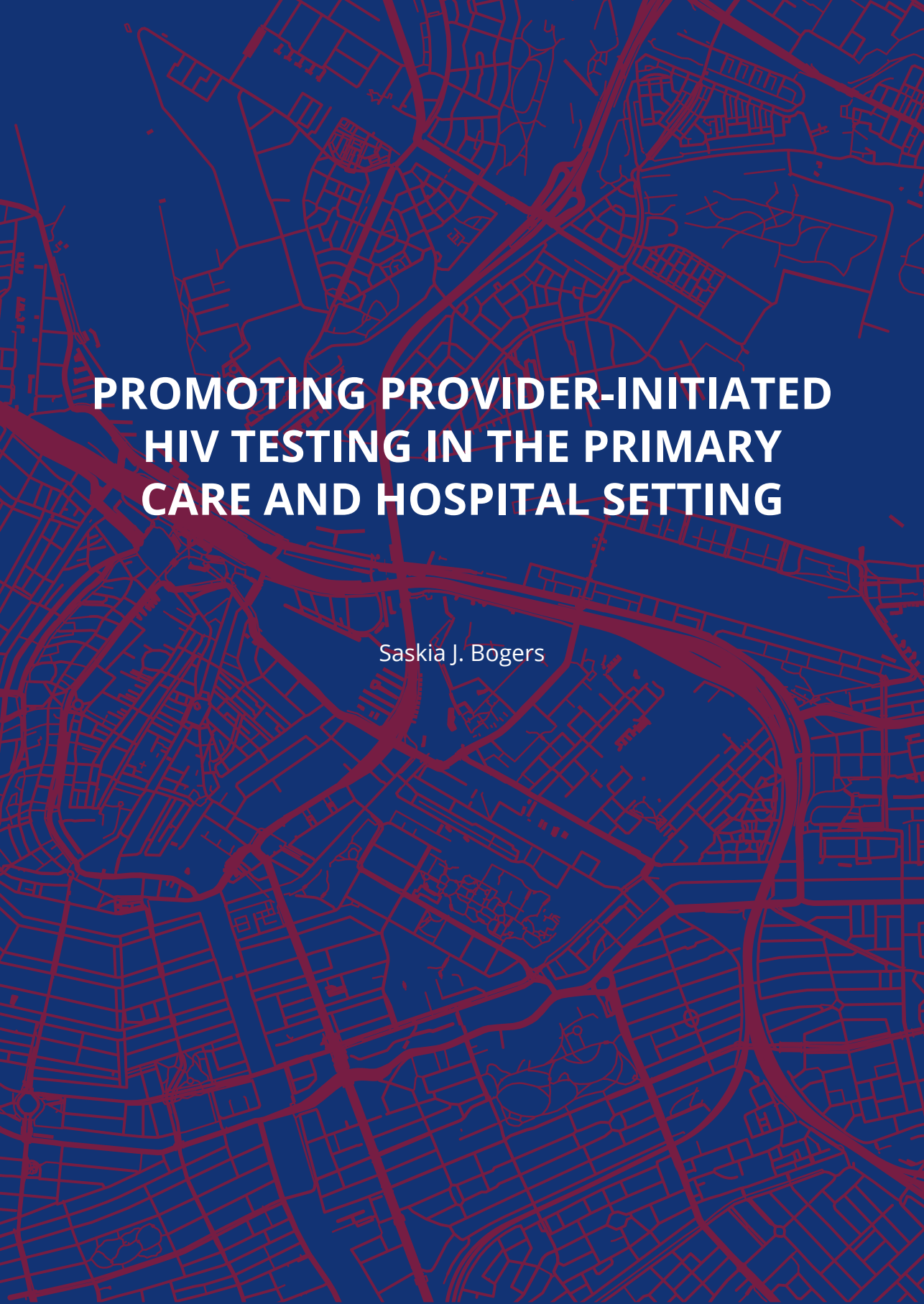

PROMOTING PROVIDER-INITIATED HIV TESTING IN THE PRIMARY CARE AND HOSPITAL SETTING

Saskia J. Bogers

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Faculteit der Geneeskunde

Voor mijn moeder,
Voor mijn zus,
Voor mijn nichtjes,
Voor alle vrouwen in de wetenschap

En voor mezelf

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I

Introduction

Chapter 1

General introduction and outline of this thesis

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

State of the HIV epidemic

Since the emergence of the Human Immunodeficiency Virus (HIV) as a public health threat in the early 80's of the last century, HIV has grown to be an epidemic with a major burden of disease. HIV disproportionally affects certain communities, including men who have sex with men (MSM), people who inject drugs, transgender people and young women in sub-Saharan Africa[1]. In 2020, an estimated 37.7 million people were living with HIV worldwide, of whom 27% were not on treatment. That same year, 1.5 million new HIV infections occurred, and 680.000 people died from causes related to the acquired immunodeficiency syndrome (AIDS) following their HIV infection[1]. However, major advances have been made in the last decade that will help curb the epidemic. First, early start of antiretroviral therapy (ART) improved the outcomes for people living with HIV[2]. Second, the proof of concepts for Undetectable = Untransmittable, and Treatment as Prevention demonstrate that adequate therapy will prevent onward transmission of HIV through sexual contact[3-5]. Third, the introduction of Pre-Exposure Prophylaxis (PrEP) as an effective biochemical strategy to prevent HIV is a valuable addition to traditional prevention strategies such as condom-use, and has a major impact on HIV prevention among key groups[6,7]. Finally, with the development of state-of-the-art HIV treatment options, including long-acting antiretroviral therapy, the burden of living with HIV may be significantly reduced and therapy adherence may be facilitated, as the regimen of lifelong daily pills can be decreased to only six intramuscular injections per year[8,9]. With these solutions, timely HIV diagnosis remains key to prevent HIV transmission and thereby ending the epidemic.

HIV in the Netherlands

The first HIV diagnoses in the Netherlands were made in 1981[10,11]. Thereafter, the annual number of individuals newly diagnosed with HIV increased to nearly 1,270 in 2008, after which a decline in incidence set in[12]. Several interventions have likely contributed to this decline, including needle-exchange programs for injection drug users, the introduction of opt-out testing for HIV at sexual health centers (SHCs) and during antenatal care, early ART initiation, online test facilities for MSM, and, more recently, the introduction of PrEP[13]. Over the last decade, the annual number of new HIV infections decreased by 82%, and in 2020 an estimated 24,000 people were living with HIV in the Netherlands, while 411 individuals were newly diagnosed[12]. However, 52% of individuals newly diagnosed had a late-stage HIV infection (a CD4 count below 350 cells/mm^3 or an AIDS-defining event regardless of CD4 count), and 33% had advanced HIV disease (a CD4 count below 200 cells/mm^3 or AIDS)[14]. This is disappointing, as late diagnosis is associated with increased morbidity, mortality, and onward HIV transmission[15,16]. The percentage diagnosed with late-stage HIV was highest among older individuals, among individuals from sub-Saharan Africa, and among heterosexual men and women[12].

City-based approach

In the Netherlands, the majority of people with HIV and the majority of new HIV diagnoses are concentrated in the four largest cities. Overall, 22% of people newly diagnosed and an estimated 27% of all people with HIV live in the region of Amsterdam[12]. Moreover, the majority of HIV infections diagnosed in Amsterdam were estimated to come from a local source[17]. From other major cities with a relatively high HIV burden such as San Francisco, we have learned that using a comprehensive city-based approach when implementing interventions is highly successful in curbing the number of new HIV diagnoses[18]. This strategy is likely to be most effective as it builds on existing community, organizational, and healthcare structures[19]. Therefore, the city of Amsterdam signed the Paris Declaration on Fast-Track Cities Ending the AIDS Epidemic, committing to ending the AIDS epidemic through a city-based approach. In 2014, a consortium of stakeholders in HIV prevention and care launched the HIV Transmission Elimination AMsterdam (H-TEAM) initiative[13]. The H-TEAM aims to deploy a city-based combination intervention strategy focused on all factors that maintain the epidemic, including prevention of new infections through PrEP, immediate treatment of acute HIV infections, awareness campaigns among key populations, and improving community and healthcare provider's HIV testing strategies to identify undiagnosed individuals living with HIV[13,20,21].

HIV testing and care services

Several HIV testing strategies are available in the Netherlands. Provider-initiated HIV testing and counseling (PITC) is mainly offered by general practitioners (GPs), during antenatal care, in the hospital setting, and at the SHCs. The latter perform opt-out testing for HIV for key groups only, including people being notified for a sexually transmitted infection (STI), people having STI symptoms, MSM, people with a non-Western migration background and people aged <25 years. MSM can also get tested through a free, online service. Additionally, in the context of client-initiated HIV testing and counseling (CITC), HIV self-tests and self-sampling kits are available for the public at pharmacies and online. In 2020, 30% of individuals received their first HIV-positive test result at an SHC, 35% at a general practice, and 29% at a hospital, thereby making these three sites the key providers for PITC[12]. However, this distribution differs by transmission group; the majority of MSM were diagnosed at an SHC, while the majority of heterosexual men were diagnosed at a general practice, and the majority of women were diagnosed at a hospital[22]. Only 7% of women were diagnosed at an SHC, and 13% were diagnosed during antenatal care. These different distributions by transmission group underline the need for tailored testing strategies that meet the preferences and needs of the populations of interest.

Indicator-condition guided testing for HIV

One strategy to improve HIV testing and facilitate earlier diagnosis is routine PITC among all persons presenting with a selection of symptoms or conditions that indicate a possible HIV infection, regardless of any other risk factors for HIV. These indicator conditions (ICs) can be divided into three categories[23]:

1. Conditions which are AIDS defining among people living with HIV
2. Conditions associated with an undiagnosed HIV prevalence of >0.1%
3. Conditions in which an undiagnosed HIV infection may have significant adverse implications for the individual's clinical management

The ICs that are currently recognized were identified by numerous studies, including the HIV indicator diseases across Europe studies (HIDES)[23-25]. In total, sixty ICs are currently recognized, and over fifteen medical specialties are involved in the care of persons presenting with ICs, including primary care, internal medicine, emergency medicine, gynecology, ophthalmology, dentistry, neurology and dermatology.

The list of AIDS defining conditions, the first category of ICs, includes non-Hodgkin lymphoma, cervical cancer, tuberculosis, and several other infectious diseases. There is a large body of evidence to support the importance of HIV testing and immediate treatment of any HIV infection identified among persons presenting with AIDS defining conditions. Offering an HIV test to such people is therefore considered routine good clinical practice[23]. The second category includes conditions that are associated with an undiagnosed HIV prevalence of >0.1%, as studies have shown that routine HIV testing is cost-effective above this threshold[23,26-28]. Among this category are several infectious diseases and infection-associated conditions, including STI, hepatitis A, B and C, anal and cervical dysplasia, herpes zoster and Guillain-Barre syndrome, as well as conditions that cannot be otherwise explained, including weight loss, lymphadenopathy, chronic diarrhea and leukocytopenia. Among the final category are conditions that require aggressive immunosuppressive therapy that may further impair the immune system of a person with HIV, including cancer and auto-immune diseases.

The main advantage of IC-guided HIV testing is that it bypasses several barriers to testing, including low perceived risk when a person is not believed to belong to one of the key populations and HIV-related stigma by the patient or the healthcare provider[29,30]. Instead, this testing strategy allows healthcare providers to emphasize its routine nature, rather than inadvertently referring to a patients' background or risk-factors. Furthermore, this testing strategy is of particular importance among individuals who do not belong to, or identify with key groups, including heterosexual native Dutch men and women and older individuals, as they are at increased risk of late-stage HIV due to low perceived risk[31,32].

HIV testing in primary care

GPs are the primary access point to healthcare in the Netherlands, and 75% of people contact their GP at least once per year[33]. GPs are the largest provider of sexual health consultations, accounting for over 70% of consultations, while the remainder of consultations are provided by the SHCs[22]. Additionally, HIV and STI self-tests and self-sampling tests are available through commercial providers, but the number of tests ordered through such providers are not monitored[22]. While data on HIV testing by SHCs are routinely reported, limited data are available on the number of HIV tests ordered by GPs, and their indications[22]. According to the Dutch guideline

on STI consultations for primary care, GPs should take a proactive attitude in offering HIV testing[34]. The guideline recommends to test for HIV in patients requesting STI testing or presenting with symptoms and who belong to one of the key populations, including MSM, persons with multiple sexual partners, migrants from HIV endemic countries, sex workers, and persons with a partner belonging to a key group. It additionally recommends testing for HIV in the presence of another STI or ICs, and to periodically offer HIV testing to all patients from key groups, as well as to all patients when holding practice in areas with an HIV prevalence of >0.2%[34]. Disappointingly, previous research showed that GPs in the Netherlands did not perform an HIV test in one third of STI consultations among persons from key groups[35]. Notably, the initiative for HIV testing was not taken by the GP in the majority of those with positive test results[35]. Moreover, 83% of people diagnosed with HIV had visited their GP at least once in the 5 years prior to HIV diagnosis, while only 35% had been offered an HIV test during this time[36]. Possible explanations for these missed opportunities are low perceived risk and a lack of adequate risk assessment by the GP, time-restraints during consultations and financial barriers[30,35,36]. While the cost of HIV and STI testing and care ordered by GPs is covered by the mandatory health insurance, a set annual deductible (€385 since 2016) is to be covered by the patient, so that patients will have to pay for any testing done if this deductible has not been depleted. Finally, HIV-related stigma may have hampered optimal testing practices, as both GPs and patients have reported HIV-related stigma in the past[30,37]. These missed opportunities are reflected by the fact that late-stage HIV was observed in 46% of diagnoses made at a general practice, compared to 28% at the SHCs.

HIV testing in the hospital setting

The largest proportion of late-stage HIV diagnoses in the Netherlands is observed in the hospital setting, where 70% of diagnoses among MSM, 83% among women and 86% among other men were at a late stage[12]. As nearly a third of new HIV diagnoses are made in hospitals, strategies to improve HIV testing and facilitate earlier diagnosis in this setting are likely to have a great impact. Therefore, adequate implementation of IC-guided testing in the hospital setting is crucial. However, this strategy is currently not adopted proficiently. For example, 21% of persons diagnosed with TB in 2020 had an unknown HIV status and HIV testing is currently not recommended in the Dutch guidelines for the diagnosis and management of cervical cancer, even though both are AIDS defining conditions[38,39]. In fact, the majority of international and European guidelines for ICs do not recommend HIV testing, likely hampering this strategy's implementation[40-42]. As a result, many studies have reported on persons presenting with late-stage HIV that had previously presented in hospitals with an IC[43-46]. Adapting guidelines, and implementing additional solutions to promote timely HIV testing is therefore needed.

Getting to zero through timely testing for HIV

The city of Amsterdam has set the goal of reaching zero new HIV infections by 2026[47]. To this end, HIV testing practices in the primary care and hospital setting need to be further improved. Reducing the proportion of undiagnosed people living with HIV and the proportion presenting with late-stage infection through PITC will help

the city of Amsterdam reach its ambitious goals. Interventions should build upon existing evidence on effective strategies to change healthcare providers' behavior. In addition to guideline adaptations, examples are the use of multifaceted educational interventions for healthcare providers, the use of graphical audit and feedback on their HIV testing behavior and additional solutions that facilitate HIV testing in the context of a busy healthcare practice[48-54]. Ultimately, making HIV testing a routine practice is paramount to prevent missed opportunities to diagnose individuals living with HIV. The efficiency of routine testing strategies in preventing missed opportunities for HIV testing is illustrated by the fact that since 2004, all pregnant women in the Netherlands are offered HIV testing on an opt-out basis, and the number opting out is negligible[55].

AIM AND OUTLINE OF THIS THESIS

The aim of the studies in this thesis is to evaluate the implementation and effect of interventions to improve provider-initiated testing for HIV in the primary care and hospital setting in Amsterdam, the Netherlands. Optimal testing strategies may lead to earlier HIV diagnosis and prevent adverse outcomes associated with late-stage diagnosis, while also preventing onward HIV transmission.

Part II – Primary care setting
In **Chapter 2**, we compare HIV testing and HIV positivity by GPs versus SHCs in five regions in the Netherlands to gain insight into strategies to improve HIV testing, to enable timely detection of HIV infections, and how this varies by region.

In **Chapter 3**, we describe the design and implementation of an educational intervention to improve HIV testing by GPs in Amsterdam. We additionally explore trends in GPs' HIV, chlamydia and gonorrhea testing behavior from 2011 through 2017 using diagnostic laboratory data from the seven largest primary care diagnostic laboratories in Amsterdam.

In **Chapter 4**, we evaluate the effect of the educational intervention on HIV and STI testing rates by GPs in Amsterdam, the Netherlands, using laboratory data from 2011 through 2020. We compare HIV testing by GPs who participated in the program to GPs who have not yet participated to evaluate changes in HIV, chlamydia and gonorrhea testing following the educational intervention, to assess its effectivity.

In **Chapter 5**, we report on a mixed-methods study using questionnaires and semi-structured interviews from GPs who participated in the educational intervention. Our objective was to acquire a deeper understanding of how the quality of GPs' HIV and STI testing knowledge, attitudes and behavior changed following the intervention. Additionally, we aimed to identify contextual factors influencing GP's HIV and STI testing behavior that need to be addressed in the future.

Part III – Hospital setting

In **Chapter 6**, we report on the adoption of IC-guided testing strategies among various healthcare settings in Western countries through a systematic review and meta-analysis. We additionally report on the outcomes of this testing strategy (i.e. the percentage positive), as an indication for its cost-effectiveness.

In **Chapter 7**, we present our protocol for an intervention study to improve awareness of IC-guided testing and increase HIV testing in patients presenting with a selection of seven ICs at five different medical specialties, in five hospitals in the region of Amsterdam.

In **Chapter 8**, we evaluate determinants for IC-guided HIV testing in a variety of hospital settings through a survey study performed in five hospitals in the region of Amsterdam. By using the theory of planned behavior framework, we assess what domains have the largest contribution to planned behavior and actual self-reported behavior.

In **Chapter 9**, we evaluate the effect of our intervention on the proportion of patients diagnosed with an IC who were tested for HIV within 3 months before or after IC diagnosis. We additionally assess whether reasons for not testing were reported, and details on individuals newly diagnosed with HIV through this testing strategy.

In **Chapter 10**, we assess the HIV testing ratio among malignant lymphoma patients at five hospitals in Amsterdam and map factors influencing hematologists' HIV testing behavior in lymphoma patients using questionnaires and semi-structured interviews.

Part IV – Conclusions

In **Chapter 11**, we discuss the outcomes of this thesis, resulting in a final conclusion and implications for further research and policy changes.

REFERENCES

1. UNAIDS. UNAIDS data 2021. Geneva, Switzerland; 2021. Available at: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf. Last accessed 7 July 2022.
2. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;**373(9)**:795-807.
3. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;**393(10189)**:2428-38.
4. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med* 2016;**375(9)**:830-9.
5. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS* 2006;**20(10)**:1447-50.
6. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* 2015;**373(23)**:2237-46.
7. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016;**387(10013)**:53-60.
8. Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med* 2020;**382(12)**:1112-23.
9. Venkatesan P. Long-acting injectable ART for HIV: a (cautious) step forward. *Lancet Microbe* 2022;**3(2)**:e94.
10. Prummel MF, ten Berge RJ, Barrowclough H, Cejka V. [Kaposi's sarcoma and fatal opportunistic infections in a homosexual man with immunodeficiency]. *Ned Tijdschr Geneeskd* 1983;**127(19)**:820-4.
11. Reiss P, Razenberg PP, de Geus JP, Schellekens PT. [A patient with a mild form of the acquired immunodeficiency syndrome (AIDS)]. *Ned Tijdschr Geneeskd* 1983;**127(19)**:824-5.
12. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2021. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2021. Available at www.hiv-monitoring.nl. Last accessed 7 July 2022.
13. de Bree GJ, van Sighem A, Zuilhof W, et al. Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam. *Curr Opin HIV AIDS* 2019;**14(6)**:455-63.
14. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med* 2011;**12(1)**:61-4.
15. Girardi E, Sabin CA, Monforte AD. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. *J Acquir Immune Defic Syndr* 2007;**46 Suppl 1**:S3-8.
16. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). *PLoS Med* 2013;**10(9)**:e1001510.
17. Blenkinsop A, Monod M, van Sighem A, et al. Estimating the potential to prevent locally acquired HIV infections in a UNAIDS Fast-Track City, Amsterdam2022 [preprint].

18. Jones A, Cremin I, Abdullah F, et al. Transformation of HIV from pandemic to low-endemic levels: a public health approach to combination prevention. *Lancet* 2014;**384(9939)**:272-9.

19. UNAIDS. The cities report. UNAIDS Outlook 2014. Available at: https://www.unaids.org/sites/default/files/media_asset/JC2687_TheCitiesReport_en.pdf. Last accessed 7 July 2022. Geneva, Switzerland 2014.

20. Dijkstra M, van Rooijen MS, Hillebregt MM, et al. Decreased Time to Viral Suppression After Implementation of Targeted Testing and Immediate Initiation of Treatment of Acute Human Immunodeficiency Virus Infection Among Men Who Have Sex With Men in Amsterdam. *Clin Infect Dis* 2021;**72(11)**:1952-60.

21. Hoornenborg E, Coyer L, Achterbergh RCA, et al. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. *Lancet HIV* 2019;**6(7)**:e447-e55.

22. Staritsky LE, Visser M, Aar Fv, et al. Sexually transmitted infections in the Netherlands in 2020. National Institute for Public Health and the Environment (RIVM). Bilthoven 2021. Available at: https://www.rivm.nl/bibliotheek/rapporten/2021-0052.pdf. Last accessed 7 July 2022.

23. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. Available at https://www.eurotest.org/Projects-Collaborations/Indicator-Condition-Guided-HIV-Testing-HIDES/Guidance-HIV-Indicator-Conditions. Last accessed 7 July 2022.

24. Raben D, Sullivan AK, Mocroft A, et al. Improving the evidence for indicator condition guided HIV testing in Europe: Results from the HIDES II Study - 2012 - 2015. *PLoS One* 2019;**14(8)**:e0220108.

25. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.

26. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. *N Engl J Med* 2005;**352(6)**:586-95.

27. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med* 2005;**352(6)**:570-85.

28. Yazdanpanah Y, Sloan CE, Charlois-Ou C, et al. Routine HIV screening in France: clinical impact and cost-effectiveness. *PLoS One* 2010;**5(10)**:e13132.

29. Mimiaga MJ, Johnson CV, Reisner SL, Vanderwarker R, Mayer KH. Barriers to routine HIV testing among Massachusetts community health center personnel. *Public Health Rep* 2011;**126(5)**:643-52.

30. Joore IK, van Roosmalen SL, van Bergen JE, van Dijk N. General practitioners' barriers and facilitators towards new provider-initiated HIV testing strategies: a qualitative study. *Int J STD AIDS* 2017;**28(5)**:459-66.

31. Justice AC, Goetz MB, Stewart CN, et al. Delayed presentation of HIV among older individuals: a growing problem. *Lancet HIV* 2022;**9(4)**:e269-e80.

32. van Opstal SEM, van der Zwan JS, Wagener MN, et al. Late Presentation of HIV Infection in the Netherlands: Reasons for Late Diagnoses and Impact on Vocational Functioning. *AIDS Behav* 2018;**22(8)**:2593-603.

33. Nielen M, Weesie, Y, Davids, R, Winckers, M, Korteweg, L, Leeuw, E de, Urbanus, T, Dijk, L van, Korevaar, J, Hasselaar, J, Hek, K. Zorg door de huisarts. Nivel Zorgregistraties Eerst Lijn: jaarcijfers 2020 en trendcijfers 2016-2020. NIVEL. Utrecht 2021. Available at: https://nivel.nl/sites/default/files/bestanden/1004116.pdf. Last accessed 7 July 2022.

34. Van Bergen J, Dekker J, Boeke A, et al. NHG-Standaard Het soa-consult (Eerste herziening) (Dutch). *Huisarts Wet* 2013;**56(9)**:450-63.

35. Joore IK, Reukers DF, Donker GA, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. *BMJ Open* 2016;**6(1)**:e009194.

36. Joore IK, Geerlings SE, Brinkman K, van Bergen JE, Prins JM. The importance of registration of sexual orientation and recognition of indicator conditions for an adequate HIV risk-assessment. *BMC Infect Dis* 2017;**17(1)**:178.

37. Stutterheim SE, Kuijpers KJR, Walden MI, Finkenflugel RNN, Brokx PAR, Bos AER. Trends in HIV Stigma Experienced by People Living With HIV in the Netherlands: A Comparison of Cross-Sectional Surveys Over Time. *AIDS Educ Prev* 2022;**34(1)**:33-52.

38. Slump E, Beurden KMv, Boogaard Jvd, et al. Tuberculose in Nederland 2020. Surveillancerapport. National Institute for Public Health and the Environment (RIVM). Bilthoven2021. Available at: https://www.rivm.nl/bibliotheek/rapporten/2021-0192.pdf. Last accessed 7 July 2022.

39. Nederlandse Vereniging van Obstetrie en Gynaecologie (NVOG). Richtlijn Cervixcarcinoom (Dutch). In: Federatie van Medisch Specialisten, editor. 2022. Available at https://richtlijnendatabase.nl/richtlijn/cervixcarcinoom/startpagina_-_cervixcarcinoom.html. Last accessed 7 July 2022.

40. Lin YD, Eades L, Nair A, Korman TM, Woolley I. Review of HIV testing recommendations in Australian specialty guidelines for HIV indicator conditions: a missed opportunity for recommending testing? *Intern Med J* 2020;**50(3)**:293-8.

41. Lord E, Stockdale AJ, Malek R, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. *HIV Med* 2017;**18(4)**:300-4.

42. Jordans CCE, Vasylyev M, Rae C, et al. National medical specialty guidelines of HIV indicator conditions in Europe lack adequate HIV testing recommendations: a systematic guideline review. *Eurosurveillance* 2022;**27(48)**:2200338.

43. Levy I, Maor Y, Mahroum N, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. *BMJ Open* 2016;**6(11)**:e012721.

44. Lin YD, Garner SE, Lau JSY, Korman TM, Woolley IJ. Prevalence of HIV indicator conditions in late presenting patients with HIV: a missed opportunity for diagnosis? *QJM* 2019;**112(1)**:17-21.

45. Powell M, Krentz HB, Eagles ME, Gill MJ. Missed opportunities within healthcare for an earlier diagnosis of HIV. *Int J STD AIDS* 2020;**31(12)**:1169-77.

46. van den Bogaart L, Ranzani A, Oreni L, et al. Overlooked cases of HIV infection: An Italian tale of missed diagnostic opportunities. *Eur J Intern Med* 2020;**73**:30-5.

47. Sedee M. Amsterdam wil naar nul hiv-infecties. NRC Handelsblad. 2020, June 10. Available at: https://www.nrc.nl/nieuws/2020/06/10/amsterdam-wil-naar-nul-hiv-infecties-a4002458.

48. Desai S, Tavoschi L, Sullivan AK, et al. HIV testing strategies employed in health care settings in the European Union/European Economic Area (EU/EEA): evidence from a systematic review. *HIV Med* 2020;**21(3)**:163-79.

49. Sokhi DS, Oxenham C, Coates R, Forbes M, Gupta NK, Blackburn DJ. Four-Stage Audit Demonstrating Increased Uptake of HIV Testing in Acute Neurology Admissions Using Staged Practical Interventions. *PLoS One* 2015;**10(9)**:e0134574.

50. Spoorenberg V, Hulscher ME, Geskus RB, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. *PLoS One* 2015;**10(12)**:e0142672.

51. van Daalen FV, Prins JM, Opmeer BC, et al. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. *Clin Microbiol Infect* 2017;**23(7)**:485 e1- e8.

52. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013;**8**:35.

53. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;**362(9391)**:1225-30.

54. Apers H, Nostlinger C, Van Beckhoven D, et al. Identifying key elements to inform HIV-testing interventions for primary care in Belgium. *Health Promot Int* 2020;**35(2)**:301-11.

55. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Prenatale Screening, Infectieziekten en Erytrocytenimmunisatie (PSIE) procesmonitor 2019 (Dutch). 2019. Available at https://www.pns.nl/documenten/proces-monitor-psie. Last accessed 7 July 2022.

Part

II

Primary care setting

Chapter 2

Who is providing HIV diagnostic testing? Comparing HIV testing by general practitioners and sexual health centres in five regions in the Netherlands, 2011-2018

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ABSTRACT

Objectives
General practitioners (GPs) and sexual health centres (SHCs) are the main providers of HIV testing and diagnose two-thirds of HIV infections in the Netherlands. We compared regional HIV testing and positivity by GPs versus SHCs to gain insight into strategies to improve HIV testing, to enable timely detection of HIV infections.

Methods
Laboratory data (2011–2018) on HIV testing by GPs and SHCs in five Dutch regions with varying levels of urbanisation were evaluated. Regional HIV testing rates per 10 000 residents ≥15 years (mean over period and annual) were compared between providers using negative binomial generalised additive models and additionally stratified by sex and age (15–29 years, 30–44 years, 45–59 years, ≥60 years). $\chi 2$ tests were used to compare positivity percentage between the two groups of providers.

Results
In the study period, 505 167 HIV tests (GP 36%, SHC 64%) were performed. The highest HIV testing rates were observed in highly urbanised regions, with large regional variations. The HIV testing rates ranged from 28 to 178 per 10 000 residents by GPs and from 30 to 378 per 10 000 by SHCs. Testing rates by GPs were lower than by SHCs in three regions and comparable in two. In all regions, men were tested less by GPs than by SHCs; for women, this varied by region. Among those aged 15–29 years old, GPs' testing rates were lower than SHCs', while this was reversed in older age categories in four out of five regions. The overall mean HIV positivity was 0.4%. In contrast to other regions, positivity in Amsterdam was significantly higher among individuals tested by GPs than by SHCs.

Conclusions
This retrospective observational study shows that besides SHCs, who perform opt-out testing for key groups, GPs play a prominent role in HIV testing, especially in non-key populations, such as women and older individuals. Large regional variation exists, requiring region-specific interventions to improve GPs' HIV testing practices.

INTRODUCTION

In the Netherlands, a declining trend in annual number of newly diagnosed HIV infections has been observed since 2008[1]. By the end of 2018, an estimated 23,300 people were living with HIV, of whom a substantial proportion (n=1900, 8%) were estimated to be unaware of their infection[1]. In that same year, about half of newly diagnosed HIV infections were late-stage infections[1]. An important step towards zero new HIV infections is ensuring timely diagnosis and treatment through optimal HIV testing strategies. As the Dutch HIV epidemic is not affecting all regions equally, with clustering in very highly urbanised regions such as the cities of Amsterdam and Rotterdam[2], region-specific tailored approaches for optimised HIV testing and care are warranted.

Nearly 70% of STI consultations are performed by general practitioners (GPs) in the Netherlands[3]. In addition, sexual health centres (SHCs) provide client-initiated STI testing and care for key groups, such as people being notified for an STI, people having STI symptoms, men who have sex with men (MSM), people with a non-Western migratory background and people aged <25 years. GPs and SHCs are therefore the main access points for STI testing and care, but there are important differences in accessibility between GPs and SHCs. The GP is readily accessible for all, while the SHC is only accessible for key groups. GPs usually test for HIV at the request of the patient, and guidelines recommend testing for HIV based on risk assessment and symptoms and in the presence of HIV indicator conditions[4]. The cost of HIV testing by a GP is not covered by health insurance if the obligatory annual deductible (currently €385) has not been reached. In contrast, at the SHC, testing and care are free of charge. Since 2015, SHCs have been offering HIV testing for key groups on an opt-out basis, with the exception of heterosexual attendees <25 years who are tested for HIV on indication only[5]. The number of SHC attendees is limited by financial restrictions imposed by national policy[5].

GPs and SHCs diagnose 36% and 27% of new HIV infections in the Netherlands, respectively, with the remainder being diagnosed in hospitals or other settings such as antenatal care services[1,6]. However, the number of HIV tests performed by GPs and their contribution to HIV testing compared with SHCs in the Netherlands are unknown. Insight into this contribution is needed to identify opportunities for improved HIV testing strategies. Therefore, this study aimed to compare HIV testing and positivity by GPs versus SHCs in five Dutch regions with different levels of urbanisation. We expect that opportunities for improved HIV testing predominantly lie with GPs due to their accessibility in all geographical areas and because HIV testing by SHCs is already done on an opt-out basis in key populations.

METHODS

Design and setting

In this retrospective observational study, we used laboratory data (2011–2018) on HIV testing and HIV positivity by healthcare provider (GP or SHC) from five regions in the Netherlands (Amsterdam, Rotterdam, Maastricht, Twente, North Netherlands). The five participating regions accounted for 24% of the total Dutch population of 17.2 million in 2018[7]. These regions were selected because a collaboration was already established[8], and to provide an overview of HIV testing in settings with varying levels of urbanisation in the Netherlands. As shown in figure 1, each region consists of one or more municipalities, varying in level of urbanisation (number of residents per square kilometre, based on 2018 data). The regions ranged from rural (North Netherlands, N-NL: 208 residents/km^2) to very highly urbanised (Amsterdam: 5160 residents/km^2; Rotterdam: 2936 residents/km^2).

Data collection

All laboratories performing diagnostics for GPs and SHCs in participating regions were approached for data collection. The annual number of HIV tests performed by GPs and SHCs and the number of positive HIV tests were collected, stratified by sex and age category (15–29, 30–44, 45–59 and ≥60 years). HIV tests as part of antenatal screening were excluded. The aggregated laboratory data were combined with the number of residents and level of urbanisation per region, as publicly available from Statistics Netherlands[9]. Data were included if both the patient's and the healthcare provider's postal code were within the region. For GPs in Amsterdam, the patient's postal code was not available; thus, inclusion was based only on the postal code of the GP. For the N-NL region, all GP laboratory data were included irrespective of postal code. SHC data for N-NL in 2015 were missing as diagnostics for SHCs were performed by a foreign laboratory in that year and could not be retrieved.

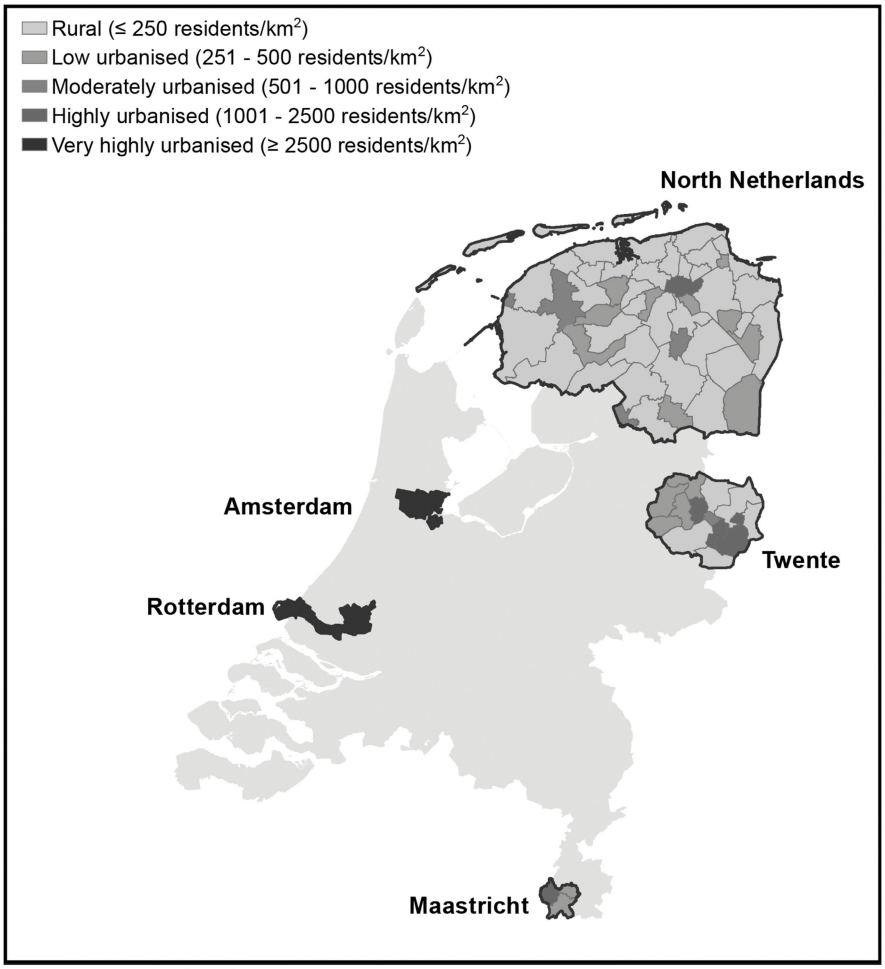
Case definition

An HIV test was defined as a serum HIV antibody test, antigen test or a combination test (HIV antibody and p24 antigen). Multiple HIV tests performed within 21 days were counted as one to exclude repeat or confirmation tests. The HIV test result was defined as the result of the last test performed within a 21-day window to exclude possible false positive and false negative test results.

Data coverage

The SHC data coverage was 100%, since laboratory services for SHCs are performed by a single laboratory per region. GPs may contract various diagnostic laboratories. As we were not able to collect data from all laboratories that perform diagnostics for GPs, GP data coverage was estimated by each region to adjust for incomplete data. The estimated GP data coverage ranged from 72% to 92% (figure 1).

Figure 1 Urbanisation map of the Netherlands and study region descriptives[1].



Region	Total no. of residents ≥15 years	Population density[2]	Urbanisation[3]	Age distribution (%) 15-29y, 30-44y, 45-59y, ≥60y	GP test data coverage[4]
Netherlands	**14,418,460**	**510**	**Moderately urbanised**	**22.4%, 21.6%, 26.1%, 30.0%**	**NA**
Amsterdam	728,040	5,160	Very highly urbanised	28.2%, 28.6%, 22.8%, 20.4%	91%
Rotterdam	535,290	2,936	Very highly urbanised	26.8%, 25.4%, 23.3%, 24.5%	92%
Maastricht	146,363	967	Moderately urbanised	27.8%, 16.9%, 22.9%, 32.4%	81%
Twente	524,526	422	Low urbanised	22.4%, 20.6%, 25.9%, 31.1%	72%
North Netherlands	1,456,292	208	Rural	22.0%, 19.6%, 26.0%, 32.4%	92%

[1]Based on 2018. [2]Number of residents per square kilometre. [3]Level of urbanisation by region; each region consists of one or more municipalities. [4]Estimated GP test data coverage to adjust for incomplete HIV test data, as we were not able to collect data from all laboratories that perform diagnostics for GPs. GP, general practitioner; NA, not applicable.

Statistical analysis

Overall mean and annual HIV testing rates (number of tests per 10 000 residents) were calculated for each region and stratified by provider group, sex and age category. We compared HIV testing rates between provider groups with SHC as reference, calculating rate ratios (RR) and their 95% CI. Rates were modelled using generalised additive models (GAM), with the log of total number of residents as offset. Since outcomes were overdispersed, they were modelled assuming a negative binomial distribution. To correct for missing data, HIV testing rates and GAM analyses including GP data were adjusted for regional GP data coverage by multiplying the number of tests with 1/ coverage for each region. Overall mean positivity percentages (number of positive tests out of tests performed) were calculated for each region, and compared between providers using χ^2 tests, or Fisher's exact tests when more than 20% of the cells had an expected frequency below five. For all calculations in the region of N-NL, GP and SHC data for 2015 were excluded as SHC data were missing. All analyses were performed using R V.3.6.3. A p value <0.05 was considered statistically significant.

RESULTS

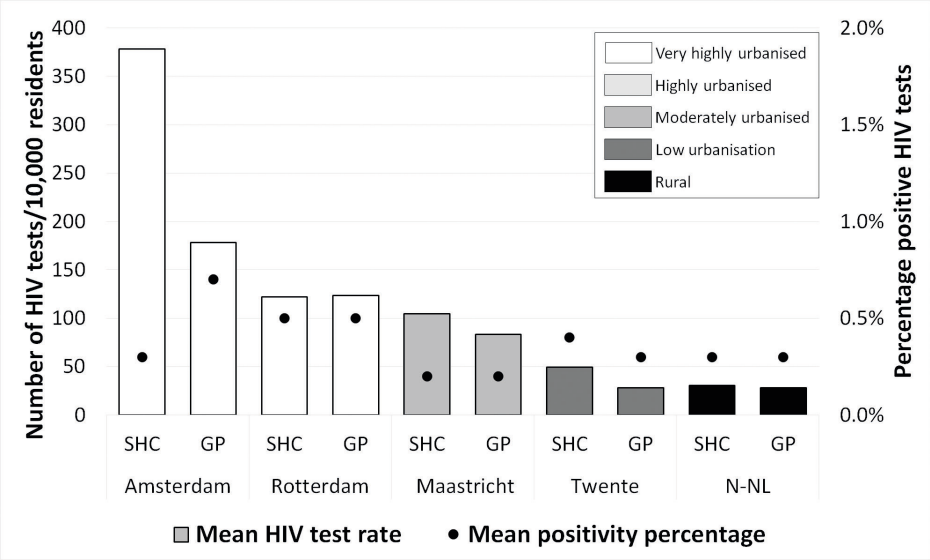
Laboratory data

We analysed 505,167 HIV tests performed by GPs and SHCs from the five included regions from 2011 to 2018 (supplementary table 1). GPs and SHCs from the very highly urbanised regions of Amsterdam and Rotterdam performed the largest proportion of tests of the included study regions (59% from Amsterdam and 19% from Rotterdam, respectively). SHCs conducted more tests compared with GPs (323,370 (64%) vs 181,797 (36%)), with the vast majority of SHC tests done in Amsterdam (65%, 209,610 of 323,370). In total, 2128 HIV tests were positive, 1156 (54%) from SHCs and 972 (46%) from GPs. The largest number of positive HIV tests was reported in Amsterdam (1268, 60%), followed by Rotterdam (508, 24%), N-NL (200, 9%), Twente (117, 6%) and Maastricht (35, 2%).

Mean HIV testing rates

Figure 2 and table 1 show the overall mean HIV testing rates per 10,000 residents by provider per region. The mean HIV testing rates decreased with decreasing level of urbanisation. In three regions with varying levels of urbanisation—Amsterdam, Maastricht and Twente—GPs' testing rates were lower than SHCs', with the biggest difference between providers observed in Amsterdam (RR 0.47, 95% CI 0.44 to 0.50). In the very highly urbanised region of Rotterdam and in the rural region of N-NL, mean testing rates were comparable between GPs and SHCs (RR 1.01, 95% CI 0.97 to 1.05 and RR 0.93, 95% CI 0.88 to 0.97, respectively).

Figure 2 Mean number of HIV tests per 10,000 residents ≥15 years and mean HIV positivity percentage, by provider, in five regions in the Netherlands, 2011–2018.



GP test data were corrected for estimated HIV test data coverage per region. Data in 2015 for N-NL are missing and not included in the calculations. GP, general practitioner; N-NL, North Netherlands; SHC, sexual health centre.

Table 1 Mean HIV testing rate per 10,000 residents ≥15 years and comparison between GPs and SHC in five regions in the Netherlands, total and by sex and age category, 2011-2018.

	GP[1]	SHC	GP versus SHC
	Mean HIV testing rate (n/10,000)	Mean HIV testing rate (n/10,000)	RR (95%CI)[2]
Very highly urbanised regions			
Amsterdam			
Total	178	378	0.47 (0.44 - 0.50)
Men	195	453	0.43 (0.39 - 0.46)
Women	163	306	0.53 (0.49 - 0.57)
15 – 29 years	208	850	0.24 (0.20 - 0.28)
30 – 44 years	268	357	0.75 (0.71 - 0.79)
45 – 59 years	144	143	1.00 (0.94 - 1.07)
60+ years	43	30	1.42 (1.29 - 1.55)
Rotterdam			
Total	123	122	1.01 (0.97 - 1.05)
Men	124	154	0.81 (0.76 - 0.86)
Women	122	91	1.34 (1.28 - 1.40)
15 – 29 years	209	298	0.70 (0.65 - 0.75)
30 – 44 years	179	122	1.47 (1.40 - 1.54)
45 – 59 years	74	38	1.94 (1.82 - 2.05)
≥60 years	16	8	2.12 (1.87 - 2.37)

Table 1 Mean HIV testing rate per 10,000 residents ≥15 years and comparison between GPs and SHC in five regions in the Netherlands, total and by sex and age category, 2011-2018. (continued)

	GP[1]	SHC	GP versus SHC
	Mean HIV testing rate (n/10,000)	Mean HIV testing rate (n/10,000)	RR (95%CI)[2]
Moderately urbanised region			
Maastricht			
Total	83	104	0.80 (0.72 - 0.88)
Men	88	116	0.76 (0.65 - 0.87)
Women	79	93	0.84 (0.73 - 0.96)
15 – 29 years	156	288	0.54 (0.44 - 0.65)
30 – 44 years	140	86	1.62 (1.45 - 1.80)
45 – 59 years	52	42	1.25 (1.02 - 1.47)
≥60 years	13	8	1.67 (1.24 - 2.10)
Low urbanised region			
Twente			
Total	28	50	0.57 (0.50 - 0.64)
Men	29	61	0.48 (0.38 - 0.57)
Women	28	38	0.72 (0.62 - 0.82)
15 – 29 years	48	128	0.38 (0.28 - 0.48)
30 – 44 years	52	58	0.90 (0.79 - 1.02)
45 – 59 years	20	27	0.73 (0.57 - 0.90)
≥60 years	3	4	0.62 (0.22 - 1.02)
Rural region			
North Netherlands[3]			
Total	28	30	0.93 (0.88 - 0.97)
Men	27	32	0.86 (0.79 - 0.92)
Women	29	29	1.00 (0.93 - 1.07)
15 – 29 years	56	91	0.62 (0.55 - 0.68)
30 – 44 years	48	28	1.72 (1.63 - 1.81)
45 – 59 years	18	15	1.22 (1.10 - 1.34)
≥60 years	3	2	1.35 (1.07 - 1.64)

[1]GP test data were corrected for estimated HIV test data coverage per region. [2]Reference = SHC. [3]2015 data were missing for this region and not included in the calculations. GP, general practitioner; RR, rate ratio; SHC, sexual health centre.

In all regions, men were tested less by GPs than by SHCs. This pattern was also observed for women in Amsterdam, Twente and Maastricht, but not in Rotterdam and N-NL. In general, RR increased with increasing patient age categories. In the youngest age category (15–29 years), testing rates by GPs were lower than those by SHCs (RR ranging from 0.24, 95% CI 0.20 to 0.28, to 0.70, 95% CI 0.65 to 0.75), while in the older age categories this was reversed for all regions except Twente.

Annual HIV testing rates

Comparing annual HIV testing rates by GPs and SHCs revealed that GPs' rate relative to that of SHCs decreased over time in the very highly urbanised region of Amsterdam and the low urbanised region of Twente (table 2). In Amsterdam the RR comparing GP versus SHC decreased most: from 0.72 (95% CI 0.70 to 0.75) in 2011 to 0.40 (95% CI 0.38 to 0.43) in 2018. This decrease was caused by a strong increase in testing by SHCs (HIV testing rate of 314.7 in 2011 to 430.1 per 10,000 residents in 2018). The decrease in RR was observed in all subgroups in Amsterdam and most subgroups in Twente, with the strongest decrease among men and those aged 15–29 years old. In other regions, the RR remained more stable (Rotterdam and Maastricht) or increased over time (N-NL).

Mean HIV positivity percentage

The overall mean HIV positivity percentage for all provider groups and regions was 0.4%. As shown in figure 2, the highest mean positivity percentages were reported in the very highly urbanised regions of Amsterdam (GP 0.7%, SHC 0.3%) and Rotterdam (GP 0.5%, SHC 0.5%), while the lowest positivity percentages were reported in the urbanised area of Maastricht (GP 0.2%, SHC 0.2%). In Amsterdam, the positivity percentages were statistically significantly higher among people tested by GPs compared with those tested by SHCs ($p<0.001$). No statistically significant difference in positivity was found in the other regions.

Table 2 Annual rate ratios comparing HIV testing rates per 10,000 residents ≥15 years between GPs[1] and SHC in five regions in the Netherlands, total and by sex and age categories, 2011-2018.

	Amsterdam RR (95% CI)[2]	Rotterdam RR (95% CI)[2]	Maastricht RR (95% CI)[2]	Twente RR (95% CI)[2]	N-NL RR (95% CI)[2]
Total					
2011	0.72 (0.70 - 0.75)	1.03 (0.99 - 1.07)	0.67 (0.59 - 0.74)	0.86 (0.79 - 0.92)	0.64 (0.59 - 0.68)
2012	0.63 (0.60 - 0.66)	0.98 (0.94 - 1.02)	0.97 (0.90 - 1.05)	0.70 (0.63 - 0.76)	0.77 (0.72 - 0.82)
2013	0.50 (0.47 - 0.53)	0.93 (0.89 - 0.97)	0.79 (0.72 - 0.87)	0.50 (0.43 - 0.56)	0.70 (0.65 - 0.75)
2014	0.35 (0.32 - 0.38)	0.94 (0.90 - 0.98)	0.66 (0.58 - 0.74)	0.40 (0.33 - 0.47)	0.57 (0.52 - 0.62)
2015	0.45 (0.42 - 0.48)	1.12 (1.08 - 1.16)	1.02 (0.93 - 1.11)	0.54 (0.46 - 0.62)	NA
2016	0.43 (0.40 - 0.46)	1.05 (1.01 - 1.10)	0.89 (0.80 - 0.98)	0.53 (0.45 - 0.60)	1.45 (1.39 - 1.50)
2017	0.39 (0.36 - 0.42)	0.95 (0.91 - 0.99)	0.77 (0.69 - 0.86)	0.57 (0.50 - 0.64)	1.31 (1.26 - 1.36)
2018	0.40 (0.38 - 0.43)	1.14 (1.10 - 1.18)	0.75 (0.66 - 0.84)	0.56 (0.49 - 0.63)	1.68 (1.63 - 1.74)
Men					
2011	0.67 (0.63 - 0.70)	0.94 (0.89 - 1.00)	0.69 (0.59 - 0.80)	0.78 (0.69 - 0.87)	0.61 (0.54 - 0.68)
2012	0.58 (0.55 - 0.62)	0.84 (0.78 - 0.89)	1.01 (0.90 - 1.12)	0.59 (0.50 - 0.68)	0.70 (0.63 - 0.77)
2013	0.50 (0.46 - 0.54)	0.83 (0.77 - 0.88)	0.83 (0.73 - 0.93)	0.44 (0.35 - 0.53)	0.67 (0.60 - 0.74)
2014	0.39 (0.35 - 0.43)	0.84 (0.78 - 0.89)	0.67 (0.57 - 0.78)	0.37 (0.27 - 0.46)	0.59 (0.52 - 0.65)
2015	0.43 (0.39 - 0.47)	0.82 (0.76 - 0.87)	0.80 (0.69 - 0.92)	0.42 (0.31 - 0.52)	NA
2016	0.37 (0.33 - 0.40)	0.75 (0.70 - 0.80)	0.76 (0.65 - 0.88)	0.43 (0.33 - 0.53)	1.14 (1.07 - 1.21)
2017	0.32 (0.29 - 0.36)	0.69 (0.64 - 0.74)	0.65 (0.54 - 0.77)	0.43 (0.34 - 0.52)	0.96 (0.90 - 1.02)
2018	0.34 (0.31 - 0.38)	0.81 (0.76 - 0.86)	0.65 (0.53 - 0.77)	0.45 (0.36 - 0.54)	1.50 (1.43 - 1.56)
Women					
2011	0.79 (0.75 - 0.83)	1.12 (1.07 - 1.18)	0.65 (0.55 - 0.75)	0.95 (0.86 - 1.04)	0.65 (0.59 - 0.71)
2012	0.68 (0.65 - 0.72)	1.17 (1.11 - 1.22)	0.94 (0.83 - 1.04)	0.84 (0.74 - 0.93)	0.83 (0.77 - 0.90)
2013	0.49 (0.45 - 0.53)	1.06 (1.01 - 1.12)	0.75 (0.65 - 0.86)	0.57 (0.48 - 0.66)	0.72 (0.66 - 0.79)

Table 2 Annual rate ratios comparing HIV testing rates per 10,000 residents ≥15 years between GPs[1] and SHC in five regions in the Netherlands, total and by sex and age categories, 2011-2018. (continued)

	Amsterdam RR (95% CI)[2]	Rotterdam RR (95% CI)[2]	Maastricht RR (95% CI)[2]	Twente RR (95% CI)[2]	N-NL RR (95% CI)[2]
2014	0.31 (0.27 - 0.35)	1.07 (1.02 - 1.13)	0.65 (0.54 - 0.75)	0.44 (0.33 - 0.54)	0.55 (0.48 - 0.62)
2015	0.49 (0.45 - 0.53)	1.71 (1.65 - 1.78)	1.40 (1.26 - 1.53)	0.79 (0.67 - 0.91)	NA
2016	0.54 (0.50 - 0.58)	1.70 (1.64 - 1.77)	1.10 (0.96 - 1.23)	0.72 (0.60 - 0.83)	1.96 (1.89 - 2.04)
2017	0.52 (0.48 - 0.56)	1.54 (1.48 - 1.60)	0.97 (0.84 - 1.10)	0.88 (0.77 - 0.98)	2.09 (2.01 - 2.16)
2018	0.54 (0.50 - 0.58)	1.94 (1.88 - 2.01)	0.91 (0.77 - 1.05)	0.79 (0.68 - 0.89)	1.99 (1.91 - 2.06)
15 - 29 years					
2011	0.43 (0.39 - 0.46)	0.74 (0.69 - 0.79)	0.50 (0.41 - 0.59)	0.67 (0.59 - 0.76)	0.43 (0.37 - 0.49)
2012	0.35 (0.31 - 0.38)	0.70 (0.65 - 0.75)	0.70 (0.61 - 0.80)	0.47 (0.38 - 0.56)	0.54 (0.47 - 0.60)
2013	0.25 (0.21 - 0.29)	0.63 (0.58 - 0.68)	0.56 (0.47 - 0.66)	0.33 (0.24 - 0.42)	0.44 (0.38 - 0.51)
2014	0.15 (0.10 - 0.19)	0.61 (0.55 - 0.66)	0.45 (0.35 - 0.55)	0.25 (0.15 - 0.36)	0.36 (0.30 - 0.43)
2015	0.21 (0.17 - 0.26)	0.80 (0.74 - 0.85)	0.78 (0.66 - 0.90)	0.38 (0.26 - 0.50)	NA
2016	0.22 (0.18 - 0.27)	0.74 (0.68 - 0.80)	0.60 (0.49 - 0.72)	0.36 (0.24 - 0.48)	1.11 (1.04 - 1.18)
2017	0.20 (0.15 - 0.24)	0.67 (0.61 - 0.72)	0.47 (0.35 - 0.59)	0.29 (0.17 - 0.41)	0.99 (0.92 - 1.06)
2018	0.21 (0.17 - 0.25)	0.79 (0.73 - 0.84)	0.35 (0.22 - 0.49)	0.33 (0.21 - 0.44)	1.24 (1.17 - 1.31)
30 - 44 years					
2011	1.17 (1.12 - 1.21)	1.47 (1.41 - 1.54)	1.42 (1.26 - 1.58)	1.22 (1.10 - 1.33)	1.42 (1.33 - 1.51)
2012	1.06 (1.02 - 1.10)	1.45 (1.38 - 1.51)	2.06 (1.88 - 2.23)	1.17 (1.05 - 1.28)	1.66 (1.57 - 1.76)
2013	0.87 (0.83 - 0.91)	1.51 (1.44 - 1.58)	1.85 (1.68 - 2.01)	0.88 (0.77 - 0.99)	1.51 (1.42 - 1.61)
2014	0.66 (0.62 - 0.70)	1.57 (1.50 - 1.65)	1.37 (1.21 - 1.54)	0.76 (0.64 - 0.88)	1.23 (1.14 - 1.32)
2015	0.74 (0.70 - 0.79)	1.51 (1.44 - 1.58)	1.64 (1.46 - 1.81)	0.82 (0.70 - 0.95)	NA
2016	0.65 (0.61 - 0.69)	1.42 (1.35 - 1.48)	1.66 (1.47 - 1.85)	0.77 (0.64 - 0.89)	2.03 (1.94 - 2.12)
2017	0.57 (0.53 - 0.61)	1.30 (1.23 - 1.37)	1.40 (1.23 - 1.57)	0.92 (0.81 - 1.03)	1.78 (1.69 - 1.87)
2018	0.57 (0.53 - 0.60)	1.56 (1.49 - 1.62)	1.76 (1.57 - 1.94)	0.78 (0.67 - 0.89)	2.57 (2.48 - 2.66)

Table 2 Annual rate ratios comparing HIV testing rates per 10,000 residents ≥15 years between GPs[1] and SHC in five regions in the Netherlands, total and by sex and age categories, 2011-2018. (continued)

	Amsterdam RR (95% CI)[2]	Rotterdam RR (95% CI)[2]	Maastricht RR (95% CI)[2]	Twente RR (95% CI)[2]	N-NL RR (95% CI)[2]
45 - 59 years					
2011	1.43 (1.36 - 1.50)	2.10 (1.97 - 2.22)	1.03 (0.79 - 1.26)	1.12 (0.94 - 1.30)	0.92 (0.79 - 1.05)
2012	1.32 (1.25 - 1.39)	2.12 (2.00 - 2.24)	1.41 (1.21 - 1.61)	0.94 (0.77 - 1.10)	0.91 (0.78 - 1.04)
2013	1.27 (1.20 - 1.34)	2.07 (1.95 - 2.19)	1.12 (0.90 - 1.34)	0.80 (0.63 - 0.97)	1.06 (0.94 - 1.19)
2014	1.10 (1.04 - 1.17)	2.11 (1.99 - 2.24)	1.08 (0.87 - 1.30)	0.51 (0.34 - 0.69)	0.75 (0.63 - 0.87)
2015	1.03 (0.97 - 1.10)	2.06 (1.94 - 2.19)	1.07 (0.85 - 1.29)	0.62 (0.43 - 0.80)	NA
2016	0.83 (0.77 - 0.90)	1.82 (1.70 - 1.93)	1.30 (1.07 - 1.54)	0.64 (0.47 - 0.81)	1.58 (1.47 - 1.70)
2017	0.79 (0.73 - 0.85)	1.60 (1.49 - 1.70)	1.41 (1.17 - 1.64)	0.70 (0.55 - 0.85)	1.54 (1.44 - 1.65)
2018	0.76 (0.71 - 0.82)	1.82 (1.71 - 1.93)	1.73 (1.49 - 1.97)	0.71 (0.56 - 0.86)	1.79 (1.68 - 1.90)
≥60 years					
2011	1.59 (1.44 - 1.75)	2.92 (2.63 - 3.22)	1.80 (1.32 - 2.29)	0.64 (0.13 - 1.15)	0.78 (0.40 - 1.16)
2012	2.01 (1.86 - 2.16)	2.68 (2.40 - 2.96)	1.36 (0.77 - 1.96)	0.71 (0.24 - 1.18)	0.83 (0.44 - 1.21)
2013	1.77 (1.62 - 1.92)	1.85 (1.59 - 2.10)	1.68 (1.18 - 2.18)	NE	0.88 (0.54 - 1.22)
2014	1.68 (1.53 - 1.82)	2.41 (2.14 - 2.68)	1.26 (0.86 - 1.67)	NE	0.59 (0.18 - 0.99)
2015	1.51 (1.37 - 1.64)	1.89 (1.65 - 2.14)	1.58 (1.10 - 2.05)	NE	NA
2016	1.38 (1.26 - 1.51)	1.97 (1.74 - 2.20)	2.01 (1.62 - 2.39)	0.47 (0.05 - 0.89)	1.90 (1.58 - 2.22)
2017	1.18 (1.06 - 1.30)	1.61 (1.39 - 1.83)	1.65 (1.29 - 2.02)	1.19 (0.88 - 1.50)	1.68 (1.45 - 1.90)
2018	1.03 (0.92 - 1.13)	2.31 (2.08 - 2.54)	1.91 (1.54 - 2.28)	0.95 (0.67 - 1.24)	1.92 (1.71 - 2.13)

[1]GP test data were corrected for estimated HIV test data coverage per region. [2]Reference = SHC. GP, general practitioner; NA, not applicable; data is missing; NE, not estimated (N too small for reliable estimates); N-NL, North Netherlands; RR, rate ratio; SHC, sexual health centre.

DISCUSSION

This laboratory-based observational study comparing HIV testing and positivity by GPs and SHCs in five Dutch regions showed considerable regional differences in testing by these providers, while the positivity percentages between GPs and SHCs within regions were generally comparable. The difference between GPs' and SHCs' HIV testing rates largely depended on subgroups by sex and age, with GPs' testing rates being especially lower than SHCs' testing rates in men and those aged 15–29 years old.

Our data show that GPs are an important provider of HIV testing and that they contribute a substantial proportion of positive tests while having lower or comparable testing rates compared with SHCs in all regions. This suggests that, although SHC services are in place as an additional service for key groups for HIV testing, there are valuable opportunities for HIV testing in primary care. This is especially the case among populations that are not typically considered key HIV risk groups in the Netherlands, such as women and older people. However, the GP remains an important HIV test provider among key populations as well. In countries such as the UK, Spain, France, Belgium and the USA, the important role of GPs in optimal HIV testing and earlier diagnosis is increasingly recognised. As GPs are the primary service for (early) detection of disease in general and typically have a wide reach among residents, various interventions to improve HIV testing in this setting have been implemented in these countries[10-13].

The notable regional variation in HIV testing observed in our study is likely due to differences in the level of urbanisation, populations' cultural composition and local policy, as well as patients' and providers' attitudes. Not surprisingly, we observed higher HIV testing rates with higher levels of urbanisation, with the highest testing rates observed in the very highly urbanised regions of Amsterdam and Rotterdam. One explanation for this observation is the fact that key populations for HIV predominantly reside in highly urbanised regions. For example, in the Netherlands, 45% of MSM live in very highly urbanised regions, and over 30% of the residents of these highly urbanised regions are people with a non-Western migratory background[14,15]. Additionally, more HIV testing campaigns are implemented among these communities, likely affecting their HIV awareness and testing behaviour. Healthcare providers in highly urbanised regions might also have higher awareness of HIV testing due to higher HIV prevalence and more focus on sexual healthcare compared with less urbanised regions, where healthcare providers are only incidentally faced with HIV-related concerns. However, although both Amsterdam and Rotterdam have similar levels of urbanisation and population composition, testing rates among both GPs and SHCs are much higher in Amsterdam than in Rotterdam. For SHCs, this discrepancy is largely explained by difference in consultation capacity. In 2018, SHCs in Amsterdam performed over 50,000 STI consultations, while SHCs in Rotterdam performed over 12,000[16,17]. This difference in capacity is partially historically explained; the SHC in Amsterdam is better known among residents due to its longer existence and there are large regional differences

in governmental funding, with the highest proportion allocated to Amsterdam. For GPs, the difference might be explained by higher awareness regarding HIV testing among GPs in Amsterdam: several HIV testing and care campaigns aimed at GPs have been implemented by the HIV Transmission Elimination in Amsterdam (H-TEAM) consortium, which has been working towards zero new HIV infections in the Amsterdam region since 2014, among others. This is reflected in Amsterdam GPs' HIV testing time trends; after an initial decline in testing from 2011 to 2014, testing partially recovered from 2014 onwards[18]. Meanwhile, trends in Rotterdam GPs' HIV testing remained stable from 2011 to 2018.

The results from this study highlight opportunities for improved HIV testing strategies. Since SHCs already offer HIV testing to attendees from key groups on an opt-out basis, GPs' HIV testing strategies have the most room for improvement. Moreover, as GPs perform over twice as many STI consultations compared with SHCs and make 79% of annual STI diagnoses, they are the primary access to sexual healthcare[6,8]. In contrast, the contribution of GPs and SHCs to the annual number of HIV diagnoses is much more equal. This is partly explained by a difference in client population between GPs and SHCs, with only key populations for STI and HIV attending SHCs and because many STI consultations by GPs do not include the performance of an HIV test. Nevertheless, this discrepancy also indicates missed opportunities for HIV testing in the primary care setting. These missed opportunities are the results of previously identified barriers such as time constraints, stigma, financial barriers and low perceived risk, as well as poor adherence to the current guidelines for STI consultations[10,19,20]. In addition, as the Dutch HIV epidemic is shrinking over time, positive test results will become sparser, making a sustained proactive HIV testing strategy by GPs increasingly challenging. The observed regional differences in this study, as well as the underlying differences in policy, barriers and population, should be considered when designing strategies for improved HIV testing. In these strategies, locally targeted approaches to engage GPs are warranted, not only focusing on highly urbanised regions but also engaging lower urbanised regions, where GPs are only incidentally faced with new HIV diagnoses, and the distance to SHCs makes their accessibility more cumbersome[21]. Lessons taken from successful region-specific interventions to improve HIV testing strategies in primary care, such as an educational intervention implemented in Amsterdam by the H-TEAM, could serve as an example[18].

Strengths

This is the first laboratory-based observational study on HIV testing by GPs versus SHCs in the Netherlands, allowing for a novel, objective assessment of the number of HIV tests performed per provider. Previous surveillance on HIV testing in primary care used data from sentinel networks, patient records, questionnaires or interviews[19,22-24]. We compared our laboratory-based GP testing rates with data collected in the Dutch Sentinel General Practice Network from 1988 to 2009 and found large discrepancies in HIV testing between their results from 2009 and our results from 2011[22]. This discrepancy may be due to registration bias in the sentinel network study, as they used patient records and additional questionnaires

completed by GPs. With laboratory data, there is no risk of recall or registration bias, ensuring a more accurate assessment of the contribution of GPs to HIV testing.

Limitations

A limitation of this study is that we used the annual number of tests per healthcare provider, not the annual number of unique patients tested per healthcare provider. As some key groups such as MSM are advised to test for HIV biannually[5], and the SHCs only accommodate key groups while the GPs are widely accessible, it is possible that GPs' testing rates include more unique patients than SHCs'. Second, as we used anonymised aggregated laboratory data, no data on patients' HIV risk factors such as sexual behaviour and migratory background or reason for testing were available. Data on patients' risk factors are available for SHCs and extensively described elsewhere[6], but not for primary care, as they are not routinely registered by GPs. We could therefore not explain differences in GPs' and SHCs' HIV testing based on patient risk factors other than age and sex. Combining risk factors and reasons for consultation with laboratory data could give more insight into indications for HIV testing that are being missed in both settings and pinpoint additional opportunities for improvement. Finally, the results of this study might not be generalizable to all other Western countries due to differences in the organisation of sexual health services and primary care.

CONCLUSIONS

Our results show that GPs, in addition to SHCs, play a significant role in HIV testing and HIV diagnoses, but there is large variation between regions. Lessons drawn from regions with the most proactive testing strategies could serve as a basis for broader implementation of optimal testing strategies. However, the observed heterogeneity highlights the need for regionally tailored interventions to improve HIV testing, considering all regional challenges, on our way to zero new HIV infections.

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Competing interests
The authors declare no competing interests. The funders were not involved in the design or evaluation of this project.

Contributors
SB and JB designed the project. SB and DT collected the aggregated data. DT, MK, AO, ML, ND, CH, CK and FB contributed to data collection. SB and DT collaborated in designing the analyses and writing the manuscript and contributed equally to this work. DT performed all statistical analyses. LB, HG, AM, MK, EH, AO, ML, ND, CH, FB, KK, MS, SG and JB revised the manuscript before submission. All authors read and approved the final manuscript.

REFERENCES

1. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, Reiss P. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2019.
2. Op de Coul ELM, Joore IK, van Sighem A, Bom BCJ, Hillebregt M, Prins JM, et al. Hiv-bestrijding begint met GIS-werk. Ned Tijdschr Geneeskd. 2017;161.
3. Staritsky LE, Van Aar F, Visser M, Op de Coul ELM, Heijne JCM, Götz HM, et al. Sexually transmitted infections in the Netherlands in 2019. Bilthoven: National Institute for Public Helath and the Environment (RIVM); 2020.
4. Heijnen A, Hermanussen R, Verlee L, van Bergen J. Hiv - verdieping naast NHG-Standaard 'Het Soa-Consult'. Amsterdam: Huisarts Advies Groep Seksuele Gezondheid; 2019.
5. LCI-RIVM. Seksuele gezondheid, het consult - 6. Testbeleid Bilthoven: RIVM; 2019 [updated July 11, 2019; cited 2021 March]. Available from: https://lci.rivm.nl/draaiboeken/consult-seksuele-gezondheid.
6. Slurink IAL, van Aar F, Op de Coul ELM, Heijne JCM, van Wees DA, Hoenderboom BM, et al. Sexually transmitted infections in the Netherlands in 2018. Bilthoven: National Institute for Public Health and the Environment; 2019.
7. Statistics Netherlands. Regionale kerncijfers Nederland - Bevolkingssamenstelling 2020 [updated March 2020; cited 2021 March]. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70072NED/table?fromstatweb.
8. Slurink I, Groen K, Gotz HM, Meima A, Kroone MM, Hogewoning AA, et al. Contribution of general practitioners and sexual health centres to sexually transmitted infection consultations in five Dutch regions using laboratory data of Chlamydia trachomatis testing. Int J STD AIDS. 2020:956462420905275.
9. Statistics Netherlands. Kerncijfers wijken en buurten 2004-2019 2018 [updated 2019; cited 2021 March]. Available from: https://www.cbs.nl/nl-nl/reeksen/kerncijfers-wijken-en-buurten-2004-2019.
10. Foundation Federation of Dutch Medical Scientific Societies. Code of Conduct for Health Research [cited 2021 March]. Available from: https://www.federa.org/sites/default/files/bijlagen/coreon/code_of_conduct_for_medical_research_1.pdf.
11. Deblonde J, Van Beckhoven D, Loos J, Boffin N, Sasse A, Nostlinger C, et al. HIV testing within general practices in Europe: a mixed-methods systematic review. BMC Public Health. 2018;18(1):1191.
12. Leber W, Panovska-Griffiths J, Martin P, Morris S, Capelas Barbosa E, Estcourt C, et al. Evaluating the impact of post-trial implementation of RHIVA nurse-led HIV screening on HIV testing, diagnosis and earlier diagnosis in general practice in London, UK. EClinicalMedicine. 2020;19:100229.
13. Mahoney MR, Fogler J, Weber S, Goldschmidt RH. Applying HIV testing guidelines in clinical practice. Am Fam Physician. 2009;80(12):1441-4.
14. Dominguez-Berjon MF, Pichiule-Castaneda M, Garcia-Riolobos MC, Esteban-Vasallo MD, Arenas-Gonzalez SM, Moran-Arribas M, et al. A feasibility study for 3 strategies promoting HIV testing in primary health care in Madrid, Spain (ESTVIH project). J Eval Clin Pract. 2017;23(6):1408-14.
15. Den Daas C, Zuilhof W, Van Bijnen A, Vermey K, Dörfler T, De Wit J. Rapport Survey Mannen & Seksualiteit 2018. 2018.

16. Statistics Netherlands. Hoeveel mensen met een migratieachtergrond wonen in Nederland? 2019 [updated March 2021; cited 2021 March]. Available from: https://www.cbs.nl/nl-nl/dossier/dossier-asiel-migratie-en-integratie/hoeveel-mensen-met-een-migratieachtergrond-wonen-in-nederland-.

17. Public Health Service Amsterdam. Jaarcijfers 2018 - Soa polikiniek GGD Amsterdam. 2019.

18. Public Health Service Rotterdam. Jaarcijfers 2018 regionaal Centrum voor Seksuele Gezondheid zuidelijk Zuid-Holland. 2019.

19. Bogers SJ, Schim van der Loeff MF, van Dijk N, Groen K, Groot Bruinderink ML, de Bree GJ, et al. Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care. Fam Pract. 2020.

20. Joore IK, Reukers DF, Donker GA, van Sighem AI, Op de Coul EL, Prins JM, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. BMJ open. 2016;6(1):e009194.

21. Joore IK, van Roosmalen SL, van Bergen JE, van Dijk N. General practitioners' barriers and facilitators towards new provider-initiated HIV testing strategies: a qualitative study. Int J STD AIDS. 2017;28(5):459-66.

22. Twisk DE, Meima A, Nieboer D, Richardus JH, Gotz HM. Distance as explanatory factor for sexual health centre utilisation in an infrastructure-rich urban area in the Netherlands: A population-based multilevel study. Research Square [Preprint]. November 2020.

23. Donker G, Dorsman S, Spreeuwenberg P, van den Broek I, van Bergen J. Twenty-two years of HIV-related consultations in Dutch general practice: a dynamic cohort study. BMJ open. 2013;3(4).

24. Joore IK, Geerlings SE, Brinkman K, van Bergen JE, Prins JM. The importance of registration of sexual orientation and recognition of indicator conditions for an adequate HIV risk-assessment. BMC infectious diseases. 2017;17(1):178.

25. van Opstal SEM, van der Zwan JS, Wagener MN, Been SK, Miedema HS, Roelofs P, et al. Late Presentation of HIV Infection in the Netherlands: Reasons for Late Diagnoses and Impact on Vocational Functioning. AIDS Behav. 2018;22(8):2593-603.

Supplementary Table 1 Crude number[1] of HIV tests and positive tests among patients ≥15 years by GPs and SHCs in five regions in the Netherlands, total and by sex and age categories, 2011-2018.

	Amsterdam Number of HIV tests (number positive)		Rotterdam Number of HIV tests (number positive)		Maastricht Number of HIV tests (number positive)		Twente Number of HIV tests (number positive)		N-NL Number of HIV test (number positive)	
	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC
Total										
2011	13,629 (108)	20,676 (107)	6,198 (37)	6,569 (41)	1,126 (2)	2,080 (3)	1,402 (5)	2,275 (9)	3,336 (16)	5,693 (9)
2012	12,655 (85)	22,129 (92)	6,164 (32)	6,830 (34)	1,213 (1)	1,539 (2)	1,249 (6)	2,495 (11)	3,280 (9)	4,610 (10)
2013	10,977 (80)	24,293 (83)	6,046 (31)	7,055 (37)	1,158 (0)	1,808 (1)	1,169 (3)	3,259 (13)	3,203 (8)	4,988 (12)
2014	9,414 (68)	29,774 (88)	5,590 (28)	6,472 (17)	987 (1)	1,847 (5)	893 (3)	3,126 (9)	2,772 (20)	5,296 (19)
2015	10,063 (68)	24,399 (73)	5,681 (32)	5,523 (43)	879 (1)	1,068 (3)	758 (4)	1,949 (10)	2,922 (13)	NA
2016	10,842 (66)	27,757 (84)	5,725 (27)	5,901 (42)	845 (1)	1,170 (1)	836 (6)	2,203 (11)	4,163 (16)	3,131 (1)
2017	10,377 (53)	29,272 (80)	5,748 (31)	6,562 (23)	819 (1)	1,306 (5)	1,035 (1)	2,516 (15)	4,406 (11)	3,664 (14)
2018	11,513 (51)	31,310 (82)	6,150 (30)	5,868 (23)	742 (4)	1,223 (4)	1,065 (1)	2,658 (10)	4,767 (12)	3,076 (30)
Men										
2011	6,651 (81)	10,951 (98)	3,047 (27)	3,512 (37)	541 (2)	963 (3)	683 (5)	1,222 (9)	1,319 (14)	2,339 (9)
2012	6,294 (58)	11,879 (85)	2,970 (27)	3,857 (32)	607 (1)	741 (2)	610 (6)	1,435 (11)	1,316 (6)	2,044 (8)
2013	5,690 (59)	12,475 (77)	2,984 (26)	3,922 (32)	601 (0)	892 (1)	579 (3)	1,822 (13)	1,482 (7)	2,405 (10)
2014	5,251 (59)	14,849 (83)	2,801 (23)	3,645 (17)	488 (1)	894 (5)	473 (3)	1,792 (8)	1,406 (18)	2,609 (16)
2015	5,636 (53)	14,434 (67)	2,748 (30)	3,663 (41)	447 (1)	686 (3)	392 (3)	1,305 (10)	1,463 (9)	NA
2016	5,978 (54)	17,825 (81)	2,771 (23)	4,017 (41)	444 (1)	719 (1)	458 (5)	1,469 (11)	2,062 (16)	1,968 (0)
2017	5,781 (41)	19,639 (76)	2,887 (27)	4,542 (23)	423 (1)	802 (5)	538 (1)	1,728 (15)	2,245 (8)0	2,539 (14)
2018	6,707 (44)	21,552 (79)	3,098 (25)	4,162 (22)	407 (1)	770 (40)	577 (1)	1,795 (9)	2,624 (12)	1,905 (30)
Women										
2011	6,978 (27)	9,725 (9)	3,151 (10)	3,057 (4)	585 (0)	1,117 (0)	719 (0)	1,053 (0)	2,017 (2)	3,354 (0)
2012	6,361 (27)	10,250 (7)	3,194 (5)	2,973 (2)	606 (0)	798 (0)	639 (0)	1,060 (0)	1,964 (3)	2,566 (2)
2013	5,287 (21)	11,818 (6)	3,062 (5)	3,133 (5)	557 (0)	916 (0)	590 (0)	1,437 (0)	1,721 (1)	2,583 (2)

Supplementary Table 1 Crude number[1] of HIV tests and positive tests among patients ≥15 years by GPs and SHCs in five regions in the Netherlands, total and by sex and age categories, 2011-2018. (continued)

	Amsterdam Number of HIV tests (number positive)		Rotterdam Number of HIV tests (number positive)		Maastricht Number of HIV tests (number positive)		Twente Number of HIV tests (number positive)		N-NL Number of HIV test (number positive)	
	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC
2014	4,163 (9)	14,925 (5)	2,789 (5)	2,827 (0)	499 (0)	953 (0)	420 (0)	1,334 (1)	1,366 (2)	2,687 (3)
2015	4,427 (15)	9,965 (6)	2,933 (2)	1,860 (2)	432 (0)	382 (0)	366 (1)	644 (0)	1,459 (4)	NA
2016	4,864 (12)	9,932 (3)	2,954 (4)	1,884 (1)	401 (0)	451 (0)	378 (1)	734 (0)	2,101 (0)	1,163 (1)
2017	4,596 (12)	9,633 (4)	2,861 (4)	2,020 (0)	396 (0)	504 (0)	497 (0)	788 (0)	2,161 (3)	1,125 (0)
2018	4,806 (7)	9,758 (3)	3,052 (5)	1,706 (1)	335 (3)	453 (0)	488 (0)	863 (1)	2,143 (0)	1,171 (0)
15 - 29 years										
2011	5,094 (25)	13,118 (26)	3,059 (9)	4,485 (21)	660 (0)	1,641 (1)	692 (0)	1,427 (6)	1,661 (4)	4,206 (2)
2012	4,518 (18)	14,363 (27)	3,045 (14)	4,736 (15)	651 (0)	1,141 (0)	528 (0)	1,560 (1)	1,599 (3)	3,239 (4)
2013	3,615 (11)	16,111 (21)	2,854 (8)	4,937 (17)	635 (0)	1,394 (1)	500 (0)	2,127 (0)	1,447 (3)	3,536 (2)
2014	2,704 (10)	20,378 (29)	2,539 (7)	4,540 (7)	506 (0)	1,376 (2)	364 (0)	1,992 (0)	1,215 (2)	3,628 (5)
2015	2,894 (12)	15,055 (31)	2,511 (9)	3,428 (17)	418 (0)	662 (2)	278 (0)	1,016 (4)	1,286 (4)	NA
2016	3,351 (9)	16,453 (35)	2,414 (9)	3,546 (11)	402 (1)	822 (1)	289 (1)	1,123 (7)	1,745 (3)	1,713 (1)
2017	3,007 (5)	16,809 (33)	2,425 (5)	3,950 (12)	341 (0)	893 (2)	265 (0)	1,270 (4)	1,814 (3)	1,993 (3)
2018	3,307 (6)	17,197 (32)	2,517 (10)	3,479 (11)	252 (2)	881 (3)	301 (0)	1,276 (4)	1,876 (2)	1,650 (10)
30 - 44 years										
2011	5,942 (46)	5,604 (61)	2,197 (16)	1,620 (16)	305 (0)	265 (2)	496 (1)	566 (1)	1,211 (5)	929 (4)
2012	5,581 (43)	5,790 (47)	2,143 (13)	1,612 (14)	343 (0)	206 (2)	494 (3)	588 (7)	1,191 (4)	779 (5)
2013	4,876 (34)	6,153 (44)	2,204 (12)	1,589 (11)	347 (0)	232 (0)	468 (1)	737 (8)	1,170 (4)	840 (2)
2014	4,298 (30)	7,176 (39)	2,124 (15)	1,466 (7)	287 (1)	258 (1)	375 (1)	689 (3)	1,067 (9)	943 (5)
2015	4,583 (28)	6,780 (26)	2,179 (18)	1,565 (17)	281 (0)	212 (1)	336 (2)	567 (3)	1,056 (6)	NA
2016	4,768 (22)	8,047 (33)	2,279 (9)	1,747 (20)	244 (0)	181 (0)	352 (3)	639 (2)	1,525 (6)	817 (0)
2017	4,567 (25)	8,838 (32)	2,264 (11)	1,892 (6)	276 (0)	244 (3)	481 (0)	729 (6)	1,531 (3)	935 (7)

Supplementary Table 1 Crude number[1] of HIV tests and positive tests among patients ≥15 years by GPs and SHCs in five regions in the Netherlands, total and by sex and age categories, 2011-2018. (continued)

	Amsterdam Number of HIV tests (number positive)		Rotterdam Number of HIV tests (number positive)		Maastricht Number of HIV tests (number positive)		Twente Number of HIV tests (number positive)		N-NL Number of HIV test (number positive)	
	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC	GPs	SHC
2018	5,088 (18)	9,886 (36)	2,489 (10)	1,737 (7)	265 (1)	186 (0)	459 (0)	820 (3)	1,742 (6)	737 (10)
45 - 59 years										
2011	2,148 (31)	1,650 (19)	778 (11)	403 (3)	123 (2)	148 (0)	196 (3)	243 (2)	419 (6)	495 (3)
2012	2,026 (21)	1,690 (16)	801 (5)	411 (5)	198 (1)	173 (0)	205 (3)	304 (3)	445 (2)	533 (0)
2013	2,016 (31)	1,745 (15)	825 (10)	433 (8)	142 (0)	157 (0)	191 (2)	332 (5)	527 (1)	539 (8)
2014	1,901 (24)	1,893 (19)	756 (5)	389 (3)	149 (0)	170 (1)	141 (1)	381 (3)	455 (7)	660 (7)
2015	2,038 (23)	2,173 (15)	815 (4)	429 (8)	143 (1)	165 (0)	136 (1)	306 (2)	523 (2)	NA
2016	2,105 (27)	2,773 (15)	829 (5)	496 (9)	134 (0)	127 (0)	171 (1)	370 (2)	788 (7)	541 (0)
2017	2,185 (18)	3,056 (15)	859 (14)	585 (5)	139 (1)	122 (0)	223 (1)	440 (4)	859 (4)	605 (4)
2018	2,425 (25)	3,498 (12)	908 (10)	541 (4)	157 (0)	112 (1)	235 (1)	460 (3)	907 (4)	552 (9)
≥60 years										
2011	428 (6)	295 (1)	164 (1)	61 (1)	38 (0)	26 (0)	18 (1)	39 (0)	45 (1)	63 (0)
2012	512 (3)	280 (2)	175 (0)	71 (0)	21 (0)	19 (0)	22 (0)	43 (0)	45 (0)	59 (1)
2013	451 (4)	280 (2)	163 (1)	96 (1)	34 (0)	25 (0)	10 (0)	63 (0)	59 (0)	73 (0)
2014	484 (4)	317 (2)	171 (1)	77 (0)	44 (0)	43 (1)	13 (1)	64 (3)	35 (2)	65 (2)
2015	533 (5)	389 (1)	176 (1)	101 (1)	37 (0)	29 (0)	8 (1)	60 (1)	57 (1)	NA
2016	602 (7)	478 (1)	203 (4)	112 (2)	65 (0)	40 (0)	24 (1)	71 (0)	105 (0)	60 (0)
2017	610 (5)	567 (0)	200 (1)	135 (0)	63 (0)	47 (0)	66 (0)	77 (1)	202 (1)	131 (0)
2018	680 (2)	728 (2)	236 (0)	111 (1)	68 (1)	44 (0)	70 (0)	102 (0)	242 (0)	137 (1)

Abbreviations: GP, general practitioner; NA, data is missing; N-NL, North Netherlands; SHC, sexual health centre. [1]Number of HIV tests by GPs are unadjusted for GPs' HIV test data coverage.

Chapter 3

Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care

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ABSTRACT

Objectives
In the Netherlands, general practitioners (GPs) perform two-thirds of sexually transmitted infection (STI) consultations and diagnose one-third of HIV infections. GPs are, therefore, a key group to target to improve provider-initiated HIV testing. We describe the design and implementation of an educational intervention to improve HIV testing by Amsterdam GPs and explore trends in GPs' testing behaviour.

Methods
Interactive sessions on HIV and STI using graphical audit and feedback started in 2015. Participating GPs developed improvement plans that were evaluated in follow-up sessions. Laboratory data on STI testing by Amsterdam GPs from 2011 to 2017 were collected for graphical audit and feedback and effect evaluation. The primary outcome was the HIV testing rate: number of HIV tests per 10 000 person-years (PY). Secondary endpoints were chlamydia and gonorrhoea testing rates and HIV positivity ratios.

Results
Since 2015, 41% of GPs participated. HIV testing rate declined from 2011 to 2014 (from 175 to 116 per 10 000 PY), more in women than men (176 to 101 versus 173 to 132), and stabilized from 2015 to 2017. The HIV positivity ratio declined from 0.8% in 2011 to 0.5% in 2017. From 2011 to 2017, chlamydia and gonorrhoea testing rates declined in women (from 618 to 477 per 10 000 PY) but remained stable in men (from 270 to 278).

Conclusions
The stabilization of the downward trend in HIV testing coincided with this educational intervention. Follow-up data are needed to formally assess the intervention's impact on GP testing behaviour whilst considering contextual factors and secular trends.

Key Messages
- An educational intervention is used to improve HIV testing by general practitioners.
- The HIV testing rate stabilized after the implementation of the intervention.
- Follow-up analyses will formally assess long-term impact on HIV testing practices.

BACKGROUND

General practitioners (GPs) play a pivotal role in provider-initiated testing and counselling (PITC) for HIV in the Netherlands. About two-thirds of sexually transmitted infection (STI) consultations take place in primary care, and GPs diagnose a third of HIV infections[1]. However, opportunities for earlier diagnosis through primary care are often missed. Over 60% of people newly diagnosed with HIV visited their GP in the year prior to diagnosis, and 61% had been diagnosed with indicator conditions (i.e. conditions where HIV testing is recommended) in the 5 years prior to diagnosis[2]. This is disappointing, as the STI consultation guideline for GPs, as updated in 2013, includes guidance on appropriate HIV testing strategies[3]. Research showed that GPs still perceive barriers towards HIV testing[4-7]. Thus, a key approach to eliminating HIV is improving HIV testing strategies by GPs and addressing their barriers to timely testing[7,8].

There were an estimated 23,300 people living with HIV (PLHIV) in the Netherlands in 2018, with 660 new HIV diagnoses, and 47% presenting with a late-stage infection (CD4 <350 cells/mm^3 or an AIDS-defining event[9]). In Amsterdam, the HIV prevalence is over five times higher than the national prevalence, warranting a city-based approach to curbing the epidemic[10]. In 2014, a consortium of stakeholders in HIV prevention and care launched the HIV Transmission Elimination AMsterdam (H-TEAM) initiative[11]. The H-TEAM aims to eliminate HIV in Amsterdam through innovative interventions, focussing on all parts of the cascade. Previous studies on educational interventions to improve HIV and STI testing in primary care yielded varying results[12-14]. Effects were often of limited size and not sustained. The H-TEAM, therefore, designed a novel educational intervention programme for GPs in Amsterdam using a combination of previously successful and evidence-based elements for educational interventions[15-22]. This programme is currently ongoing. The primary research questions in this programme are: '*what is the uptake and evaluation of the intervention by GPs in Amsterdam?*' and '*what is the impact of the intervention on HIV, chlamydia and gonorrhoea testing rates by GPs in Amsterdam?*' Here, we describe the design and implementation of this educational intervention programme, as well as observed trends in HIV and STI testing from 2011 to 2017.

METHODS

Setting and participants

In 2017, Amsterdam had 844,947 residents and 534 GPs. Over 80% of GPs in Amsterdam work part time. Nearly all residents of the Netherlands are registered with a GP and 78% contact their GP at least once every year[23]. All Amsterdam GPs were invited to participate in the educational intervention. For recruitment, we collaborated with Elaa, which is the key organization for regional primary care support and a well-known and trusted party for GPs. Participating GPs receive accreditation points, which are required for ongoing registration in their specialty.

Educational intervention

The intervention, in the form of a diagnostic audit meeting (in Dutch: Diagnostisch Toets Overleg; DTO) was designed by a group of GPs and experts on medical education and HIV. Evidence-based elements for effective continuing medical education (CME) to improve physician performance were used in the design, including interactive audit and feedback, multiple educational tools, multiple exposures and small-group sessions (Table 1)[16,21,24].

The intervention is organized for existing groups of 5 to 20 GPs and consists of two 2-hour sessions (DTO I and DTO II). During the sessions, trends in HIV and STI prevalence and current guidelines are discussed, as well as appropriate HIV testing strategies, including proactive HIV testing, screening of at-risk groups, indicator condition-based testing and routine HIV testing in new patients. Additionally, practical tips are addressed through interactive discussions, such as strategies to overcome barriers to discussing sexual risk behaviour, and practical tools to facilitate quality STI consultations in the context of busy primary care facilities. Graphical audit and feedback is used to demonstrate differences in testing behaviour between participating GPs relative to the calculated average number of tests by a full-time Amsterdam GP (Figure 1). The session's outline and background information are provided in workbooks, which are distributed prior to the session.

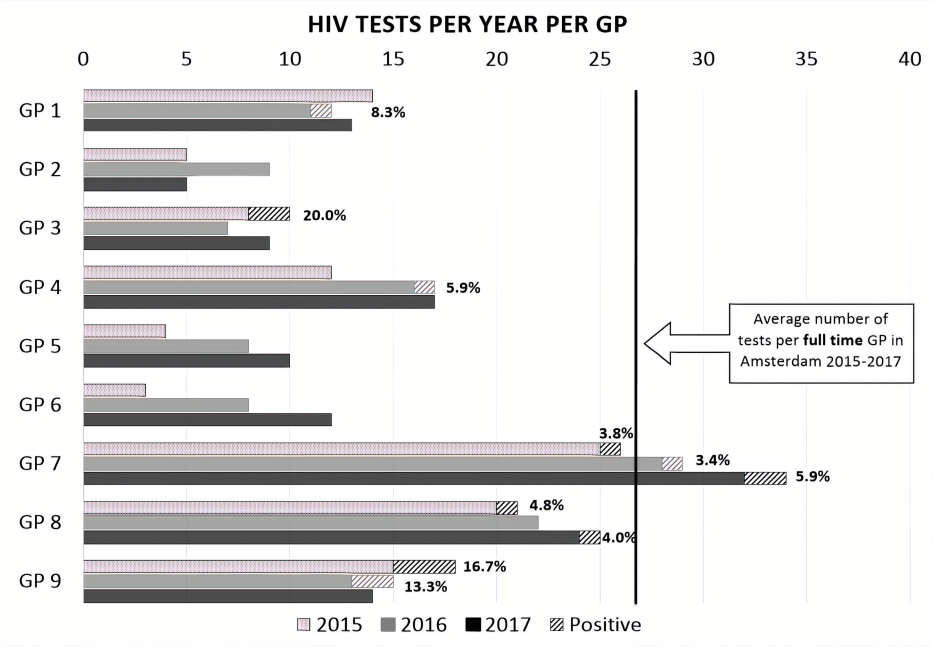
Moderation of the sessions is done by GPs that are trained through a specially designed 2-hour teach-the-teacher session to develop extensive knowledge of the topics discussed. A member of the national expert group on HIV and STI in primary care attends to answer in-depth questions. At the end of DTO I, the GPs develop a quality improvement plan for their own practice. In DTO II, approximately 1 year after DTO I depending on the availability of the group, the GPs evaluate its implementation and discuss barriers and facilitators for implementation, further points of improvement and whether HIV and STI testing has improved based on the updated graphical audit and feedback.

Table 1: Evidence-based elements of successful innovation in health care and their implementation in the H-TEAM's educational intervention to improve the HIV testing behaviour of GPs in Amsterdam.

Evidence-based elements of effective education	**Implementation in the design**
Small-scale educational meetings	GPs participate in their local peer-group of 5-20 GPs per group.
Implementation process follow-up	DTOs are divided into two consecutive sessions. Implementation of improvement plans made in the first session is evaluated in the second.
Integration of implementation in existing work-structures	Improvement plans are made by the GPs for their own practices to ensure effective implementation.
Intrinsic motivational factor focus	GPs choose relevant subjects as a group, receive feedback on their own performance and acquire new competencies through education.
Extrinsic motivational factor focus	GPs are provided with information on differences in testing compared to peers as a form of intercollegiate auditing. GPs participating in the DTOs receive accreditation points for two hours.
Target audience involvement	GPs are invited to participate by a well-known and trusted party (Elaa); the sessions are led by a GP from within the group and the expert attending the sessions is from a national GP organisation.
Support for the cause	A GP organises the DTO for their own group of peers to ensure applicability and relevance.
Expert peer trainers	The organising GP attends a 2-hour teach-the-teacher session to develop a command of the topics discussed.
Interactive sessions	Discussions about differences in testing and barriers and facilitators to implementation are encouraged by the organising GP; audit and feedback elements are used during the sessions.
Inclusion of multiple teaching strategies	In the sessions, unilateral education by the expert, interactive discussions, quizzes on knowledge, take-home materials and graphical audit and feedback are used to include multiple teaching strategies.

Elaa: key organisation for regional primary care support in Amsterdam; GP: general practitioner; DTO: diagnostic audit meeting (in Dutch: Diagnostisch Toets Overleg)

Figure 1: Example of a graphical audit and feedback slide as used in the diagnostic audit meeting to show differences in HIV testing between the participating general practitioners (adapted from a graphical feedback slide used in the session).



GP = general practitioner.

Evaluation of the intervention

After DTO I, the moderating GP completes a questionnaire evaluating the DTO session, including scoring statements on a 10-point scale and open questions, and summarizes the quality improvement plans made. After DTO II, all participating GPs complete a questionnaire evaluating the programme, the self-perceived effect on testing behaviour and adherence to their quality improvement plans. Additional data on the characteristics of these GPs (age, sex, years practising as a GP, type of practice, days working per week and the number of PLHIV in their practice) are collected through this questionnaire.

Laboratory data

Data on HIV and STI testing by Amsterdam GPs from 2011 onwards are obtained from primary care diagnostic laboratories in Amsterdam. All GPs were given the opportunity to object to the use of their test data for this programme. Data variables include the type of test (HIV, gonorrhoea or chlamydia), anatomical site (blood, urogenital, oral or anorectal), date and outcome of the test, year of birth and sex of the patient and the name and zip code of the ordering GP. Data on tests performed in other contexts, such as antenatal screening, and tests performed by health care

professionals other than GPs are excluded. We calculate the HIV, chlamydia and gonorrhoea testing rates per 10,000 person-years (PY; number of tests per 10,000 Amsterdam residents) and the HIV positivity ratios (i.e. the proportion positive among tests performed). To estimate our data coverage, we assess which laboratory participating GPs use for their diagnostics through the evaluative questionnaires. Based on this, we estimate the proportion of Amsterdam GPs that utilize a laboratory that is not included in the dataset.

Analysis

We analysed the initial results of this ongoing intervention and trends in HIV and STI testing by GPs from 2011 to 2017. Scoring statements in the DTO I questionnaires were summarized as means. Open questions were summarized by identified themes. We used a Poisson regression model to examine differences in laboratory testing rates by year with incidence rate ratios (IRRs). Additional analyses stratified by patients' sex and age categories (<20, 20-34, 35-49, 50-64 and ≥65) were performed. Because the estimated laboratory data coverage was 90-95%, the use of confidence intervals was not deemed appropriate. An effect with a P-value of <0.05 was considered statistically significant. Data analysis and effect evaluation were performed using Stata 15[25].

RESULTS

Participating GPs

From February 2015 to October 2019, 30 DTOs were organized, including 22 DTO I and 8 DTO II sessions. In total, 220 GPs attended one or both sessions. This accounts for 41.2% of all GPs in Amsterdam in 2017 (220/534). DTO I was attended by 204 GPs and 71 attended DTO II. The DTO II sessions are still ongoing. The mean number of participants per session was 9.

Evaluation of DTO I

Of the 22 groups attending DTO I (including 208 participants), 20 (partially) completed the evaluation (91% of groups; including 181 participants). Overall, the DTO was rated 8.5/10. The content was rated 8.4/10, the method 8.4/10, and the materials 8.6/10. All groups made quality improvement plans for their practice. Six main topics (three on HIV testing and three on STI testing) were identified (Table 2). Five strengths and five points of improvement for the programme were identified (Supplementary Table 1).

Table 2: Main topics identified in the quality improvement plans made at the end of DTO I.

Quality improvement plans concerning HIV testing	**n/N (%)**
Offer more provider-initiated HIV testing, e.g. by offering an HIV test at consultations concerning other complaints, at the intake procedure, when performing diagnostics for different reasons and through suggesting HIV testing on the TV-screens in the waiting room	10/20 (50.0)
Specifically screen high-groups for HIV proactively, including men who have sex with men, people from HIV-endemic countries and patients with positive STI tests in the past	8/20 (40.0)
Test for HIV more when diagnosing or suspecting an HIV indicator condition, including other STI	7/20 (35.0)
Quality improvement plans concerning STI testing	**n/N (%)**
Be more alert on extragenital STI testing (oral, anal) when indicated	12/20 (60.0)
Choose type and anatomical location of testing (urogenital, oral, anorectal or blood) based on the guidelines and diagnostic decision tool more	11/20 (55.0)
Take more detailed sexual histories, to more accurately assess risk-behaviour to choose the appropriate diagnostics accordingly	9/20 (45.0)

DTO = diagnostic audit meeting (in Dutch: Diagnostisch Toets Overleg).

HIV and STI testing trends

Seven laboratories provided data on STI testing from 2011 onwards, yielding an estimated 90-95% coverage of tests performed by all Amsterdam GPs. Two GPs opted out; their data were excluded. Data from 2011 to 2017 are reported.

HIV testing rates declined from 2011 to 2014 (from 174.8 to 116.1 per 10,000 PY, IRR 0.69; Figure 2). This decline was more pronounced in female patients (176.2 to 101.2 per 10,000 PY, IRR 0.62) than in male patients (173.3 to 131.5 per 10,000 PY, IRR 0.76, Supplementary Table 2). HIV testing rates stabilised from 2014 to 2017 (from 116.1 to 122.8 per 10,000 PY, IRR 1.06). The rates were lowest in the extreme age categories (<20 and ≥65). In most age categories (35-49, 50-64 and ≥65), the rates were higher in men than women (Figure 3). In both sexes, testing in the age categories of 20-34 years and 35-49 years declined from 2011 to 2014. This decline was more pronounced in women than in men.

The overall HIV positivity ratio was low, but higher in men than in women. The HIV positivity ratio declined from 2011 to 2017. This decline was more pronounced in men (from 1.2% to 0.7%) than in women (from 0.4% to 0.3%; Supplementary Figure 1 and Supplementary Table 3).

Figure 2: Trends in HIV tests performed by GPs per 10,000 residents of Amsterdam per year by sex and key interventions. GP = general practitioner, STI = sexually transmitted infection.

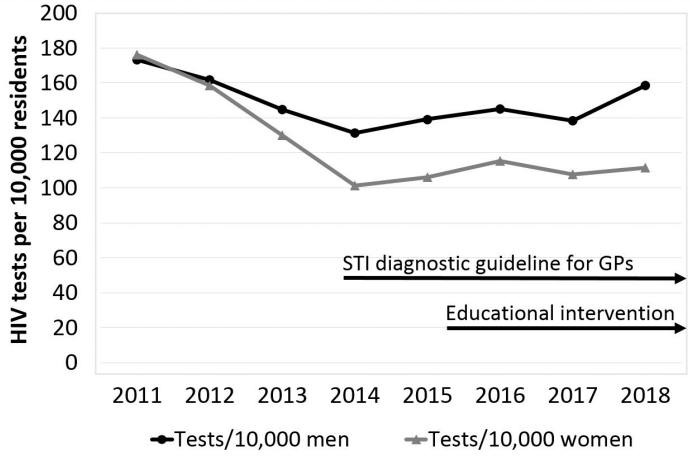
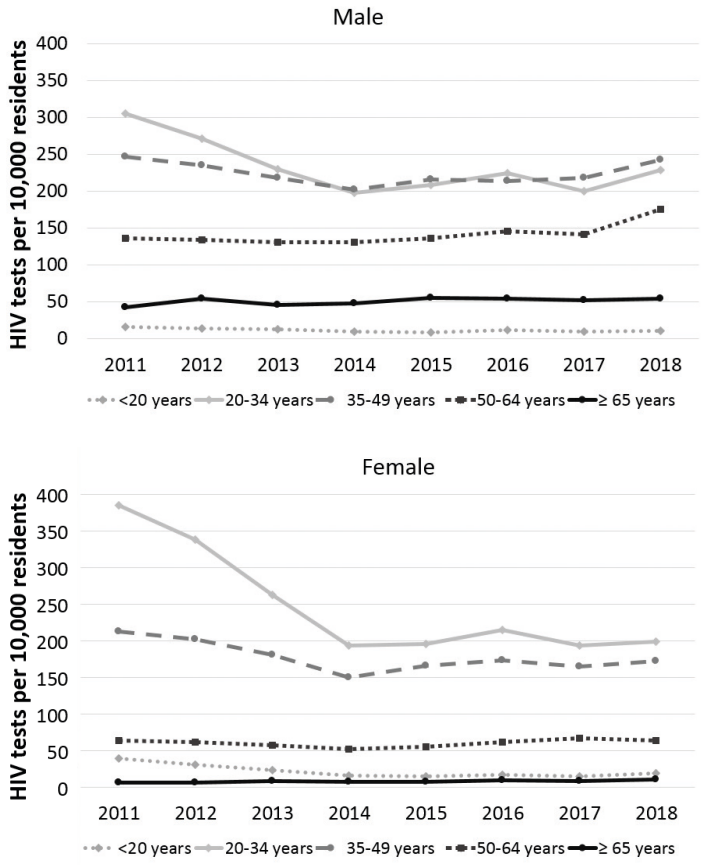


Figure 3: Trends in HIV tests performed by GPs per 10,000 residents of Amsterdam per year by age category and sex.



Chlamydia and gonorrhoea testing rates were higher in women than men. For men, testing rates remained stable for chlamydia (from 269.9 to 286.6 per 10,000 PY, IRR 1.06) and gonorrhoea (from 269.9 to 268.7 per 10,000 PY, IRR 1.00) from 2011 to 2017 (Supplementary Figure 2 and Supplementary Table 4). For women, they showed a similar pattern as the HIV testing trends, with a decline from 2011 to 2014 (chlamydia: from 615.5 to 471.1, IRR 0.77; gonorrhoea: from 620.8 to 432.7, IRR 0.70) and a partial recovery and stabilisation from 2014 to 2017. The recovery was stronger in chlamydia than gonorrhoea, resulting in a difference in testing rates between the two in 2017 (chlamydia: 511.2 per 10,000 PY versus gonorrhoea: 442.9 per 10,000 PY). Although low overall, the testing increased for anorectal chlamydia from 2011 to 2017, (from 4.5 to 16.3 per 10,000 PY, IRR 3.67) and anorectal gonorrhoea (from 4.5 to 15.9 per 10,000 PY, IRR 3.53). This increase was stronger in men than women for both anorectal chlamydia (from 7.1 to 26.6 per 10,000 PY, IRR 3.72 versus from 1.8 to 6.3 per 10,000 PY, IRR 3.42) and anorectal gonorrhoea (from 7.1 to 26.5 per 10,000 PY in men, IRR 3.72, versus from 1.9 to 5.4 per 10,000 PY in women, IRR 2.82; Supplementary Figure 3 and Supplementary Table 4).

DISCUSSION

Our educational programme to improve GPs' HIV testing has been attended by over 41% of Amsterdam GPs since 2015 and has been positively evaluated with an average rating of 8.5/10. Laboratory data showed declining HIV testing by Amsterdam GPs from 2011 to 2014, with a subsequent stabilization from 2014 onwards. The decline was more pronounced in women and in the young and middle age categories (20-34 and 35-49). The HIV positivity ratio declined from 2011 to 2017. There was a decline in chlamydia and gonorrhoea testing rates in women from 2011 to 2014 but, in men, they remained stable. Anorectal chlamydia and gonorrhoea testing rates increased from 2011 to 2017, especially in men.

The initial decline in HIV testing rates coincides with the increase of the Dutch compulsory annual deductible for patients from €170 to €385. GP diagnostics are paid out-of-pocket by patients who have not exhausted their deductible. Meanwhile, HIV testing at STI clinics, which is free for the patient, increased[1]. The stabilization of HIV testing from 2014 onwards coincides with the start of our intervention. As such, it might have contributed to this stabilization. Meanwhile, as part of the H-TEAM initiative, GPs received periodic newsletters on appropriate HIV testing from 2014 and contributed to annual free HIV testing weeks from 2015 onwards. Furthermore, the STI consultation guideline for GPs was implemented in September 2013 (Figure 2)[3]. The stabilization in HIV testing also coincides with the implementation of a ceiling on government funding for STI clinics in 2015, leading to constrained access to these clinics. Thus, multiple H-TEAM interventions and contextual factors on the national level could have contributed to the observed trend in HIV testing. As such, no causality of the stabilization in HIV testing can be attributed to this programme. Analyses comparing pre- and post-intervention testing rates and

comparing participants and non-participants are needed to determine the effect of this intervention.

The stronger recovery in chlamydia testing rates compared to gonorrhoea testing rates from 2014 onwards is in accordance with the STI consultation guideline for GPs, as it recommends testing only for chlamydia in the absence of STI risk factors[3]. In the presence of risk factors, GPs are advised to test for the 'Big Five' (chlamydia, gonorrhoea, syphilis, HIV and hepatitis B), with additional testing for STIs like *Trichomonas vaginalis*, lymphogranuloma venereum, *Mycoplasma genitalium* and hepatitis C, if indicated. The guideline also emphasizes the importance of a detailed sexual history to identify indications for extragenital STI testing. Accordingly, our data reveal increased anorectal chlamydia and gonorrhoea testing, predominantly in men, although these rates remain low.

Comparing HIV testing by Amsterdam GPs to other high prevalence areas in Europe reveals mixed results. In Haringey, London, an area with a similar HIV prevalence as Amsterdam (7.5 versus 7.3 per 1,000 residents, respectively[9,26]), an intervention amongst GPs yielded a testing rate of 59.9 per 10,000 PY in 2012[17]. That year, the testing rate by Amsterdam GPs was over 2.5 times higher. Conversely, the HIV testing rate by GPs in France in 2013 was 580.7 per 10,000 PY in residents aged 15-70 years[27], while the testing rate by Amsterdam GPs was 137.3 per 10,000 PY for all ages. This difference is possibly due to diagnostics being free in France, while, in the Netherlands, a deductible is compulsory.

Our ongoing programme has several strengths. The intervention uses multiple evidence-based elements for performance improvement (Table 1): graphical audit and feedback is a proven effective intervention[28]; small-scale interactive sessions are more successful than traditional strategies such as one-time lectures; and multifaceted programmes are recommended, including elements such as group discussion and designing quality improvement plans[15-21]. We aimed to create a sustainable effect by adopting those elements that were proven sustainably effective in comparable settings[29]. Additionally, a GP moderating the DTO for its peers elicits a more open discussion, allowing for more effective adherence to the quality improvement plans[30]. During the sessions, we address other STIs aside from HIV to make participation more rewarding and to improve GPs' STI consultations as a whole. Dutch GPs experience heavy workloads and have limited time for professional development[31], so the high participation ratio so far indicates that GPs are interested in these topics. This high participation ratio could additionally be explained by our collaboration with the regional primary care support organization Elaa for the recruitment of participants as they are a well-known and trusted party for GPs. As this project is ongoing, the number of participants to DTO II is still rising. For this project, a unique dataset was assembled, providing novel and valuable insight into the role of primary care in HIV testing. Data on HIV and STI testing were not readily available for primary care, and only data on HIV and STI diagnoses made in primary care are provided through national surveillance. Retrieving data from laboratories yielded an estimated 90-95% of STI tests ordered by Amsterdam GPs

since 2011. Finally, as these data contain actual test data, there is no risk of recall bias (as in interviews) or registration bias (as for electronic health records).

Our study is limited by the fact that there is considerable variation in practice size between GPs (e.g. GPs working part time) and over time (e.g. maternity leave). Consequently, differences in testing behaviour by GPs in the graphical feedback shown during the sessions warrant cautious interpretation. This is reflected in the DTO I evaluations, where 35% of participants named the skewed or incomplete graphical feedback as a point of improvement. We additionally present the calculated mean number of tests per full-time GP so that GPs can compare their testing behaviour to this mean considering their own practice size. Additionally, although we aim to improve PITC by GPs, we cannot distinguish between provider-initiated tests and patient-requested tests[32]. It is possible that changes in HIV testing are due to changes in patients requesting HIV testing as opposed to changes in GPs proactively testing for HIV. Furthermore, the changes in testing rates could not be corrected for patients' risk factors for HIV acquisition (e.g. ethnicity or sexual behaviour). Consequently, a declining testing rate is not incompatible with a more targeted testing strategy by GPs. Data on these risk factors could help more accurately assess whether testing behaviour is improving, but collection of these data is limited by European privacy regulations. However, the declining HIV incidence in Amsterdam is reflected in the declining HIV positivity ratio in our data. This suggests that GPs testing behaviour is not becoming more targeted as we would then find a more stable positivity ratio. Although the number of undiagnosed PLHIV in the Netherlands is decreasing, 47% of new HIV diagnoses are late-stage infections[9]. Thus, improving GPs' testing strategies to ensure timely testing of patients at risk, presenting with symptoms of acute HIV or with an indicator condition, remains of utmost importance. Finally, we did not include electronic prompts as a strategy to increase HIV testing. During the design of this intervention, GPs were resistant to such an intervention due to '*prompt fatigue*'. Although current evidence on this approach shows variable results[33-35], this strategy might further improve GPs' testing practices in the future.

CONCLUSIONS

We described the rationale, design and implementation of an evidence-based educational intervention to improve provider-initiated HIV testing by GPs in Amsterdam. A stabilization in HIV testing coincided with the start of our intervention, although no inference on causality can be made. Analyses of follow-up data from this ongoing project, including qualitative and quantitative data, will determine the intervention's effectiveness to improve GPs' testing behaviour, whilst considering contextual factors and secular trends. Facilitating earlier diagnosis and treatment of HIV in primary care will ultimately help achieve our ambitious goal of eliminating HIV in Amsterdam, the Netherlands.

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Ethics approval
The Medical Ethics Committee of the Amsterdam UMC determined that this study does not meet the definition of medical research involving human subjects under Dutch law. All GPs were given opportunity to object to use of their data. Participating GPs provided informed consent for the use of their evaluations for research purposes.

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Conflict of interest
Funders were not involved in the project's design/evaluation. The authors report no competing interests

REFERENCES

1. Visser M, van Aar F, Op de Coul E, et al. *Sexually transmitted infections in the Netherlands in 2017.* RIVM official reports, Rijksinstituut voor Volksgezondheid en Milieu RIVM2018.
2. Joore IK, Arts DL, Kruijer MJ, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. Sex Transm Infect. 2015;91(7):467-472.
3. Van Bergen J, Dekker J, Boeke A, et al. NHG-Standaard Het soa-consult(Eerste herziening) (Dutch). Huisarts Wet. 2013;56(9):450-463.
4. Joore IK, van Roosmalen SL, van Bergen JE, van Dijk N. General practitioners' barriers and facilitators towards new provider-initiated HIV testing strategies: a qualitative study. Int J STD AIDS. 2017;28(5):459-466.
5. Kesten JM, Davies CF, Gompels M, et al. Qualitative evaluation of a pilot educational intervention to increase primary care HIV-testing. BMC Fam Pract. 2019;20(1):74.
6. Apers H, Nostlinger C, Van Beckhoven D, et al. Identifying key elements to inform HIV-testing interventions for primary care in Belgium. Health Promot Int. 2019.
7. Tan K, Black BP. A Systematic Review of Health Care Provider-Perceived Barriers and Facilitators to Routine HIV Testing in Primary Care Settings in the Southeastern United States. J Assoc Nurses AIDS Care. 2018;29(3):357-370.
8. Deblonde J, Van Beckhoven D, Loos J, et al. HIV testing within general practices in Europe: a mixed-methods systematic review. BMC Public Health. 2018;18(1):1191.
9. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. Monitoring Report 2018. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring;2018.
10. Op de Coul ELM, Joore IK, van Sighem A, et al. [Mapping HIV prevalence in the Netherlands with geographic information systems]. Ned Tijdschr Geneeskd. 2017;161:D965.
11. H-TEAM. https://hteam.nl/]. Accessed Last accessed 3 April 2019.
12. Bos-Bonnie LHA, van Bergen J, Te Pas E, Kijser MA, van Dijk N. Effectiveness of an individual, online e-learning program about sexually transmitted infections: a prospective cohort study. BMC Fam Pract. 2017;18(1):57.
13. Pillay K, Gardner M, Gould A, et al. Long term effect of primary health care training on HIV testing: A quasi-experimental evaluation of the Sexual Health in Practice (SHIP) intervention. PLoS One. 2018;13(8):e0199891.
14. Davies CF, Kesten JM, Gompels M, et al. Evaluation of an educational intervention to increase HIV-testing in high HIV prevalence general practices: a pilot feasibility stepped-wedged randomised controlled trial. BMC Fam Pract. 2018;19(1):195.
15. Spoorenberg V, Hulscher ME, Geskus RB, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. PLoS One. 2015;10(12):e0142672.
16. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362(9391):1225-1230.
17. Pillay TD, Mullineux J, Smith CJ, Matthews P. Unlocking the potential: longitudinal audit finds multifaceted education for general practice increases HIV testing and diagnosis. Sex Transm Infect. 2013;89(3):191-196.

18. Forsetlund L, Bjorndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database Syst Rev. 2009(2):CD003030.

19. Verstappen WH, van der Weijden T, Sijbrandij J, et al. Effect of a practice-based strategy on test ordering performance of primary care physicians: a randomized trial. JAMA. 2003;289(18):2407-2412.

20. Joore IK, van Bergen J, Ter Riet G, van der Maat A, van Dijk N. Development and evaluation of a blended educational programme for general practitioners' trainers to stimulate proactive HIV testing. BMC Fam Pract. 2018;19(1):36.

21. Grol R, Wensing M. [Implementatie. Effectieve verbetering van de patiëntenzorg] (Dutch). 5th ed. Amsterdam: Reed Business; 2013.

22. Ivers NM, Grimshaw JM, Jamtvedt G, et al. Growing literature, stagnant science? Systematic review, meta-regression and cumulative analysis of audit and feedback interventions in health care. J Gen Intern Med. 2014;29(11):1534-1541.

23. Boersma-van Dam ME, Weesie YM, Hek K, et al. Zorg door de huisarts - Nivel Zorgregistraties eerste lijn: Jaarcijfers 2017 en trendcijfers 2011-2017 [Dutch]. In: NIVEL Zorgregistraties eerste lijn; 2018.

24. Cervero RM, Gaines JK. The impact of CME on physician performance and patient health outcomes: an updated synthesis of systematic reviews. J Contin Educ Health Prof. 2015;35(2):131-138.

25. StataCorp. 2017. Stata Statistical Software: Release 15. College Station TX: StataCorp LLC. In.

26. Public Health England. Sexual and Reproductive Health Profile - Haringey. 2015.

27. Sicsic J, Saint-Lary O, Rouveix E, Pelletier-Fleury N. Impact of a primary care national policy on HIV screening in France: a longitudinal analysis between 2006 and 2013. Br J Gen Pract. 2016;66(653):e920-e929.

28. van Braak M, Visser M, Holtrop M, Statius Muller I, Bont J, van Dijk N. What motivates general practitioners to change practice behaviour? A qualitative study of audit and feedback group sessions in Dutch general practice. BMJ Open. 2019;9(5):e025286.

29. Chauhan BF, Jeyaraman MM, Mann AS, et al. Behavior change interventions and policies influencing primary healthcare professionals' practice-an overview of reviews. Implement Sci. 2017;12(1):3.

30. Lillis S. The educational value of peer groups from a general practitioner perspective. J Prim Health Care. 2011;3(3):218-221.

31. Boekee S, Hoekstra H. Workload GP threatens kwality of care [Dutch]. In. Enschede: Landelijke Huisartsen Vereniging; 2018.

32. World Health Organization. Guidance on provider-initiated HIV testing and counselling in health facilities. In. Geneva, Zwitzerland2007.

33. Cayuelas Redondo L, Ruiz M, Kostov B, et al. Indicator condition-guided HIV testing with an electronic prompt in primary healthcare: a before and after evaluation of an intervention. Sex Transm Infect. 2019;95(4):238-243.

34. Chadwick DR, Hall C, Rae C, et al. A feasibility study for a clinical decision support system prompting HIV testing. HIV Med. 2017;18(6):435-439.

35. Marcelin JR, Tan EM, Marcelin A, et al. Assessment and improvement of HIV screening rates in a Midwest primary care practice using an electronic clinical decision support system: a quality improvement study. BMC Med Inform Decis Mak. 2016;16:76.

Supplementary Table 1: Strengths and points of improvement for the DTO I sessions mentioned in evaluation by 20 participating groups.

Strengths of the DTO sessions	**n (%)**
Gaining more knowledge and awareness on the several topics	8 (40)
Interactive design of the session	4 (20)
Discussing the diagnostic decision tool for STI testing	3 (15)
Graphical audit and feedback and discussion	2 (10)
Group discussion on stigma and barriers to discussing STI with the patient	2 (10)
Points of improvement for the DTO sessions	**n (%)**
The graphical feedback showed incomplete or skewed data	7 (35)
Participants wanted more information on epidemiology of STI in their area	3 (15)
Participants wanted more exemplary practice cases	2 (10)
Participants wanted a shorter session	2 (10)
Participants wanted a longer session	2 (10)

DTO = diagnostic audit meeting (in Dutch: Diagnostisch Toets Overleg). STI = sexually transmitted infection.

Supplementary Table 2: HIV testing rates by GPs per 10,000 person-years by age category and sex.

Male						
	<20 years	**20-34 years**	**35-49 years**	**50-64 years**	**≥ 65 years**	**Total male**
2011	15.49	305.20	246.40	135.95	42.55	173.29
2012	14.07	271.61	234.78	133.42	54.59	161.80
2013	12.89	229.65	218.21	131.15	45.89	144.69
2014	8.89	198.19	202.55	130.31	47.43	131.46
2015	8.73	208.93	215.77	136.41	54.66	139.20
2016	12.01	224.17	213.52	145.80	53.59	145.24
2017	9.60	199.49	217.86	141.75	52.23	138.26
Female						
	<20 years	**20-34 years**	**35-49 years**	**50-64 years**	**≥ 65 years**	**Total female**
2011	39.77	385.58	213.08	63.27	6.51	176.21
2012	30.26	338.81	201.80	61.64	5.74	158.59
2013	22.89	263.01	180.43	57.04	7.94	130.22
2014	15.36	193.28	149.99	51.78	7.40	101.16
2015	15.28	195.76	166.42	55.59	7.65	106.20
2016	16.48	215.42	173.91	61.29	9.16	115.26
2017	14.78	193.77	164.56	67.23	8.45	107.68

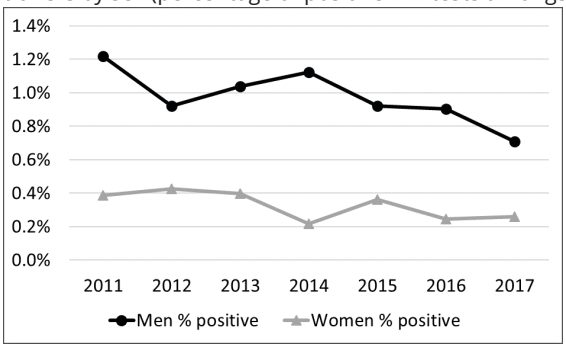
Supplementary Table 3: Positivity ratio of all HIV tests ordered by Amsterdam GPs per year by sex.

	Male % positive	Female % positive	Total % positive
2011	1.22	0.39	0.79
2012	0.92	0.42	0.67
2013	1.04	0.40	0.73
2014	1.12	0.22	0.72
2015	0.92	0.36	0.68
2016	0.90	0.25	0.61
2017	0.71	0.26	0.51

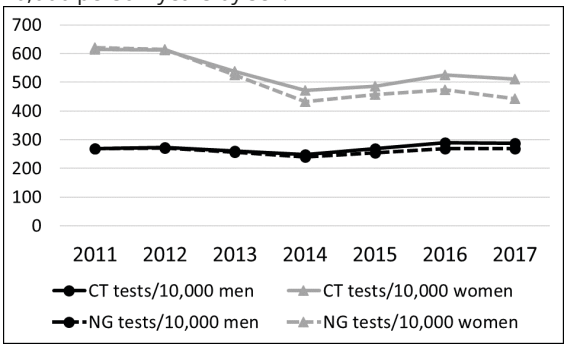
Supplementary Table 4: Chlamydia and gonorrhoea testing rates by GPs per 10,000 person-years by sex.

	Chlamydia			Gonorrhoea		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
2011	269.85	615.50	445.38	269.93	620.80	448.11
2012	272.90	613.28	445.70	271.80	614.63	445.84
2013	260.82	538.43	401.84	256.67	525.35	393.16
2014	248.86	471.12	361.64	239.19	432.72	337.40
2015	269.68	486.55	379.70	254.84	457.72	357.76
2016	288.99	525.15	408.54	269.07	473.92	372.77
2017	286.61	511.20	400.06	268.72	442.90	356.71
	Anorectal chlamydia			**Anorectal gonorrhoea**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
2011	7.14	1.84	4.45	7.14	1.92	4.49
2012	8.30	1.57	4.89	8.38	1.65	4.96
2013	8.42	2.00	5.16	8.34	2.04	5.14
2014	11.62	2.21	6.84	11.54	2.07	6.73
2015	15.88	4.22	9.97	15.96	4.03	9.91
2016	21.21	6.47	13.75	21.31	5.62	13.36
2017	26.55	6.30	16.32	26.52	5.41	15.86

Supplementary Figure 1: Trends in positivity ratio of HIV tests performed by general practitioners by sex (percentage of positive HIV tests amongst all HIV tests performed).

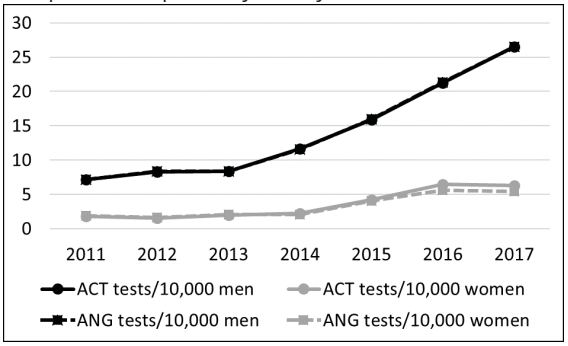


Supplementary Figure 2: Trends in chlamydia & gonorrhoea tests performed by GPs per 10,000 person-years by sex.



CT = chlamydia trachomatis, NG = Neisseria gonorrhoeae

Supplementary Figure 3: Trends in anorectal chlamydia & gonorrhoea tests performed by GPs per 10,000 person-years by sex.



ACT = anorectal chlamydia trachomatis, ANG = anorectal Neisseria gonorrhoeae

Chapter 4

Improving provider-initiated testing for HIV and other STI in the primary care setting in Amsterdam, the Netherlands: results from a multifaceted, educational intervention programme

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ABSTRACT

Background
In the Netherlands, general practitioners (GPs) play a key role in HIV testing. However, the proportion of people diagnosed with late-stage HIV remains high, and opportunities for earlier diagnosis are being missed. We implemented an educational intervention to improve HIV and STI testing in primary care in Amsterdam, the Netherlands.

Methods
GPs were invited to participate in an educational program between 2015 and 2020, which included repeat sessions using audit and feedback and quality improvement plans. Data on HIV, chlamydia and gonorrhoea testing by GPs were collected from 2011 through 2020. The primary outcome was HIV testing frequency, which was compared between GPs before and after participation using Poisson regression. Secondary outcomes were chlamydia and gonorrhoea testing frequencies, and positive test proportions. Additional analyses stratified by patient sex and age were done.

Findings
GPs after participation performed 7% more HIV tests compared to GPs before participation (adjusted relative ratio [aRR] 1.07, 95%CI 1.04-1.09); there was no change in the proportion HIV positive tests (aRR 0.87, 95%CI 0.63-1.19). HIV testing increased most among patients who were female and ≤19 or 50-64 years old. After participation, HIV testing continued to increase (aRR 1.02 per quarter, 95%CI 1.01-1.02). Chlamydia testing by GPs after participation increased by 6% (aRR 1.06, 95%CI 1.05-1.08), while gonorrhoea testing decreased by 2% (aRR 0.98, 95%CI 0.97-0.99). We observed increases specifically in extragenital chlamydia and gonorrhoea testing.

Conclusions
The intervention was associated with a modest increase in HIV testing among GPs after participation, while the proportion positive HIV tests remained stable. Our results suggest that the intervention yielded a sustained effect.

INTRODUCTION

Globally, the annual number of new HIV infections has been reduced by 52% since its peak in 1997, but an estimated 1.5 million new HIV infections still occurred in 2021[1]. In the Netherlands, the number of newly-diagnosed HIV infections has declined by 53% since 2015, with 427 newly-diagnosed HIV infections in 2021[2]. The Netherlands has thus reached one of their goals set by the national action plan on sexually transmitted infections (STI), HIV and sexual health: to achieve a 50% reduction in the annual number of newly-diagnosed HIV infections by 2022, compared with 2015[3]. However, an estimated 6% of people living with HIV (PLHIV) in the Netherlands in 2021 were unaware of their diagnosis, and over half of individuals newly diagnosed were at a late-stage of HIV infection, defined as having a CD4 count below 350 cells/mm^3 or an AIDS-defining event[2]. Since studies have shown that the majority of HIV transmissions come from persons with undiagnosed HIV and adequate treatment of HIV prevents onward transmission, reduction of the proportion undiagnosed and timely diagnosis of HIV are crucial in ending the HIV epidemic[4-6].

In the Netherlands, general practitioners (GPs) provide the majority of sexual health consultations (71%)[7]. GPs may therefore play a key role in diagnosing HIV. Additionally, GPs may be the first healthcare provider to recognize symptoms indicating acute HIV infection, as well as HIV indicator conditions[8,9]. Since 2019, 32% of PLHIV were diagnosed by GPs, while 28% were diagnosed at sexual health centres (SHCs) and 35% in the hospital setting. The proportions of PLHIV that were diagnosed at a late stage of infection in these settings were 46%, 30% and 81%, respectively[2]. While SHCs provide routine HIV testing for key populations on an opt-out basis, HIV diagnoses in hospitals are generally made among patients presenting with HIV indicator conditions or AIDS-defining illnesses, usually after referral by the GP. Thus, it is likely that GPs can facilitate earlier diagnosis by applying optimal HIV testing strategies. However, it has been previously shown that there were missed opportunities for earlier HIV diagnosis in the primary care setting, and that barriers and HIV related stigma hampering proactive HIV testing by GPs may delay HIV diagnosis[9-11].

The Dutch HIV epidemic is mostly concentrated in urban areas, with 26% of PLHIV, and an estimated 12% of undiagnosed PLHIV living in the city of Amsterdam[2]. In response to this epidemiological context, the HIV Transmission Elimination in Amsterdam (H-TEAM) consortium was founded in 2014 to deliver a multifaceted city-based approach to end the HIV-epidemic[12]. One of the H-TEAM's objectives is facilitating timely and frequent HIV testing in primary care. To achieve this goal, the H-TEAM implemented a multifaceted educational intervention programme for GPs in Amsterdam as part of their efforts to improve HIV testing in primary care. To extend the impact of the intervention on quality of sexual health consultations and to make participation more rewarding for GPs, the educational programme additionally focused on other STI, including chlamydia and gonorrhoea. In this study, we evaluated the effect of the educational intervention on HIV, chlamydia and gonorrhoea testing by GPs in Amsterdam, the Netherlands.

MATERIAL AND METHODS

Setting and participants

All Amsterdam GPs were invited to participate in an educational intervention by a partner organisation that facilitates integrated healthcare services in primary care. The educational sessions were delivered between February 2015 and December 2020, when saturation in interest to participate was achieved (i.e. no more GPs were interested to participate). The sessions were attended by practicing groups of GPs attending continuing medical education (CME) sessions together. One GP from each group attended a teach-the-teacher session for the programme and moderated the sessions. GPs received points for participation, which are needed to remain accredited.

Intervention

The educational intervention was designed by CME coordinators in conjunction with experts in the field of sexual health and HIV/STI. This intervention used evidence-based elements for effective interventions, including interactive audit and feedback, multiple exposures, and small-group sessions[13]. The programme consisted of two consecutive educational sessions. During the first session, several topics on sexual health and appropriate HIV and STI testing strategies were discussed, including indications for extragenital chlamydia and gonorrhoea testing, and testing for HIV in the case of HIV indicator conditions or symptoms associated with acute HIV infection. A member of the national expert group on HIV and STI in primary care provided updates on state-of-the-art HIV and STI testing and care. Interactive graphical audit and feedback was then given to the participants on their HIV, chlamydia and gonorrhoea testing frequency and positivity, compared to the city average[13]. At the end of the first session, each group established quality improvement plans for optimal HIV and STI testing and care in their practice. During the second session, the implementation of these quality improvement plans was evaluated, updates on HIV and STI epidemiology, diagnosis, prevention and treatment were provided, and updated graphical audit and feedback was given to participants. During both sessions, participants received educational materials including workbooks, STI testing flowcharts, information flyers, and further reading materials. Finally, in the context of this educational intervention programme, GPs received digital newsletters several times a year with relevant news updates on HIV and STI testing and care. More details on the educational programme are described elsewhere[13].

Data collection

Laboratory data on HIV, chlamydia and gonorrhoea tests ordered by all GPs in Amsterdam from 2011 through 2020 were collected from seven major diagnostic laboratories for primary care using a standardized data request form. These data were used to generate the graphical audit and feedback for each session and to evaluate the effect of the intervention. Participating laboratories provided data on the ordering GP (i.e., 4-digit postal code of their practice), test ordered (i.e., date, anatomical site of sampling, and test result), and the patient who was tested (i.e., age and sex). During the educational sessions, we assessed which laboratories the

participating GPs were using through a questionnaire. Based on the responses, we estimated that 90-95% of all HIV, chlamydia and gonorrhoea tests ordered by GPs in Amsterdam were included in the data provided by these laboratories.

Outcomes

The primary outcome was the number of HIV tests ordered per GP per quarter. Secondary outcomes were the number of HIV tests that were positive, the overall number of chlamydia and gonorrhoea tests ordered per GP per quarter, the number of urogenital, anorectal and oropharyngeal chlamydia and gonorrhoea tests ordered per GP per quarter, and their respective proportions positive.

Statistical analysis

Overall trends in HIV, chlamydia and gonorrhoea testing over time were calculated per 10,000 residents of Amsterdam. We modelled outcomes by quarter-year periods using Poisson regression. Each record represented a quarter-year period of one GP. A record could concern (1) a GP prior to participation, (2) a GP after participation, or (3) a GP who never participated. The model was used to estimate the relative ratio (RR) and its 95% confidence interval (CI) of the mean number of tests or proportion positive comparing between (2) GPs after participation and (3) GPs who never participated in the intervention with GPs before participation (1; reference group). For participants, time after participation started on the date a GP first attended a session in the programme, regardless of whether they attended one or both sessions. Due to the disruption of healthcare service delivery from COVID-19, data from quarters 2-4 in 2020 were excluded from analysis, and follow-up therefore ended on March 31st, 2020. We added city district of the ordering GP (as the HIV and STI incidence and prevalence vary by district) and year of testing (to correct for any secular trends) as covariates to the model. For the primary outcome, a sensitivity analysis was performed by excluding GPs who ordered >30 HIV tests per quarter-year before participation (among participants) or before the start of the programme (among GPs who never participated), as both participation and effect of the intervention were expected to be low since these GPs already had high levels of HIV testing activity. Additional analyses using the same models stratified by patient sex and age categories (<20 years, 20-34 years, 35-49 years, 50-64 years and ≥65 years) were performed. Finally, we estimated the effect of the intervention over time by regressing the outcomes by GPs after participation on quarter-years, adjusted for city district and year of testing. A p-value of <0.05 was considered statistically significant. Data analysis was performed using Stata (v15.1, College Station, Texas, USA).

Ethics statement

All GPs in Amsterdam were provided with the opportunity to object to use of their laboratory data through a written opt-out procedure. All participating GPs provided written informed consent for the use of the results of the educational sessions and their evaluations for research purposes. The Medical Ethics Committee of the Amsterdam University Medical Centres, University of Amsterdam determined

that this study does not meet the definition of medical research involving human subjects under Dutch law (file W18_230, #18.274, 24 July 2018).

RESULTS

Participation in the programme

The mean annual number of registered GPs practicing in Amsterdam in 2011-2018 was 504[14]. In total, 36 first and second educational sessions were conducted, with 229 unique GPs attending. A third (75/229) of GPs attended both sessions of the programme. First sessions were conducted between February 2015 and April 2019 and second sessions were conducted between November 2017 and December 2020.

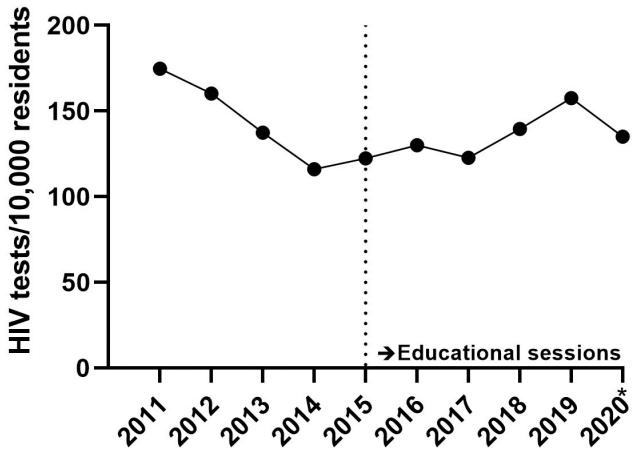
Data collected

Data on 106,424 HIV tests, 343,648 chlamydia tests and 321,345 gonorrhoea tests by Amsterdam GPs from January 2011 through March 2020 were collected. Of these, 684 HIV tests, 24,318 chlamydia tests and 6,984 gonorrhoea tests were positive, resulting in 0.6%, 7.1% and 2.2% positive tests, respectively. Overall, the data collected during the study period concerned tests ordered by 725 GPs, with a mean of 464 GPs per year (i.e. 464/504; 92% of the mean number of registered GPs).

HIV testing

From 2011-2014, overall HIV testing by GPs decreased with 34%, from 175 to 116 per 10,000 residents of Amsterdam. From 2015 onward, overall HIV testing increased by 10%, from 123 to 135 per 10,000 residents (Figure 1).

Figure 1: Trends in HIV tests performed by GPs per 10,000 residents of Amsterdam, 2011-2020.



*2020 data only include the first quarter. The dotted vertical line represents the transition to the period in which the educational sessions were implemented.

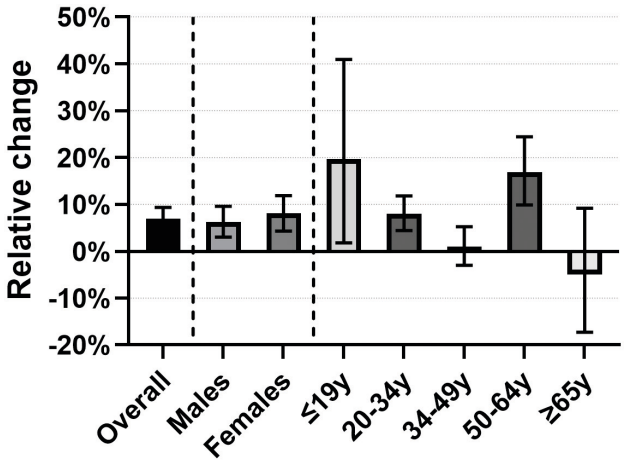
The overall mean number of HIV tests ordered per GP per quarter was 5, interquartile range (IQR) 2-9. By GP group, this was 5, IQR 2-9 for GPs before participation and 5, IQR 3-9 for GPs after participation in the intervention. We observed a 7% increase in HIV testing among GPs after participation, compared to before participation (relative ratio [RR] adjusted for calendar year and city district 1.07, 95%CI 1.04-1.09, p<0.001), Table 1, Figure 2).

Table 1: Adjusted relative HIV test ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.

	Main analysis		Sensitivity analysis*	
	Relative HIV Test Ratio	**95% CI**	**Relative HIV Test Ratio**	**95% CI**
Overall	1.07	1.04 - 1.09	1.09	1.07 - 1.12
By sex				
Males	1.06	1.03 - 1.10	1.07	1.03 - 1.10
Females	1.08	1.04 - 1.12	1.13	1.09 - 1.17
By age categories				
≤19 years	1.20	1.02 - 1.41	1.26	1.06 - 1.49
20-34 years	1.08	1.04 - 1.12	1.10	1.06 - 1.14
34-49 years	1.01	0.97 - 1.05	1.03	0.99 - 1.08
50-64 years	1.17	1.10 - 1.24	1.23	1.15 - 1.32
≥65 years	0.95	0.83 - 1.09	0.94	0.80 - 1.10
Males by age categories				
≤19 years	1.15	0.87 - 1.50	1.17	0.88 - 1.56
20-34 years	1.05	1.00 - 1.10	1.04	0.99 - 1.10
34-49 years	1.02	0.97 - 1.08	1.02	0.96 - 1.08
50-64 years	1.17	1.09 - 1.26	1.23	1.13 - 1.33
≥65 years	0.99	0.85 - 1.15	0.99	0.83 - 1.19
Females by age categories				
≤19 years	1.23	1.01 - 1.51	1.32	1.06 - 1.65
20-34 years	1.12	1.07 - 1.18	1.17	1.12 - 1.24
34-49 years	0.99	0.93 - 1.06	1.05	0.98 - 1.12
50-64 years	1.15	1.02 - 1.30	1.21	1.06 - 1.38
≥65 years	0.78	0.54 - 1.11	0.69	0.47 - 1.03

Relative test ratios were adjusted for city district of the ordering GP and year of testing. *Excluding GPs that had already ordered >30 HIV tests per quarter before participation in the educational intervention.

Figure 2: Relative change and 95% confidence intervals in HIV testing among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.



By patient sex, this increase was 6% among men and 8% among women. By age categories, the largest increases in HIV testing among GPs after participation were observed in those ≤19 or 50-64 years old. Among men, significant increases in HIV testing by GPs after participation were only observed among patients aged 50-64 years old. Among women, significant increases were observed among patients aged ≤19, 20-34 and 50-64 years old (Table 1, Figure 2). In sensitivity analyses excluding GPs who ordered >30 HIV tests per quarter-year at baseline (n=9 among GPs who participated and n=22 among GPs who never participated in the programme), we observed a 9% increase in overall HIV testing among GPs after participation in the intervention, a 7% increase among male patients, a 13% increase among female patients, and increases among all groups of patients aged <65 years old, Table 1.

The overall mean number of HIV tests ordered was 4, IQR 2-8 for GPs who never participated in the intervention. This group ordered 18% more HIV tests compared to GPs before participation (aRR 1.18, 95%CI 1.16-1.20, p<0.001). However, in sensitivity analyses excluding GPs who ordered >30 HIV tests per quarter-year at baseline, we observed no difference in testing among GPs who never participated compared to GPs before participation (aRR 0.98, 95% CI 0.97-1.00, p=0.07).

HIV positivity

Overall, 174/25,909 (0.7%) HIV tests ordered by GPs before participation, and 72/15,509 (0.5%) tests ordered by GPs after participation in the intervention were positive; no significant change was observed in the proportion positive HIV tests ordered per quarter by GPs after participation compared to GPs before participation (aRR 0.87, 95%CI 0.63-1.19, p=0.39). Similar results were found in analyses when stratified by patients' sex and age, Table 2.

Table 2: Adjusted relative HIV positivity ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.

	Main analysis		Sensitivity analysis*	
	Relative HIV Positivity Ratio	95% CI	Relative HIV Positivity Ratio	95% CI
Overall	0.87	0.63 - 1.19	0.88	0.61 - 1.26
By sex				
Males	0.82	0.58 - 1.16	0.90	0.60 - 1.34
Females	1.03	0.47 - 2.22	0.84	0.37 - 1.93
By age categories				
≤19 years	n/a	n/a	n/a	n/a
20-34 years	0.76	0.39 - 1.48	0.60	0.29 - 1.24
34-49 years	1.06	0.66 - 1.72	1.27	0.73 - 2.19
50-64 years	0.72	0.40 - 1.30	0.73	0.37 - 1.46
≥65 years	n/a	n/a	n/a	n/a

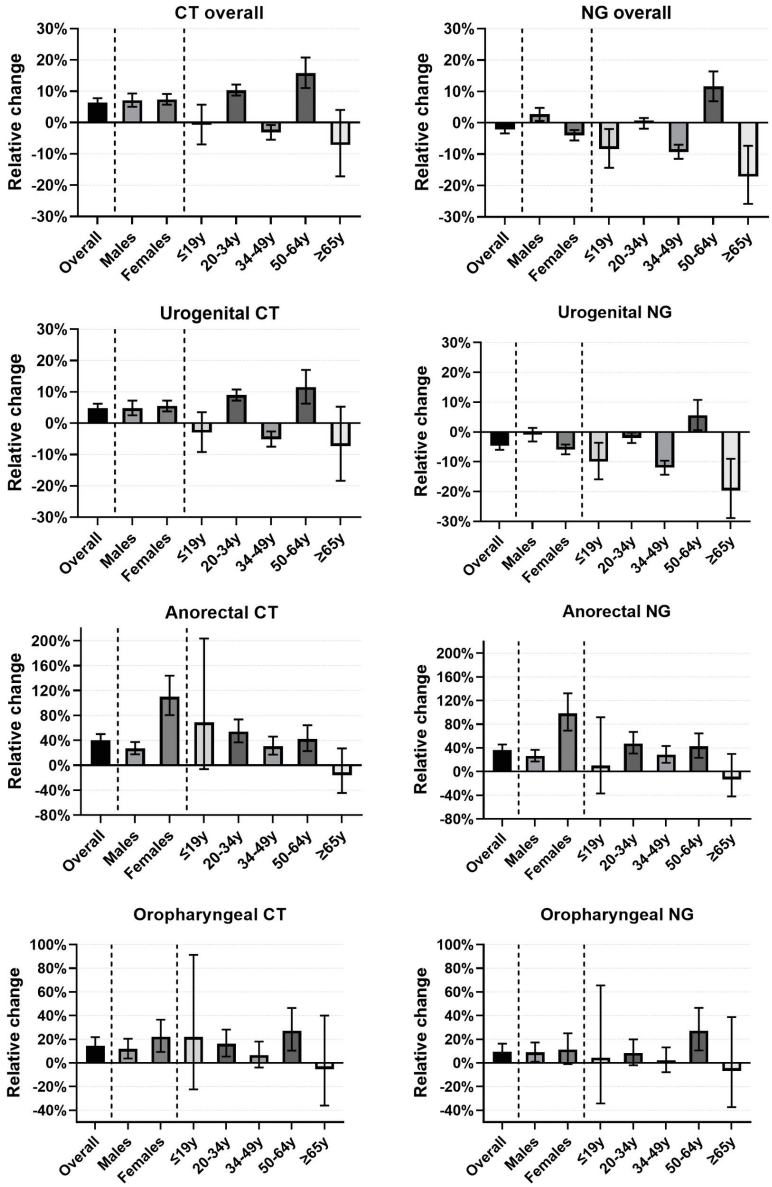
Relative test ratios were adjusted for city district of the ordering GP and year of testing. *Excluding GPs that had already ordered >30 HIV tests per quarter before participation in the educational intervention. n/a: parameter estimates could not be obtained due to low numbers

Chlamydia testing and positivity

From 2011-2014, overall chlamydia testing decreased with 18%, from 453 to 373 per 10,000 residents of Amsterdam. From 2015 onward, overall chlamydia testing increased by 44%, from 397 to 569 per 10,000 residents. The overall mean number of chlamydia tests ordered per GP per quarter was 17, IQR 9-27. By GP group, this was 17, IQR 10-27 for GPs before participation and 20, IQR 11-33 for GPs after participation in the intervention. We observed a 6% increase in chlamydia testing among GPs after participation, compared to GPs before participation (aRR 1.06, 95%CI 1.05-1.08, p<0.001, Figure 3, Supplementary Table 1), which did not vary by patient sex. By patient age categories, 10% and 16% increases in chlamydia testing were observed among patients aged 20-34 and 50-64 years old, respectively, while a 3% decrease was observed among 34-49 year olds. By anatomical site, we observed a 5% increase in urogenital chlamydia testing among GPs after participation, while there was a 40% increase in anorectal chlamydia testing and a 15% increase in oropharyngeal chlamydia testing. The largest increase in chlamydia testing was observed for anorectal chlamydia in women (aRR 2.10, 95% CI 1.81-2.44, p<0.001, Figure 3, Supplementary Table 1).

Overall, 5,668/85,611 (6.6%) chlamydia tests ordered by GPs before participation and 4,346/60,018 (7.2%) tests ordered by GPs after participation were positive. No significant change was observed in the overall proportion positive chlamydia tests ordered by GPs after participation (aRR 1.02, 95% CI 0.98-1.07, p=0.36, Supplementary Table 1), but we did observe an increase in positivity among patients aged 50-64 years (aRR 1.37, 95% CI 1.10-1.70, p=0.01). By anatomical site, no change in the overall proportion positive chlamydia tests was observed.

Figure 3: Relative change and 95% confidence intervals in overall, urogenital, anorectal and oropharyngeal chlamydia and gonorrhoea testing among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.



CT: Chlamydia trachomatis. NG: Neisseria gonorrhoeae. Axis ranges vary by panel.

Gonorrhoea testing and positivity

From 2011-2014, overall gonorrhoea testing decreased with 23%, from 456 to 349 per 10,000 residents of Amsterdam. From 2015 onward, overall gonorrhoea testing increased by 34%, from 375 to 504 per 10,000 residents. The overall mean number of gonorrhoea tests ordered per GP per quarter was 15, IQR 8-25. By GP group, this was 17, IQR 10-26 for GPs before participation and 17, IQR 10-27 for GPs after participation in the intervention. We observed a 2% decrease in gonorrhoea testing among GPs after participation, compared to GPs before participation (aRR 0.98, 95% CI 0.97-0.99, p<0.001, Figure 3, Supplementary Table 2). This decrease was only observed among women, while a 3% increase was observed among men. By age, 8% and 9% decreases in gonorrhoea testing were observed among patients aged ≤19 and 34-49 years old, respectively, while a 12% increase was observed among 50-64 year olds. By anatomical site, we observed a 5% decrease in urogenital gonorrhoea testing among GPs after participation, while there was a 36% increase in anorectal gonorrhoea testing, and a 9% increase in oropharyngeal gonorrhoea testing. The largest increase in gonorrhoea testing was observed for anorectal gonorrhoea in women (aRR 1.98, 95% CI 1.69-2.32, p<0.001), while the largest decrease in gonorrhoea testing was observed in ≥65 year-old patients being tested for urogenital gonorrhoea (aRR 0.80, 95% CI 0.71-0.91, p<0.001, Figure 3, Supplementary Table 2).

Overall, 1,347/81,974 (1.6%) gonorrhoea tests ordered by GPs before participation and 1,392/50,616 (2.8%) tests ordered by GPs after participation were positive. No significant change was observed in the overall proportion positive gonorrhoea tests results by GPs after participation, compared to GPs before participation (aRR 1.09, 95% CI 1.00-1.19, p=0.052, Supplementary Table 2), but we did observe an increase in positivity among patients aged 35-49 years (aRR 1.23, 95% CI 1.04-1.46, p=0.02). By anatomical site, no change in the overall proportion positive gonorrhoea tests was observed.

Trends in testing over time after participation

The median number of quarter-years of data following participation was 6, IQR 3-9 and a range of 1-19. In an analysis estimating the effect of the intervention over time among GPs after participation, we observed an increase in HIV testing over time since participation (aRR 1.02 per quarter, 95% CI 1.01-1.02, p<0.001); the same was observed for chlamydia and gonorrhoea testing overall and by anatomical site (Supplementary Table 3). This increase over time was largest among anorectal chlamydia tests (aRR 1.09, 95% CI 1.08-1.10, p<0.001), while it was smallest for urogenital gonorrhoea tests (aRR 1.00, 95% CI 1.00-1.01, p=0.01, Supplementary Table 3).

DISCUSSION

We implemented an educational intervention to improve HIV and STI testing by GPs in Amsterdam. The educational intervention yielded a modest increase in the

number of HIV tests ordered by GPs after participation. This increase was largest among patients who were female and those ≤19 or 50-64 years old. There was no change in the proportion positive HIV tests.

The differences in effect of the intervention by patient characteristics may suggest increased HIV testing among groups that were often overlooked previously when considering HIV testing, including women and older patients. This assertion is supported by the fact that in the Netherlands, older patients and heterosexual men and women are more commonly diagnosed at a late stage of infection compared to MSM and younger patients[2]. However, we also observed an increase in HIV testing among ≤19 year-olds, suggesting that GPs became more proactive in offering HIV tests to teenagers attending sexual health consultations. In primary care, patients <25 years old consisted of about a third of sexual health consultations and about 40% of STI diagnoses in 2019[7]. The increase in HIV testing among ≤19 year olds may therefore have been due to an increase in adherence to the guideline for GPs on STI consultations, which recommends testing for HIV in the presence of other STI[15]. However, only 9% of new HIV diagnoses in 2020 were made among <25 year-olds, reflecting the low risk of HIV in this age group. Conversely, as 30% of individuals diagnosed with HIV in 2021 were aged 50 years or older[2], the decrease in HIV tests ordered among ≥65 year-old patients may lead to missed opportunities for HIV diagnosis if this group is inadequately tested in the future.

We observed no effect of the intervention on the proportion positive HIV tests. Given the observed increase in HIV test frequency and the strong decline in HIV incidence in the Netherlands over the last decade[2], a decline in the proportion positive test results would have been expected had the testing strategy remained the same. It is therefore likely that HIV testing became more targeted. Moreover, the percentage positive tests observed in our study means that provider-initiated HIV testing in primary care is a cost-effective strategy, as it exceeded the previously identified cost-effectiveness threshold for routine HIV testing of 0.1% positivity[16-18].

In contrast to findings from other intervention studies that aimed to improve HIV and STI testing in primary care[19,20], the findings from our study suggested that the effect on testing among participants did not wane over time. This may have been the result of the quality improvement plans that GPs were encouraged to make during the sessions, as well as the graphical audit and feedback, making GPs intrinsically motivated to improve their testing behaviour, as was suggested previously[21-23]. This finding may be of particular importance in the context of a shrinking HIV epidemic, in which keeping GPs motivated for proactive HIV testing may be challenging in the future, when incidence and therefore perceived risk may decline.

The observed increase in the number of HIV tests ordered by GPs after participation was modest. A previous educational intervention to improve HIV testing rates in primary care in the UK showed no increase in testing which the authors ascribed to the fact that it was a single session without performance feedback, and time constraints among GPs[19]. More recently, a study using on-screen prompts to

test for HIV in patients presenting with indicator conditions in Spain yielded a 3% increase (from 18% to 21%) in HIV testing rates, and the authors suggested that additional education among healthcare providers might further improve HIV testing[24]. In contrast, an intervention to improve nurse-led routine rapid HIV testing in general practice in the UK, which used a combination of training and follow-up sessions, external support, prompts and incentive payments to the practices yielded a 85% increase in testing rates. However, testing rates declined after the trial was completed[25]. These results from interventions to increase HIV testing in primary care in countries similar to the Netherlands in terms of HIV prevalence highlight the challenges of designing and implementing interventions that yield a large, sustainable increase in HIV testing in low-prevalence settings, as has been recognized by several studies that qualitatively assessed factors for success in this setting[21,26-28].

A secondary goal of our educational intervention programme was to improve testing for other STI. We found that while overall chlamydia testing increased among GPs after participation, overall gonorrhoea testing decreased. This is in accordance with GP guidelines on STI consultations, as it recommends gonorrhoea testing only when selected risk factors are present. Therefore, the observed decrease in gonorrhoea testing may indicate closer adherence to this guideline[15]. Most notably, large increases were observed in extragenital chlamydia and gonorrhoea testing by GPs after participation; extragenital testing and the role of autoinoculation in persistent or recurrent chlamydia infections were explicitly addressed during the sessions[29]. In the past years, an increase in anorectal and oropharyngeal chlamydia and gonorrhoea diagnoses has been observed at SHCs[7]. Previous research has shown that compared to SHCs, GPs rarely ordered extragenital tests[30]. Therefore, extragenital infections are likely often being missed in primary care, particularly in women, possibly leading to suboptimal treatment. Nevertheless, the clinical relevance of asymptomatic extragenital chlamydia infections currently remains unclear[31,32].

Strengths and limitations

Strengths of this study include the large proportion of GPs in Amsterdam participating in the intervention, as well as the collection of comprehensive data on HIV and STI testing by nearly all Amsterdam GPs over the past 20 years. This collection allowed a more precise assessment of the intervention's impact on HIV and STI testing frequencies. Additionally, as we collected up to nearly five years of follow-up data on GPs after participation in the intervention, we were able to assess its impact over a longer period of time, thereby estimating the sustainability of the intervention's effect. We do, however, recognize several limitations of this study. Foremost, our data did not include any parameters on patient HIV and STI risk, and therefore no risk-based stratification of our outcomes could be made. Furthermore, we could not collect additional data on patients testing HIV positive, and therefore could not determine whether the proportion diagnosed at a late stage of HIV infection decreased among GPs after participation in the intervention. Such data, as well as qualitative analyses among GPs who participated, could further indicate

how the quality of HIV and STI testing improved among participants, in addition to the quantity of testing reported. While the overall participation to this programme was good, only a third of participating GPs participated in both sessions. This may have hampered the programme's potential, but it also indicates that GPs may have been too constrained for time to attend a second session on this topic. Finally, while we included year of testing in our model to correct for any secular trends, we could not correct for any other factors that may have influenced individual GP's testing behaviour. This educational intervention was part of several H-TEAM initiatives to improve provider-initiated HIV testing in Amsterdam. Consequently, Amsterdam GPs were exposed to multiple initiatives, including local HIV test weeks, pre-exposure prophylaxis (PrEP) campaigns, newsletters on HIV and STI, and media coverage of H-TEAM activities[12,13]. We previously reported that after an initial decline in HIV testing by GPs in Amsterdam, a stabilization in testing coincided with the start of our intervention[13], and this trend may therefore reflect the overall effect from a multilevel and comprehensive city-based approach.

CONCLUSIONS

The educational intervention was associated with a significant, but modest increase in HIV testing among GPs after participation, while the proportion positive HIV tests remained stable. Our results suggest that the effect of the intervention was sustained over time.

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Competing interests
The authors declare that they have no competing interests related to this work.

REFERENCES

1. UNAIDS: Joint United Nations Programme on HIV/AIDS. IN DANGER: UNAIDS Global AIDS Update 2022. Geneva 2022. Available at: https://www.unaids.org/en/resources/documents/2022/in-danger-global-aids-update. Last accessed 22 December 2022.
2. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2022. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2022. Available at www.hiv-monitoring.nl. Last accessed 22 December 2022.
3. David S, van Benthem B, Deug F, van Haastrecht P. Nationaal Actieplan Soa, Hiv En Seksuele Gezondheid 2017-2022. National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport; 2018. Available from: https://www.rivm.nl/bibliotheek/rapporten/2018-0034.pdf. Last accessed 22 December 2022.
4. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;**393(10189)**:2428-38.
5. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS* 2006;**20(10)**:1447-50.
6. Ratmann O, van Sighem A, Bezemer D, et al. Sources of HIV infection among men having sex with men and implications for prevention. *Sci Transl Med* 2016;**8(320)**:320ra2.
7. van Wees D, Visser M, van Aar F, et al. Sexually transmitted infections in the Netherlands in 2021. Rijksinstituut voor Volksgezondheid en Milieu RIVM; 2022. Available from: https://www.rivm.nl/bibliotheek/rapporten/2022-0023.pdf. Last accessed 22 December 2022.
8. Bogers SJ, Twisk DE, Beckers LM, et al. Who is providing HIV diagnostic testing? Comparing HIV testing by general practitioners and sexual health centres in five regions in the Netherlands, 2011-2018. *Sex Transm Infect* 2022;**98(4)**:262-8.
9. Joore IK, Twisk DE, Vanrolleghem AM, et al. The need to scale up HIV indicator condition-guided testing for early case-finding: a case-control study in primary care. *BMC Fam Pract* 2016;**17(1)**:161.
10. Joore IK, Reukers DF, Donker GA, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. *BMJ Open* 2016;**6(1)**:e009194.
11. Bedert M, Davidovich U, de Bree G, et al. Understanding Reasons for HIV Late Diagnosis: A Qualitative Study Among HIV-Positive Individuals in Amsterdam, The Netherlands. *AIDS Behav* 2021;**25(9)**:2898-906.
12. de Bree GJ, van Sighem A, Zuilhof W, et al. Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam. *Curr Opin HIV AIDS* 2019;**14(6)**:455-63.
13. Bogers SJ, Schim van der Loeff MF, van Dijk N, et al. Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care. *Fam Pract* 2021;**38(4)**:441-7.
14. Batenburg R. Beroepenregistraties in de Gezondheidszorg. NIVEL. Available from: https://www.nivel.nl/nl/panels-en-registraties/beroepenregistraties-de-gezondheidszorg. Last accessed: 06-07-2022. Utrecht 2022.
15. van Bergen J, Dekker J, Boeke A, et al. NHG-Standaard Het soa-consult (Eerste herziening). *Huisarts Wet* 2013;**56**:450-63.

16. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. *N Engl J Med* 2005;**352(6)**:586-95.

17. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med* 2005;**352(6)**:570-85.

18. Yazdanpanah Y, Sloan CE, Charlois-Ou C, et al. Routine HIV screening in France: clinical impact and cost-effectiveness. *PLoS One* 2010;**5(10)**:e13132.

19. Davies CF, Kesten JM, Gompels M, et al. Evaluation of an educational intervention to increase HIV-testing in high HIV prevalence general practices: a pilot feasibility stepped-wedged randomised controlled trial. *BMC Fam Pract* 2018;**19(1)**:195.

20. Town K, McNulty CA, Ricketts EJ, et al. Service evaluation of an educational intervention to improve sexual health services in primary care implemented using a step-wedge design: analysis of chlamydia testing and diagnosis rate changes. *BMC Public Health* 2016;**16**:686.

21. Apers H, Nostlinger C, Van Beckhoven D, et al. Identifying key elements to inform HIV-testing interventions for primary care in Belgium. *Health Promot Int* 2020;**35(2)**:301-11.

22. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013;**8**:35.

23. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;**362(9391)**:1225-30.

24. Agusti C, Cunillera O, Almeda J, et al. Efficacy of an electronic reminder for HIV screening in primary healthcare based on indicator conditions in Catalonia (Spain). *HIV Med* 2022;**23(8)**:868-79.

25. Leber W, Panovska-Griffiths J, Martin P, et al. Evaluating the impact of post-trial implementation of RHIVA nurse-led HIV screening on HIV testing, diagnosis and earlier diagnosis in general practice in London, UK. *EClinicalMedicine* 2020;**19**:100229.

26. Cervero RM, Gaines JK. The impact of CME on physician performance and patient health outcomes: an updated synthesis of systematic reviews. *J Contin Educ Health Prof* 2015;**35(2)**:131-8.

27. Allison RL, Ricketts EJ, Hartney T, et al. Qualitative impact assessment of an educational workshop on primary care practitioner attitudes to NICE HIV testing guidelines. *BJGP Open* 2018;**2(1)**:bjgpopen18X101433.

28. Deblonde J, Van Beckhoven D, Loos J, et al. HIV testing within general practices in Europe: a mixed-methods systematic review. *BMC Public Health* 2018;**18(1)**:1191.

29. Dukers-Muijrers N, Schim van der Loeff M, Wolffs P, et al. Incident urogenital and anorectal Chlamydia trachomatis in women: the role of sexual exposure and autoinoculation: a multicentre observational study (FemCure). *Sex Transm Infect* 2022.

30. den Heijer CD, van Liere GA, Hoebe CJ, et al. Who tests whom? A comprehensive overview of Chlamydia trachomatis test practices in a Dutch region among different STI care providers for urogenital, anorectal and oropharyngeal sites in young people: a cross-sectional study. *Sex Transm Infect* 2016;**92(3)**:211-7.

31. Dukers-Muijrers NH, Schachter J, van Liere GA, Wolffs PF, Hoebe CJ. What is needed to guide testing for anorectal and pharyngeal Chlamydia trachomatis and Neisseria gonorrhoeae in women and men? Evidence and opinion. *BMC Infect Dis* 2015;**15**:533.

32. Dukers-Muijrers N, Evers YJ, Hoebe C, et al. Controversies and evidence on Chlamydia testing and treatment in asymptomatic women and men who have sex with men: a narrative review. *BMC Infect Dis* 2022;**22(1)**:255.

Supplementary Table 1: Adjusted relative overall, urogenital, anorectal and oropharyngeal chlamydia test ratios and positivity ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.

	Chlamydia overall		Urogenital chlamydia		Anorectal chlamydia		Oropharyngeal chlamydia	
	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI
Overall	1.06	1.05 - 1.08	1.05	1.03 - 1.06	1.40	1.31 - 1.50	1.15	1.08 - 1.22
By sex								
Males	1.07	1.05 - 1.09	1.05	1.03 - 1.07	1.27	1.18 - 1.37	1.12	1.04 - 1.20
Females	1.07	1.06 - 1.09	1.05	1.04 - 1.07	2.10	1.81 - 2.44	1.22	1.09 - 1.36
By age categories								
≤19 years	0.99	0.93 - 1.06	0.97	0.91 - 1.04	1.69	0.94 - 3.04	1.22	0.78 - 1.91
20-34 years	1.10	1.09 - 1.12	1.09	1.07 - 1.11	1.54	1.37 - 1.74	1.16	1.05 - 1.28
34-49 years	0.97	0.95 - 0.99	0.95	0.92 - 0.97	1.31	1.17 - 1.46	1.07	0.96 - 1.18
50-64 years	1.16	1.11 - 1.21	1.12	1.06 - 1.17	1.42	1.23 - 1.64	1.27	1.10 - 1.46
≥65 years	0.93	0.83 - 1.04	0.93	0.82 - 1.05	0.84	0.56 - 1.27	0.95	0.64 - 1.40
Males by age categories								
≤19 years	1.19	1.04 - 1.36	1.14	0.99 - 1.31	0.94	0.37 - 2.43	n/a	n/a
20-34 years	1.09	1.06 - 1.12	1.08	1.05 - 1.11	1.40	1.19 - 1.65	1.12	0.97 - 1.29
34-49 years	0.99	0.95 - 1.03	0.96	0.92 - 1.00	1.22	1.08 - 1.37	1.06	0.94 - 1.18
50-64 years	1.18	1.12 - 1.25	1.15	1.08 - 1.22	1.33	1.14 - 1.54	1.23	1.06 - 1.43
≥65 years	0.90	0.79 - 1.03	0.90	0.78 - 1.05	0.81	0.53 - 1.23	0.96	0.65 - 1.43

Supplementary Table 1: Adjusted relative overall, urogenital, anorectal and oropharyngeal chlamydia test ratios and positivity ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020. (continued)

	Chlamydia overall		Urogenital chlamydia		Anorectal chlamydia		Oropharyngeal chlamydia	
	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI
Females by age categories								
≤19 years	0.95	0.88 - 1.02	0.94	0.87 - 1.01	2.97	1.27 - 6.95	0.95	0.57 - 1.59
20-34 years	1.12	1.10 - 1.14	1.10	1.08 - 1.12	1.79	1.49 - 2.14	1.22	1.06 - 1.39
34-49 years	0.96	0.93 - 1.00	0.95	0.92 - 0.98	2.34	1.69 - 3.24	1.12	0.89 - 1.41
50-64 years	1.12	1.04 - 1.20	1.07	0.99 - 1.15	4.74	2.48 - 9.04	1.82	1.13 - 2.93
≥65 years	0.92	0.72 - 1.18	0.93	0.72 - 1.19	n/a	n/a	n/a	n/a
Positivity								
Overall	1.02	0.98 - 1.07	1.00	0.96 - 1.05	1.12	0.90 - 1.38	1.15	0.73 - 1.81
Males	1.00	0.93 - 1.07	0.99	0.92 - 1.07	1.02	0.80 - 1.31	1.40	0.76 - 2.58
Females	1.03	0.97 - 1.10	1.01	0.95 - 1.07	1.43	0.91 - 2.25	0.88	0.45 - 1.73

Relative test ratios are adjusted for city district of the ordering GP and year of testing. n/a: parameter estimates could not be obtained due to low numbers.

Supplementary Table 2: Adjusted relative overall, urogenital, anorectal and oropharyngeal gonorrhoea test ratios and positivity ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020.

	Gonorrhoea overall		Urogenital gonorrhoea		Anorectal gonorrhoea		Oropharyngeal gonorrhoea	
	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI
Overall	0.98	0.97 - 0.99	0.95	0.94 - 0.97	1.36	1.27 - 1.46	1.09	1.03 - 1.16
By sex								
Males	1.03	1.01 - 1.05	0.99	0.97 - 1.01	1.26	1.17 - 1.37	1.09	1.01 - 1.17
Females	0.96	0.94 - 0.98	0.94	0.93 - 0.96	1.98	1.69 - 2.32	1.11	0.99 - 1.25
By age categories								
≤19 years	0.92	0.86 - 0.98	0.90	0.84 - 0.96	1.10	0.63 - 1.92	1.04	0.66 - 1.66
20-34 years	1.00	0.98 - 1.01	0.98	0.96 - 1.00	1.48	1.30 - 1.67	1.08	0.98 - 1.20
34-49 years	0.91	0.88 - 0.93	0.88	0.86 - 0.90	1.28	1.15 - 1.43	1.02	0.92 - 1.13
50-64 years	1.12	1.07 - 1.16	1.06	1.01 - 1.11	1.43	1.23 - 1.65	1.27	1.11 - 1.47
≥65 years	0.83	0.74 - 0.93	0.80	0.71 - 0.91	0.87	0.58 - 1.30	0.93	0.63 - 1.39
Males by age categories								
≤19 years	1.14	0.99 - 1.32	1.10	0.95 - 1.27	0.90	0.37 - 2.19	n/a	n/a
20-34 years	1.03	0.99 - 1.06	1.01	0.98 - 1.04	1.39	1.18 - 1.63	1.07	0.93 - 1.24
34-49 years	0.95	0.92 - 0.99	0.91	0.87 - 0.95	1.19	1.06 - 1.34	1.02	0.91 - 1.14
50-64 years	1.17	1.11 - 1.24	1.12	1.05 - 1.19	1.35	1.16 - 1.57	1.24	1.07 - 1.44
≥65 years	0.88	0.77 - 1.00	0.86	0.74 - 1.00	0.86	0.57 - 1.30	0.95	0.63 - 1.42

Supplementary Table 2: Adjusted relative overall, urogenital, anorectal and oropharyngeal gonorrhoea test ratios and positivity ratios among GPs in Amsterdam after participation in an educational intervention, compared to GPs before participation, overall and by patient sex and age, 2011-2020. (continued)

	Gonorrhoea overall		Urogenital gonorrhoea		Anorectal gonorrhoea		Oropharyngeal gonorrhoea	
	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI	Relative Ratio	95% CI
Females by age categories								
≤19 years	0.87	0.81 - 0.94	0.86	0.80 - 0.93	1.35	0.65 - 2.82	0.79	0.46 - 1.35
20-34 years	1.00	0.98 - 1.02	0.98	0.96 - 1.00	1.73	1.42 - 2.11	1.11	0.96 - 1.28
34-49 years	0.88	0.85 - 0.91	0.87	0.84 - 0.90	2.39	1.70 - 3.36	1.03	0.81 - 1.32
50-64 years	1.02	0.94 - 1.10	0.97	0.90 - 1.05	3.79	2.06 - 6.96	1.70	1.05 - 2.75
≥65 years	0.66	0.53 - 0.82	0.66	0.52 - 0.82	n/a	n/a	n/a	n/a
Positivity								
Overall	1.09	1.00 - 1.19	1.07	0.97 - 1.19	0.85	0.67 - 1.08	1.04	0.78 - 1.40
Males	1.04	0.94 - 1.16	1.04	0.92 - 1.18	0.91	0.71 - 1.16	1.10	0.80 - 1.51
Females	1.07	0.90 - 1.27	1.05	0.88 - 1.26	0.82	0.25 - 2.69	0.90	0.40 - 2.01

Relative test ratios are adjusted for city district of the ordering GP and year of testing. n/a: parameter estimates could not be obtained due to low numbers.

Supplementary Table 3: Relative trends in HIV, chlamydia and gonorrhoea testing over quarter-year periods among GPs in Amsterdam after participation in an educational intervention, 2011-2020.

Test ordered	Relative Test Ratio*	95% CI
HIV	1.02	1.01 - 1.02
Chlamydia		
Overall	1.02	1.02 - 1.03
Urogenital	1.01	1.01 - 1.02
Anorectal	1.09	1.08 - 1.10
Oropharyngeal	1.07	1.06 - 1.08
Gonorrhoea		
Overall	1.02	1.01 - 1.02
Urogenital	1.00	1.00 - 1.01
Anorectal	1.09	1.08 - 1.10
Oropharyngeal	1.07	1.06 - 1.08

*The relative test ratio indicates the number of ordered tests by a GP who participated in the intervention in one quarter, relative to the previous quarter

Chapter 5

Understanding the effect of an educational intervention to optimize HIV testing strategies in primary care in Amsterdam – Results of a mixed-methods study

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ABSTRACT

Background
In the Netherlands, general practitioners (GPs) play a key role in provider-initiated HIV testing, but opportunities for timely diagnosis are regularly missed. We implemented an educational intervention to improve HIV testing by GPs from 2015 to 2020, and observed a 7% increase in testing in an evaluation using laboratory data. The objective for the current study was to gain a deeper understanding of whether and how practices and perceptions of GPs' HIV/sexually transmitted infection (STI) testing behaviour changed following the intervention.

Methods
We performed a mixed-methods study using questionnaires and semi-structured interviews to assess self-reported changes in HIV/STI testing by participating GPs. Questionnaires were completed by participants at the end of the final educational sessions from 2017 through 2020, and participating GPs were interviewed from January through March 2020. Questionnaire data were analysed descriptively, and open question responses were categorised thematically. Interview data were analysed following thematic analysis methods.

Findings
In total, 101/103 participants completed questionnaires. Of 65 participants that were included in analyses on the self-reported effect of the programme, forty-seven (72%) reported it had changed their HIV/STI testing, including improved STI consultations, adherence to the STI consultation guideline, more proactive HIV testing, and more extragenital STI testing. Patients' risk factors, patients' requests and costs were most important in selecting STI tests ordered. Eight participants were interviewed and 15 themes on improved testing were identified, including improved HIV risk-assessment, more proactive testing for HIV/STI, more focus on HIV indicator conditions and extragenital STI testing, and tools to address HIV during consultations. However, several persistent barriers for optimal HIV/STI testing by GPs were identified, including HIV-related stigma and low perceived risk.

Conclusions
Most GPs reported improved HIV/STI knowledge, attitude and testing, but there was a discrepancy between reported changes in HIV testing and observed increases using laboratory data. Our findings highlight challenges in implementation of effective interventions, and in their evaluation. Lessons learned from this intervention may inform follow-up initiatives to keep GPs actively engaged in HIV testing and care, on our way to zero new HIV infections.

INTRODUCTION

HIV transmission remains an important public health issue, with 104,765 people newly diagnosed with HIV in the European Region in 2020[1]. As transmission is prevented through adequate therapy, most transmissions come from persons with undiagnosed HIV[2,3]. Optimal HIV testing strategies are therefore crucial to end the HIV epidemic.

In the Netherlands, general practitioners (GPs) perform two thirds of sexually transmitted infections (STI) consultations and diagnose one third of HIV infections[4]. GPs therefore play a crucial role in provider-initiated HIV testing, in particular among people not attending sexual health centres (SHCs) and among those presenting with HIV indicator conditions or symptoms suggestive of an acute HIV infection[5]. SHCs provide free-of-charge HIV testing on an opt-out basis for key groups only; in contrast, HIV testing by GPs is not covered by health insurance if the obligatory annual deductible (currently €385) has not been reached[5].

Previous research indicated that opportunities for earlier HIV diagnosis are being missed in primary care[6]. Implementing optimal HIV testing practices in primary care is an ongoing challenge, especially in a low-prevalence setting and in the context of a shrinking epidemic[7]. In 2014, a consortium of stakeholders in HIV care launched the HIV Transmission Elimination in Amsterdam (H-TEAM) initiative, which aims to implement innovative interventions for improved HIV prevention, testing and care though a city-based approach[8]. From 2015 to 2020, the H-TEAM implemented an educational intervention programme aiming to improve HIV testing strategies by GPs as well as the quality of GPs' STI consultations in general[9]. We previously reported the effect of the programme by assessing changes in HIV/STI testing frequencies by participating GPs compared to non-participating GPs as the primary outcome, using laboratory data. The intervention was associated with a 7% increase in HIV testing among participating GPs and has been described elsewhere[10]. Although an increase in HIV testing indeed was the primary objective of the intervention, the quality of HIV/STI testing by GPs can only partially be assessed from anonymised laboratory data as no information was available on risk factors and reasons for testing. To put the results from the laboratory-based evaluation in perspective, we used questionnaires and interviews with participating GPs to gain a deeper understanding of their practices and the perceptions of their testing behaviour. Additionally, we aimed to identify contextual factors influencing GPs' HIV/STI testing behaviour that need to be addressed in the future.

MATERIAL AND METHODS

Design and setting

We performed a mixed-methods study using questionnaires and semi-structured interviews among Amsterdam-based GPs who participated in the intervention. The educational intervention programme consisted of two consecutive small group sessions; all Amsterdam GPs were invited to participate. During the sessions, trends in incidence and prevalence of HIV/STI and current guidelines were discussed in existing groups of 5 to 20 GPs who regularly attend continuing medical education (CME) sessions together. Barriers to appropriate HIV/STI testing that were previously identified by our group were addressed during these discussions[11]. Competitive graphical audit and feedback based on laboratory data was presented to discuss differences in test-ordering between participants as a stimulant to improving testing[12]. At the end of the first educational session (Session-I), participating GPs developed quality improvement plans for HIV/STI testing in their own practice, and their implementation was discussed in the second educational session (Session-II). Further details on the design and implementation of the programme are described elsewhere[9].

Questionnaire recruitment and design

All GPs attending Session-II were invited to complete a questionnaire containing four sections: (1) participant characteristics, (2) perceived effect of the programme, (3) implementation of quality improvement plans, and (4) programme evaluation (Supplementary Table 1). The questionnaire was developed by a group of experts on HIV medicine, primary care and medical education, led by NvD and JvB and updated after piloting in the first two sessions.

Interview recruitment and design

GPs who participated in both educational sessions were eligible to participate in semi-structured interviews, and were invited by email. No additional selection based on GPs' characteristics was applied. GPs were invited until data saturation was achieved. The interviews were structured by a topic guide, consisting of open-ended questions on (1) effect of the programme, (2) reflection on trends in HIV/STI testing by Amsterdam GPs, (3) experienced barriers and facilitators to HIV/STI testing, and (4) programme evaluation (Supplementary Table 2). The topic guide was developed by experts in the field of medical psychology, primary care, infectious diseases, HIV medicine, and medical education (PN, NvD, JvB, SG, MSvdL and SJB). After four interviews, the topic guide was reviewed and updated based on interim analyses.

Data collection

The questionnaire was completed on paper at each Session-II (2017-2020), and data were entered into Castor Electronic Data Capture. Interview data were collected through individual interviews conducted by SJB between January and March 2020. The duration of the interviews ranged from 25 to 54 minutes. Interviews took place at a location of choice of the participant or by telephone, and were audio recorded. Interviews were transcribed verbatim and data were anonymised.

Analysis

All questionnaires completed by GPs were included for analysis, regardless of missing items. For items on the programme's effect on HIV/STI testing behaviour, only responses from GPs who participated in both sessions were included, as those who only attended Session-II could not yet report on changes in testing behaviour. Data on participant characteristics, implementation of the quality improvement plans and the programme's evaluation were analysed descriptively. Open question responses were categorised thematically (SJB), and checked for agreement (MSvdL). All questionnaire data analyses were performed using Stata v15.1 (StataCorp LLC, College Station, Texas, USA).

Interview transcripts were analysed by two independent researchers (SJB and PN) following thematic analysis methods by Braun and Clarke[13]. The researchers started an open coding process using the first three interviews, which resulted in a preliminary code system through consensus discussion that was built upon. The final categorization of identified themes was reached through consensus discussion. Interview data were analysed using MaxQDA 2022 (VERBI Software, Berlin, Germany).

RESULTS

Participant characteristics

Overall, 36% (229/632) of Amsterdam-based GPs active in 2015-2020 attended one or both sessions (154 attended one of the two and 75 attended both), including 103 Session-II participants. In total, 101/103 (98%) participants of Session-II completed the questionnaire. Of these, 65 (64%) reported they had participated in both sessions and therefore could be included in analyses on the self-reported effect of the programme. Of these 65, eight (12%) participated in the interviews. Participant characteristics are described in Table 1.

Questionnaire-reported effect of the programme

Forty-five participants (69%) reported that Session-I provided eye-openers on HIV/STI testing. Ten eye-opener themes were identified, including becoming motivated to offer more extragenital STI tests (i.e. oropharyngeal or anorectal chlamydia and gonorrhoea testing), to improve STI testing based on a proper risk-assessment and the GPs' guideline for STI consultations, to offer HIV testing more proactively and gaining awareness on HIV indicator conditions (Table 2). Forty-seven (72%) GPs reported the programme had changed their HIV/STI testing behaviour. Forty-two elaborated on these changes, and seven themes were identified, including improved STI consultations and adherence to the guidelines, more proactive HIV testing or -offering, and more extragenital STI testing when indicated (Table 3).

The percentages of GPs who reported increased testing frequency for chlamydia, gonorrhoea and HIV were 27% (16/60), 23% (14/60), and 54% (31/58), respectively. The percentages who reported no change in testing for chlamydia, gonorrhoea and

HIV were 73% (44/60), 50% (30/60), and 43% (25/58), respectively. The percentages who reported decreased testing for chlamydia, gonorrhoea and HIV were 0% (0/60), 27% (16/60) and 4% (2/58), respectively. Of the 24 GPs who reported no change in HIV testing, three made additional comments. One GP stated they offered HIV testing more frequently, but it was regularly refused by patients due to financial barriers. One GP stated they offered HIV testing only at the patients' request. Another GP reported that despite their intention to increase HIV testing, they still did not test for HIV very often due to lack of time.

Sixty-seven GPs elaborated on when they would test their patient for the 'Big 5' (i.e. chlamydia, gonorrhoea, HIV, hepatitis B, and syphilis; the most common and relevant STIs[14]), and six themes were identified. Forty-one (61%) reported that the patient's risk assessment was an important factor in deciding to test for the Big 5, while 23 (34%) reported that the patient's request was a factor, and 10 (15%) reported that costs of testing were a factor (Supplementary Table 3).

Implementation of quality improvement plans

GPs formulated up to five quality improvement plans for HIV/STI testing and counselling in their practice at the end of Session-I. GPs reported after Session-II that of these, 82% (139/169) were reportedly partially or completely implemented.

By theme, reported implementation was highest among plans to improve extragenital testing and STI consultations in general (Supplementary Table 4). Implementation was lowest among plans to improve HIV testing and counselling, especially among GPs who had planned to inform patients about HIV testing on waiting room screens and those who had planned to offer HIV testing during routine health-checks. Seventeen GPs provided additional commentary. Fear of worrying patients when providing information about HIV on waiting room screens, language barriers, rarely encountering HIV indicator conditions, becoming less proactive over time, and financial barriers were mentioned as barriers to implementation.

Ninety-one GPs (90%) completed an open question on further improvement plans for HIV/STI testing after attending Session-II. More focus on HIV, more frequent offering of HIV and extragenital STI testing, and further improving HIV/STI consultations in general, were among the themes that emerged. Additionally, 25% reported planning to start or to expand their prescribing of pre-exposure prophylaxis for HIV (PrEP) (Table 4).

Table 1: Characteristics of the participating Amsterdam-based GPs that completed the questionnaire, and participated in the interviews evaluating the effect of the educational intervention, 2017-2020.

Questionnaire participants (n = 101)	**n (%)**
Female sex	63 (62%)
Age categories	
30-44 years	39 (37%)
45-59 years	40 (40%)
60+ years	22 (22%)
Years work experience	
0-5 years	13 (13%)
6-10 years	21 (21%)
11-15 years	12 (12%)
>15 years	54 (54%)
missing	1 (1%)
No. of days working per week	
<3 days	5 (5%)
3-4 days	84 (84%)
5 days (full-time)	11 (11%)
missing	1 (1%)
Est. no. of PLHIV in the practice	
<5 PLHIV	7 (7%)
5-10 PLHIV	41 (41%)
11-25 PLHIV	27 (27%)
>25 PLHIV	9 (9%)
Don't know	14 (14%)
missing	3 (3%)
Participated in the first session	65 (64%)
Interview participants (n = 8)	**n (%)**
Female sex	3 (38%)
Age categories	
30-44 years	0 (0%)
45-59 years	6 (75%)
60+ years	2 (25%)
Years work experience	
0-5 years	0 (0%)
6-10 years	1 (13%)
11-15 years	0 (0%)
>15 years	7 (88%)
Est. no. of PLHIV in the practice	
<5 PLHIV	0 (0%)
5-10 PLHIV	5 (63%)
11-25 PLHIV	1 (13%)
>25 PLHIV	2 (25%)
Additional HIV/STI related activities	3 (38%)

GP: general practitioner. PLHIV: people living with HIV. STI: sexually transmitted infection.

Table 2: Identified themes from the 45 Amsterdam GPs that reported Session-I provided eye-openers in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Theme	n (%*)
Motivation for more proactive extragenital STI testing (including oropharyngeal and anorectal)	28 (62%)
Motivation to improve STI testing based on risk assessment and the guidelines for STI testing	14 (31%)
Motivation for more proactive HIV testing	6 (13%)
Awareness of HIV indicator conditions	6 (13%)
Motivation for more HIV/STI testing in general	5 (11%)
Awareness of other STI (syphilis, hepatitis C, *Mycoplasma genitalium*)	4 (9%)
Awareness of the (undiagnosed) HIV prevalence	4 (9%)
Awareness of the clinical symptoms of acute HIV infection	2 (4%)
Less HIV test ordering in low-risk populations	1 (2%)
Awareness that too little HIV/STI testing is being done	1 (2%)

* Percentages add up to >100% as GPs could provide more than one eye-opener example. GP: general practitioner. Session-I: First session of the educational intervention. STI: sexually transmitted infection.

Table 3: Identified themes from the 42 Amsterdam GPs that reported how attending Session-I changed their HIV/STI testing behaviour in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Theme	n (%*)
Improved STI consultation; better history taking, following the guidelines	24 (57%)
More extragenital STI testing when indicated	14 (33%)
More proactive HIV testing or addressing HIV	11 (26%)
More HIV/STI testing in general	7 (17%)
More hepatitis C testing	2 (5%)
More indicator condition-guided HIV testing	2 (5%)
Started prescribing pre-exposure prophylaxis for HIV	1 (2%)

* Percentages add up to >100% as GPs could provide as many examples of change as they wanted. GP: general practitioner. Session-I: First session of the educational intervention. STI: sexually transmitted infection.

Table 4: Identified themes from the 91 Amsterdam GPs who reported on what they planned to improve upon further after attending the second and final session of this programme in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Theme	n (%*)
More HIV testing or focus on HIV during consultations	38 (42%)
More extragenital chlamydia/gonorrhoea testing including anorectal testing	35 (39%)
Further improve HIV/STI testing and consultations in general	31 (34%)
Start/expand prescribing of pre-exposure prophylaxis	23 (25%)
More indicator condition-guided testing for HIV (including in case of another STI)	8 (9%)
More testing or focus on hepatitis B/C during consultations	8 (9%)
Improved *Mycoplasma genitalium* testing strategies (i.e. usually less testing)	7 (8%)
More retesting for chlamydia after treatment for a chlamydia-infection	6 (7%)

* Percentages add up to >100% as GPs could provide multiple examples of what they planned to improve. GP: general practitioner. SHC: sexual health centre.

Effects of the programme as reported by interviewees

From the interviews, fifteen themes on self-reported changes in HIV/STI testing following the intervention were identified. Some GPs reported less frequent HIV testing in low-risk patients, while others reported more frequent HIV testing, even in low-risk patients:

"Some patients that definitely have a low risk I now test less. Sometimes people want HIV testing done themselves, then it's fine, but I'm less proactive."

"I was already proactive, but really exclusively in key groups and now I think, I should also test the low-risk groups. You kind of want to screen all of Amsterdam."

GPs reported being more alert and more proactive in HIV testing, and being more alert on HIV indicator conditions:

"I diagnosed someone with HIV recently. He had very severe eczema, one of those indicator conditions. You recognise this faster now."

Additionally, GPs reported that they became more motivated to increase HIV testing in men who have sex with men (MSM) and (undocumented) migrants, and to increase awareness on HIV and HIV testing among their patient population.

Other themes on self-reported changes in HIV/STI testing that emerged were gaining more skills on how to discuss HIV testing and sexual health including sexual behaviour to determine the need for extragenital STI testing, and more awareness on extragenital STI. Finally, GPs reported having gained more knowledge on indications for STI testing.

Interviewees' reflection on trends in HIV testing

Fifteen themes regarding reflections on trends in HIV testing by GPs in Amsterdam were identified (Figure 1). Reflections on the initial decrease in HIV testing included a declining prevalence, less perceived risk of HIV and financial barriers. Reflections on the increase in HIV testing from 2015 onward included increased condomless sex, lower threshold for HIV testing due to HIV becoming a treatable, chronic condition, HIV awareness campaigns, and GPs prescribing PrEP.

Barriers and facilitators

Twenty-seven themes on persistent barriers and facilitators for HIV/STI testing were identified from the interviews and divided into barriers and facilitators at the patient-level (10), provider-level (8) and system-level (10) (Supplementary Table 5).

Patient-level

Participants mentioned perceiving patients' fearful response to offering an HIV test as a barrier:

"I used to test very proactively, but I'm less on top of it now. But that's also because people get very frightened when I bring it up. Sometimes I'll just let them mull it over for a while."

Patient-level facilitators included easy discussion of HIV testing with key groups including MSM, while the fact that sexuality and homosexuality are taboo in some cultures was perceived as a patient-level barrier. Symptoms and HIV indicator conditions were frequently mentioned facilitators for testing:

"When someone has non-specific symptoms, such as weight loss or malaise, then at some point you think about who is in front of you, could it be an HIV infection?"

Provider-level

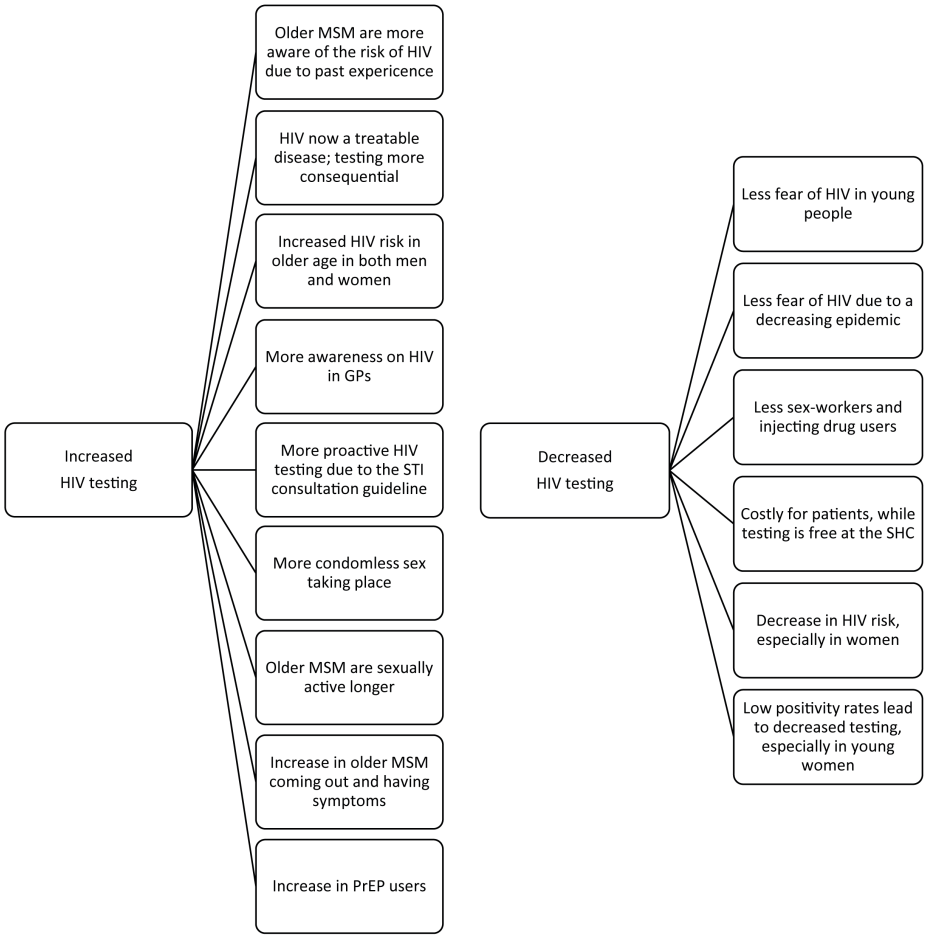
Provider-level barriers included lack of training on sexual health in the GP vocational training programme, GPs sticking to old patterns in testing strategies, and GPs feeling less motivated to test for HIV due to decreasing HIV prevalence in the Netherlands.

System-level

Participants mentioned cost of testing as a system-level barrier, which sometimes lead to less frequent testing, or referral to the SHC or other free testing services. Two participants reported that the comprehensiveness of the STI consultation guideline posed a barrier to adherence:

"We are a group that pre-eminently works based on past experience. So naturally, training and guidelines are important, but the guidelines are so elaborate that you don't know them by heart, and then experience is leading."

Figure 1: Themes identified in the interviews with eight GPs in Amsterdam regarding their reflections on trends in HIV testing, 2020.



GP: general practitioner. MSM: men who have sex with men. PrEP: Pre-exposure prophylaxis. SHC: sexual health centre. STI: sexually transmitted infection

Evaluation of the programme

In the questionnaire, the programme received a mean grade of 8.4 (SD 0.7, range 7-10) on a 10-point scale. Thirty-six GPs (36%) completed an open question on what could be improved, and eight themes were identified. Change in duration of the session, more practical sessions, receiving more detailed or more recent audit and feedback, discussing a wider range of sexual health-related topics and repeat sessions were themes that emerged (Supplementary Table 6). In an evaluation by interviewees, several strengths and recommendations for improvement for the programme were identified (Figure 2). Strengths included using already established training structures and using competitive audit and feedback to motivate sustained improvement:

"You usually already attend continued medical education sessions with the same group of GPs, so you are allowed to be bewildered by other participants' testing strategies, and to ask awkward questions, and to be vulnerable. So I think that's very important."

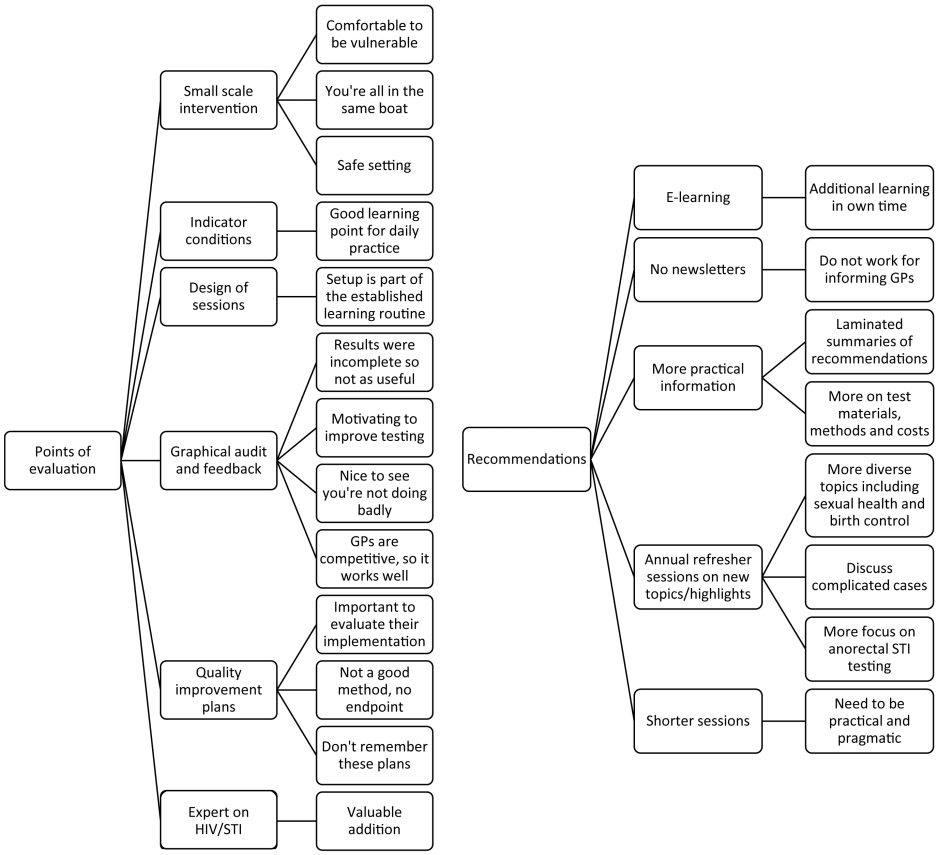
"The funny thing is, GPs, however big-mouthed they are, they're always a bit afraid that they are underperforming. I have that too. But then we get our audit and feedback and then it turns out we're not doing too bad at all. That's really motivating to see."

"You really get a big mirror held up to your own testing behaviour. So I think it really lasts, because it's more than a quick fix, so it would really work in the long run."

The use of quality improvement plans received additional feedback:

"I think we have about fifty practice improvement plans in our practice currently. You have to be careful about all these plans that sort of hang around, they start and never finish. It's better to ask the group what they need, or one or two real take home messages, and address those in follow-up sessions, then it can be really effective."

Figure 2: Themes identified in the interviews with eight GPs in Amsterdam on the evaluation and recommendations for improvement of the educational intervention, 2020.



GP: general practitioner. STI: sexually transmitted infection

DISCUSSION

In our study, we aimed to gain a deeper understanding of whether and how the quality and perceptions of GPs' HIV/STI testing behaviour changed by the programme. While analyses of laboratory data showed a 7% increase in HIV testing frequency among participating GPs[10], the results of this mixed-methods study suggest that self-reported knowledge, attitude and testing by participating GPs in Amsterdam changed more substantially.

More than two-thirds of participants reported that the programme provided eye-openers on HIV/STI testing, and that it changed their testing behaviour. Over half of participants reported to have increased their HIV testing frequency, while the rest reported no change in frequency, or even a decrease in HIV testing. Reported improvements in HIV/STI testing behaviour included improved STI consultations and improved adherence to the guidelines, including testing for HIV/STI less when it is not indicated. GPs also reported increased willingness to start prescribing PrEP. The interactive, small-scale design of the sessions and the use of audit and feedback were positively evaluated and helped establish intrinsic motivation to improve HIV/STI testing behaviour. Additionally, inclusion of repeat sessions in the programme made sustainable improvement more likely[15-17].

We identified several system-level barriers including financial barriers (i.e. cost of HIV testing by GPs is only covered by health insurances if the annual deductible has been reached), and the STI consultation guideline being perceived as too extensive to be useful. Some GPs reported not having implemented their quality improvement plan to discuss HIV testing more frequently or to inform patients about HIV testing on waiting room screens, because they feared their patients would worry. This shows that HIV-related stigma remains an important issue[11,18,19], obstructing optimal HIV testing in primary care. This study further confirmed previous findings that both GPs' and patients' perceived risk remains one of the most important motivators for HIV testing[20,21]. A shrinking HIV epidemic was mentioned as a reason for GPs to test for HIV less proactively, especially among low-risk groups. As we are entering a new era in the HIV epidemic, i.e. 'the last mile' towards reaching (micro)elimination of HIV in the Netherlands, a decreasing HIV prevalence will likely decrease GPs' and patients' perceived risk of HIV, compromising appropriate testing behaviour in the future.

The discrepancy between the modest increase in HIV testing frequency assessed with laboratory data and the more considerable self-reported improvements in HIV/STI testing behaviour found in this study may also be an indication that participants report intention rather than actual behaviour (i.e. "wishful thinking"), or that they overestimate the quality of their own testing behaviour, which in practice may have not improved considerably. This has been reported in other studies, that showed that self-assessment of quality of delivered care by healthcare providers is not always accurate[22-24]. Conversely, some participants reported intentional decreases in HIV/STI testing among low-risk patients, which might also explain the described

discrepancy. Increased testing frequency does not necessarily mean improved HIV testing, which is more complex to assess as it may depend on the patient's risk-profile, their symptoms and/or diagnoses and any findings during physical or laboratory examination. Moreover, decreased testing in asymptomatic, low-risk patients is only justified after a thorough risk-assessment, and previous research has shown that GPs are often unaware of certain risk-factors[25].

In recent years, the role of primary care physicians in optimal HIV testing is increasingly recognised, leading to several intervention studies to improve testing among GPs[15,16,26-29]. These studies yielded mixed results, including considerable increases in testing[26], as well as no effect, or even decreases in testing after implementation[15,30]. In most of these studies, sustainability or generalisability of the effect was compromised due to limitations including temporary financial incentives, lack of follow-up and lack of combination approaches. In our study, willingness to participate in the educational programme posed a challenge in its implementation, as illustrated by the fact that only a third of the participants attended both sessions. GPs in the Netherlands are currently heavily overburdened[31], and have a wide range of topics to choose from in attending CME sessions. Combined with a diminished sense of urgency due to the shrinking HIV epidemic, this may make proper attention for HIV testing challenging. Therefore, designing CME projects that are specifically focused on sustainability of quality improvement, by incorporating a combination of audit and feedback, repeat sessions, and IT solutions such as electronic prompts will be key moving forward.

Strengths and limitations

An important strength of our study is the fact that we used multiple data sources to gain a deeper understanding of the effect of the intervention on testing behaviour than laboratory data alone would have. Our study has several limitations, the most important being reporting bias and recall bias; participants may have given socially desirable answers and may have overestimated the quality of their testing behaviour. As questionnaires were completed anonymously, we could not compare self-reported changes in testing from questionnaire data to laboratory data per GP. Finally, selection bias may have occurred during the interviews, as several participants were involved in additional HIV/STI related activities. However, we did achieve theoretical data saturation with the included interviews, mitigating selection bias as much as possible.

Conclusions

The majority of GPs attending an educational intervention programme reported improved HIV/STI testing behaviour, but stigma, decreasing perceived risk and several structural barriers hamper sustained improvement.

Ethics approval and consent to participate

Participants provided written informed consent and did not receive compensation. The Medical Ethics Committee of the Amsterdam UMC determined that this study does not meet the definition of medical research involving human subjects under Dutch law.

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Authors' contributions

NvD and JvB designed the educational intervention sessions. SB, PN, NvD, MSL, SG and JvB designed this study evaluating its results. SG and JvB acquired funding. SB collected data, supervised the junior researchers collecting data, and wrote the first and final draft of the manuscript. MSL collaborated in the statistical analysis. SB performed all data cleaning and analyses, which was all subsequently checked by MSL. PN was involved in the design of the questionnaire and the interview guide and collaborated in their analysis. All authors had access to the data used in this study. All authors interpreted the data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2021 - 2020 data. Stockholm; 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/2021-Annual_HIV_Report_0.pdf. Last accessed: 24 December 2022.
2. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS* 2006;**20(10)**:1447-50.
3. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;**393(10189)**:2428-38.
4. Staritsky L, van Aar F, Visser M, et al. Sexually transmitted infections in the Netherlands in 2019. *Rijksinstituut voor Volksgezondheid en Milieu (RIVM)* 2020;**Report number 2020-0052**.
5. Bogers SJ, Twisk DE, Beckers LM, et al. Who is providing HIV diagnostic testing? Comparing HIV testing by general practitioners and sexual health centres in five regions in the Netherlands, 2011-2018. *Sex Transm Infect* 2021:Published Online First: 27 July 2021.
6. Joore IK, Reukers DF, Donker GA, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. *BMJ Open* 2016;**6(1)**:e009194.
7. van Bergen JE. Normalizing HIV testing in primary care. Commentary on: Late HIV diagnoses in Europe: a call for increased testing and awareness among general practitioners. *Eur J Gen Pract* 2012;**18(3)**:133-5.
8. de Bree GJ, van Sighem A, Zuilhof W, et al. Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam. *Curr Opin HIV AIDS* 2019;**14(6)**:455-63.
9. Bogers SJ, Schim van der Loeff MF, van Dijk N, et al. Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care. *Fam Pract* 2021;**38(4)**:441-7.
10. S. Bogers, M. Schim van der Loeff, A. Boyd, et al. Improving HIV testing in the primary care setting: Results from a multifaceted, educational intervention study in Amsterdam, the Netherlands [abstract]. *AIDS 2022, the 24th International AIDS conference; July 29-August 2, Montreal, Canada* 2022.
11. Joore IK, van Roosmalen SL, van Bergen JE, van Dijk N. General practitioners' barriers and facilitators towards new provider-initiated HIV testing strategies: a qualitative study. *Int J STD AIDS* 2017;**28(5)**:459-66.
12. van Braak M, Visser M, Holtrop M, Statius Muller I, Bont J, van Dijk N. What motivates general practitioners to change practice behaviour? A qualitative study of audit and feedback group sessions in Dutch general practice. *BMJ Open* 2019;**9(5)**:e025286.
13. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;**3(2)**:77-101.
14. Van Bergen J, Dekker J, Boeke A, et al. NHG-Standaard Het soa-consult(Eerste herziening) (Dutch). *Huisarts Wet* 2013;**56(9)**:450-63.
15. Davies CF, Kesten JM, Gompels M, et al. Evaluation of an educational intervention to increase HIV-testing in high HIV prevalence general practices: a pilot feasibility stepped-wedged randomised controlled trial. *BMC Fam Pract* 2018;**19(1)**:195.

16. Allison RL, Ricketts EJ, Hartney T, et al. Qualitative impact assessment of an educational workshop on primary care practitioner attitudes to NICE HIV testing guidelines. *BJGP Open* 2018;**2(1)**:bjgpopen18X101433.

17. Kesten JM, Davies CF, Gompels M, et al. Qualitative evaluation of a pilot educational intervention to increase primary care HIV-testing. *BMC Fam Pract* 2019;**20(1)**:74.

18. Simmons EM, Brown MJ, Sly K, Ma M, Sutton MY, McLellan-Lemal E. Barriers and facilitators to HIV testing in primary care among health care providers. *J Natl Med Assoc* 2011;**103(5)**:432-8.

19. Apers H, Nostlinger C, Van Beckhoven D, et al. Identifying key elements to inform HIV-testing interventions for primary care in Belgium. *Health Promot Int* 2020;**35(2)**:301-11.

20. Bedert M, Davidovich U, de Bree G, et al. Understanding Reasons for HIV Late Diagnosis: A Qualitative Study Among HIV-Positive Individuals in Amsterdam, The Netherlands. *AIDS Behav* 2021.

21. van Opstal SEM, van der Zwan JS, Wagener MN, et al. Late Presentation of HIV Infection in the Netherlands: Reasons for Late Diagnoses and Impact on Vocational Functioning. *AIDS Behav* 2018;**22(8)**:2593-603.

22. Davis DA, Mazmanian PE, Fordis M, Van Harrison R, Thorpe KE, Perrier L. Accuracy of physician self-assessment compared with observed measures of competence: a systematic review. *JAMA* 2006;**296(9)**:1094-102.

23. Ludikhuize J, Dongelmans DA, Smorenburg SM, Gans-Langelaar M, de Jonge E, de Rooij SE. How nurses and physicians judge their own quality of care for deteriorating patients on medical wards: self-assessment of quality of care is suboptimal*. *Crit Care Med* 2012;**40(11)**:2982-6.

24. Curry LA, Nembhard IM, Bradley EH. Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation* 2009;**119(10)**:1442-52.

25. Joore IK, Geerlings SE, Brinkman K, van Bergen JE, Prins JM. The importance of registration of sexual orientation and recognition of indicator conditions for an adequate HIV risk-assessment. *BMC Infect Dis* 2017;**17(1)**:178.

26. Leber W, Panovska-Griffiths J, Martin P, et al. Evaluating the impact of post-trial implementation of RHIVA nurse-led HIV screening on HIV testing, diagnosis and earlier diagnosis in general practice in London, UK. *EClinicalMedicine* 2020;**19**:100229.

27. Dominguez-Berjon MF, Pichiule-Castaneda M, Garcia-Riolobos MC, et al. A feasibility study for 3 strategies promoting HIV testing in primary health care in Madrid, Spain (ESTVIH project). *J Eval Clin Pract* 2017;**23(6)**:1408-14.

28. Pillay K, Gardner M, Gould A, et al. Long term effect of primary health care training on HIV testing: A quasi-experimental evaluation of the Sexual Health in Practice (SHIP) intervention. *PLoS One* 2018;**13(8)**:e0199891.

29. Agusti C, Cunillera O, Almeda J, et al. Efficacy of an electronic reminder for HIV screening in primary healthcare based on indicator conditions in Catalonia (Spain). *HIV Med* 2022;**23(8)**:868-79.

30. Joore IK, van Bergen J, Ter Riet G, van der Maat A, van Dijk N. Development and evaluation of a blended educational programme for general practitioners' trainers to stimulate proactive HIV testing. *BMC Fam Pract* 2018;**19(1)**:36.

31. Landelijke Huisartsen Vereniging. Worries about burden of work [Dutch]. Utrecht2021. Available from: https://www.lhv.nl/nieuws/huisartsen-met-handen-in-het-haar-om-bezetting-rond-te-krijgen/. Last accessed: 5 January 2023.

Supplementary Table 1: Questionnaire for Amsterdam-based GPs that attended Session-II of the educational programme, to evaluate the effect and acceptance of the programme, 2017-2020.

1. Participant characteristics	
Sex of participant	Male/Female
Age of participant	20-24 years/25-29 years/30-34 years/ 35-39 years/40-44 years/45-49 years/ 50-54 years/55-59 years/60-64 years/ ≥65 years
Job description of participant	General practitioner / other, i.e.:
Number of years working as a general practitioner	GP in training/0-5 years/6-10 years/11-15 years/>15 years/ not a GP
Type of practice of participant	Single/Dual/Group/Health centre/other, i.e.:
Number of days per week working as a GP	*[Open question]*
Number of people living with HIV registered in the participant's practice	<5 patients/5-10 patients/11-25 patients/>25 patients/Don't know

2a. Effect of the previous educational session	
1. To what extent do you recall topics that were discussed during Session-I?	a. I don't remember Session-I at all b. I don't remember much from Session-I c. I remember a few topics that were discussed d. I remember many topics that were discussed e. I remember most topics that were discussed f. I remember everything from Session-I g. I did not attend Session-I - Skip to question 5
2. Did Session-I provide eye-openers on HIV/STI testing?	a. No b. I don't remember c. Yes, i.e.:
3. To what extent did the educational sessions change your HIV/STI testing behaviour?	a. I did not change my HIV STI testing behaviour at all due to the educational sessions b. I changed my HIV STI testing behaviour somewhat due to the educational sessions, i.e.: c. I changed my HIV STI testing behaviour a lot due to the educational sessions, i.e.: d. I don't know

Supplementary Table 1: Questionnaire for Amsterdam-based GPs that attended Session-II of the educational programme, to evaluate the effect and acceptance of the programme, 2017-2020. (continued)

4a. To what extent did you change your chlamydia testing behaviour? Please elaborate	a. Much less testing b. Less testing c. No change d. More testing e. Much more testing
4b. To what extent did you change your gonorrhoea testing behaviour? Please elaborate	a. Much less testing b. Less testing c. No change d. More testing e. Much more testing
4c. To what extent did you change your HIV testing behaviour? Please elaborate	a. Much less testing b. Less testing c. No change d. More testing e. Much more testing
2b. Reported changes in HIV/STI testing in thirteen hypothetical clinical consultation situations ***(leave 'before Session-I blank if you did not attend Session-I)***	
5. I test a high-risk patient for the Big 5. a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
6a. When I perform an STI test I also perform an anorectal test in MSM a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
6b. When I perform an STI test I also perform an anorectal test in women with anorectal sexual contact a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
7. I advise a patient with chlamydia to do a repeat chlamydia test within 3-12 months a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know

Supplementary Table 1: Questionnaire for Amsterdam-based GPs that attended Session-II of the educational programme, to evaluate the effect and acceptance of the programme, 2017-2020. (continued)

8. When I order a chlamydia test I also order a gonorrhoea test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
9. I offer a patient with gonorrhoea an HIV test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
10a. I offer all my patients an HIV test when I am performing a blood test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
10b. I offer MSM an HIV test when I am performing a blood test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
10c. I offer migrants from HIV endemic countries an HIV test when I am performing a blood test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
11. I offer patients aged <60 years with herpes zoster (shingles) an HIV test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
12. I offer patients with a hepatitis B infection an HIV test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know

Supplementary Table 1: Questionnaire for Amsterdam-based GPs that attended Session-II of the educational programme, to evaluate the effect and acceptance of the programme, 2017-2020. (continued)

13. I consider HIV infection in patients presenting with mononucleosis-like symptoms a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know
14. I offer patients with unexplained symptoms such as chronic diarrhoea or weight loss an HIV test a. Before attending Session-I b. After attending Session-I	1. Never 2. Rarely 3. Regularly 4. Often 5. Always 6. Don't know

3. Implementation of quality improvement plans for HIV/STI testing in practice (During Session-I, your group established the below listed quality improvement plans. Please report how well they were implemented)	
[Quality improvement plan 1]	a. Not implemented/b. Partially implemented/c. Completely implemented Explanation …
[Quality improvement plan 2]	a. Not implemented/b. Partially implemented/c. Completely implemented Explanation …
[Quality improvement plan 3]	a. Not implemented/b. Partially implemented/c. Completely implemented Explanation …
[Quality improvement plan 4]	a. Not implemented/b. Partially implemented/c. Completely implemented Explanation …

4. Evaluation of the educational programme	
1. What did you gain from attending this educational programme?	*[Open question]*
2. How would you grade the quality if this programme on a 10-point scale?	1/2/3/4/5/6/7/8/9/10
3. How can the programme be improved in the future?	*[Open question]*
4. Are you planning on making any (further) changes in your HIV/STI testing behaviour after attending this Session-II? If so, which?	*[Open question]*

Big 5: chlamydia, gonorrhoea, HIV, hepatitis B, and syphilis. GP: general practitioner. MSM: men who have sex with men. STI: sexually transmitted infection

Supplementary Table 2: Interview topic guide for interviews with Amsterdam-based GPs that attended both sessions of the educational programme, to evaluate the effect and acceptance of the programme, 2020.

Topic	Addressed questions
(0) Participant characteristics	• Age, sex, number of years working as a GP, type of practice, neighbourhood of practice, estimated number of patients with HIV in practice, additional activities related to HIV/STI care
(1) HIV/STI testing behaviour, barriers and facilitators	• How would you describe your HIV/STI testing behaviour? • Which barriers and facilitators to HIV/STI testing do you experience? • Which other factors have influenced your HIV/STI testing behaviour over time?
(2) Changes in HIV/STI testing behaviour following the educational intervention	• How has your HIV/STI testing behaviour changed following the educational intervention? • Has your providerinitiated HIV/STI testing behaviour changed (how)? • Are there patient groups that you test more often or less often following the intervention (which, why)? • Has the educational intervention changed your perceived barriers and facilitators to HIV/STI testing (how)? • Are any perceived changes likely to be sustainable?
(3) Reflection on observed changes in HIV/STI testing trends by GPs in Amsterdam using graphs based on laboratory data	• How would you explain the observed changed in HIV/STI testing and positivity percentages by Amsterdam GPs over time? And when stratified by sex and age categories? (graphs for trends in HIV, chlamydia and gonorrhoea – both genitourinary and anorectal – testing and positivity are discussed) • Which influencing factors could have played a role in these changes (how)? Could the intervention have played a role (how)?
(4) Evaluation of the educational intervention programme	• How would you evaluate the educational intervention programme? • Are there specific topics that you remember most from the educational intervention? • What was most useful in the design? What was least useful? What did you miss? • How would you evaluate the use of graphical audit and feedback in the sessions? • How would you evaluate the use of quality improvement plans in the sessions? • How would you evaluate the attendance of an expert in the field of HIV/STI in primary care in the sessions? • How would you evaluate the sessions being held in a small group of peers/colleagues? • How would you improve the sessions? Do you have any other advice/tips?

GP: general practitioner. STI: sexually transmitted infection

Supplementary Table 3: Identified themes from the 67 Amsterdam-based GPs that elaborated on their reasons to test for the Big 5 in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Theme	n (%*)
My risk assessment of the patient is a factor in deciding to test for the Big 5 or not	41 (61%)
The patient's request or choice is a factor in deciding to test for the Big 5 or not	23 (34%)
A positive HIV/STI result or symptoms are a factor in deciding to test for the Big 5 or not	13 (19%)
The costs of STI tests are a factor in deciding to test for the Big 5 or not	10 (15%)
Whether the patient attends the SHC is a factor in deciding to test for the Big 5 or not	4 (6%)
I routinely test all patients for the Big 5 when I perform STI testing	3 (5%)

* Percentages add up to >100% as GPs could provide as many reasons to test for the Big 5 as they wanted. Big 5: chlamydia, gonorrhoea, HIV, hepatitis B, and syphilis. GP: general practitioner. STI: sexually transmitted infection. SHC: sexual health centre.

Supplementary Table 4: Implementation of quality improvement plans by theme reported by Amsterdam-based GPs that attended both educational session in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Quality improvement plan		No. of respondents	Implementation of plans: Not n (%)	Partially n (%)	Completely n (%)
Theme 1: Improved STI consultation and testing					
1.	Improved history-taking during STI consultations	20	1 (5%)	9 (45%)	10 (50%)
2.	Always perform STI test according to the STI consultation guideline	15	0 (0%)	11 (73%)	4 (27%)
3.	No more over-the-counter STI testing, always perform a consultation	9	1 (11%)	4 (44%)	4 (44%)
4.	Only test for chlamydia in patients at low-risk for STI	8	1 (13%)	0 (0%)	7 (88%)
5.	Instruct assistance/create awareness on appropriate STI testing	3	2 (67%)	1 (33%)	0 (0%)
6.	Repeat chlamydia testing in patients with chlamydia after 6 months	2	1 (50%)	0 (0%)	1 (50%)
	Total theme 1: Improved STI consultation and testing	57	6 (11%)	25 (44%)	26 (46%)
Theme 2: Improved HIV consultation and testing					
7.	Offer HIV testing to risk-groups (incl. migrants from endemic countries)	26	5 (19%)	19 (73%)	2 (8%)
8.	Offer HIV testing more proactively	11	2 (18%)	6 (55%)	3 (27%)
9.	Offer HIV testing in the case of HIV indicator conditions	10	2 (20%)	5 (50%)	3 (30%)
10.	Inform patients about HIV (testing) on waiting room screens	8	5 (63%)	0 (0%)	3 (38%)
11.	Offer HIV testing during routine 'health-checks'	3	1 (33%)	2 (67%)	0 (0%)
12.	Offer HIV testing to new patients during intake	3	0 (0%)	0 (0%)	3 (100%)
	Total theme 2: Improved HIV consultation and testing	61	15 (25%)	32 (53%)	14 (23%)
Theme 3: Continued learning on HIV/STI					
13.	Repeat this learning session in 1-2 years	14	2 (14%)	4 (29%)	8 (57%)
14.	Send out a quarter-year newsletter on appropriate HIV/STI testing	7	2 (29%)	4 (57%)	1 (14%)
15.	Evaluate our quality improvements in one year	3	2 (67%)	1 (33%)	0 (0%)
	Total theme 3: Continued learning on HIV/STI	24	6 (25%)	9 (38%)	9 (38%)
Theme 4: Improved extragenital testing					
16.	Improved extragenital testing when indicated	22	2 (9%)	13 (59%)	7 (32%)
17.	Always perform extragenital chlamydia/gonorrhoea testing in MSM	5	1 (20%)	1 (20%)	3 (60%)
	Total theme 4: Improved extragenital testing	27	3 (11%)	14 (52%)	10 (37%)

GP: general practitioner. STI: sexually transmitted infection. MSM: men who have sex with men.

Supplementary Table 5: Themes identified in the interviews with eight GPs in Amsterdam regarding patient level, provider level and system level barriers and facilitators for HIV/STI testing, 2020.

Barriers	Facilitators
Patient level	
It worries the patient to bring it up	Easy to discuss with MSM
I do not test in the case of a low HIV risk heterosexual patient	Key groups do not mind getting tested regularly
Discussing (homo)sexuality is taboo in some cultures	Additional STI testing in case of a positive test result
Patients never ask for HIV testing themselves, I have to bring it up	Amsterdam has a higher concentration of key groups
	HIV/STI testing depends on the patients risk profile and request
	HIV/STI testing depends on symptoms or HIV indicator conditions
Provider level	
Discussing STI testing with patients you are not familiar with is harder	I routinely test chlamydia and gonorrhea together
Discussing STI testing with patients you are very familiar with is harder	I am MSM, so I have a low threshold to offer extragenital testing
Too little training on sexual health consultations in medical education	
Decreasing HIV epidemic makes testing less rewarding	
Old patterns of HIV stigma in older GPs	
I regularly forget discussing extragenital sexual contact	
System level	
Communication and collaboration with the SHC is suboptimal	Only selected key groups have access to the SHC
Chlamydia and gonorrhea are now separate on the order form	Publications in medical journals for primary care improve testing
Costs of testing influences test-ordering	Informed consent is no longer needed for HIV testing
Sex workers are not in the picture due to restrictive regulations	Increased testing due to increased PrEP prescribing in primary care
Other testing services for key groups such as online services and SHC are (more) popular	
STI guideline is too elaborate and comprehensive to be useful	

GP: general practitioner. SHC: sexual health centre. STI: sexually transmitted infection. MSM: men who have sex with men. PrEP: pre-exposure prophylaxis for HIV.

Supplementary Table 6: Identified themes from the 36 Amsterdam GPs who reported on what could be improved in the programme in questionnaires evaluating the effect of the educational intervention, 2017-2020.

Theme	n (%*)
More time/longer sessions	9 (25%)
Audit and feedback per GP practice, not per individual GP	8 (22%)
Shorter/more practical/succinct sessions	6 (17%)
Additional specific audit and feedback (e.g. per number of patients, as percentage, by sex)	5 (14%)
Discussion of additional topics (e.g. syphilis, HPV, SHC data)	4 (11%)
More recent audit and feedback	4 (11%)
Periodic repeat sessions (after the two sessions of this programme)	2 (6%)
More interactive discussion of clinical cases	1 (3%)

* Percentages add up to >100% as GPs could provide multiple examples of what could be improved. GP: general practitioner. HPV: human papillomavirus. SHC: sexual health centre.

Part

III

Hospital setting

Chapter 6

Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis

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ABSTRACT

Background
Indicator condition (IC) guided testing for HIV is an effective way to identify undiagnosed people living with HIV, but studies suggest its implementation is lacking. This systematic review provides an overview of the adoption of IC-guided testing in Western countries.

Methods
Seven ICs were selected: tuberculosis (TB), malignant lymphoma, hepatitis B, hepatitis C, cervical/vulvar carcinoma/intraepithelial neoplasia grade 2+ (CC/CIN2+, VC/VIN2+), and peripheral neuropathy (PN). Embase and Ovid MEDLINE were searched up to November 20th, 2020. Publications of all types, using data from ≥2009, reporting on HIV test ratios in patients ≥18 years in all settings in Western countries were eligible. HIV test ratios and positivity were reported per IC. A random effects-model for proportions was used to calculate estimated proportions (ES) with 95% CIs. This study was registered at PROSPERO, registration number CRD42020160243.

Findings
Fifty-seven references, including 23 full-text articles and 34 other publications were included. Most (28/57) reported on HIV testing in TB. No reports on HIV testing in VC/VIN2+ or PN patients were eligible for inclusion. Large variation in HIV test ratios was observed between and within ICs, resulting from different testing approaches. Highest HIV test ratios (pooled ratio: 0·72, 95%CI 0·63-0·80) and positivity (0·05, 95% CI 0·03-0·06) were observed among TB patients, and lowest among CC/CIN2+ patients (pooled ES test ratio: 0·12, 95%CI 0·01-0·31, positivity: 0·00, 95%CI 0·00-0·00).

Interpretation
IC-guided HIV testing is insufficiently implemented in Western countries. The large variation in test ratios provides insight into priority areas for implementing routine IC-guided HIV testing in the future.

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RESEARCH IN CONTEXT

Evidence before this study

Identifying and treating people living with HIV is key to control the HIV epidemic. Opportunities to identify undiagnosed HIV through indicator condition guided testing are being missed in various healthcare settings. We have found no systematic review on the extent to which indicator condition guided testing has been adopted in Western countries.

We searched Embase and Ovid MEDLINE for evidence published up to November 20th, 2020 for evidence on the extent to which indicator condition guided testing for HIV is implemented in all healthcare settings in the Western world. All publication types, including full-text peer reviewed articles, as well as abstracts, short communications, and correspondence reporting on HIV testing in a selection of seven indicator conditions in or after 2009 in all healthcare settings in Western Countries were eligible for inclusion. No language restrictions were applied. The search included terms for HIV testing, the selected indicator conditions, and the term 'indicator condition'.

Added value of this study

This systematic review revealed that indicator condition guided testing for HIV is unevenly and insufficiently adopted across indicator conditions and healthcare settings in Western countries. We found that even in AIDS defining conditions, such as tuberculosis or cervical cancer, HIV testing strategies need to be further improved. Additionally, for some indicator conditions such as peripheral neuropathy, no evidence on HIV testing was identified, suggesting that in some conditions, this testing strategy might be lacking even more. Overall, this review revealed that adopting these strategies is an effective way to identify undiagnosed HIV, as in most conditions positivity percentages exceeded the established cost-effectivity threshold of 0·1%.

Implications of all the available evidence

Indicator condition guided testing for HIV remains insufficiently practiced, and results from settings where this strategy is best implemented reveal opportunities for improvement. Lessons on effective implementation can be learned from these settings, such as the high HIV test ratio observed when opt-out testing strategies are used. Adopting these strategies could lead to improved indicator condition guided HIV testing strategies across healthcare settings in Western countries.

INTRODUCTION

In our global efforts to complete the 'last mile' towards ending the HIV epidemic, timely diagnosis remains an important challenge. In the European Union/European Economic Area (EU/EEA), an estimated 14% of people living with HIV (PLHIV) is unaware of their diagnosis and late diagnosis (CD4 count <350 cells/mm^3) is reported in almost half of all new cases.[1] These figures are of particular concern, as late presentation is associated with higher morbidity, mortality, and onward transmission of HIV.[2,3]

In the last decade, growing evidence on the potential role of indicator condition guided testing for HIV to improve timely testing has emerged. Indicator conditions (ICs) are defined as conditions that are either (1) AIDS-defining, (2) associated with an undiagnosed HIV prevalence of >0·1%, the cut-off for cost-effective screening for HIV,[4,5] or (3) conditions where failure to identify an HIV infection may have significant adverse implications for the patient.[6] In 2007 the World Health Organization recommended provider-initiated HIV testing in conditions that could indicate HIV infection,[7] and in 2014 the HIV in Europe-initiative published a guidance on IC-guided HIV testing in adults,[6] based on the HIV Indicator Diseases across Europe Study (HIDES) and subsequent HIDES II study, that were performed in Europe.[8,9]

In recent years numerous studies have shown that IC-guided HIV testing is an effective approach to identify undiagnosed PLHIV.[10-17] Additionally, IC-guided testing has the advantage of bypassing barriers on both the patient and provider level, such as discussing sexual behaviour and risk factors for HIV.[8] As a consequence, HIV guidelines recommend IC-guided testing as one of the strategies to reduce the proportion undiagnosed PLHIV. However, recent studies on implementation of IC-guided testing consistently show missed opportunities for earlier HIV diagnosis due to lack of adherence to- or absence of- local protocols on IC-guided testing, but no overview of the adoption of IC-guided testing has been reported.[18-25]

The main objective of this systematic review was to assess the proportion of patients presenting with indicator conditions that are tested for HIV (i.e. the HIV test ratio). The secondary objective was to assess the outcomes of this testing strategy (i.e. the percentage positive).

METHODS

Protocol and guidelines

The protocol for this review was published at PROSPERO (supplementary appendix 1), and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (supplementary appendix 2).

Review topics
Seven ICs from various medical specialties were selected for inclusion: tuberculosis (TB), cervical cancer (CC) or cervical intraepithelial neoplasia (CIN) grade 2+, vulvar cancer (VC) or vulvar intraepithelial neoplasia (VIN) grade 2+, malignant lymphoma, hepatitis B (HBV), hepatitis C (HCV), and peripheral neuropathy (PN). These ICs were selected as they are diagnosed and managed by various medical specialties (i.e. pulmonology, gynecology, hematology, gastroenterology/ hepathology and neurology), ensuring a wide scope of the extent to which IC-guided testing is adopted, and they can all be objectively diagnosed using diagnostic tests.

Search strategy
With assistance of a clinical librarian, Ovid MEDLINE and Embase were searched for studies published up to November 20th, 2020. The search contained terms for HIV testing, the selected ICs, and the term 'indicator condition' (supplementary appendix 3). No language or date restrictions were applied. Additionally, all articles referring to the HIDES studies,[8,9] and abstracts identified in Embase were included for screening.

Selection criteria
Studies reporting HIV test ratios among patients ≥18 years (directly available or through calculation with presented data), all settings (e.g. primary care (PC), hospital care, registry surveillance), and all publication types (e.g. research article, abstract, correspondence) were eligible for inclusion. Only studies performed in Western countries (Western Europe, USA, Canada, Australia, New Zealand, and Japan) were included, as HIV epidemiology and the standard of healthcare are comparable in these countries. No language restrictions were applied. Studies among persons known HIV positive, with unconfirmed disease (e.g. suspected TB), or conditions not meeting the IC definition (e.g. latent TB infection), and studies with a sample size <10 per subgroup per IC were excluded. Studies with data on HIV testing before 2009 only were excluded, as IC-guided testing was globally implemented around 2009.

Selection process
Search results were exported through an EndNote database (version 19·1, Thomson Reuters, Philadelphia, USA) and duplicates were removed. All titles and abstracts were screened for inclusion by SJB, and 10% were independently screened by SHH. A maximum of 2·5% discrepancy was allowed for. Differences were resolved through discussion, and, if needed, SEG was consulted as a third reviewer to resolve differences of opinion. If after discussion the discrepancy remained >2·5%, all titles and abstracts would be screened by SHH. Subsequently, the full text of all selected references was assessed for eligibility by both reviewers. Differences were again resolved through discussion. For all eligible abstracts, subsequent full-text publications were searched for.

Data extraction
For data extraction, a form in Microsoft Excel (Version 2016, Microsoft Corporation, USA) was used. The form was piloted in the first 10% of eligible studies, and adjusted accordingly. Data extraction was independently performed by SJB and SHH and

discrepancies were resolved through discussion, with consultation of SEG as a third reviewer, if needed. Type of publication (i.e. full-text peer-reviewed article or 'other publication types', including abstracts, short communications, and correspondence), first author, year, title, setting, aim, recruitment site, definition of the IC and of being HIV tested, inclusion and exclusion criteria, number of subjects, number tested for HIV, and data on the percentage positive were extracted, supplementary appendix 4. When HIV test ratios were presented separately by sex or time periods (e.g. before and after intervention), they were extracted separately. Missing data were requested from authors if needed.

Quality assessment

Risk of bias assessment per included full-text study was performed independently by SJB and SHH using an adaptation of the Joanna Briggs checklist for prevalence studies, with consultation of SEG as a third reviewer, if needed.[26] The item on statistical analysis was dropped as it was deemed not relevant, and an item on objective measurement of being HIV tested was added (supplementary appendix 5). Risk of bias was scored out of 10. Discrepancies were resolved by discussion. No risk of bias was assessed for the other publication types (including abstracts, short communications, and correspondence, as insufficient information was available in these publications.

Statistical analysis

HIV test ratios, percentage positive, and quality assessments per reference were reported by IC. Summary statistics across studies were reported as medians with interquartile ranges (IQR). Test ratios and positivity were pooled by IC, regardless of publication type and assessed risk of bias. A random effects-model for proportions by Nyaga et al. was used,[27] as considerable heterogeneity between studies was expected due to the broad inclusion criteria. No limit for heterogeneity as expressed by the I^2 statistic was used. Results were reported as estimated proportions (ES) and 95% confidence intervals (CI) and displayed as forest plots. In sensitivity analyses, pooling of test ratio was performed using only low risk of bias full-text articles, and stratified by sex. A risk of bias score of ≥7/10 was chosen as cutoff for low risk by the researchers. Additionally, meta-regression analyses of the HIV test ratio per study by date of data collection (as a continuous variable) were performed to assess whether HIV test ratio varied by time, overall and by IC. For date of data collection, the midpoint of reported periods were taken. Permuted tests with an iteration of 1000 were used to confirm the findings. Analyses were performed using STATA 15 (StataCorp LLC, College Station, USA).

Role of funding sources

The funders of this study had no role in the study's design, conduct, analysis and interpretation of results, the writing of the report, or the decision to publish.

RESULTS

A total of 3405 records, including 992 abstracts and 62 records referencing the HIDES studies were identified through the search. Eighty-three were excluded because they were duplicates and 3219 based on title/abstract. Less than 2·5% discrepancy was found between the two screening authors during independent screening (5/341, 1·5%), which was resolved through discussion. Of the remaining 103 references, 46 were excluded based on full-text screening.

Of the 57 included references reporting on one or more IC, 23 were full-text articles and 34 were other publication types including abstracts, short communications, and correspondence (Figure 1).

Three of the 57 included citations reported on four or five of selected ICs, two reported on three ICs, ten reported on two ICs and 42 reported on one. Most included records (28/57) reported on HIV testing in TB patients (Table 1). No records on HIV testing in VC/VIN2+ patients or PN patients were eligible for inclusion. Most records were from the UK (24), followed by the USA (14) and Canada (5). Twenty-four records had included data from prior to 2009. There was considerable variation between records in how 'tested for HIV' was defined; 37% of studies (21) had defined a timeframe for being tested, using varying timeframes. Forty percent (23) described how HIV testing was defined, but did not define a timeframe, and 23% (13) described no definition of 'HIV tested', despite HIV test ratios being reported.

Tuberculosis

Of 16 included full-text articles on TB, eight were performed in a hospital/TB clinic setting, seven in the setting of a TB registry database, and one in the PC setting. Median number of study subjects was 603 (IQR 340-1355). HIV test ratios ranged from 44% to 95% in the hospital/registry setting, and was 8% in the PC setting. Median positivity percentage was 4·9% (IQR 4·4%-5·8%). Risk of bias was low; 77% of full-text references (13/16) had a low risk assessment (7/10 or higher). Across the 12 included other publication types, median number of subjects was 219 (IQR 28-463) and median HIV test ratio was 72% (IQR 56%-92%), Table 2.

Hepatitis B and C

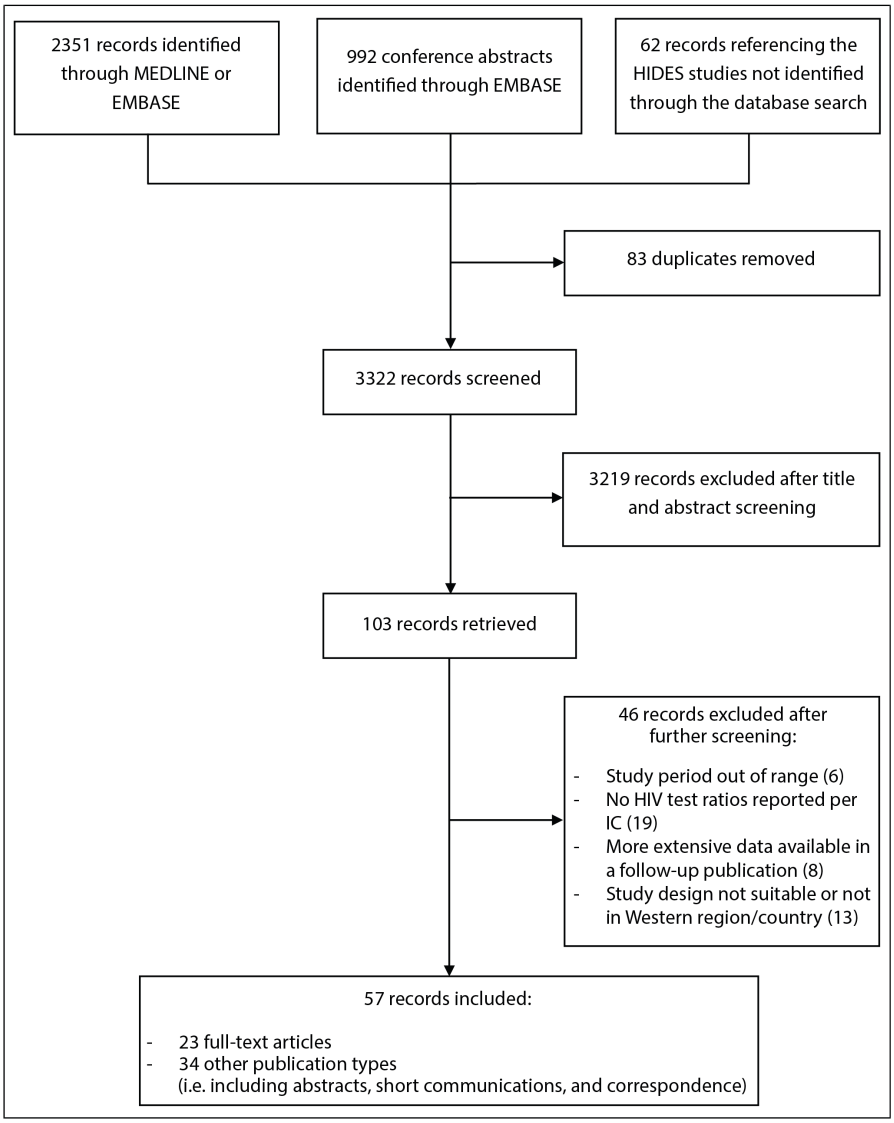
Of three full-text references on HBV, one was performed in the PC setting, and the other two in hospitals. Median number of subjects was 3091 (IQR 71-9746). HIV test ratios were 23% and 74% in the hospital setting, and 29% in the PC setting. Median positivity was 2·6% (IQR 1·2%-3·9%). No studies were scored high risk of bias. Across the nine included other publications, median number of subjects was 157 (IQR 88-385) and median HIV test ratio was 46% (IQR 45%-60%).

Of five full-text references on HCV, one was performed in the PC setting, and the others in hospitals. Median number of subjects was 624 (IQR 165-5305). HIV test ratios ranged from 14% to 83% in the hospital setting, and was 29% in the PC setting. Median positivity was 4·7% (IQR 3·0%-6·4%). One study was scored high risk of bias.

Across the 13 included other publications, median number of subjects was 384 (IQR 88-756) and median HIV test ratio 56% (IQR 45%-62%).

Two full-text references and one abstract did not distinguish between HBV and HCV. The full-text studies reported HIV test ratios of 13% and 87%, the abstract reported 21%, Table 2.

Figure 1: Search results and inclusions.



HIDES: HIV Indicator Diseases across Europe Study. IC: Indicator condition.

Table 1: Included records per indicator condition and publication type*

	Number of included full-text publications	Number of included other publication types **	Total included citations
Tuberculosis	16	12	28
Hepatitis B	3	9	12
Hepatitis C	5	13	18
Hepatitis B or C	2	1	3
Cervical carcinoma or CIN2+	6	3	9
Vulvar carcinoma or VIN2+	0	0	0
Malignant lymphoma	4	7	11
Peripheral neuropathy	0	0	0
Total	**23**	**34**	**57**

*Numbers add up more than the total number of included citations, as some reported on more than one indicator condition. **(i.e. abstracts, short communications, and correspondence). CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia.

Cervical carcinoma or CIN2+

Of six full-text references on CC/CIN2+, one was performed in the PC setting, one in the context of a cancer surveillance program, and four in hospitals. Median number of subjects was 489 (IQR 245-583). The HIV test ratio was 2% in the PC setting. HIV test ratios ranged from 1% to 14% in four studies in the hospital/surveillance setting, and the fifth reported 76%, but risk of bias was deemed high. Of four studies reporting on positivity, three reported 0% and one 0·2% positivity. Three other publications were included, with a median number of 64 subjects (IQR 57-94) and median HIV test ratio of 11% (range 2%-36%), Table 2.

Malignant lymphoma

Of four full-text references on malignant lymphoma, one was performed in the PC setting, the others in hospitals. Median number of subjects was 869 (IQR 276-1629). HIV test ratios ranged from 6% to 89% in the hospital setting, and was 3% in the PC setting. Median positivity percentage was 3·6% (IQR 1·4%-8·3%). One study was high risk of bias. Across seven included other publications, median number of subjects was 179 (IQR 135-281) and median HIV test ratio was 32% (IQR 13%-75%), Table 2.

Table 2: Study characteristics, summary of findings and risk of bias by indicator condition

Tuberculosis								
Full-text articles								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)****	**Positivity ratio (%)****	**Risk of bias score***
Anderson (2013)[33]	Retrospective cohort study in UK TB clinics – before cohort implementation	July 2009 - June 2010	All TB cases of all ages from 5 London clinics were included	Patients notified as having TB disease	Uptake of HIV testing	Before: 510/557 (91·6%)	NA	7/10
	Retrospective cohort study in UK TB clinics – after cohort implementation	July 2010 - December 2011				After: 687/752 (91·4%)		
Augusti (2016)[19]	Cross-sectional cohort in primary care, Spain	January 2010 - August 2012	Patients aged 16-65 years were included; known HIV positive patients excluded	Using either their ICD-10 codes or a positive laboratory result	HIV test within 4 months of diagnosis date	Men: 112/1287 (8·7%)	Men: 0/112 (0%)	9/10
						Women: 63/840 (7·5%)	Women: 1/63 (1·6%)	
Basham (2018)[28]	Audit of a Canadian provincial tuberculosis program	2008 - 2010	All active TB cases of all ages in the TB registry	Active TB	HIV test recorded in TB registry database	250/428 (58·4%)	12/250 (4·8%)	9/10
Basham (2019)[38]	Audit of First Nations tuberculosis program in Canada	2008 - 2012	First Nations of all ages recorded in the TB registry	Recorded TB in registry	HIV test recorded in TB registry database	95/149 (63·8%)	NA	8/10
Clark (2013)[39]	Retrospective cohort to assess HIV testing in TB surveillance database in US	2008 - 2010	Living patients with TB of all ages	Reported TB cases surviving with TB	Known (positive or negative) or unknown (refused testing/ not offered testing) HIV status	208/273 (76·2%)	12/208 (5·8%)	7/10

Clerk (2013)[40]	Cross-sectional study on HIV testing in TB patients in the UK	NA	TB cases of all ages were included	Confirmed active TB cases	NA	27/31 (87·1%)	NA	6/10
Gardner (2012)[41]	Retrospective cohort after implementation of opt-out HIV testing in US TB clinic	June 2010 - June 2011	Excluded: Patients <14 years, known HIV positive, no chart available, diagnosed prior to study period	New TB cases presenting at the clinic	Tested for HIV in the clinic after presentation	458/939 (48·8%)	1/458 (0·2%)	9/10
Gupta (2011)[35]	First audit of IC-guided testing in UK general hospital	First audit: August 2008 - July 2009	Patients of all ages testing positive for TB	Patients tested positive for tuberculosis	HIV testing was double checked using the electronic pathology records system and a separate database of HIV testing	First audit: 19/25 (76·0%)	NA	7/10
	Re-audit of IC-guided testing in UK general hospital	Re-audit: August 2009 - June 2010				Re-audit: 12/29 (41·4%)		
Long (2014)[29]	Retrospective cohort of tuberculosis patients in Canada	2003-2012	Patients of all ages in the TB registry	Persons meeting the Canadian case definition for TB	Already known or newly diagnosed with HIV	1317/1453 (90·6%)	74/1317 (5·6%)	8/10
Post (2015)[42]	Retrospective cohort among patients with tuberculosis in Australia	2009	Patients of all ages with TB	Microbiologically confirmed TB and patients that were treated for TB without microbiological confirmation	HIV status was categorised as known or unknown (not tested or declined testing)	2009: 56/80 (70·0%)	2009: 3/56 (5·4%)	6/10
		2010				2010: 79/100 (79·0%)	2010: 5/79 (6·3%)	
		2011				2011: 72/98 (73·5%)	2011: 4/72 (5·6%)	
		2012				2012: 56/73 (76·7%)	2012: 1/56 (1·8%)	
		2013				2013: 61/70 (87·1%)	2013: 3/61 (4·9%)	
Raben (2015)[9]	Retrospective cohort on HIV testing in ICs in Europe	May 2013	Patients in participating centres, >18 and <65 years of age, not known HIV positive, presenting within the previous year/last 100+ patients	Patients with tuberculosis	Participating centres reviewed retrospectively how many patients presenting with the IC were tested for HIV	1041/1401 (74·3%)	46/1041 (4·4%)	2/10

Ribeiro (2018)[43]	Retrospective cohort study on HIV screening of TB patients in Portugal	2008 - 2014	Notified TB cases of all ages in the Portuguese Tuberculosis Surveillance System	Notified TB	NA	Men: 10,629/12,115 (87·7%)	Men: NA	7/10
						Women: 5,414/6,330 (85·5%)	Women: NA	
Rivest (2014)[44]	Retrospective cohort on HIV-TB co-infection and predictors of HIV screening among incident TB cases in Canada	2004 - 2009	Incident TB cases of all ages reported to the TB reporting database	Cases confirmed by culture or diagnosed on the basis of clinical and radiological signs	HIV testing done from one month before to six months after date of TB diagnosis	Men: 226/422 (53·6%)	Men: 26/226 (11·5%)	8/10
						Women: 169/356 (47·5%)	Women: 7/169 (4·1%)	
Roy (2013)[36]	Cluster randomised controlled trial on the impact of implementing universal HIV testing in TB patients in the UK	September 2009 - March 2010	Patients of all ages in centres using a selective HIV testing policy, not known HIV infected	All patients seen and diagnosed with TB in participating centres	The date the HIV test was conducted was recorded and these patients were classified as having "accepted" the test	Women (selective testing): 269/417 (64·5%)	NA	7/10
						Men (selective testing): 376/544 (69·1%)		
			Patients of all ages in centres using a universal HIV testing policy, not known HIV infected			Women (universal testing): 111/149 (74·5%%)		
						Men (universal testing): 152/198 (76·8%)		
Sewell (2014)[45]	Retrospective cohort in a UK TB clinic	January 2009 - July 2012	TB patients of all ages at a TB medical outpatient service	Clinical or laboratory TB diagnosis	Tested < 3 months of attending the clinic or starting TB treatment	389/410 (94·9%)	27/389 (6·9%)	9/10

William (2011)[46]	Audit on HIV testing in TB patients after HIV testing guideline implementation in the UK	April 2008 - March 2009	Patients <18 years, private patients, on chemoprophylaxis, non TB mycobacteria were excluded.	TB patients in the database	HIV testing in the six months prior to and following TB notification	Men: 101 / 214 (47·2%) Women: 76 / 193 (39·4%)	NA	9/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	
Aguayo (2010)[47]	Retrospective study on Extrapulmonary TB in Spain	NA	NA	Extrapulmonary tuberculosis	NA	11/20 (55·0%)	NA	
Hubbard (2020)[48]	Retrospective study on HBV and HCV prevalence in TB in a US hospital	September 2016 - May 2019	Adult cases of active or latent TB	positive QuantiFERON-TB Gold In-Tube test	Tested for HIV	375/453 (82·8%)	22/375 (5·9%)	
Patel (2019)[49]	Retrospective study on mortality risk factors and delays in TB mortality cases in New Mexico, US	2007 - 2017	NA	TB mortality cases	Offered HIV testing	48/83 (57·8%)	NA	
Perch (2013)[50]	Retrospective cohort on HIV testing in TB in Denmark	2009 (Total study included 2007-2009)	Notified TB of all ages cases were included	All cases of notified tuberculosis in database	NA	204/324 (63·0%)	8/204 (3·9%)	
Phillips (2010)[51]	Audit of IC-guided testing in UK hospital	October 2008 - November 2009	Patients of all ages with tuberculosis	Confirmed mycobacterium tuberculosis	HIV tested within the audit period	1/11 (9·1%)	NA	
Potter (2014)[52]	Audit on HBV, HCV and HIV infection among new TB cases in UK	2013	Patients of all ages with active TB	Active tuberculosis	HIV screened	447/472 (94·7%)	15/447 (3·4%)	
Qasim (2012)[53]	Audit on diagnosis and management of TB patients in the UK	January 2009 - December 2010	Patients with a positive Acid-Fast Bacillus test	A positive Acid-Fast Bacillus test	NA	21/21 (100%)	NA	
Reina (2015)[54]	Cross sectional study on unknown HIV status in TB patients in Portugal	2006 - 2012	TB cases reported	Registered tuberculosis cases	Known HIV status	6804/7683 (88·8%)	NA	

Ricci (2010)[55]	Audit on HIV testing and coinfection in TB patients in Italy	2004 - 2009	Patients with tuberculosis	Culture-confirmed cases of tuberculosis	Tested for HIV at any time	412/526 (78·3%)	67/412 (16·3%)
Stolagiewicz (2015)[56]	Audit to quantify the local prevalence of HIV in patients with TB in the UK	2014	Patients diagnosed with or treated for TB	Diagnosed or treated for tuberculosis	Tested for HIV	114/114 (100%)	3/114 (2·6%)
Thorburn (2012)[57]	Audit on HIV testing in TB patients in the UK	2010 (before implementation multidisciplinary TB meeting)	Confirmed TB cases in 2010	Confirmed TB cases	HIV tested in the year before or after TB diagnosis	2010: 141/234 (60·3%)	2010: 7/141 (5·0%)
		2011 (after implementation multidisciplinary TB meeting)	Confirmed TB cases in 2011			2011: 81/105 (77·1%)	2011: 2/81 (2·5%)
Vas (2012)[58]	Audit on HIV testing in TB patients in a UK hospital	2009	Patients attending the chest clinic with TB	NA	Patients offered and accepted an HIV test	9/34 (26·5%)	NA

Hepatitis B

Full-text articles

Reference (year)	Design and setting	Included study period	Population and exclusion criteria	IC definition	HIV tested definition	HIV test ratio (%)**	Positivity ratio (%)**	Risk of bias score*
Augusti (2016)[19]	Cross-sectional cohort in primary care, Spain	January 2010 - August 2012	Patients aged 16-65 years were included; known HIV positive patients excluded	Using either their ICD-10 codes or a positive laboratory result	HIV test within 4 months of diagnosis date	Men: 1792/6034 (29·7%)	Men: 27/1792 (1·5%)	9/10
						Women: 1058/3712 (28·5%)	Women: 8/1058 (0·8%)	
Gupta (2011)[35]	First audit of IC-guided testing in UK general hospital	First audit: August 2008 - July 2009	Patients of all ages testing positive for HBV	Patients with a positive hepatitis B surface antigen test	HIV testing was double checked using the electronic pathology records system and a separate database of HIV testing	First audit: 6/27 (22·2%)	First audit: NA	7/10
	Re-audit of IC-guided testing in UK general hospital	Re-audit: August 2009 - June 2010				Re-audit: 10/44 (22·7%)	Re-audit: NA	

Hallager (2018)[31]	Retrospective cohort study on HIV coinfection among HBV and HCV patients in 18 hospitals in Denmark	January 2002 - July 2015	Patients registered in the Danish hepatitis database of 16 years or older	Positive HBV surface antigen	HIV antibody/antigen tests performed before or within 6 months of database enrolment	2287 / 3091 (74·0%)	89/2287 (3·9%)	9/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	
Deshpande (2015)[59]	Retrospective study on HIV testing in patients on Tenofovir monotherapy in Australia	January 2014 - June 2014	Patients with HBV on Tenofovir	Medical record or pathology confirmed chronic HBV infection	HIV test recorded before start of Tenofovir monotherapy	72/157 (45·9%)	NA	
Ireland (2018)[60]	Retrospective cross-sectional study on HIV testing in HBV patients in the UK	2010 - 2014	Patients of 15 years or over with HBV. Patients with known HIV and diagnosed with HBV at antenatal services were excluded	Hepatitis B virus (HBV) surface antigen positive	HIV tested on the same day or within 6 months following HBV diagnosis	7315/16,086 (45·5%)	NA	
Lander (2014)[61]	Audit on HIV testing in HBV and HCV patients in a hepatitis clinic in the UK	September 2012 - August 2013	HBV patients in the clinic	NA	Uptake of HIV testing in the clinic during the audit time period	205/362 (56·6%)	NA	
Lynn (2014)[62]	Audit on HIV testing in HBV patients in the Rochester Epidemiology Project (REP) in the US	1994 - 2010	HBV patients in the REP cohort	NA	All HIV screening tests and their results	273/607 (45·0%)	NA	
Pavlides (2011)[63]	Audit on HIV testing in HBV patients in the UK	October 2008 - September 2009	HBV patients	HBV surface antigen positive	Whether these patients had an HIV test	63/99 (63·6%)	6/63 (9·5%)	

Perera (2011)[64]	Audit On HIV testing in HBV patients in the UK	NA	HBV patients in a teaching hospital	NA	HIV test performed	53/88 (60·2%)	4/53 (7·5%)
Phillips (2010)[51]	Audit on HIV testing in indicator conditions in the UK	October 2008 - November 2009	HBV patients at one hospital	Confirmed HBV infection	HIV tests taken within the same time period as inclusion	2/32 (6·3%)	NA
Su (2015)[65]	Audit on HBV treatment and care at an Asian health center in the US	2012	New patients presenting with chronic hepatitis B	NA	Offered HIV screening	362/385 (94·0%)	NA
Vas (2012)[58]	Audit on HIV testing in HBV patients in a hospital in the UK	2009	Patients attending the gastroenterology clinic with HBV	NA	Patients offered and accepted an HIV test	2/25 (8·0%)	NA

Hepatitis c

Full-text articles

Reference (year)	Design and setting	Included study period	Population and exclusion criteria	IC definition	HIV tested definition	HIV test ratio (%)**	Positivity ratio (%)**	Risk of bias score*
Augusti (2016)[19]	Cross-sectional cohort in primary care, Spain	January 2010 - August 2012	Patients aged 16-65 years were included; known HIV positive patients excluded	Using either their ICD-10 codes or a positive laboratory result	HIV test within 4 months of diagnosis date	Men: 1995/6333 (31·5%)	Men: 67/1995 (1·1%)	9/10
						Women: 828/3493 (23·7%)	Women: 18/828 (2·2%)	
Bolther (2014)[30]	Cross-sectional cohort at a university hospital and outpatient clinics in Denmark	1996 - 2011	HCV patients of all ages; Patients no longer registered at the clinic were excluded	Chronic HCV patients with HCV RNA positive test outcome	HIV screening performance within 180 days of the HCV diagnosis	360/624 (57·7%)	NA	9/10
Gupta (2011)[35]	First audit of IC-guided testing in UK general hospital	First audit: August 2008 - July 2009	Patients of all ages testing positive for HCV	Patients with a positive hepatitis C antibody test	HIV testing was double checked using the electronic pathology records system and a separate database of HIV testing	First audit: 18/93 (19·4%)	First audit: NA	7/10
	Re-audit of IC-guided testing in UK general hospital	Re-audit: August 2009 - June 2010				Re-audit: 5/72 (6·9%)	Re-audit: NA	

Hallager (2018)[31]	Retrospective cohort study on HIV coinfection among HBV and HCV patients in 18 hospitals in Denmark	January 2002 - July 2015	Patients registered in the Danish hepatitis database of 16 years or older	HCV-RNA before or within 6 months after enrolment in the database	HIV antibody/ antigen tests performed before or within 6 months of enrolment in the database	4400/5305 (82·9%)	281/4400 (6·4%)	9/10
King (2019)[66]	Intervention study among patients with an IC admitted to an acute General Medicine Unit in Australia	July 2017 - October 2017	Patients recently HIV tested, known HIV positive and with an alternative explanation for the IC were excluded	Hepatitis C antibody positive	Pathology lab data	5 / 11 (45·5%)	NA	4/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	
Cowan (2020)[67]	Retrospective review of testing and care of HCV mono- and HIV co-infected patients in a US emergency department	June 2018 - December 2019	Patients aged 18 years or older with active HCV infection, triaged to the ED and able to provide consent for testing	HCV viral load positive	Known HIV status	386/427 (90·4%)	56/386 (14·5%)	
Fleischer (2018)[68]	Retrospective cohort on HIV testing in HCV patients in a US hospital	July 2015 - March 2017	Patients with hepatitis C	HCV antibody positive	HIV antibody tested at any time	252/445 (56·6%)	6/252 (2·4%)	
Gilbert (2011)[69]	Audit to evaluate HIV testing in Canada	2007 - 2009	Patients diagnosed with HCV	NA	Tested for HIV within 3 months of diagnosis	8,183/15,981 (51·2%)	NA	
Ireland (2018)[60]	Retrospective cross-sectional study on HIV testing in HCV cases in the UK	2010 - 2014	Patients of 15 years or over with HCV. Patients with known HIV were excluded	HCV antibody positive	HIV tested on the same day or within 6 months following HCV diagnosis	14,587/32,114 (45·4%)	NA	

Lander (2014)[61]	Audit on HIV testing in HBV and HCV patients in a hepatitis clinic in the UK	September 2012 - August 2013	HCV patients in the clinic	NA	Uptake of HIV testing in the clinic during the audit time period	40/72 (55·6%)	NA
Lynn (2014)[62]	Audit on HIV testing in HCV patients in the Rochester Epidemiology Project in the US	1994 - 2010	HCV patients	NA	All HIV screening tests and their results	553/965 (57·3%)	NA
Oraka (2016)[70]	Retrospective cohort on prevalence of HIV testing among adults with HCV in the US	1999 - 2014	Patients with HCV aged 20-59 years	HCV RNA positive test result	Ever tested for HIV	248/384 (64·6%)	NA
Pavlides (2011)[63]	Audit on HIV testing in HCV patients in the UK	October 2008 - September 2009	HCV patients	Positive hepatitis C antibody or PCR	Whether these patients had an HIV test	51/102 (50·0%)	6/51 (11·8%)
Perera (2011)[64]	Audit on HIV testing in HCV patients in the UK	NA	HCV patients in a teaching hospital	NA	HIV test performed	40/92 (43·5%)	3/40 (7·5%)
Phillips (2010)[51]	Audit on HIV testing in indicator conditions in the UK	October 2008 - November 2009	HCV patients at one hospital	Confirmed HCV infection	HIV tests taken within the same time period as inclusion	25/88 (28·4%)	NA
Sterling (2017)[71]	Retrospective cohort on HIV testing in HCV patients in the PROP UP cohort in the US	NA	HCV patients on DAA therapy enrolled in the PROP UP study, not known HIV positive	NA	HIV tested at some point in their history or prior to initiating DAA therapy	472/756 (62·4%)	NA
Tunney (2018)[72]	Audit on management of HCV patients in the UK	March 2012 - March 2017	HCV patients (acute, chronic or past resolved) at the clinic, not known HIV positive	NA	HIV status	23/35 (65·7%)	NA

Vas (2012)[58]	Audit on HIV testing in HCV patients in a hospital in the UK	2009	Patients attending the gastroenterology clinic with HCV	NA	Patients offered and accepted an HIV test	1/29 (3·4%)	NA

Hepatitis B or C								
Full-text articles								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)****	**Positivity ratio (%)****	**Risk of bias score***
Cayuelas Redondo (2019)[34]	Prospective interventional study on IC-guided HIV testing with an electronic prompt in primary healthcare in Spain	2013 (pre intervention)	Patients aged 18-65, with no known HIV infection, with acute or chronic hepatitis B or C	NA	HIV infection	Pre intervention: 2/26 (7·7%)	NA	8/10
		July 2014 - May 2015 (intervention)				During intervention: 5/17 (29·4%)		
		June 2015 - May 2016 (post intervention)				Post intervention: 1/21 (4·8%)		
Raben (2015)[9]	Retrospective cohort on HIV testing in ICs in Europe	May 2013	Patients in participating centres, >18 and <65 years of age, not known HIV positive, presenting within the previous year/ last 100+ patients	Patients with hepatitis B or C	Participating centres reviewed retrospectively how many patients presenting with the IC were tested for HIV	2325/2681 (86·7%)	23/2325 (1·0%)	2/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	

Adlington (2014)[32]	An audit of HIV testing in acute medical patients with HIV clinical indicator conditions in the UK	January 2012	Patients with hepatitis B or C	Hepatitis B or C, registered as ICD-10 code	Whether HIV test had been performed during admission	January 2012: 10/39 (25·6%)	NA	
		January 2013				January 2013: 7/41 (17·1%)		

Cervical carcinoma or cervical intraepithelial neoplasia grade 2+								
Full-text articles								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)****	**Positivity ratio (%)****	**Risk of bias score***
Alldredge (2020)[73]	Retrospective cohort study on HIV screening in women with newly diagnosed invasive cervical cancer in a large comprehensive US gynecologic oncology practice	January 2007 - December 2017	Women >18 years with invasive cervical cancer were included; cervical dysplasia, non-cervical or recurrent cancer and presenting at another specialty were excluded	International Classification of Diseases codes 180.9 and C53.9 for invasive cervical cancer	HIV-1/2 antibody or 4th generation p24 antigen test undertaken within 12 months before diagnosis, or within 30 days of the encounter.	38 / 492 (7·7%)	0/38 (0%)	9/10
Augusti (2016)19	Cross-sectional cohort in primary care, Spain	January 2010 - August 2012	Patients aged 16-65 years were included; known HIV positive patients excluded	Using either their ICD-10 codes or a positive laboratory result	HIV test within 4 months of diagnosis date	15/615 (2·4%)	0/15 (0%)	9/10
Gupta (2011)[35]	First audit of IC-guided testing in UK general hospital	First audit: August 2008 - July 2009	Patients of all age with cervical intraepithelial neoplasia	Patients of all ages with a positive pathology sample for CIN II or III	HIV testing was double checked using the electronic pathology records system and a separate database of HIV testing	First audit: 2/146 (1·4%)	NA	7/10
	Re-audit of IC-guided testing in UK general hospital	Re-audit: August 2009 - June 2010				Re-audit: 4/340 (1·2%)		

Hwang (2015)[74]	Retrospective cohort on HIV testing in patients with cancer at the initiation of therapy at a large US comprehensive cancer centre	January 2004 - April 2011	Patients treated at a large comprehensive cancer centre. Patients on oral chemotherapy and enrolled in clinical trials were excluded	Patients with cervical cancer who received systemic cancer therapy	HIV-1/2 antibody test and/or confirmatory Western blot testing after registration at the centre.	23 / 245 (9·4%)	0/23 (0%)	10/10
McGee-Avila(2020)[75]	Retrospective study on patterns of HIV testing and determinants of non-receipt of HIV testing among women with cervical cancer in the New Jersey Medicaid program, US	January 2012 - December 2014	Patients with cervical cancer aged 21-64 years. Cases identified post-mortem, non-New Jersey residence at diagnosis and with previous primary cancer or known HIV positive were excluded.	Primary, histologically confirmed invasive cervical cancer	Tested at any point during the study period	78/242 (32·2%)	NA	10/10
					Tested 6 months before diagnosis to 6 months after diagnosis of cervical cancer	33/242 (13·6%)		
Raben (2015)[9]	Retrospective cohort on HIV testing in ICs in Europe	May 2013	Patients in participating centres, >18 and <65 years of age, not known HIV positive, presenting within the previous year/ last 100+ patients	Patients with cervical cancer	Participating centres reviewed retrospectively how many patients presenting with the IC were tested for HIV	444/583 (76·2%)	1/444 (0·2%)	2/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	

Butler (2014)[76]	Retrospective cohort study on HIV testing in patients with CIN 2+ in the UK	July 2012 - June 2013	Patients with CIN2+ at colposcopy, not known to be HIV positive	Cervical intraepithelial neoplasia grade 2 and above at colposcopy	The most recent HIV test at the service prior to their attendance for colposcopy (last 3 years)	34/94 (36·2%)	NA	
Lebari (2012)[77]	Retrospective review of HIV testing in patients with AIDS defining malignancies in the UK	March 2007 - July 2011	Patients referred or initially diagnosed with cervical cancer	NA	Tested for HIV	1/64 (1·6%)	NA	
Mosimann (2014)[78]	Retrospective cohort study on HIV testing rates among patients treated for AIDS defining cancers and HL in Switzerland	January 2002 - July 2012	Patients aged ≥ 18 years treated for invasive cervical cancer	Invasive cervical cancer	HIV tested within 90 days before and 90 days after the cancer diagnosis date	6/57 (10·5%)	0/6 (0%)	

Malignant lymphoma

Full-text articles

Reference (year)	Design and setting	Included study period	Population and exclusion criteria	IC definition	HIV tested definition	HIV test ratio (%)**	Positivity ratio (%)**	Risk of bias score*
Augusti (2016)[19]	Cross-sectional cohort in primary care, Spain	January 2010 - August 2012	Patients aged 16-65 years were included; known HIV positive patients excluded	Using either their ICD-10 codes or a positive laboratory result	HIV test within 4 months of diagnosis date	Patients with HL 0/86 (0%) Men with NHL 6/250 (2·4%) Women with NHL 6/214 (2·8%)	Patients with HL NA Men with NHL 1/6 (16·7%) Women with NHL 0/6 (0%)	9/10
Gupta (2011)[35]	First audit of IC-guided testing in UK general hospital	First audit: August 2008 - July 2009	Patients of all ages with lymphoma	Patients with a positive pathology sample for lymphoma	HIV testing was double checked using the electronic pathology records system and a separate database of HIV testing	First audit: 3/42 (7·1%)	NA	7/10
	Re-audit of IC-guided testing in UK general hospital	Re-audit: August 2009 - June 2010				Re-audit: 2/46 (4·3%)		

Hwang (2015)[74]	Retrospective cohort on HIV testing in patients with cancer at the initiation of therapy at a large US comprehensive cancer centre	January 2004 - April 2011	Patients treated at a large comprehensive cancer centre. Patients on oral chemotherapy and enrolled in clinical trials were excluded	Patients with NHL on systemic cancer therapy	HIV-1/2 antibody test and/or confirmatory Western blot testing after registration at the centre.	NHL: 1439/1628 (88·4%)	NHL: 23/1439 (1·6%)	10/10
				Patients with HL on systemic cancer therapy		HL: 322/356 (90·4%)	HL: 2/322 (0·6%)	
Raben (2015)[9]	Retrospective cohort on HIV testing in ICs in Europe	May 2013	Patients in participating centres, >18 and <65 years of age, not known HIV positive, presenting within the previous year/ last 100+ patients	Patients with NHL	Participating centres reviewed retrospectively how many patients presenting with the IC were tested for HIV	577/1274 (45·3%)	21/577 (3·6%)	2/10
Other publication types***								
Reference (year)	**Design and setting**	**Included study period**	**Population and exclusion criteria**	**IC definition**	**HIV tested definition**	**HIV test ratio (%)**	**Positivity ratio (%)**	
Bishin (2017)79	Longitudinal cohort study to assess treatment guidelines for diffuse large B-cell lymphoma in the US	2005 - 2016	All patients diagnosed and treated for diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma	HIV serology testing	165/179 (92·2%)	NA	
Bowman (2010)80	Cohort study on HIV testing in lymphoma patients in the UK	6 month pilot period (date not reported)	All lymphoma patients seen in the 6 month pilot period at the study site	NA	NA	27/214 (12·6%)	0/27 (0%)	

Buxton (2011)81	Cross-sectional study to assess treatment in lymphoma patients in the UK	2009	All patients newly diagnosed with lymphoma	New lymphoma diagnosis	NA	91/281 (32·4%)	3/91 (3·3%)
Datta (2015)82	Audit on treatment in Primary Central Nervous System lymphoma patients in the UK	2008 - 2013	All patients with Primary Central Nervous System lymphoma, excluding metastatic disease	Biopsy-proven Primary Central Nervous System lymphoma	HIV status	1/20 (5%)	NA
Davies (2018)83	Audit on HIV testing in lymphoma patients in the UK	2016 - 2017	All patients newly diagnosed with lymphoma	New lymphoma diagnosis	Tested for HIV at first clinic/ specialist review	101/135 (74·8%)	0/101 (0%)
Lebari (2012)77	Retrospective review of HIV testing in patients with AIDS defining malignancies in the UK	March 2007 - July 2011	Patients referred or initially diagnosed with Non-Hodgkin's lymphoma	NA	Tested for HIV	34/158 (21·5%)	NA
Mosimann (2014)78	Retrospective cohort study on HIV testing rates among patients treated for AIDS defining cancers and HL in Switzerland	January 2002 - July 2012	Patients aged ≥ 18 years treated for HL	Hodgkin's Lymphoma	HIV tested within 90 days before and 90 days after the cancer diagnosis date	HL: 79/133 (59·4%)	HL: 0/79 (0%)
			Patients aged ≥ 18 years treated for NHL	non-Hodgkin lymphoma		NHL: 392/653 (60·0%)	NHL: 4/392 (1·0%)

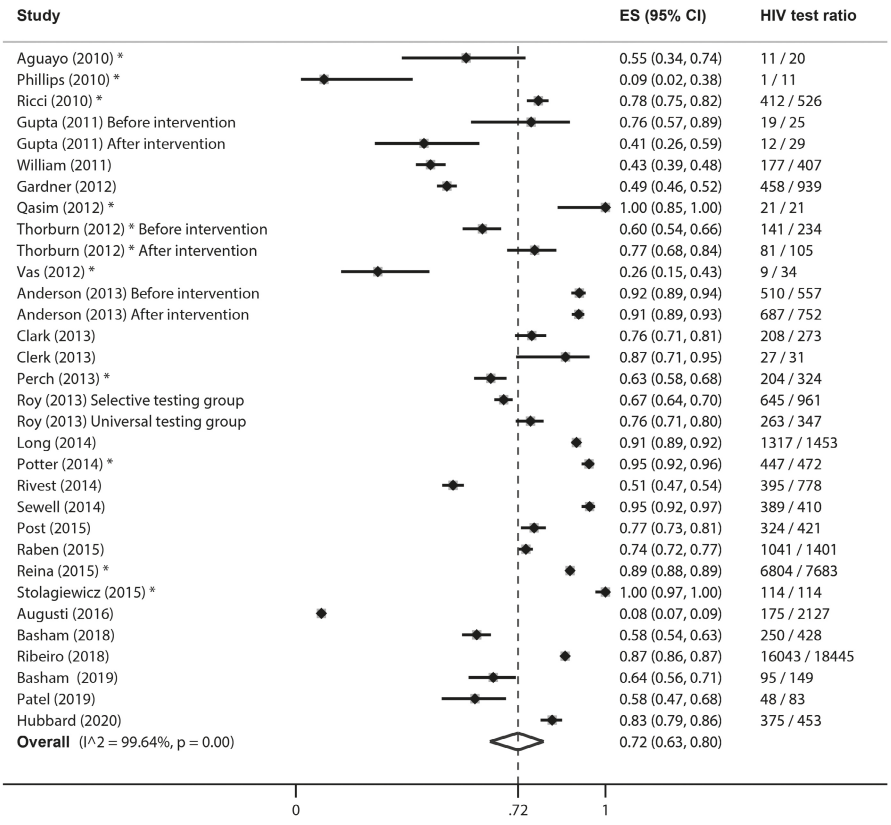
* Risk of bias was assessed for all included full-text references using an adapted version of the Joanna Briggs Institute checklist for prevalence studies, and scored out of 10. A risk of bias score of ≥7/10 was considered low risk by the researchers. ** If articles reported data on HIV test ratio and positivity ratio by subgroup (e.g. sex, before and after intervention), then the data of that article are provided by subgroup here. *** Including abstracts, short communications, and correspondence. CIN = cervical intraepithelial neoplasia; DAA = direct-acting antivirals; ED = emergency department; HBV = hepatitis B virus; HCV = hepatitis C virus; HL = Hodgkin's lymphoma; IC = indicator condition; ICD-10 = 10th revision of the International Classification of Diseases and Related Health Problems; NA = not reported/not applicable; NHL = Non-Hodgkin lymphoma; PCR = Polymerase chain reaction; REP = Rochester Epidemiology Project; RNA = ribonucleic acid; TB = tuberculosis.

Pooled results

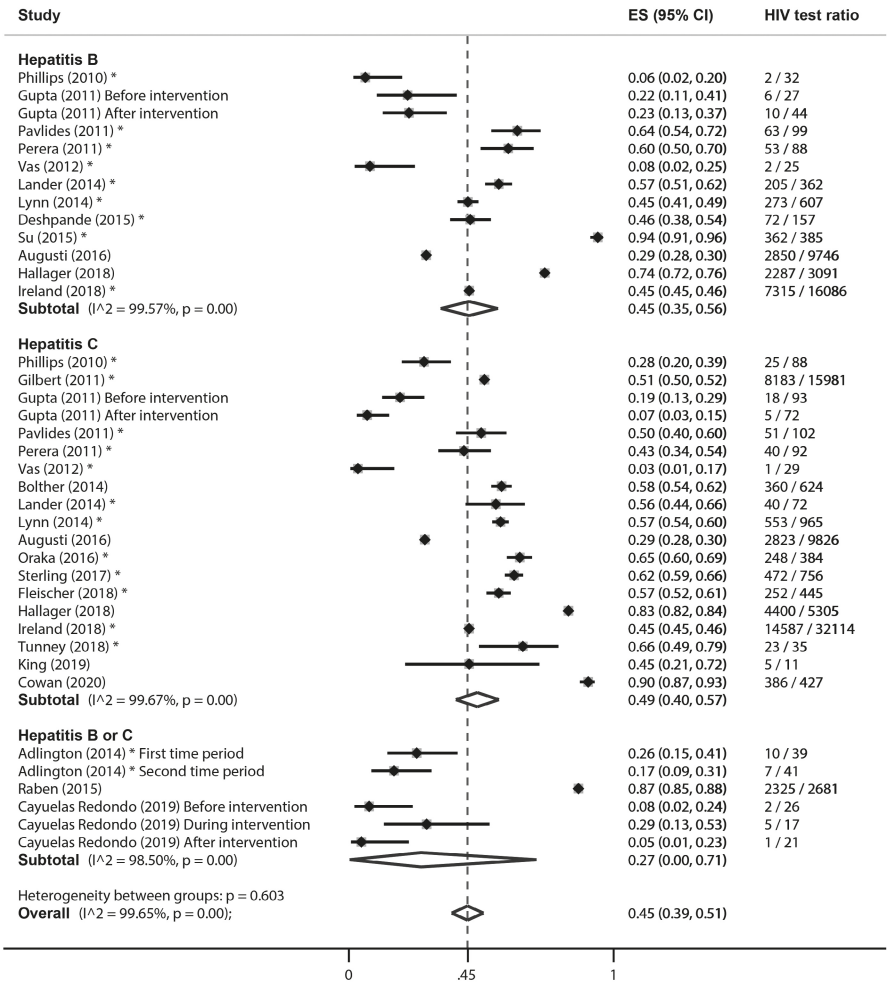
Meta-analyses of HIV test ratios by IC, including all publication types, regardless of risk of bias were performed. Heterogeneity between studies within ICs was very large, with the I^2 test for heterogeneity exceeding 99% in all analyses. The overall estimated proportion (ES) tested for HIV was 0·49 (95% CI 0·43-0·54). By IC, this proportion was highest in TB; ES 0·72 (0·63-0·80), followed by HCV (ES 0·49, 0·40-0·57), HBV (ES 0·45, 0·35-0·56), malignant lymphoma (ES 0·35, 0·16-0·58) and studies reporting hepatitis B or C (ES 0·27, 0·0-0·71). Lowest ES were observed in CC/CIN2+ (ES 0·12, 0·01-0·31), Figure 2.

Figure 2: Pooled results and estimated proportion tested for HIV per indicator condition

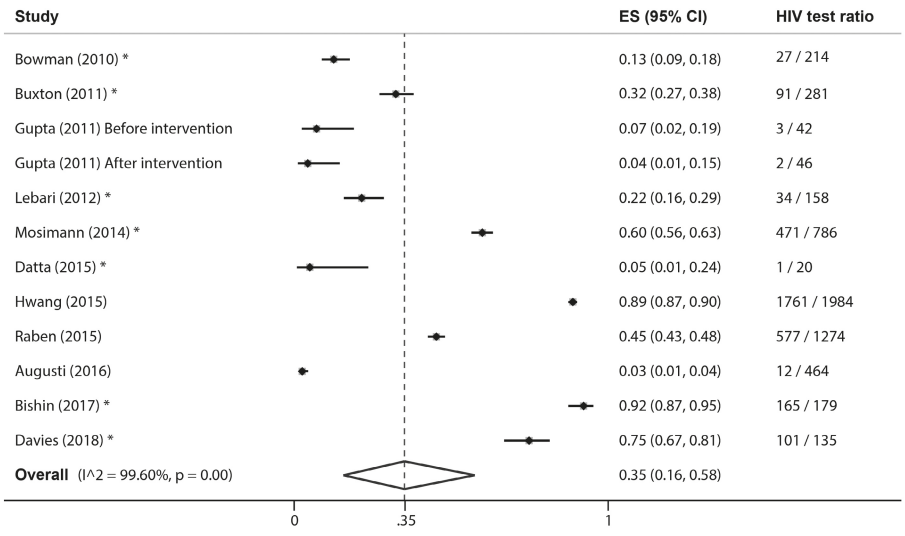
2A: Tuberculosis



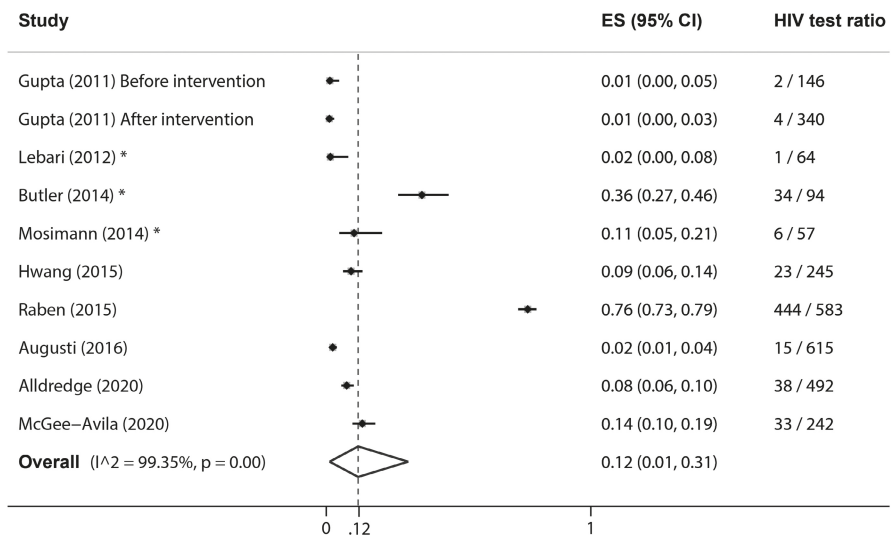
2B: Hepatitis B and C



2C: Malignant lymphoma



2D: Cervical carcinoma or cervical intraepithelial neoplasia grade 2+



*Other publication types than full-text articles (i.e. abstracts, short communications, and correspondence). CIN: cervical intraepithelial neoplasia. ES: estimated proportion.

A sensitivity analysis including only low risk of bias full-text publications showed lower proportions, with an overall ES of 0·40 (0·29-0·52), and 0·68 (0·51-0·83), 0·38 (0·10-0·71), 0·37 (0·10-0·69), 0·21 (0·00-0·87), 0·12 (0·02-0·27), and 0·05 (0·02-0·09) for TB, HCV, HBV, malignant lymphoma, HBV/HCV, and CC/CIN2+, respectively. Five studies reported HIV test ratios stratified by sex; four on TB, and one on TB, HBV, HCV, and malignant lymphoma. When pooling studies among TB patients by sex, overall ES were similar in women (ES 0·49, 0·13-0·85) and men (ES 0·53, 0·15-0·89).

Meta-analyses of HIV positivity by IC, including all publication types, regardless of risk of bias were performed. Heterogeneity between studies within ICs was large for most ICs (e.g. I^2 test for heterogeneity 96% for HBV/HCV), but low for CC/CIN2+ (I^2=0%). The overall estimated positivity ranged between 0% (CC/CIN2+) and 5% (TB) (supplementary appendix 6).

Meta-regression analyses showed no significant association between date of data collection and overall HIV test ratio (β=1·05%, 95%CI=-0·96%–3·06%, p=0·30). When stratified by IC, a significant association was observed in studies on CC/CIN2+ only (β=6·14%, 95%CI=0·75%–11·53%, p=0·03). However, this association was largely influenced by the most recent study, that reported the highest test ratio, but was also deemed high risk of bias.[9] In a sensitivity analysis excluding high risk of bias studies, this association was lost (β=0·47%, 95%CI=-2·86%–3·79%, p=0·72).

DISCUSSION

This systematic review provides an overview of the adoption of IC-guided testing in seven selected ICs in Western countries. Results show a large variation in HIV test ratios per IC, but overall HIV test ratios are low. The highest test ratios were observed in TB patients, followed by patients with HCV, HBV, and malignant lymphoma, respectively. Lowest test ratios were observed in patients with CC/CIN2+. No data on the extent of IC-guided testing in patients with VC/VIN2+ and PN was found.

Large differences in HIV test ratios between studies concerning the same IC were observed. Some outliers were studies with a high risk of bias, but among studies with low risk of bias, considerable variation was still observed. An explanation may be the difference in design of studies and how being tested for HIV was defined: some studies assessed evidence of any HIV testing, while others had a set timeframe around IC diagnosis to assess IC-guided testing. Another explanation could be the difference in setting between studies. For example, in malignant lymphoma, the lowest test ratio was observed in a study performed in the PC setting, while the highest ratio was observed in a study performed in a comprehensive cancer center. Variation was also observed within countries. Among TB patients in Canada, an audit performed in the province of Manitoba showed much lower HIV test ratios than one in Alberta (59% versus 91%, respectively[28,29]). This discrepancy is probably due to the 'opt out' HIV testing procedure for TB patients in Alberta, which was not used in Manitoba, suggesting its effectivity to optimize HIV testing. Two studies

performed among HCV patients in Denmark also showed very different results, with an HIV test ratio of 58% in one university hospital,[30] compared to 83% in 18 Danish hospitals.[31] This discrepancy might be due to an increase in HIV test ratio over time, attributed to national efforts to increase HIV testing in risk groups, as the latter study concerned a later period (2002-2015) than the former (1996-2011). However, we found no association between data collection period and HIV test ratio in meta-regression analyses, suggesting that adherence to this testing strategy has not improved over time, and underlining the urgency of implementing strategies to improve IC-guided testing for HIV.

When comparing HIV test ratio before- and after interventions to increase HIV testing, some studies reported an improvement,[32,33] while others did not.[34,35] One UK study showed that HIV test ratios among patients with TB, HCV, cervical carcinoma and malignant lymphoma were lower in 2009-2010 than in 2008-2009 despite educational and promotional efforts by the researchers.[35] Studies showed that a universal HIV testing policy among TB patients yielded higher HIV test ratios than a selective testing policy based on risk-assessment,[36] a result in line with the high success rate of the 'opt out' testing procedure for TB patients in Alberta.[29]

HIV positivity was highest among TB patients, followed by HBV, HCV, and malignant lymphoma, respectively, but again large variation was observed. Among CC/CIN2+ patients, one study reported a positivity of 0·2%,[9] while positivity was 0% in the others. However, in view of the small number of studies and the low test ratios, this should not be interpreted as HIV screening not being cost-effective among CC/CIN2+ patients[4,5].

This review confirms previous reporting on missed opportunities for earlier diagnosis through IC-guided testing. A barrier to optimal IC-guided testing might be the large number of ICs, the large variety in types of conditions and the many medical specialties involved. This variety requires tailored strategies to assure routine IC-guided testing is implemented across ICs. Moreover, an evaluation of IC-guided HIV testing recommendations in specialty guidelines in the UK and Europe revealed that the majority of IC guidelines do not recommend HIV testing, and physicians are not always aware of current HIV testing recommendations.[18,37] This is supported by the observation that the highest HIV test ratio were found in TB, HBV and HCV; HIV testing is recommended most prominently in the specialty guidelines for these conditions, and as pulmonologists and gastroenterologists commonly collaborate with infectious disease specialists, they may be more likely to focus on possible underlying HIV. Adoption of HIV testing in specialty guidelines and creating awareness of this strategy among involved specialties is an important first step to optimize testing.[38] As educational interventions to optimize testing showed varying results, additionally implementing previously proven successful strategies, such as opt-out testing or universal testing without detailed pre-test discussion, as described in the studies mentioned earlier,[29,36] is likely more effective than only educating involved medical professionals on IC-guided testing. In addition, sustained effect must be aimed for when designing interventions. For example, a digital case

note prompt suggesting HIV testing when the patient has an IC diagnosis lead to a significant increase in HIV test ratios during the intervention period in two studies, but the effect was lost when the prompts were deactivated.[24,34] Thus, continuous implementation of a combination of the aforementioned strategies would likely be most effective.

Strengths and limitations

A major strength of this review is the variety of settings and countries included. Second, by including not only published full-text articles, but also other publication types, we gained a more comprehensive picture of actual IC-guided HIV testing practices.

Although the retrospective design of included studies posed a potential risk of bias, most full-text studies were assessed as low risk of bias. We further addressed this possible limitation in a sensitivity analysis including only full-text articles with low risk of bias and found lower estimated proportions, suggesting that the IC-guided HIV test ratio outside study settings might be even lower. Very large heterogeneity was observed in the meta-analyses by IC, probably reflecting true heterogeneity across settings and Western countries. Thus, exact inferences on HIV test ratios by ICs could not be made, but conclusions can be drawn from the heterogeneity itself; testing practices are both inconsistently reported and inconsistently adopted. These findings should be considered when evaluating efforts to improve HIV testing strategies. Finally, a selection of only seven ICs was included in this review. Although not all ICs were included, it is unlikely that the HIV test ratios in other ICs will be much higher, as well-established and guideline-supported ICs such as TB and HCV were included in this study, and it is evident that even in those improvement is still needed.

This systematic review shows that a decade after its introduction, IC-guided testing for HIV is still insufficiently implemented in Western countries. Lessons on effective strategies from ICs with the highest test ratios, such as universal testing strategies, should be used to design effective implementation strategies for optimal IC-guided testing, to reduce underdiagnosis and late presentation of HIV.

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Contributors statement
Geerlings acquired financial support for the project leading to this publication. Geerlings, Schim van der Loeff, van Bergen and Bogers were involved in the conceptualisation and design of methodology of the study. Bogers performed the literature search. Bogers and Hulstein performed data curation including screening of search results, data extraction, and performing quality assessments. Bogers analysed the data and designed the figures. Schim van der Loeff performed quality controls and validation on all data analyses. De Bree and Reiss provided commentary and revisions on the original draft. All authors were involved in the interpretation of the data and the preparation of the final manuscript.

REFERENCES

1. European Centre for Disease Prevention and Control. HIV/AIDS surveillance in Europe 2019 – 2018 data. Copenhagen, Denmark: 2018. https://www.ecdc.europa.eu/sites/default/files/documents/hiv-surveillance-report-2019.pdf. Accessed 17 November 2020.
2. Girardi E, Sabin CA, Monforte AD. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. *J Acquir Immune Defic Syndr* 2007;**46 Suppl 1**:S3-8.
3. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). *PLoS Med* 2013;**10(9)**:e1001510.
4. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med* 2005;**352(6)**:570-85.
5. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. *N Engl J Med* 2005;**352(6)**:586-95.
6. HIV in Europe. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark; 2014. http://www.hiveurope.eu/Portals/0/Documents/Guidance.pdf.pdf?ver=2014-01-29-113626-000. Accessed 13 October 2020.
7. World Health Organization. Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva, Switzerland; 2007. Report No.: ISBN 978 92 4 159556 8.
8. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.
9. Raben D, Mocroft A, Rayment M, et al. Auditing HIV Testing Rates across Europe: Results from the HIDES 2 Study. *PLoS One* 2015;**10(11)**:e0140845.
10. Menacho I, Sequeira E, Muns M, et al. Comparison of two HIV testing strategies in primary care centres: indicator-condition-guided testing vs. testing of those with non-indicator conditions. *HIV Med* 2013;**14 Suppl 3**:33-7.
11. Read P, Armstrong-James D, Tong CY, Fox J. Missed opportunities for HIV testing--a costly oversight. *QJM* 2011;**104(5)**:421-4.
12. Scognamiglio P, Chiaradia G, De Carli G, et al. The potential impact of routine testing of individuals with HIV indicator diseases in order to prevent late HIV diagnosis. *BMC Infect Dis* 2013;**13**:473.
13. Wohlgemut J, Lawes T, Laing RB. Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study. *BMC Infect Dis* 2012;**12**:72.
14. Lin YD, Garner SE, Lau JSY, Korman TM, Woolley IJ. Prevalence of HIV indicator conditions in late presenting patients with HIV: a missed opportunity for diagnosis? *QJM* 2019;**112(1)**:17-21.
15. Levy I, Maor Y, Mahroum N, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. *BMJ Open* 2016;**6(11)**:e012721.
16. Joore IK, Arts DL, Kruijer MJ, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. *Sex Transm Infect* 2015;**91(7)**:467-72.

17. Ellis S, Curtis H, Ong EL, British HIV Association. HIV diagnoses and missed opportunities. Results of the British HIV Association (BHIVA) National Audit 2010. *Clin Med (Lond)* 2012;**12(5)**:430-4.

18. Lord E, Stockdale AJ, Malek R, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. *HIV Med* 2017;**18(4)**:300-4.

19. Agusti C, Montoliu A, Mascort J, et al. Missed opportunities for HIV testing of patients diagnosed with an indicator condition in primary care in Catalonia, Spain. *Sex Transm Infect* 2016;**92(5)**:387-92.

20. Bull L, Rayment M. HIV-indicator-condition-driven HIV testing: clinically effective but still rarely implemented. *Clin Med (Lond)* 2016;**16(2)**:175-9.

21. Gullon A, Verdejo J, de Miguel R, Gomez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. *AIDS Care* 2016;**28(10)**:1296-300.

22. Page I, Phillips M, Flegg P, Palmer R. The impact of new national HIV testing guidelines at a district general hospital in an area of high HIV seroprevalence. *J R Coll Physicians Edinb* 2011;**41(1)**:9-12.

23. Ruutel K, Lemsalu L, Latt S. Monitoring HIV-indicator condition guided HIV testing in Estonia. *HIV Med* 2018;**19 Suppl 1**:47-51.

24. Youssef E, Sanghera T, Bexley A, Hayes M, Perry N, Dosekun O. HIV testing in patients presenting with indicator conditions in outpatient settings: offer and uptake rates, and educational and active interventions. *Int J STD AIDS* 2018;**29(13)**:1289-94.

25. Tominski D, Katchanov J, Driesch D, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. *HIV Med* 2017;**18(2)**:125-32.

26. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015;**13(3)**:147-53.

27. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014;**72(1)**:39.

28. Basham CA, Elias B, Fanning A, Cook C, Orr P. Performance measurement of a Canadian provincial tuberculosis programme: Manitoba, 2008-2012. *International Journal of Tuberculosis & Lung Disease* 2018;**22(4)**:437-43.

29. Long R, Niruban S, Heffernan C, et al. A 10-year population based study of 'opt-out' HIV testing of tuberculosis patients in Alberta, Canada: national implications. *PLoS ONE [Electronic Resource]* 2014;**9(6)**:e98993.

30. Bolther M, Dalgaard LS, Kristensen LH, Tarp BD, Jensen-Fangel S. Testing for hepatitis B virus and HIV in patients with chronic hepatitis C: screening performance and outcome. *Scandinavian Journal of Infectious Diseases* 2014;**46(10)**:686-92.

31. Hallager S, Lundh A, Ladelund S, et al. The Prevalence of Human Immunodeficiency Virus Coinfection Among Patients Newly Diagnosed With Chronic Hepatitis B or C in Denmark: A Nationwide Cohort Study. *Open Forum Infect Dis* 2018;**5(12)**:ofy310.

32. Adlington K, Mackie N. An audit of HIV testing in acute medical patients with HIV clinical indicator conditions: Are guidelines being ignored? *HIV Medicine* 2014;**15**:102 (abstr).

33. Anderson C, White J, Abubakar I, et al. Raising standards in UK TB control: introducing cohort review. *Thorax* 2014;**69(2)**:187-9.

34. Cayuelas Redondo L, Ruiz M, Kostov B, et al. Indicator condition-guided HIV testing with an electronic prompt in primary healthcare: a before and after evaluation of an intervention. *Sexually Transmitted Infections* 2019;**95(4)**:238-43.

35. Gupta ND, Lechelt M. Assessment of the implementation and knowledge of the UK National Guidelines for HIV Testing (2008) in key conditions at a UK district general hospital. *International Journal of STD & AIDS* 2011;**22(2)**:102-4.

36. Roy A, Anaraki S, Hardelid P, et al. Universal HIV testing in London tuberculosis clinics: a cluster randomised controlled trial. *European Respiratory Journal* 2013;**41(3)**:627-34.

37. Martinez Sanz J, Perez Elias MJ, Muriel A, et al. Outcome of an HIV education program for primary care providers: Screening and late diagnosis rates. *PLoS One* 2019;**14(7)**:e0218380.

38. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282(15)**:1458-65.

39. Basham CA, Elias B, Fanning A, Orr P. Tuberculosis among northern Manitoba First Nations, 2008-2012: program performance on- and off-reserve. *Canadian Journal of Public Health Revue Canadienne de Sante Publique* 2019;**8**:08.

40. Clark IT, Lobato MN, Gutierrez J, Sosa LE. HIV status among patients with tuberculosis and HIV testing practices by Connecticut health care providers. *Journal of the International Association of Providers of AIDS Care* 2013;**12(4)**:261-5.

41. Clerk N, Antunes G, Williams J, Dibble W. Improving the uptake of HIV testing in patients with tuberculosis. *British Journal of Nursing* 2013;**22(11)**:634-7.

42. Gardner A, Naureckas C, Beckwith C, Losikoff P, Martin C, Carter EJ. Experiences in implementation of routine human immunodeficiency virus testing in a US tuberculosis clinic. *International Journal of Tuberculosis and Lung Disease* 2012;**16(9)**:1241-6.

43. Post JJ, Goldberg H, Kaufman G, Plit M, Ressler KA, Ferson MJ. HIV testing rates and co-infection among patients with tuberculosis in south-eastern Sydney, 2008-2013. *Medical Journal of Australia* 2015;**202(5)**:255-7.

44. Ribeiro L, Gomes M, Gaio R, Duarte R. HIV screening of tuberculosis patients in Portugal: what are we missing? *International Journal of Tuberculosis & Lung Disease* 2018;**22(10)**:1216-9.

45. Rivest P, Sinyavskaya L, Brassard P. Burden of HIV and tuberculosis co-infection in Montreal, Quebec. *Canadian Journal of Public Health Revue Canadienne de Sante Publique* 2014;**105(4)**:e263-e7.

46. Sewell J, Capocci S, Johnson J, et al. Expanded blood borne virus testing in a tuberculosis clinic. A cost and yield analysis. *Journal of Infection* 2015;**70(4)**:317-23.

47. William ST, Taylor R, Osman H. Changes in HIV testing rates among patients with tuberculosis in a large multiethnic city in the United Kingdom in 2008/09. *HIV Medicine* 2010;**1**:57.

48. Aguayo C, Leon L, Sanchez A, Reguera A. Analysis of Extrapulmonary Tuberculosis (ETB) Registred in a Spanish hospital. Retrospective study 1999-2009. *Internal Medicine Journal* 2010;**40**:66 (abstr).

49. Hubbard A, Garcia E, Chitnis A, Wong R. High Prevalence of Hiv, Hbv, and Hcv Co-Infection among Adults with Tb Infection: An Urban Safety-Net Hospital Experience. *Chest* 2020;**158**:A329 (abstr).

50. Patel R, Makaretz A, Fortune D, et al. Factors associated with high mortality during TB treatment in New Mexico: 2007-2017. *American Journal of Respiratory and Critical Care Medicine Conference* 2019;**199(9)** (abstr).

51. Perch M, Andersen P, Kok-Jensen A. HIV testing of patients diagnosed with tuberculosis increased in Denmark during the period from 2007 to 2009. *HIV Medicine* 2013;**14**:42-3.

52. Phillips M, Page I, Sweeney J, Flegg P, Palmer R, Wasef W. A year on from UK national guidelines: An audit of HIV testing in patients diagnosed with a clinical indicator disease. *HIV Medicine* 2010;**1**:111-2 (abstr).

53. Potter JL, Hyams C, Shaukat M, et al. Should screening for chronic viral hepatitis in patients with tuberculosis be introduced to nice guidelines? *Thorax* 2014;**69**:A159 (abstr).

54. Qasim M, Nadama R, Adeloye O. Clinical study: Diagnosis and management of tuberculosis patients as per national institute of clinical excellence (NICE) United Kingdom guidelines. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2012;**185** (abstr).

55. Reina S, Silva C, Correia AM, Duarte R. HIV screening in tuberculosis patients, in the northern region of Portugal. *European Respiratory Journal Conference: European Respiratory Society Annual Congress* 2015;**46**.

56. Ricci A, Buelli F, Pinsi G, et al. Reported HIV-status in TB patients attended in a infectious diseases department in Brescia. *Infection* 2010;**38**:68 (abstr).

57. Stolagiewicz N, Goodman A, Milburn H, Breen R. Are rates of HIV infection falling in patients with TB in inner London? *HIV Medicine* 2015;**16**:42-3 (abstr).

58. Thorburn F. The impact of a multi-disciplinary meeting on the rates of HIV in testing in TB patients. *HIV Medicine* 2012;**13**:64 (abstr).

59. Vas A, Morgan E, Padmakumar K, Bradley B, Williams M, Thornton-Chan J. HIV testing in TB and Hepatitis services in a district general hospital. *HIV Medicine* 2012;**13**:65 (abstr).

60. Deshpande S, Ko T, Roberts E, et al. Tenofovir Therapy for Hepatitis B May Be Commonly Prescribed Without HIV Testing. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2016;**71(2)**:e53-e4.

61. Ireland G, Ogaz D, Kirwan P, et al. HIV testing in persons diagnosed with hepatitis B and C. *HIV Medicine* 2018;**19(3)**:e54-e5.

62. Lander M, Tohani A, Dias A, O'Connell R. Assessing HIV testing in hepatitis: An audit of HIV testing uptake in a specialist hepatology clinic in an area of high prevalence for hepatitis B and C. *HIV Medicine* 2014;**15**:96-7 (abstr).

63. Lynn AM, Larson JJ, Leise MD. Population-based HIV screening rates in patients with viral hepatitis. *Gastroenterology* 2014;**146(5)**:S1003 (abstr).

64. Pavlides M, Madhotra R, Raza MM. HIV testing in patients with hepatitis B and C infection in the United Kingdom. *Clinical Microbiology and Infection* 2011;**17**:S802-S3 (abstr).

65. Perera S, Lallemant C, Gilleece Y, Verma S. HIV testing in patients with hepatitis B and/or C. *HIV Medicine* 2011;**12**:41-2 (abstr).

66. Su C, Bannister N, Huang V. Evaluation of chronic hepatitis B treatment and assessment of chronic hepatitis B care at an Asian community health center in New York City, 2012. *Hepatology* 2015;**62**:993A (abstr).

67. King K, Seah J, Cheng A, Whiting S, Hoy J. Missed Opportunities for HIV testing persist despite a single educational intervention: How can we close this evidence-practice gap? *Internal Medicine Journal* 2019;**5**:05.

68. Cowan E, Hardardt J, Brandspiegel S, Calderon Y. Linkage Outcomes for HIV/HCV Co-Infected and HCV Mono-Infected Patients Participating in an Emergency Department Screening Program. *Annals of Emergency Medicine* 2020;**76**:S49 (abstr).

69. Fleisher I, Geboy A, Nichols W, et al. HCV Antibody Positive Patients in a Large Healthcare System: HIV Testing Rates and Compliance with CDC Guidelines. *Gastroenterology* 2018;**154**:S1201 (abstr).

70. Gilbert M, Barrios R, Wong E, et al. Use of provincial laboratory and surveillance data to inform strategies for expanding provider-initiated HIV testing and to assess their impact. *Canadian Journal of Infectious Diseases and Medical Microbiology* 2011;**22**:86B (abstr).

71. Oraka E, Abara W, Pitasi M, Van Handel M, DiNenno E. Prevalence of HIV testing among adults with a hepatitis c diagnosis: Findings from the national health and nutrition examination survey 1999-2014. *Sexually Transmitted Diseases* 2016;**43**:S217 (abstr).

72. Sterling RK, Amador J, Stewart P, et al. HIV testing in patients starting HCV treatment and factors associated with adherence to AASLD-IDSA guidelines. *Hepatology* 2017;**66**:531A-2A (abstr).

73. Tunney R, Saxon C. Characteristics and audit of the management of all new hepatitis C diagnoses made in a level 3 genitourinary medicine clinic over the last 5 years. *HIV Medicine* 2018;**19**:S148 (abstr).

74. Alldredge J, Leaf MC, Patel P, et al. Prevalence and predictors of HIV screening in invasive cervical cancer: a 10 year cohort study. *Int J Gynecol Cancer* 2020;**30(6)**:772-6.

75. Hwang JP, Granwehr BP, Torres HA, et al. HIV Testing in Patients With Cancer at the Initiation of Therapy at a Large US Comprehensive Cancer Center. *Journal of oncology practice/American Society of Clinical Oncology* 2015;**11(5)**:384-90.

76. McGee-Avila JK, Doose M, Nova J, Kumar R, Stroup AM, Tsui J. Patterns of HIV testing among women diagnosed with invasive cervical cancer in the New Jersey Medicaid Program. *Cancer Causes & Control* 2020;**31(10)**:931-41.

77. Butler M, Black C, Cumming J, Groom T, Fargie F. HIV testing in patients with cervical intraepithelial neoplasia grade 2 and above: A clinical indicator disease. *HIV Medicine* 2014;**15**:105 (abstr).

78. Lebari D, Kaczmarski E. HIV testing in cancer: Experience from a tertiary oncology hospital. *HIV Medicine* 2012;**13**:34 (abstr).

79. Mosimann V, Cavassini M, Hugli O, et al. Patients with AIDS-defining cancers are not universally screened for HIV: A 10-year retrospective analysis of HIV-testing practices in a Swiss university hospital. *HIV Medicine* 2014;**15(10)**:631-4.

80. Bishin A, Vishnu P, Mandelson M, Aboulafia DM. Guidelines in clinical practice: Appraisal of quality metrics in the management of newly diagnosed diffuse large b-cell lymphoma based on the American Society of hematology practice improvement module. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH* 2017;**130** (abstr).

81. Bowman CA, Olarinde O, Wright J. Routine HIV testing in lymphoma patients - Overcoming the challenges. *HIV Medicine* 2010;**1**:59-60 (abstr).

82. Buxton JK, Davidson KL, Davies JM, Scott FM, Tucker J. South East Scotland experience of HIV testing in patients newly diagnosed with lymphoma. *Journal of the Royal College of Physicians of Edinburgh* 2011;**41(3)**:284.

83. Datta S, Lee R, Webb T, Ismail A, Jung A. 5 years experience of primary central nervous system lymphoma (PCNSL): A retrospective pilot audit. *Journal of Neurology, Neurosurgery and Psychiatry Conference: Association of British Neurologists, ABN* 2015;**86(11)** (abstr).

84. Davies D, Ishimwe P, Roberts M. A single centre's experience of HIV testing in patients with lymphoma. *HIV Medicine* 2018;**19**:S127 (abstr).

Supplementary Appendix 1: PROSPERO study protocol

The protocol for this review was published at PROSPERO, registration number CRD42020160243:

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

A systematic review on the HIV-testing ratio in seven selected indicator conditions in the Western world

Saskia Bogers, Suzanne Geerlings

To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.

Citation

Saskia Bogers, Suzanne Geerlings. A systematic review on the HIV-testing ratio in seven selected indicator conditions in the Western world. PROSPERO 2020 CRD42020160243 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020160243

Review question

What are the HIV-test ratios (i.e. the proportion of people diagnosed with a specific IC that are tested for HIV) for seven selected ICs in the Western world; tuberculosis, hepatitis B, hepatitis C, vulvar carcinoma, cervical carcinoma, malignant lymphoma and peripheral neuropathy of unknown cause.

Searches

The systematic literature search is performed through MEDLINE and EMBASE. Search date was August 19th, 2019. A repeat search will be performed shortly before finalising the systematic review to check for additional publications that may have been published. We limit the timeframe of studies to be included to the last 10 years (?2009). No language limitation is used in our inclusion. Conference abstracts are included to check for publication bias and selective outcome reporting or patient inclusion. When multiple publications report on the same data, only the publication reporting the most complete data is included.

Types of study to be included

Case reports are excluded from this review. All other study designs in which an HIV testing ratio in a population diagnosed with one of the selected IC is reported or can be calculated are included.

Condition or domain being studied

Domains studied

- HIV(-testing), diagnostic testing for HIV

- Indicator Conditions for HIV (-testing): tuberculosis, cervical cancer, vulva cancer, malignant lymphoma, hepatitis B, hepatitis C, peripheral neuropathy of unknown cause

- Western world countries (i.e. Western Europe, USA, Canada, Australia, New Zealand and Japan)

Participants/population

Studies must be performed amongst adults (aged 18 years or over), including those performed amongst both children and adults when data are reported separately. In all studies, subjects must be diagnosed with one or more of the selected ICs.

Intervention(s), exposure(s)

HIV testing and outcome.

Comparator(s)/control

n/a

Main outcome(s)

the HIV-test ratio (i.e. the proportion of adults diagnosed with a specific IC that are tested for HIV) for each of the seven selected ICs (i.e. tuberculosis, cervical cancer, vulva cancer, malignant lymphoma, hepatitis B, hepatitis C and peripheral neuropathy of unknown cause) in the Western world (i.e. Western Europe, USA,

Canada, Australia, New Zealand and Japan) in or after 2009.

* Measures of effect

Final relative risk

Additional outcome(s)

time trends in these HIV-test ratios (e.g. are there positive behavioural changes after the publication of the HIDES studies and subsequent guideline changes), and proportions HIV-positive among tested patients with one of the seven selected ICs.

* Measures of effect

Final relative risk

Data extraction (selection and coding)

The primary search results obtained will be imported into an EndNote X9 database (EndNote, Thomson Reuters, Philadelphia, PA, USA). All titles and abstracts of the articles obtained will be screened by one author to identify studies that potentially meet the inclusion criteria, and 10% will be independently screened by a second author through random selection (figure 1). We will allow up to 2.5% of papers per search identified by the second author as being eligible to have been missed by the first author. Differences in opinion on eligibility will be resolved by discussion. If after such discussion the difference remains more than 2.5%, all titles and abstracts will be reviewed by the second author. A data extraction sheet will be used to extract the data. Data will be retrieved on variables on study details (author name, year of publication, title, journal), country, study period, study methods (design, data collection source, recruitment, inclusion- and exclusion criteria, population, sex, age distribution, and the risk factors: sexual preference, ethnicity, socio-economic status, intravenous drug use, and sex worker), and results (sample size, ICs diagnosed, number of people diagnosed with an IC, number of those diagnosed with an IC that received an HIV test, HIV-test ratio, number tested HIV positive, HIV-positivity ratio, type of HIV test used, CD4 count at diagnosis, HIV viral load at diagnosis, and reason for not testing, if available). All data will be extracted by the first author and fully checked for accuracy by the second author. Discrepancies will be resolved through discussion.

Risk of bias (quality) assessment

The full text of all selected articles will be assessed by two independent authors. This critical appraisal of the studies to be included in our systematic review will be conducted using an adapted version of the Joanna Briggs checklist for prevalence studies; a checklist to assess quality of studies reporting prevalence data for use in a systematic review. From this checklist, we will drop item 3 ('Was the sample size adequate?')and 8 ('Was there appropriate statistical analysis?') as they are irrelevant to our review question. Item 6 ('Were valid methods used for the identification of the condition?') will be appraised both for the diagnostic method for the IC and HIV. Each item of appraisal for each study to be included in the review is discussed by the two assessing authors prior to extraction. The final assessment on quality of evidence will be done with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach by both reviewers. If the two authors disagree on the final critical appraisal and this cannot be resolved through discussion, a third author will be consulted to reach a final decision.

Strategy for data synthesis

We will describe the HIV test ratio for each of the included ICs, as well as the positivity-rates and time trends in HIV-testing ratios for each of the 7 ICs. Meta-analyses will be performed for each of the 7 separate ICs if limited heterogeneity is found in the studies (i.e. an I^2 of 40% or higher). These analyses will be performed using the random-effects model (as we expect heterogeneity between populations) and presented with 95% confidence intervals (95% CI), and subsequently displayed in a forest plot using odds ratio's as effect size.

Analysis of subgroups or subsets

Sub-analyses by sex and age of patients will be performed.

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Organisational affiliation of the review

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Review team members and their organisational affiliations
Miss Saskia Bogers. Amsterdam UMC
Professor Suzanne Geerlings. Amsterdam UMC

Type and method of review
Epidemiologic, Systematic review

Anticipated or actual start date
01 December 2019

Anticipated completion date
01 May 2020

Funding sources/sponsors
The H-TEAM initiative, of which this review is a project, is being supported by Aids Fonds (grant number: 2013169), Stichting AmsterdamDiner Foundation, Bristol-Myers Squibb International Corp. (study number: AI424-541), Gilead Sciences Europe Ltd (grant number: PA-HIV-PREP-16-0024), Gilead Sciences (protocol numbers: CO-NL-276-4222, CO-US-276-1712), Janssen Pharmaceutica (reference number: PHNL/JAN/0714/0005b/1912fde), M.A.C AIDS Fund, ViiV Healthcare (PO numbers: 3000268822, 3000747780) and ZonMw (grant number: 522002003). This review is further funded by Aids Fonds (grant number: P- 42702).

Conflicts of interest

Language
English

Country
Netherlands

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
10 July 2020

Date of first submission
27 November 2019

Stage of review at time of this submission

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
10 July 2020

Supplementary Appendix 2: PRISMA checklist for reporting Systematic Reviews and Meta-analyses

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, appendix page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, appendix page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, 6, appendix page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1, Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9, Table 2, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a (see pg. 5)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10

Section/topic	#	Checklist item	Reported on page #
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	36

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* **6(7)**: e1000097. For more information, visit: www.prisma-statement.org

Supplementary Appendix 3: Full search strategy

Ovid MEDLINE(R) ALL <1946 to November 20, 2020>		
#	**Searches**	**Results**
1	exp Tuberculosis/	189990
2	(tubercul* or tb or tbc).ti,ab,kf.	252288
3	1 or 2	277322
4	Uterine Cervical Neoplasms/	72306
5	(cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kf.	85841
6	4 or 5	104132
7	exp Vulvar Neoplasms/	8033
8	((vulva* or clitoris or clitoral) adj3 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kf.	5955
9	7 or 8	9525
10	exp Lymphoma/	167356
11	(lymphoma* or hematologic-neoplasms* or hodgkin* or non-hodgkin* or nonhodgkin* or immuno?ytom* or (hair* adj cell* adj leu*) or burkit* or sezary* or (mycos* adj fungo*) or (h?emato* adj (malign* or neoplas*))).ti,ab,kf.	219363
12	10 or 11	259698
13	hepatitis b/ or hepatitis c/	73777
14	(hepatitis or ((HBV or HCV) adj infection)).ti,ab,kf.	214749
15	13 or 14	224454
16	exp Peripheral Nervous System Diseases/	142614
17	(neuropathy or neuropathies or polyneuropathies or polyneuropathy).ti,ab,kf.	81375
18	16 or 17	187244
19	(indicator adj (diseas* or condition*)).ti,ab.	228
20	3 or 6 or 9 or 12 or 15 or 18 or 19	1043189
21	(HIV adj2 (testing or screening)).ti,ab,kf.	15936
22	20 and 21	1946
23	case reports.pt.	2038816
24	22 not 23	1886

Embase Classic + Embase <1947 to November 20, 2020>		
#	**Searches**	**Results**
1	exp tuberculosis control/ or exp tuberculosis/	258284

2	(tubercul* or tb or tbc).ti,ab,kw.	311283
3	1 or 2	362256
4	exp uterine cervix cancer/	98698
5	(cervi* adj5 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kw.	119298
6	4 or 5	144077
7	exp vulva cancer/	7040
8	((vulva* or clitoris or clitoral) adj3 (cancer* or neoplas* or carcinom* or malignan* or tumor* or tumour*)).ti,ab,kw.	8698
9	7 or 8	11137
10	exp lymphoma/	311845
11	(LYMPHOMA* or HEMATOLOGIC-NEOPLASMS* or HODGKIN* or NON-HODGKIN* or NONHODGKIN* or IMMUNO?YTOM* or (HAIR* adj CELL* adj Leu*) or BURKIT* or SEZARY* or (MYCOS* adj FUNGO*) or (H?EMATO* adj (MALIGN* or neoplas*))).ti,ab,kw.	318893
12	10 or 11	404124
13	exp Hepatitis A virus/ or exp hepatitis A/ or exp hepatitis B/ or exp Hepatitis B virus/	144399
14	(hepatitis or ((HBV or HCV) adj infection)).ti,ab,kw.	310961
15	13 or 14	338643
16	exp neuropathy/	554778
17	(neuropathy or neuropathies or polyneuropathies or polyneuropathy).ti,ab,kw.	125382
18	16 or 17	575735
19	(indicator adj (diseas* or condition*)).ti,ab.	370
20	3 or 6 or 9 or 12 or 15 or 18 or 19	1778570
21	(HIV adj2 (testing or screening)).ti,ab,kw.	20618
22	20 and 21	3195
23	case report/	2491837
24	22 not 23	3001
25	limit 24 to (conference abstracts or embase)	2621
26	limit 24 to embase	1619
27	limit 24 to conference abstracts	1002

Supplementary Appendix 4: Items included in the data extraction sheet

Data extraction was performed using a standard data extraction form created in Microsoft Excel. The items in the data extraction were:

Item	Further instruction
First author name	Name of first author
Study #	Record number from title/abstract screening results
Indicator condition	Which IC is reported on. If multiple ICs are reported on, extract each IC in a separate entry
Lymphoma type	For lymphoma: Specify which type. Use the exact specification that the article used
Article or abstract	Is the reported data from an article or abstract
Year of publication	Publication year
Title	Title of the publication
Journal	Journal or conference published/presented
Country/Countries	Country/countries in which the research took place
Study period	Period which was studied
Aim of study	Main research question
Recruitment site	Site of recruitment of patients/ data collection
Study design	Design of study
IC definition	How was the IC diagnosis defined
HIV tested definition	How was 'being tested for HIV' defined
Data collection source	Where was the data collected from (type of data source, e.g. registry, health records)
Inclusion criteria	What were the inclusion criteria
Exclusion criteria	What were the exclusion criteria
Population	Which population was studied (for the data collected in this row of the form, e.g. only the women in one row, and only the men in the next for the same study)
Age (describe what is reported, mean, median, ranges, categories)	Descriptive reporting of age distribution (as described in paper)
# with IC	Number of subjects with the IC, population in this row
# with HIV test	Number of subjects that were tested for HIV
HIV test ratio (calculation)	Calculation column for HIV test ratio
Reported HIV test ratio	HIV test ratio as reported in the record
# positive HIV tests	Number of population that were tested that were positive
Calculated HIV positivity ratio	Calculation column for HIV positivity ratio
Reported HIV positivity ratio	HIV positivity ratio as reported in article
Type of HIV test used	Type of HIV test used in the study
CD4 count at diagnosis	With unit that was used in the article
Viral load at diagnosis	With unit that was used in the article
Reasons for not testing	If reported
Author's comments	Additional comments by authors of record
Reviewer comments	Additional comments of screener

IC: Indicator condition.

Supplementary Appendix 5: Joanna Briggs Institute risk of bias checklist[1]

For assessment of risk of bias of individual included full-text studies, an adapted version of the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data was used;

The original checklist contains the following items:
1. Was the sample representative of the target population?
2. Were study participants recruited in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and setting described in detail?
5. Is the data analysis conducted with sufficient coverage of the identified sample?
6. Were objective, standard criteria used for measurement of the condition?
7. Was the condition measured reliably?
8. Was there appropriate statistical analysis?
9. Are all important confounding factors/ subgroups/differences identified and accounted for?
10. Were subpopulations identified using objective criteria?

For our risk of bias assessment, we dropped item 8 of the checklist, as it was not deemed relevant for our study question. We assessed item 6 for both the indicator condition that was studied, as well as how 'tested for HIV' was assessed. Thus, the total number of items was 10.

Scoring of all full-text articles was done by two authors (SJB and SHH) independently and any discrepancies resolved through discussion.

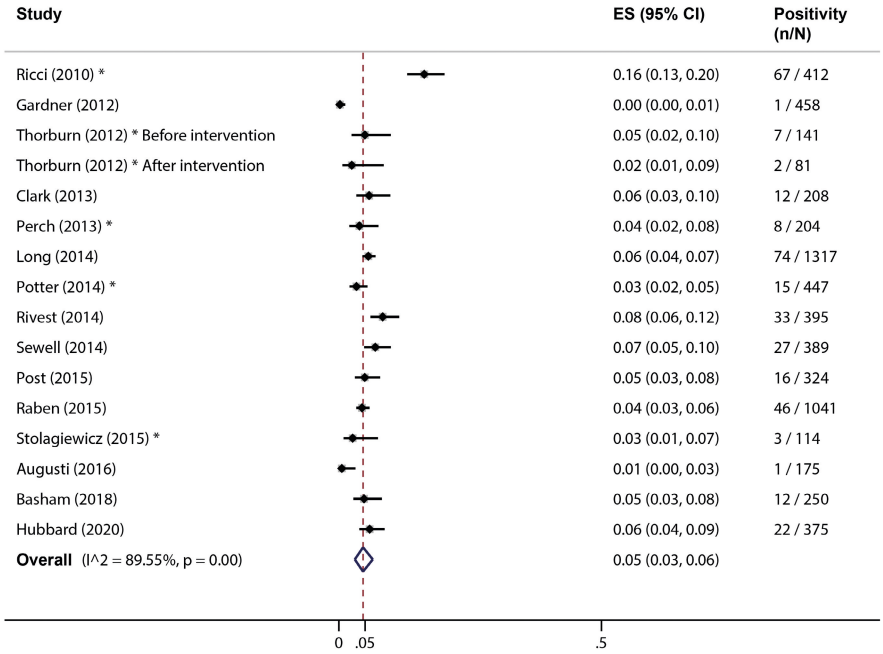
Outcome of risk of bias assessment per study was reported as a score on a 10-point scale (one point per item). As cut-off, a risk of bias score of 7/10 or higher was considered low risk, and a score of 6/10 or lower was deemed a high risk of bias by the researchers.

1. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015;**13(3)**:147-53.

Supplementary Appendix 6: Meta-analyses of HIV positivity by indicator condition

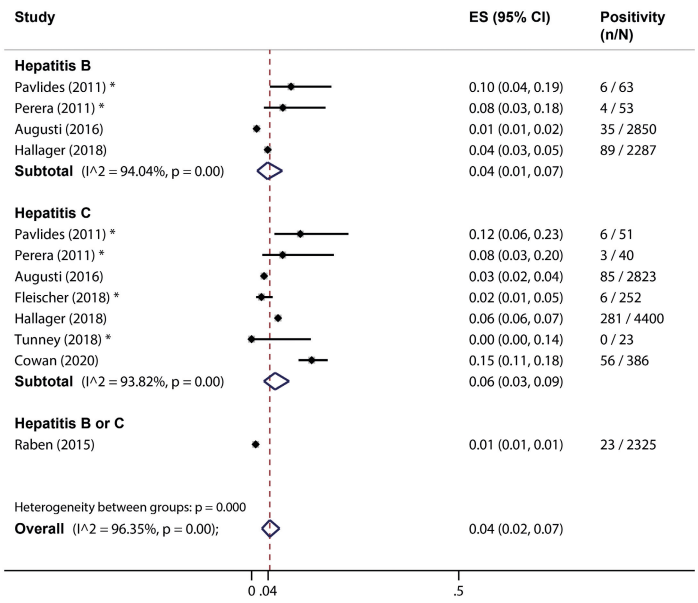
Supplementary Figure 1: Pooled results and estimated proportion tested HIV positive per indicator condition.

1A: Tuberculosis.



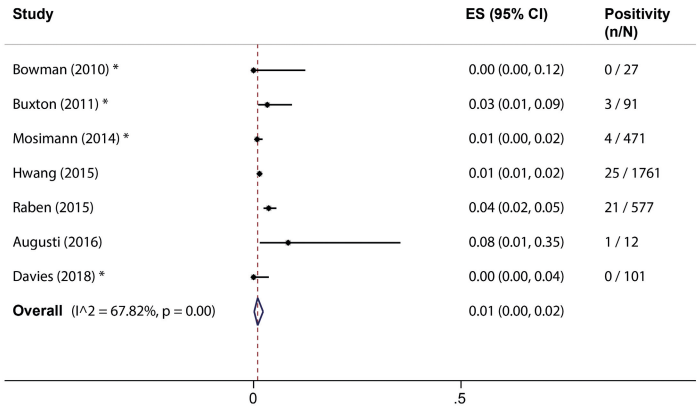
* Other publication types than full-text articles (i.e. abstracts, short communication, and correspondence). ES: estimated proportion. n=cases tested. N=cases identified.

1B: Hepatitis B and C.



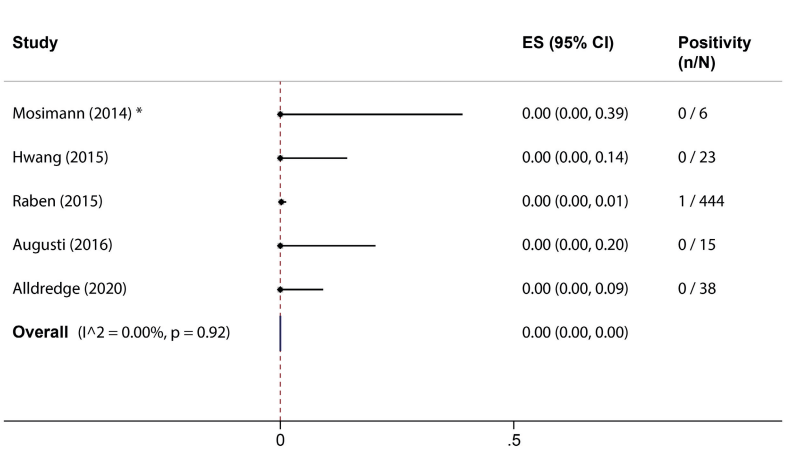
* Other publication types than full-text articles (i.e. abstracts, short communication, and correspondence). ES: estimated proportion. n=cases tested. N=cases identified.

1C: Malignant lymphoma.



* Other publication types than full-text articles (i.e. abstracts, short communication, and correspondence). ES: estimated proportion. n=cases tested. N=cases identified.

1D: Cervical carcinoma or cervical intraepithelial neoplasia grade 2+.



* Other publication types than full-text articles (i.e. abstracts, short communication, and correspondence). CIN: cervical intraepithelial neoplasia. ES: estimated proportion. n=cases tested. N=cases identified.

Supplementary Appendix 7: H-TEAM consortium members

H-TEAM Steering Committee: J.E.A.M. van Bergen[1;2;3], G.J. de Bree[4;5], P. Brokx[6], U. Davidovich[7;8], F. Deug[1], S.E. Geerlings[5], M. Heidenrijk[4], E. Hoornenborg[7], A. Oomen[1], M. Prins[5;7], P. Reiss[4;9], A. van Sighem[9], M. van der Valk[5], W. Zuilhof[1]

H-TEAM Project Management: N. Schat[4]

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Chapter 7

Promoting HIV indicator condition-guided testing in hospital settings (PROTEST 2.0): study protocol for a multicentre interventional study

Saskia J. Bogers, Maarten F. Schim van der Loeff, Udi Davidovich, Anders Boyd, Marc van der Valk, Kees Brinkman, Godelieve J. de Bree, Peter Reiss, Jan E.A.M. van Bergen and Suzanne E. Geerlings, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium

BMC Infectious Diseases. 2021 Jun 2;21(1):519

ABSTRACT

Background
Late presentation remains a key barrier towards controlling the HIV epidemic. Indicator conditions (ICs) are those that are AIDS-defining, associated with a prevalence of undiagnosed HIV >0.1%, or whose clinical management would be impeded if an HIV infection were undiagnosed. IC-guided HIV testing is an effective strategy in identifying undiagnosed HIV, but opportunities for earlier HIV diagnosis through IC-guided testing are being missed. We present a protocol for an interventional study to improve awareness of IC-guided testing and increase HIV testing in patients presenting with ICs in a hospital setting.

Methods
We designed a multicentre interventional study to be implemented at five hospitals in the region of Amsterdam, the Netherlands. Seven ICs were selected for which HIV test ratios (proportion of patients with an IC tested for HIV) will be measured: tuberculosis, cervical/vulvar cancer or high-grade cervical/vulvar dysplasia, malignant lymphoma, hepatitis B and C, and peripheral neuropathy. Prior to the intervention, a baseline assessment of HIV test ratios across ICs will be performed in eligible patients (IC diagnosed January 2015 through May 2020, ≥18 years, not known HIV positive) and an assessment of barriers and facilitators for HIV testing amongst relevant specialties will be conducted using qualitative (interviews) and quantitative methods (questionnaires). The intervention phase will consist of an educational intervention, including presentation of baseline results as competitive graphical audit and feedback combined with discussion on implementation and opportunities for improvement. The effect of the intervention will be assessed by comparing HIV test ratios of the pre-intervention and post-intervention periods. The primary endpoint is the HIV test ratio within ±3 months of IC diagnosis. Secondary endpoints are the HIV test ratio within ±6 months of diagnosis, ratio ever tested for HIV, HIV positivity percentage, proportion of late presenters and proportion with known HIV status prior to initiating treatment for their IC.

Discussion
This protocol presents a strategy aimed at increasing awareness of the benefits of IC-guided testing and increasing HIV testing in patients presenting with ICs in hospital settings to identify undiagnosed HIV in Amsterdam, the Netherlands.

Trial registration
Dutch trial registry: NL7521. Registered 14 February 2019.

BACKGROUND

In our efforts to complete the 'last mile' towards ending the HIV epidemic, timely diagnosis of HIV remains a key focal point. Globally, about 19% of the estimated 38.0 million people living with HIV (PLHIV) were unaware of their HIV status in 2019[1]. In Europe and Central Asia, one in five PLHIV remain undiagnosed and half of new diagnoses in the European Union are at a late stage of infection (CD4 count <350 cells/mm^3 or presenting with an AIDS-defining event)[2]. These figures are worrisome as late presentation is associated with higher morbidity and mortality, poorer response to combination antiretroviral therapy (cART) and onward transmission of HIV[3-6].

One of the strategies to improve timely HIV diagnosis is testing for HIV in all patients diagnosed with an indicator condition (IC). ICs are defined as conditions that are AIDS-defining, that are associated with a prevalence of undiagnosed HIV >0.1% (the threshold for cost-effectiveness in HIV testing[7,8]), or whose clinical management would be adversely affected if HIV infection were not identified. The HIV Indicator Diseases across Europe Study (HIDES) and the subsequent HIDES II study[9,10] identified various ICs associated with an HIV prevalence of over 0.1%. Currently, over 50 ICs for which HIV testing is recommended are recognized and numerous studies have shown that IC-guided HIV testing is an effective approach to identify undiagnosed PLHIV[11-15]. IC-guided testing also has the advantage that discussing patient risk factors for HIV, which still poses a barrier for some physicians[16,17], can be bypassed. As a result, HIV testing and care guidelines across Europe have now recommended IC-guided testing[18]. However, various studies have recently shown low adherence to these recommendations. Although they confirmed a prevalence of undiagnosed HIV >0.1% amongst patients diagnosed with ICs or, conversely, a high prevalence of ICs amongst newly diagnosed PLHIV, there were consistently low HIV testing ratios in patients presenting with ICs and thus missed opportunities for earlier HIV diagnosis[19-24]. Furthermore, in 2017, the majority of specialty guidelines for ICs did not recommend HIV testing, making awareness amongst medical specialties other than those actively involved in HIV care less likely[25].

In the Netherlands, an estimated 8% of PLHIV is unaware of their diagnosis and over half of all newly diagnosed cases involve late presentation[26]. In the hospital setting, 69% of new HIV diagnoses are late-stage[26]. Previous research has shown that there have been missed opportunities to identify undiagnosed PLHIV through IC-guided testing[14]. As an estimated 27% of PLHIV in the Netherlands live in Amsterdam and over one in five HIV diagnoses are made there, a city-based approach to curb the Dutch HIV epidemic is essential. This led to the establishment of the HIV Transmission Elimination Amsterdam (H-TEAM) consortium in 2014. It deploys a city-based combination intervention strategy focusing on all parts of the HIV prevention and care cascade[27]. The H-TEAM designed an interventional study to promote IC-guided HIV testing at hospitals in the region of Amsterdam. Here, we describe the details of a protocol for an interventional study to (1) generate awareness about ICs and the importance of IC-guided HIV testing amongst physicians working in hospitals,

and (2) improve the HIV test ratio in ICs amongst different medical specialties in the region of Amsterdam, the Netherlands.

METHODS

Setting and study design

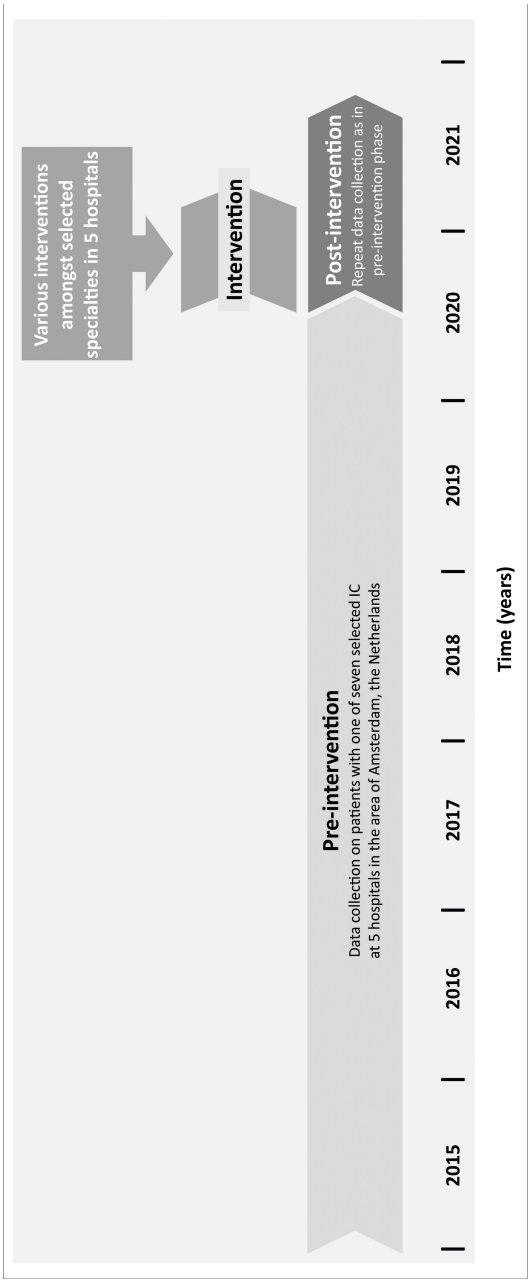
We designed a multicentre interventional study that will take place at 5 hospitals (two university hospitals, two non-academic teaching hospitals and one non-teaching hospital) in the region of Amsterdam, the Netherlands.

The development of the study consisted of three phases; an elicitation phase, a design phase, and an implementation phase. The elicitation and design phases have already been completed, while the implementation phase is currently taking place (as of June 2020). During the elicitation phase, a group of four experts, including an infectious diseases physician, a general practitioner, an epidemiologist, and a behavioural scientist, identified essential elements for an empirically based intervention. Additionally, two infectious diseases physicians from two participating hospitals were consulted on the perceived feasibility of the identified elements. During the design phase, the study protocol and evaluation plan were composed, with additional consultation from an expert on methodological approaches and statistical analysis. During the implementation phase, we will implement the educational intervention and assess its impact. The pre-intervention HIV test ratio (i.e. the proportion of patients presenting with an IC who are tested for HIV) will be compared to the post-intervention test ratio for seven selected ICs. To this end, pre-intervention test data over a period of 5.5 years (January 2015 through May 2020) will be retrospectively collected. As all participating hospitals have utilised their current electronic health record (EHR) software from 2015, allowing readily available data, the starting point of the pre-intervention period was selected at that year. The intervention period will last 6 months and its effect will be evaluated for a period of 1 year from the start of the intervention (June 2020 through May 2021, Figure 1).

Selection of indicator conditions

Seven ICs were selected for inclusion in this study: tuberculosis (TB), cervical cancer or high-grade cervical dysplasia, vulvar cancer or high-grade vulvar dysplasia, malignant lymphoma, hepatitis B (HBV), hepatitis C (HCV) and peripheral neuropathy (Table 1). These ICs were selected as they are managed by several different medical specialties (pulmonology, gynaecology, haematology, gastroenterology and neurology) and their evidence of being associated with HIV is variable. For example, the association of HIV and TB has been extensively documented, but less evidence on the association between HIV and peripheral neuropathy is available. We additionally selected these ICs based on their relatively high incidence, based on reports by the various specialty associations.

Figure 1: Intervention design to promote IC-guided testing for HIV



IC = indicator condition.

Table 1: Selected indicator conditions, associated specialties, and specific selection criteria for eligibility

Indicator condition	Main Specialty	Indicator condition-specific selection criteria
Tuberculosis	Pulmonology	Patients with latent *M. tuberculosis* infection, but no tuberculosis disease, are excluded
Cervical cancer or CIN 3+	Gynaecology	Patients without biopsy-confirmed high-grade dysplasia (CIN 3+) or carcinoma (invasive or non-invasive) are excluded
Vulvar cancer or VIN 3+	Gynaecology	Patients without biopsy-confirmed high-grade dysplasia (VIN 3+) or carcinoma (invasive or non-invasive) are excluded
Malignant lymphoma	Haematology	All types of malignant lymphoma, including all subtypes of Hodgkin's lymphoma and non-Hodgkin lymphoma are included
Hepatitis B	Gastroenterology	Both acute and chronic hepatitis B cases are included
Hepatitis C	Gastroenterology	Both acute and chronic hepatitis C cases are included
Peripheral neuropathy	Neurology	Patients with known diabetes mellitus before presenting and patients for whom no diagnostic laboratory workup was indicated are excluded

CIN: cervical intraepithelial neoplasia VIN: vulvar intraepithelial neoplasia

Patient selection and inclusion

The HIV testing ratio will be assessed using patient data from EHRs. Eligible patients will be identified using national disease billing codes. Patients of ≥18 years, diagnosed with one of the selected ICs will be eligible for inclusion (Figure 2). The following patients will be excluded: (1) patients with a known HIV infection prior to presenting with the selected IC and (2) patients that are diagnosed and treated for their IC at another hospital, and the relevant billing code was only recorded in the EHR for administrative purposes. Patients who are referred by another physician for a second opinion or transferred from another hospital will be included.

IC-specific selection criteria will additionally be applied (Table 1). In both the pre- and post-intervention period, all eligible patients from the first university hospital will be included. For the other four hospitals, data from all eligible patients will be included if there are ≤500 patients per IC; while data from a random sample of 500 patients will be assessed for eligibility and, if eligible, included if the number of patients per IC exceeds 500. This was done to keep workload manageable as the added precision of inclusions >500 is limited. Eligible patients will be given the opportunity to opt-out of the use of their EHR data.

Assessments

For all included patients, year of birth, sex, socio-economic status (SES; as derived from the postal code of residence) and whether deceased (including date of death) will be recorded. For women, any pregnancy at the time of IC diagnosis will be recorded. Additionally, the date of diagnosis and, if applicable, treatment of the specific IC will be recorded. To determine outcome measures, if, when and where an HIV test was performed will be recorded. To this end, all laboratory results, scanned documents, patient communication and referral letters in the EHR will be searched. All female patients with an EHR-recorded pregnancy after January 2004 will be assumed to have been tested for HIV during pregnancy, as all pregnant women in the Netherlands are tested for HIV on an opt-out basis, as part of the antenatal care programme, and the number opting out is negligible[28]. When no HIV test was performed during the diagnostic work-up for the IC, the EHR will be searched to assess whether a reason was given by the healthcare provider for not offering an HIV test or by the patient for declining the test. If the result of an HIV-test was positive, we will record the CD4 count at diagnosis. Electronic Case Report Forms (eCRFs) will be used for data collection using Castor (Castor Electronic Data Capture, Amsterdam, the Netherlands). As a quality control check, ten percent of eCRFs per IC and hospital will be randomly selected and verified by a second researcher. If the discrepancy in findings is >2.5%, all eCRFs for that IC and hospital will be verified by the second researcher.

Endpoints

The primary endpoint is the HIV test ratio (i.e. the proportion of patients with an IC who were tested for HIV) within ±3 months of IC diagnosis (3 months before to 3 months after diagnosis). Secondary endpoints are the HIV test ratio within ±6 months of IC diagnosis; proportion of patients presenting with an IC that were ever tested for HIV; HIV positivity ratio (i.e. number of positive HIV tests of the total number of HIV tests performed), both for the ±3 month and ±6 month window; proportion of new HIV diagnoses that are late-stage (defined as having a CD4 count <350 cells/mm^3 at diagnosis); and proportion of patients tested for HIV before initiating treatment for their IC.

Intervention strategy

A multifaceted intervention strategy will be used to improve HIV testing at different medical specialties who primarily diagnose and treat patients with the selected ICs (Table 2).

The interventions will be tailored to specialty-specific circumstances. Opportunities for intervention will be identified through qualitative and quantitative research, specifically by addressing barriers for IC-guided testing amongst professionals and their work settings[29,30]. First, an overview of IC-guided HIV testing recommendations will be made from the local and national specialty guidelines of the selected ICs. For relevant guidelines without such recommendations, the possibility to amend these guidelines will be explored. Second, all medical specialists and residents from each involved specialty at the participating hospitals will be invited to complete an online

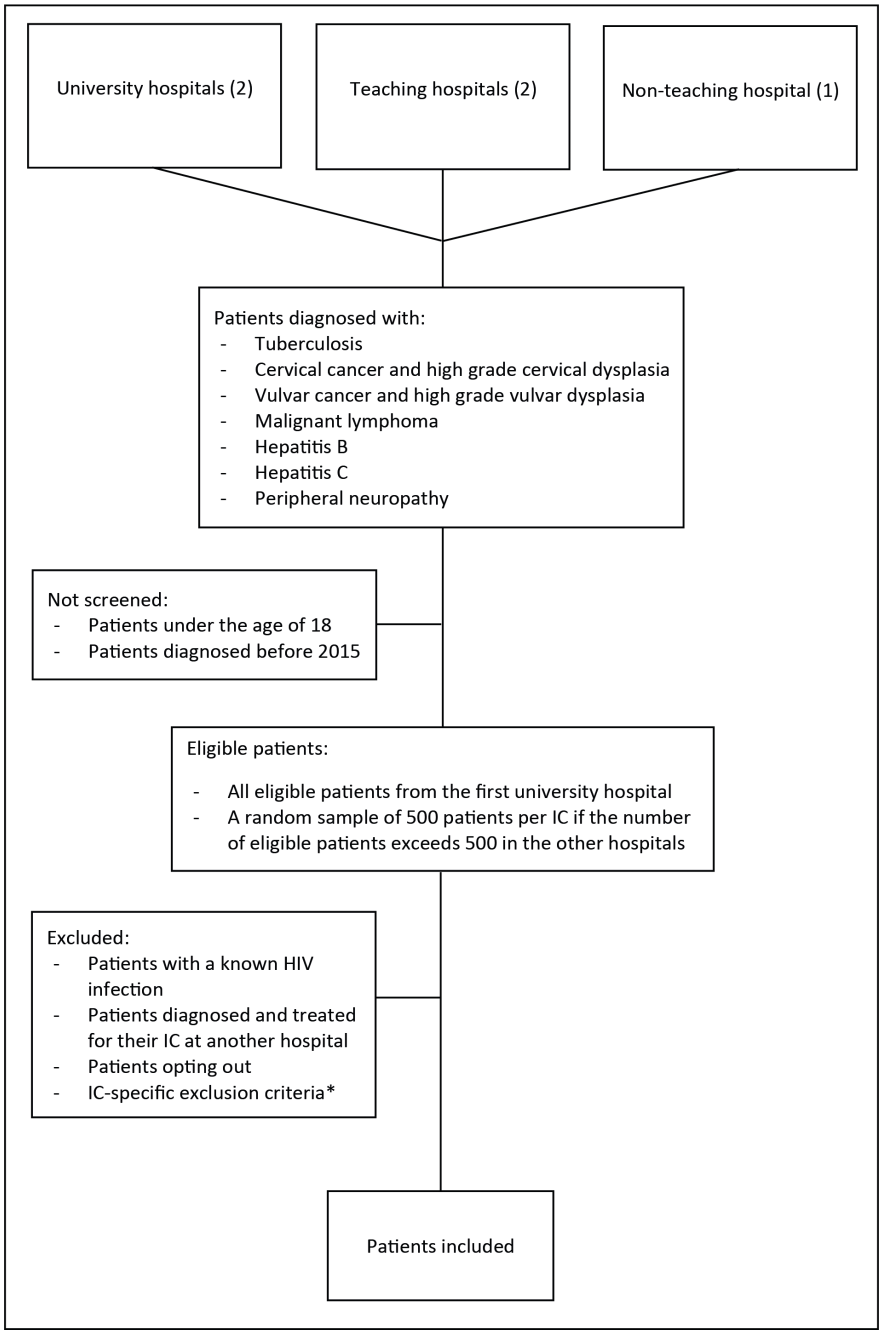
questionnaire on barriers and facilitators for HIV testing in patients with ICs related to their discipline. To this end, a questionnaire was developed based on the Attitude-Social norm-self Efficacy (ASE) model[31,32], which is an evidence-based instrument to assess behavior and its determinants in healthcare personnel (Supplementary appendix 1). The questionnaire will be distributed via email by contact persons representing each specialty at each hospital. The proportion responding will be calculated as the number of respondents divided by the number of recipients. Third, attitudes towards IC-guided HIV testing, and opportunities for improvement that fit the respondent's specialty and hospital, will be assessed through semi-structured interviews with medical specialists and residents. Individuals who respond to the online questionnaire and are willing to provide contact information will be recruited for these interviews. The contact persons of the various specialties will also be invited to participate in the interviews. The outcomes and opportunities for improvement from these interviews will be used for the educational intervention meetings (Supplementary appendix 2).

We will offer to host an educational meeting of about 30-45 minutes for each medical specialty at each participating hospital. During these educational meetings, the current state of the HIV epidemic in the Netherlands, evidence on the relation between HIV and the relevant ICs and evidence on IC-guided testing for HIV will first be presented. In addition to the ICs selected for this study, the entire list of currently recognised ICs will be presented with the aim of highlighting other ICs relevant to the specialty and bringing a more comprehensive awareness of IC-guided testing for HIV. Baseline HIV test ratios for all hospitals will be presented. This technique is known as competitive graphical audit and feedback, which was chosen because of its effectiveness in improving guideline adherence[33]. Finally, the results of the questionnaires and interviews, and identified barriers and opportunities for improvement, will be presented, followed by an interactive discussion on opportunities to improve HIV testing. When suggestions for improvement strategies are made by the participants during this discussion or other phases of the implementation period, we will offer assistance in implementation. At the end of the meeting, educational materials (pocket cards and posters) will be handed out to remind participants of the topics discussed. Participants will be informed that the effect of the intervention will be assessed through a post-intervention assessment of the HIV test ratio and that these results will be reported back to all participating hospitals.

Statistical analysis

The number of patients with ICs will be reported per IC, per hospital, and per period (in the pre- or post-intervention periods) as well as the number and percentage of patients with an IC who were tested for HIV within ±3 months of IC diagnosis. Additionally, the number and percentage of patients with an IC who were tested for HIV within ±6 months of IC diagnosis and the number and percentage of patients with an IC who were ever tested for HIV will be reported.

Figure 2: Flowchart of patient inclusion



* See Table 1 for an overview. IC = indicator condition.

Table 2: Planned study components to promote indicator condition-guided testing for HIV.

Pre-intervention
Assess recommendations for HIV testing in local and national IC specialty guidelines (literature review)
Intervention
Map barriers and facilitators to IC-guided HIV testing (online questionnaire)
Assess specialty specific opportunities to optimise HIV testing practices (semi-structured interviews)
Educational meeting for medical specialists and residents on IC-guided HIV testing (presentation)
Interactive discussion on opportunities to optimise HIV testing practices
Competitive feedback on IC-guided HIV testing performance (graphical audit and feedback)
Education material (pocket cards and posters)
Post-intervention
Reporting of post-intervention feedback on IC-guided HIV testing performance to participating specialties (graphical audit and feedback)

IC = indicator condition.

A time-series approach using segmented, Poisson regression will be used to evaluate the effect of the intervention. We will first model the HIV test ratio as a function of calendar time (in quarter-year periods), intervention period (pre- versus post-intervention), and the interaction between the two. If the interaction term in the model is significant (i.e. differences in slopes), the effect of the intervention will be determined by testing the parameter estimate of the interaction term. If the interaction term is non-significant (i.e. no difference in slopes), the interaction term of the model above will be removed and the effect of the intervention will be tested by the intervention term. Assuming no difference in slopes, average recruitment rate of 31 patients/IC per quarter, an increase in testing from 60% to 80% for four ICs (TB, HBV, HCV, malignant lymphoma) and from 12% to 30% for the three remaining ICs (cervical cancer/high-grade dysplasia, vulvar cancer/high-grade dysplasia, peripheral neuropathy) in the pre- versus post-intervention periods, respectively (unpublished data), there will be >95% power to determine a difference between intervention arms based on a simulation of 2000 runs. Potential confounding variables will also be added to the regression model. *P*-values will be obtained using a Wald X^2 test and a p-value of <0.05 will be considered statistically significant. Subgroup analyses will be performed for each IC and hospital separately, provided that there is ≥1 individual tested during each intervention period within that stratum. Analyses will be performed using Stata (v15.1, StataCorp, USA).

DISCUSSION

We describe the design of an interventional study that aims to generate awareness amongst hospital-based physicians of the importance of testing for HIV in patients

presenting with ICs and to increase the proportion of patients with an IC who are tested for HIV in various medical specialties.

The designed interventional study has several strengths. During the elicitation phase, we identified multiple intervention strategies based on qualitative and quantitative research that can be used simultaneously. This allows us to implement various innovations in healthcare that have been proven successful in other contexts[29,30]. Likewise, implementing graphical audit and feedback into the educational intervention for this study will hopefully bring about an effective strategy to increase awareness of IC-guided testing for physicians[33,34].

During the design phase, we selected a wide array of ICs, some of which have been thoroughly established as indicator conditions and already have included HIV testing as part of their specialty guidelines (e.g. TB, HCV), while for others, this has not been the case (e.g. high grade cervical dysplasia and peripheral neuropathy). Additionally, we considered that specialists from the infectious diseases department will have already been attune to HIV testing. Selecting ICs likely to be diagnosed at a broad range of other departments will ensure an intervention that has a much wider reach and thus has increased generalizability.

For the implementation phase, we will use a timeframe of 6 months around diagnosis of an IC (i.e. 3 months before and 3 months after) when calculating the primary endpoint. One previous study used a period of 3 months after IC diagnosis[35], which might inevitably exclude HIV tests performed during the workup leading to an IC diagnosis. Other studies have used 1 month or 6 months as part of their timeframe[13,36,37]. Since testing for HIV is not always the first priority after diagnosing an IC, one month may be too restrictive. Conversely, allowing up to 6 months between the diagnosis of an IC and an HIV test may be too long to prevent adverse outcomes related to undiagnosed HIV infection, especially when the patient is a late presenter of HIV infection. Nevertheless, we will use the latter cut-off as part of a secondary analysis.

One limitation that will undoubtedly arise when evaluating the effect of our intervention is the lack of control group, as no data from departments or hospitals that are unexposed to the interventions will be collected. However, the Poisson regression model used in this study will include a time component to establish any changes in HIV testing from the moment our interventions are applied. Second, because the study uses data from EHRs, certain patient characteristics, such as ethnicity and sexual risk behaviour, cannot be included, as they are not consistently reported by physicians. Consequently, no adjustment for these possible confounding variables can be made. However, as international guidelines recommend testing for HIV in all patients presenting with an IC, regardless of other patient risk factors, these are considered inessential for this study. Finally, as we will evaluate the effect of our educational intervention by comparing the HIV test ratio over a period of one year from the start of the intervention to a baseline assessment, we will be unable to assess whether any effect would be sustainable in the long term.

In conclusion, we have developed a protocol for an empirically based interventional study to create awareness of and improve IC-guided testing in a hospital setting. During the implementation phase, analysis comparing HIV testing before and after its implementation will determine whether this approach is effective in improving IC-guided testing for HIV at hospitals located in the Amsterdam region, with the aim of facilitating earlier identification of PLHIV who currently remain undiagnosed.

Ethics approval and consent to participate

The Medical Ethics Committee of the Amsterdam University Medical Centers, University of Amsterdam (Amsterdam UMC-AMC) determined that this study does not meet the definition of medical research involving human subjects as specified in Dutch law. Local feasibility was assessed and established by the Board of Directors in all study hospitals. All patients are given the opportunity to object to the consultation of their medical records and the use of their data for the purpose of this study through an opt-out procedure. All physicians participating in the questionnaires and interviews are asked for their content to participate in this study.

Competing interests

AB is a member of the editorial board of BMC infectious diseases. All other authors declare that they have no competing interests directly related to this study.

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Authors' contributions

SB, MSL, UD, MV, KB, JB and SG designed the study. SB designed the intervention materials. SG arranged funding. SB, MSL, AB and SG outlined the statistical analysis. SB, MSL and SG drafted the manuscript. All authors contributed to, read and approved this final manuscript.

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REFERENCES

1. UNAIDS. Global HIV & AIDS statistics — 2020 fact sheet. 2020. https://www.unaids.org/en/resources/fact-sheet. Accessed 1 Sept 2020.
2. Brown AE, Hayes R, Noori T, et al. HIV in Europe and Central Asia: progress in 2018 towards meeting the UNAIDS 90-90-90 targets. *Euro Surveill* 2018;**23(48)**.
3. Krentz HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4 <200 cells/microL) with HIV infection. *HIV Med* 2004;**5(2)**:93-8.
4. Sabin CA, Smith CJ, Gumley H, et al. Late presenters in the era of highly active antiretroviral therapy: uptake of and responses to antiretroviral therapy. *AIDS* 2004;**18(16)**:2145-51.
5. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;**365(6)**:493-505.
6. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). *PLoS Med* 2013;**10(9)**:e1001510.
7. Bert F, Gualano MR, Biancone P, et al. Cost-effectiveness of HIV screening in high-income countries: A systematic review. *Health Policy* 2018;**122(5)**:533-47.
8. Yazdanpanah Y, Sloan CE, Charlois-Ou C, et al. Routine HIV screening in France: clinical impact and cost-effectiveness. *PLoS One* 2010;**5(10)**:e13132.
9. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.
10. Raben D, Mocroft A, Rayment M, et al. Auditing HIV Testing Rates across Europe: Results from the HIDES 2 Study. *PLoS One* 2015;**10(11)**:e0140845.
11. Menacho I, Sequeira E, Muns M, et al. Comparison of two HIV testing strategies in primary care centres: indicator-condition-guided testing vs. testing of those with non-indicator conditions. *HIV Med* 2013;**14 Suppl 3**:33-7.
12. Omland LH, Legarth R, Ahlstrom MG, Sorensen HT, Obel N. Five-year risk of HIV diagnosis subsequent to 147 hospital-based indicator diseases: a Danish nationwide population-based cohort study. *Clin Epidemiol* 2016;**8**:333-40.
13. Scognamiglio P, Chiaradia G, De Carli G, et al. The potential impact of routine testing of individuals with HIV indicator diseases in order to prevent late HIV diagnosis. *BMC Infect Dis* 2013;**13**:473.
14. Joore IK, Arts DL, Kruijer MJ, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. *Sex Transm Infect* 2015;**91(7)**:467-72.
15. Damery S, Nichols L, Holder R, et al. Assessing the predictive value of HIV indicator conditions in general practice: a case-control study using the THIN database. *Br J Gen Pract* 2013;**63(611)**:e370-7.
16. Bagchi AD, Davis T. Clinician Barriers and Facilitators to Routine HIV Testing: A Systematic Review of the Literature. *J Int Assoc Provid AIDS Care* 2020;**19**:2325958220936014.
17. Deblonde J, De Koker P, Hamers FF, Fontaine J, Luchters S, Temmerman M. Barriers to HIV testing in Europe: a systematic review. *Eur J Public Health* 2010;**20(4)**:422-32.
18. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. http://www.eurotest.org/Finalised-Projects/Guidance-HIV-Indicator-Conditions. Accessed 12 Oct 2020.

19. Lin YD, Garner SE, Lau JSY, Korman TM, Woolley IJ. Prevalence of HIV indicator conditions in late presenting patients with HIV: a missed opportunity for diagnosis? *QJM* 2019;**112(1)**:17-21.

20. Levy I, Maor Y, Mahroum N, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. *BMJ Open* 2016;**6(11)**:e012721.

21. Agusti C, Montoliu A, Mascort J, et al. Missed opportunities for HIV testing of patients diagnosed with an indicator condition in primary care in Catalonia, Spain. *Sex Transm Infect* 2016;**92(5)**:387-92.

22. Bull L, Rayment M. HIV-indicator-condition-driven HIV testing: clinically effective but still rarely implemented. *Clin Med (Lond)* 2016;**16(2)**:175-9.

23. Ruutel K, Lemsalu L, Latt S, Opt TbH. Monitoring HIV-indicator condition guided HIV testing in Estonia. *HIV Med* 2018;**19 Suppl 1**:47-51.

24. Youssef E, Sanghera T, Bexley A, Hayes M, Perry N, Dosekun O. HIV testing in patients presenting with indicator conditions in outpatient settings: offer and uptake rates, and educational and active interventions. *Int J STD AIDS* 2018;**29(13)**:1289-94.

25. Lord E, Stockdale AJ, Malek R, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. *HIV Med* 2017;**18(4)**:300-4.

26. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, Reiss P. Monitoring Report 2019. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2018. https://www.hiv-monitoring.nl/nl/resources/monitoring-report-2019. Accessed 12 Oct 2020.

27. de Bree GJ, van Sighem A, Zuilhof W, et al. Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam. *Curr Opin HIV AIDS* 2019;**14(6)**:455-63.

28. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Prenatale Screening, Infectieziekten en Erytrocytenimmunisatie (PSIE) procesmonitor 2017 (Dutch). 2019. https://www.pns.nl/documenten/proces-monitor-psie. Accessed 12-10-2020.

29. Fleuren MA, Paulussen TG, Van Dommelen P, Van Buuren S. Towards a measurement instrument for determinants of innovations. *Int J Qual Health Care* 2014;**26(5)**:501-10.

30. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013;**8**:35.

31. de Vries H, Dijkstra M, Kuhlman P. Self-efficacy: the third factor besides attitude and subjective norm as a predictor of behavioural intentions. *Health Education Research* 1988;**3(3)**:273-82.

32. Schellart AJM, Steenbeek R, Mulders HPG, Anema JR, Kroneman H, Besseling JJM. Can self-reported disability assessment behaviour of insurance physicians be explained? Applying the ASE model. *BMC Public Health* 2011;**11(1)**:576.

33. Spoorenberg V, Hulscher ME, Geskus RB, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. *PLoS One* 2015;**10(12)**:e0142672.

34. Ivers NM, Grimshaw JM, Jamtvedt G, et al. Growing literature, stagnant science? Systematic review, meta-regression and cumulative analysis of audit and feedback interventions in health care. *J Gen Intern Med* 2014;**29(11)**:1534-41.

35. Twisk DE, Joore IK, van Bergen J. Improving early HIV diagnosis, treatment and care in Europe with healthcare provider specific HIV indicator condition list and audits. *Sex Transm Infect* 2017;**93(8)**:582.

36. Wohlgemut J, Lawes T, Laing RB. Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study. *BMC Infect Dis* 2012;**12**:72.

37. Gullon A, Verdejo J, de Miguel R, Gomez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. *AIDS Care* 2016;**28(10)**:1296-300.

Supplementary appendix 1: Online questionnaire

Development and distribution

All medical specialists and residents from each involved specialty at the participating hospitals are invited to complete an online questionnaire on barriers and facilitators for HIV testing of patients with indicator conditions (ICs) in their discipline. To this end, a questionnaire was developed based on the Attitude - Social norm - self Efficacy (ASE) model[1,2]. The questionnaire will be distributed via email by contact persons at each specialty at each hospital. For each specialty, the relevant selected IC was displayed in the questionnaire (e.g. a pulmonologist would only see questions referring to tuberculosis patients, while a neurologist would only see questions referring to peripheral neuropathy).

Content

The questionnaire consists of the following chapters:

1. Respondent's characteristics
2. Attitudes, barriers and facilitators for HIV testing based on the ASE model*
3. Invitation to a subsequent interview

Overview of questions in the questionnaire:

Chapter 1 - Respondent's characteristics

1. Respondent's sex
2. Respondent's age
3. Respondent's affiliated specialty/department
4. Respondent's position (e.g. medical specialist, resident)
5. Respondent's number of years work experience in the current specialty/department
6. Respondent's current affiliated type of hospital (e.g. university hospital, teaching hospital)
7. Respondent's estimate of HIV prevalence in their affiliated specialty/department – As expressed on a 5-point Likert scale (HIV patients are definitely not seen often – HIV patients are definitely seen often)

*Chapter 2 - Attitudes, barriers and facilitators for HIV testing**

1. In the past year, I offered patients with [IC] an HIV test [Never – Very often]
2. When I see a patient with [IC], I plan to offer them an HIV test [Completely disagree – Completely agree]
3. In the future, I expect the likelihood that I will offer a patient with [IC] an HIV test [Very unlikely – Very likely]
4. I find offering a patient with [IC] an HIV test [Very unimportant – Very important]
5. I find offering a patient with [IC] an HIV test [Very negative – Very positive]
6. I find offering a patient with [IC] an HIV test [Very uncomfortable – Very comfortable]

7. I find I am [Very incapable – Very capable] of offering a patient with [IC] an HIV test
8. I find offering a patient with [IC] an HIV test [Very difficult – Very easy]
9. My colleagues find offering a patient with [IC] an HIV test [Very unimportant – Very important]
10. Patients with [IC] [Definitely do not – Definitely do] expect me to offer them an HIV test
11. Within my specialty, HIV testing in patients with [IC] is discussed [Never – Very often]
12. HIV testing in patients with [IC] is recommended in our guidelines [Definitely not – Definitely]
13. Ordering an HIV test for a patient with [IC] is [Very hard to organize – Very easy to organize]
14. Offering a patient with [IC] an HIV test ensures better health outcomes [Definitely not – Definitely]

Chapter 3 - Invitation to a subsequent interview

1. Are you willing to participate in an interview on this topic? If so, please leave your name and contact information below.

* Questions in chapter 2 are to be answered on a 5-point Likert scale (e.g. completely disagree to completely agree, very unlikely to very likely)

1. de Vries H, Dijkstra M, Kuhlman P. Self-efficacy: the third factor besides attitude and subjective norm as a predictor of behavioural intentions. Health Education Research. 1988;3(3):273-82.

2. Schellart AJM, Steenbeek R, Mulders HPG, Anema JR, Kroneman H, Besseling JJM. Can self-reported disability assessment behaviour of insurance physicians be explained? Applying the ASE model. BMC Public Health. 2011;11(1):576.

Supplementary appendix 2: Semi-structured interview guide

Recruitment and enrollment

Contact persons from the various specialties at the participating hospitals and respondents of the online questionnaire are invited to participate in a semi-structured interview, which will take place in-person or by telephone/ videoconferencing. The interviews will be recorded with the permission of the participant.

Goal

The goal of these interviews is to gain better insight into attitudes, barriers and facilitators for indicator condition (IC)-guided HIV testing in specific specialties and hospitals, in addition to the outcomes from the questionnaire, as we hypothesize that different attitudes and barriers influence HIV testing in different ICs and different opportunities for improvement can be identified. The results of the interviews are used in the educational intervention; identified attitudes, barriers and facilitators are used as guidance during interactive discussion, with the aim of identifying tailored opportunities for improvement.

Semi-structured interview guide

1. Introduction: The interviewing researcher explains the goal of the interview, and the characteristics of the participant (work experience, specialty and hospital of employment)
2. To what extent is HIV testing in patients with this IC a point of attention in your specialty? E.g. is it discussed/checked at multidisciplinary meetings or patient rounds? Is there a standard checklist in use for HIV testing in these patients? Is HIV testing among these patients a quality indicator in your specialty?
3. Is HIV testing in these patients recommended in your local and national specialty guidelines? Why (not)? Do you think your colleagues are aware of this?
4. The proportion of patients with this IC that were tested for HIV within 3 months around IC diagnosis is … [the proportion based on the baseline assessment in this study are presented]. What is your opinion on this proportion? Why do you think it is not 100%?
5. Do you think this proportion needs to be improved?
6. Which opportunities for improvement do you see for your specialty? What would work and what would not work?

Chapter 8

Opportunities for improved indicator-based HIV testing in the hospital setting: A structural equation model analysis

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ABSTRACT

Indicator condition (IC)-guided testing for HIV is a feasible and cost-effective strategy. Assessing determinants for IC-guided testing may identify opportunities for improvement. A survey study was conducted among 163 hospital physicians from five specialties in Amsterdam, the Netherlands. The survey was Theory of Planned Behaviour (TPB) based and measured intention, behaviour and related determinants regarding IC-guided testing. Structural equation models were used to determine the association between TPB domains (i.e., attitude, belief, norms, self-efficacy and behavioural control) and (1) the intention to test as a mediator for testing behaviour (i.e., intentional model) and (2) actual testing behaviour (i.e., direct model). Both models accounted for the effect of guideline recommendations. Behaviour scored lower than intention on a five-point scale (mean score of 2.8, SD=1.6 versus 3.8, SD=1.1; $p<0.0001$). The direct model had a better fit than the intentional model based on fit statistics. Discrepancies between the determinants most important for intention versus those for behaviour led to the following recommendations: interventions to improve IC-guided testing in hospitals should primarily focus on implementation of guideline recommendations, followed by improving physicians' attitude towards IC-guided HIV testing and self-efficacy, as these were the most important correlates of actual HIV testing behaviour.

INTRODUCTION

The number of reported HIV diagnoses in the European Union (EU) has been steadily declining over the past decade, with the strongest decline among men who have sex with men (MSM) and people who inject(ed) drugs[1]. Additionally, the rate of reported cases of acquired immunodeficiency syndrome (AIDS) has more than halved in the past decade, declining from 1.3 to 0.5 cases per 100,000 individuals. Biomedical innovations, such as pre-exposure prophylaxis (PrEP) to prevent HIV transmission, alongside the treatment as prevention (TasP) strategy and promotion of the undetectable equals untransmittable (U=U) message, have greatly accelerated efforts to end the HIV epidemic[2-5].

However, an estimated 22% of people living with HIV (PLHIV) in the EU are not aware of their status and over half of individuals newly diagnosed are at a late stage of HIV infection (i.e., CD4 cell count below 350 cells/mm^3), including nearly a third with advanced HIV (i.e., CD4 cell count below 200 cells/mm^3)[1]. These data indicate that access to, and uptake of HIV testing, needs to be improved, as early diagnosis and treatment has individual health benefits and reduces onward transmission[5-7]. A feasible and cost-effective strategy for routine HIV testing is testing in patients diagnosed with health conditions associated with HIV. This strategy is known as indicator condition (IC)-guided testing[8]. While routine IC-guided testing has the advantage of bypassing several barriers to HIV testing,[9] its implementation varies widely across high-income countries and is oftentimes poor[10]. Reasons for lacking implementation may include the absence of IC-guided testing recommendations in local clinical guidelines, insufficient awareness of these recommendations, or no routine to offer testing[10-12].

In the Netherlands, about 53% of individuals are diagnosed with late-stage HIV infection, while this percentage is 81% among individuals diagnosed at a hospital[13]. Missed opportunities for earlier HIV diagnosis through IC-guided testing have been reported in the primary care setting[14], but adoption of IC-guided testing in the hospital setting, as well as its determinants, have been studied less. We performed a survey among physicians actively working at hospitals in the region of Amsterdam, the Netherlands, to examine pathways predicting IC-guided testing for HIV. This information could then be used to identify opportunities for improved IC-guided HIV testing in the hospital setting.

METHODS

Design and setting

This study was a cross-sectional survey with the aim of assessing determinants for IC-guided HIV testing in selected ICs among healthcare providers in the hospital setting. This study was conducted as part of a larger intervention study (PROTEST 2.0), which was designed to assess the implementation and improvement of IC-guided testing[15]. Five hospitals in the region of Amsterdam, the Netherlands participated, including two university hospitals, two teaching hospitals, and one non-teaching hospital. Within these hospitals, we selected five medical specialities, responsible for managing care for individuals presenting with the seven ICs studied (Table 1).

Table 1: Selected indicator conditions and associated medical specialties, PROTEST 2.0 study, Amsterdam region, 2020.

Indicator condition	Primary managing specialty
Tuberculosis	Pulmonology
Hepatitis B virus infection	Gastroenterology
Hepatitis C virus infection	Gastroenterology
Malignant lymphoma	Haematology
Cervical cancer or CIN III+	Gynaecology
Vulvar cancer or VIN III+	Gynaecology
Peripheral neuropathy	Neurology

CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia.

Recruitment of participants

From the selected specialty departments, all medical specialists and residents were invited to anonymously participate in an online survey by email in June 2020. Reminders were sent out 2-4 weeks after the first invitation. Specialist and residents from each specialty received a link to the survey with questions that were similar across specialties, yet tailored to the ICs relevant for their specialty as listed in Table 1. Individuals were required to provide consent before study participation. Data from these surveys were collected using Limesurvey (LimeSurvey GmbH, Hamburg, Germany).

Survey design, theoretical framework & assessment tools

The survey items were developed based on the Theory of Planned Behaviour (TPB) model[16,17]. This is a theoretical model evaluating the influence of factors for behavioural intention in three determinant domains: personal attitude and beliefs, social/professional/interpersonal influence or norms, and self-efficacy (i.e., personal effectiveness or capability). In turn, intention is the direct predictor of behaviour. In the context of our study, the components of the TPB model used can be interpreted as follows: *behaviour* is the self-reported IC-guided testing behaviour, and *intention* is the self-reported intention to apply IC-guided testing in the future. Through intention, behaviour is determined by the respondent's *attitude* and *belief*

regarding the need for IC-guided testing, the *professional norms* of the respondent's environment, including colleagues and patients, and the respondent's *self-efficacy*, or their confidence in their ability to successfully apply IC-guided testing. The survey contained twelve 5-point Likert-scale statement questions on attitudes, beliefs, professional norms and self-efficacy towards IC-guided testing, as well as three 5-point Likert-scale statement questions assessing behaviour and intention to test (1= lowest score; 5=highest score, Supplemental Table 1). Based on the theoretical model, the twelve questions were categorized into the four determinant domains (i.e., attitudes, beliefs, professional norms and self-efficacy). Cronbach's alpha (α) was used to confirm internal consistency between items within domains, while items were combined when α was greater than 0.7[18-20].

The *attitude* domain included items on the perceived importance and positivity of testing for HIV in patients diagnosed with the indicator condition of interest. This domain is influenced by individual's *beliefs*. The *beliefs* domain included items on respondents' perceptions regarding the prevalence of HIV in patients diagnosed with the indicator condition of interest, and whether testing for HIV in these patients would improve health outcomes.

The *professional norms* domain included items on the respondent's perceptions regarding how important colleagues and patients find IC-guided HIV testing and whether it is discussed between colleagues within the specialty. We additionally assessed whether HIV testing was recommended in the *guidelines* of the IC of interest according to the respondent. This item was considered as a determinant of professional norms as well as a direct predictor of intention to test or testing behaviour. It was therefore added as a separate co-determinant.

The *self-efficacy* domain included items on whether respondents were comfortable offering HIV testing to patients diagnosed with the indicator condition of interest, whether they considered themselves capable to do so, and whether it was easy for them to do so. We also asked whether respondents found that HIV testing was *easily arranged in their hospital*. As the response to this last item was likely a reflection of an external factor, rather than internal self-efficacy, we analysed this item as a separate co-determinant of the self-efficacy domain.

Statistical analysis

All surveys with at least one answer given were included. Data on participant characteristics and outcomes were analysed descriptively.

We utilized structural equation models (SEMs), which allowed us to explore the pathways that contributed most to behaviour. We developed an initial SEM based on the classic TPB model, in which the various determinants influence behavioural intention, while intention is the most proximal predictor of actual behaviour (i.e., intentional model)[16]. To this end, we calculated the averaged domain variables "attitude", "beliefs" and "self-efficacy" using the items representing these domains. For the "professional norms" domain, we combined item responses into one latent

variable as the items used did not measure perceived self-norms directly, but were rather a proxy of norms. Whether testing was easily arranged was added as a co-determinant between self-efficacy and reported behaviour to account for the item's effect on both. Whether testing was recommended in guidelines was added as a co-determinant between professional norms and reported behaviour to account for this item's effect on both. Parameter estimates (β) were standardized and estimated with their 95% confidence intervals (CI). We tested whether the estimates were greater than null using a Wald χ^2 test.

An important constraint to the intentional model was that, in our cross-sectional survey, behaviour was measured retrospectively, while intention was measured in relation to the upcoming future. Only the latter of these two outcomes reflects the principles of the TPB. As a result, the relation between intention and behaviour might be biased. We therefore additionally created a SEM model in which the domains from the TPB model directly contributed to self-reported HIV testing behaviour, while excluding intention from the model (i.e., direct model).

The likelihood ratio (LR) test was used to compare goodness of fit of both models compared to models with perfectly fitting covariances. Additionally, we compared the Bayesian information criteria (BIC), root mean squared error of approximation (RMSEA), standardized root mean squared residual (SRMR) and coefficient of determination (CD) between models to determine which model had the best fit.

A $p<0.05$ was considered statistically significant. All analyses were performed using Stata v15.1 (College Station, Texas, USA).

Ethics approval and consent to participate

The Medical Ethics Committee of the Amsterdam University Medical Centres, University of Amsterdam (Amsterdam UMC-AMC) determined that this study does not meet the definition of medical research involving human subjects under Dutch law. All participants consented to study participation through written consent.

RESULTS

Participation

Overall, requests to participate were sent to 378 individuals, of whom 163 responded to the questionnaire (response rate 43%; overall range by specialty: 23%-58%). The characteristics of respondents are reported in Table 2. There was no response from any neurologist at university hospitals nor from any gastroenterologist at non-teaching hospitals. Of the surveys from the 163 individuals who responded, 149 were fully completed (i.e., no missing items).

Reported behaviour, intention and domain outcomes

Overall, the mean score for frequency of testing behaviour was 2.8 (SD=1.6) and was distributed as follows: forty-five of 149 (30%) respondents reported never testing for HIV in patients diagnosed with an indicator condition of interest, 47/149 (32%) reported rarely or sometimes testing for HIV, and 57/149 (38%) reported testing for HIV often or very often (Table 3). For intention, the mean score was higher than the score for behaviour (mean score=3.8, SD=1.1, p<0.0001). Fifteen of 149 (10%) reported low or very low intention to test for HIV in patients diagnosed with the indicator condition of interest, 34/149 (23%) reported to be neutral in their intention, and 100/149 (67%) reported having high or very high intention to test for HIV (Table 3). Intention to test was significantly correlated with reported behaviour (Kendall's tau-b=0.63, p<0.0001). Mean scores and distributions of the measured determinants are reported in Table 3.

Associations between reported behaviour, intention and domains

Modelled pathways in the final SEM models are displayed in Figure 1. We compared the associations between each domain and intention to test for HIV (intentional model; panel A) or reported behaviour (direct model; panel B). The direct model had a better fit than the intentional model (Supplemental Table 2).

In the intentional model (Figure 1A, Supplemental Table 3), intention to test for HIV was associated with the *professional norms* domain (β=0.59, 95%CI=0.46,0.71, p<0.001), and the *attitude* domain (β=0.52, 95%CI=0.40,0.65, p<0.001). Intention was not associated with *self-efficacy* (β=-0.02, 95%CI=-0.12,0.08, p=0.67). Reported HIV testing behaviour was associated with intention to test (β=0.44, 95%CI=-0.28,0.60, p<0.001) and with whether HIV testing was recommended in the *guidelines* (β=0.39, 95%CI=-0.22,0.55, p<0.001), and, to a lesser extent, with whether it was *easily arranged* (β=0.16, 95%CI=0.05,0.27, p=0.003) in this model.

In the direct model (Figure 1B, Supplemental Table 3), reported HIV testing was associated with whether testing was recommended in the IC's *guidelines* (β=0.46, 95%CI=0.26,0.67; p<0.001), with the *attitude* domain (β=0.28, 95%CI=0.12,0.43, p=0.001) and with *self-efficacy* (β=0.17, 95%CI=0.03,0.30, p=0.02). HIV testing was not significantly associated with *professional norms* (β=0.16, 95%CI=-0.09,0.42, p=0.21) and only marginally by whether HIV testing was *easily arranged* (β=0.11, 95%CI=0.00,0.22, p=0.06) in this model.

Table 2: Characteristics of 163 respondents to an online survey on indicator condition-guided HIV in the hospital setting in the region of Amsterdam, the Netherlands, 2020

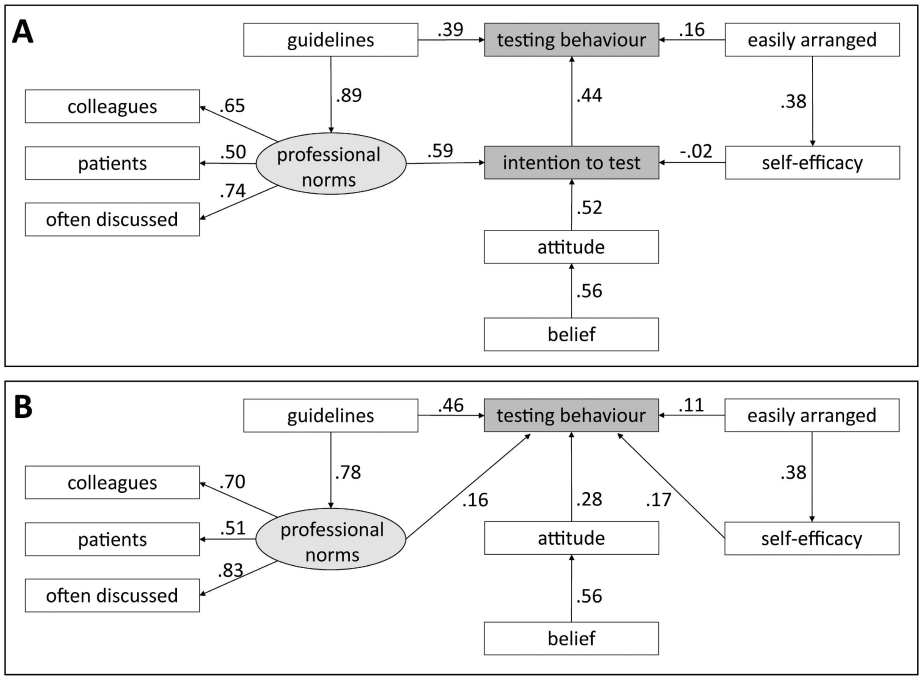
	Pulmonology	Gastroenterology	Haematology	Gynaecology	Neurology	Overall
	n = 23	n = 20	n = 43	n = 45	n = 32	n = 163
Age in years (median, IQR)	42 (36-58)	45 (36-55)	36 (31-43)	40 (34-48)	38 (31-45)	40 (33-48)
Sex (n,%)						
Male	12 (52%)	7 (35%)	16 (37%)	5 (11%)	15 (47%)	55 (34%)
Female	11 (48%)	13 (65%)	27 (63%)	40 (89%)	17 (53%)	108 (66%)
Job type (n, %)						
Resident	15 (65%)	12 (60%)	26 (61%)	28 (62%)	20 (63%)	101 (62%)
Specialist	8 (35%)	5 (25%)	17 (40%)	16 (36%)	12 (38%)	58 (36%)
Other	0 (0%)	3 (15%)	0 (0%)	1 (2%)	0 (0%)	4 (2%)
Work experience in years (median, IQR)	7 (4-20)	14 (4-18)	3 (1-10)	10 (7-16)	7 (3-11)	8 (3-15)
Type of hospital (n,%)						
University hospital	13 (57%)	7 (35%)	21 (49%)	1 (2%)	0 (0%)	42 (26%)
Teaching hospital	7 (31%)	13 (65%)	6 (14%)	39 (87%)	27 (84%)	92 (56%)
Non-teaching hospital	3 (13%)	0 (0%)	16 (37%)	5 (11%)	5 (16%)	29 (18%)

Table 3: Mean scores and distributions of reported HIV testing behaviour, intention to test for HIV, and their determinants of 163 respondents to an online survey on indicator condition-guided HIV in the hospital setting in the region of Amsterdam, the Netherlands, 2020

	Responses (n)	Mean score (SD)*	Likert score 1 n (%)*	Likert score 2 n (%)*	Likert score 3 n (%)*	Likert score 4 n (%)*	Likert score 5 n (%)*	Don't know n (%)*
Outcomes								
Testing behaviour	149	2.8 (1.6)	45 (30%)	29 (20%)	18 (12%)	20 (13%)	37 (25%)	0 (0%)
Intention to test	149	3.8 (1.1)	4 (3%)	11 (7%)	34 (23%)	42 (28%)	58 (39%)	0 (0%)
Determinants								
Attitude	149	3.8 (0.8)	0 (0%)	3 (2%)	40 (27%)	71 (48%)	35 (23%)	0 (0%)
Beliefs	163	3.5 (1.0)	3 (2%)	18 (11%)	43 (26%)	61 (37%)	38 (23%)	0 (0%)
Professional norms	149	2.9 (0.8)	1 (1%)	60 (40%)	56 (38%)	28 (19%)	4 (3%)	0 (0%)
Guidelines	149	3.7 (1.3)	7 (5%)	27 (18%)	15 (10%)	25 (17%)	57 (38%)	18 (12%)
Self-efficacy	149	3.7 (0.6)	0 (0%)	3 (2%)	54 (36%)	82 (55%)	10 (7%)	0 (0%)
Easily arranged	149	4.4 (0.6)	0 (0%)	1 (1%)	7 (5%)	74 (50%)	67 (45%)	0 (0%)

*Items were assessed using 5-point Likert-scales, where 1 represented the lowest score (e.g. strongly disagree, never, definitely not) and 5 represented the highest score (e.g. strongly agree, always, definitely yes).

Figure 1: Structural equations models on associations between determinants for behaviour and self-reported HIV testing behaviour in patients diagnosed with indicator conditions among 163 physicians in the hospital setting in the region of Amsterdam, the Netherlands, 2020



Panel A: Depiction of structural equations for the intentional model. Panel B: Depiction of structural equations for the direct model. The numbers next to the pathways are the parameter estimates (β), representing the change in modelled outcomes per standardized unit increase of the determinant. Dark grey items represent the outcomes of interest, light grey items represent latent variables.

DISCUSSION

In this study, we examined associations that could be linked to IC-guided HIV testing among 163 physicians in the region of Amsterdam. We found that in the intentional model, reported HIV testing was strongly associated with intention to test, as suggested in the classic TPB model. In turn, the domains predicting intention to test were professional norms and physician's attitudes, while self-efficacy played no role. However, when looking at the effect of the domains on reported testing behaviour in the direct model, guideline recommendations, physician's attitudes and self-efficacy were determinants for IC-guided HIV testing behaviour, while professional norms and whether testing is easily arranged played a marginal role in the direct model. It should be noted that this model had a better statistical fit than the model representing IC-guided HIV testing behaviour consequent to testing intention.

Generally, the TPB model assumes that the most proximal predictor of behaviour is behavioural intention[16], and there was indeed a strong and significant association between intent to HIV testing and HIV testing behaviour. However, the observed association between intention and behaviour was smaller than expected. This may be explained by the fact that behaviour was measured retrospectively, instead of through a prospective assessment. We therefore explored whether a direct model would better predict testing behaviour in our data. Indeed, the direct model had a better fit than the intentional model.

We were surprised to find that professional norms and attitude had a weakened association with behaviour in the direct model, while we expected them to retain, if not increase, their effect size, as intention is often known to serve as a mediator between these determinants and behaviour[21-23]. The weaker effect of norms and attitudes in the direct model highlights that the factors predicting intention are somewhat different to those influencing behaviour. One explanation could be that healthcare providers generally perceive their care, or at least the care needing to be provided, as full-scale and high-quality. These perceptions of 'professional desirability' lead them to have a high intention to test for HIV in the presence of an IC. However, actual implementation of such intentions might require the involvement of additional factors. Challenges in care delivery, restricted time for consultations, HIV related stigma and other barriers might prevent healthcare providers with high intention from actually conducting IC-guided HIV-testing[24,25].

Factors such as self-efficacy, which had no effect on intention in the intentional model, might play a larger role in the actual implementation of behaviour. The direct effect of self-efficacy on behaviour has been proposed in the past by those who developed the TPB model[16,17].

We observed similar findings to other studies applying the TPB model to understand physicians' intentions and behaviour in various clinical settings. In these studies, as in our findings, physicians' attitude was frequently and significantly associated with behavioural intention, whereas self-efficacy was inconsistently associated[26,27]. In contrast, one systematic review evaluating shared decision-making behaviour by healthcare providers observed that norms were most influential in predicting intention and behaviour[28], while we observed a key role for this domain on intention, but a weaker correlation between this domain and HIV testing behaviour in the direct model.

Based on our findings, we recommend the following for improving indicator based testing. Targeting testing norms will not be sufficient unless guidelines are developed and promoted, and providers' attitudes and self-efficacy regarding HIV testing are addressed. Therefore, interventions should focus on addressing the lack of IC-guided HIV testing recommendations in guidelines and establish clear-cut and feasible recommendations[29]. Interventions should additionally focus on improving providers' self-efficacy in implementing IC-guided testing and their attitudes towards this strategy. In turn, self-efficacy can be supported by elements

that increase actual behavioural control, such as the factual easiness of arranging an HIV test in the hospital, while providers' attitudes can be improved by raising healthcare providers' beliefs that HIV testing benefits patients' health outcomes, and that IC-guided testing is a cost-effective strategy[11,12,30-32].

We recognize some limitations to our study. First, we measured behaviour retrospectively in the survey, instead of through a prospective assessment. This may have biased its association with behaviour. We aimed to mitigate this limitation by comparing the outcomes of our intentional model with the outcomes of a model assessing the determinants for behaviour, directly. Second, we only sampled physicians from certain specialty departments, and were unable to receive responses from all sampled specialty departments in all hospital types. Our findings may therefore not be representative of all settings involved with IC-guiding testing, and could have potentially biased the factors influencing HIV testing behaviour. Additionally, our study was underpowered for stratification by specialty and other respondent characteristics. Such stratification could have provided additional understanding in how the effect of domains on HIV testing intention and behaviour could vary by specialty. Since large variation in the implementation of routine HIV testing by IC has been observed[10], stratification would have led to further insight in how to develop tailored interventions to improve HIV testing by specialty. Finally, some of the associations identified in our study may have been the result of specific clinical circumstances at the regional level, and generalisation to other settings therefore warrants caution.

CONCLUSIONS

Our findings highlight discrepancies between determinants for physicians' intention to apply IC-guided HIV testing and determinants for actual HIV testing behaviour. Interventions to improve IC-guided HIV testing in the hospital setting should focus primarily on implementation of guideline recommendations where these are lacking, followed by improving physicians' beliefs towards IC-guided HIV testing, self-efficacy and actual behavioural control, as these were strong determinants of actual HIV testing behaviour.

Conflict of interests statement
Dr. Bogers has nothing to disclose. Dr. Boyd reports grants or contracts: ANRS, ZonMW and Participation on the Data Safety Monitoring Board or Advisory Board: Amsterdam University Medical Centers, Inserm. Dr. Schim van der Loeff has nothing to disclose. Dr. Davidovich has nothing to disclose. Dr. Geerlings has nothing to disclose.

Authorship
SJB, MFSL, UD, and SEG designed the study. SEG acquired funding. SJB recruited participants, collected data, and wrote the first and final draft of the manuscript. UD and AB collaborated in the statistical analysis. All authors had access to the data used in this study. All authors interpreted the data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES

1. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2021 – 2020 data. Stockholm: ECDC 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/2021-Annual_HIV_Report_0.pdf. Last accessed: 24 December 2022.
2. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med* 2016;**375(9)**:830-9.
3. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016;**387(10013)**:53-60.
4. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* 2015;**373(23)**:2237-46.
5. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;**393(10189)**:2428-38.
6. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;**373(9)**:795-807.
7. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS* 2006;**20(10)**:1447-50.
8. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. Available from: https://www.eurotest.org/Testing-Tools/Integrated-testing-in-health-care-settings/HIV-Indicator-Conditions. Last accessed: 24 December 2022. Available at https://www.eurotest.org/Projects-Collaborations/Indicator-Condition-Guided-HIV-Testing-HIDES/Guidance-HIV-Indicator-Conditions. Last accessed 7 July 2022.
9. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.
10. Bogers SJ, Hulstein SH, Schim van der Loeff MF, et al. Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis. *EClinicalMedicine* 2021;**35**:100877.
11. Lin YD, Eades L, Nair A, Korman TM, Woolley I. Review of HIV testing recommendations in Australian specialty guidelines for HIV indicator conditions: a missed opportunity for recommending testing? *Intern Med J* 2020;**50(3)**:293-8.
12. Lord E, Stockdale AJ, Malek R, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. *HIV Med* 2017;**18(4)**:300-4.
13. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2022. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2022. Available from www.hiv-monitoring.nl. Last accessed 24 December 2022.
14. Joore IK, Twisk DE, Vanrolleghem AM, et al. The need to scale up HIV indicator condition-guided testing for early case-finding: a case-control study in primary care. *BMC Fam Pract* 2016;**17(1)**:161.

15. Bogers SJ, Schim van der Loeff MF, Davidovich U, et al. Promoting HIV indicator condition-guided testing in hospital settings (PROTEST 2.0): study protocol for a multicentre interventional study. *BMC Infect Dis* 2021;**21(1)**:519.

16. Ajzen I. The theory of planned behavior. *Organizational Behavior and Human Decision Processes* 1991;**50(2)**:179-211.

17. Ajzen I. Attitudes, Personality, and Behavior. 2nd ed. New York: Open University Press; 2005.

18. Bland JM, Altman DG. Cronbach's alpha. *BMJ* 1997;**314(7080)**:572.

19. Nunnally J, Bernstein L. Psychometric theory. New York: McGraw-Hill Higher, INC; 1994.

20. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *Int J Med Educ* 2011;**2**:53-5.

21. Mafabi S, Nasiima S, Muhimbise EM, Kasekende F, Nakiyonga C. The mediation role of intention in knowledge sharing behavior. *VINE Journal of Information and Knowledge Management Systems* 2017;**47(2)**:172-93.

22. Thorhauge M, Cherchi E, Walker JL, Rich J. The role of intention as mediator between latent effects and behavior: application of a hybrid choice model to study departure time choices. *Transportation* 2019;**46(4)**:1421-45.

23. Jemmott JB, 3rd, Stephens-Shields A, O'Leary A, et al. Mediation of effects of a theory-based behavioral intervention on self-reported physical activity in South African men. *Prev Med* 2015;**72**:1-7.

24. Deblonde J, De Koker P, Hamers FF, Fontaine J, Luchters S, Temmerman M. Barriers to HIV testing in Europe: a systematic review. *Eur J Public Health* 2010;**20(4)**:422-32.

25. Stutterheim SE, Kuijpers KJR, Walden MI, Finkenflugel RNN, Brokx PAR, Bos AER. Trends in HIV Stigma Experienced by People Living With HIV in the Netherlands: A Comparison of Cross-Sectional Surveys Over Time. *AIDS Educ Prev* 2022;**34(1)**:33-52.

26. Wang D, Zhang X, Chen H, Liu C. Applying Theory of Planned Behavior to Understand Physicians' Shared Decision-Making With Patients With Acute Respiratory Infections in Primary Care: A Cross-Sectional Study. *Front Pharmacol* 2021;**12**:785419.

27. Kortteisto T, Kaila M, Komulainen J, Mantyranta T, Rissanen P. Healthcare professionals' intentions to use clinical guidelines: a survey using the theory of planned behaviour. *Implement Sci* 2010;**5**:51.

28. Thompson-Leduc P, Clayman ML, Turcotte S, Legare F. Shared decision-making behaviours in health professionals: a systematic review of studies based on the Theory of Planned Behaviour. *Health Expect* 2015;**18(5)**:754-74.

29. Jordans CCE, Vasylyev M, Rae C, et al. National medical specialty guidelines of HIV indicator conditions in Europe lack adequate HIV testing recommendations: a systematic guideline review. *Eurosurveillance* 2022;**27(48)**:2200338.

30. Elmahdi R, Gerver SM, Gomez Guillen G, Fidler S, Cooke G, Ward H. Low levels of HIV test coverage in clinical settings in the U.K.: a systematic review of adherence to 2008 guidelines. *Sex Transm Infect* 2014;**90(2)**:119-24.

31. Raben D, Sullivan A. Implementation of indicator condition guided HIV testing still lagging behind the evidence. *EClinicalMedicine* 2021;**36**:100918.

32. Desai S, Tavoschi L, Sullivan AK, et al. HIV testing strategies employed in health care settings in the European Union/European Economic Area (EU/EEA): evidence from a systematic review. *HIV Med* 2020;**21(3)**:163-79.

Supplementary Table 1: Content of online survey on determinants for indicator condition guided testing in a selection of seven indicator conditions managed by five medical specialties in the hospital setting

Question	TPB domain	Response options
Section 1: Respondent characteristics		
Sex of respondent	n/a	Male/Female
Age of respondent	n/a	2-digit field
Specialty department of respondent	n/a	Pulmonology/gastroenterology/ gynaecology/neurology/haematology/ other, i.e....
Job description of respondent	n/a	Resident/intern/attending/other, i.e....
No. of years work experience in this specialty	n/a	2-digit field
Type of hospital of respondent	n/a	University hospital/teaching hospital/ non-teaching hospital/other, i.e....
Section 2: HIV testing outcomes and determinants		
I offered patients with [IC]* an HIV test in the last year	Behaviour	5-point Likert scale: Never - Very often
When I see patients with [IC]*, I plan to offer them an HIV test	Intention	5-point Likert scale: Strongly disagree - Strongly agree
It is likely that I will offer patients with [IC]* an HIV test in the future	Intention	5-point Likert scale: Very unlikely – Very likely
It is important that I offer patients with [IC]* an HIV test	Attitude	5-point Likert scale: Very unimportant - Very important
It is positive that I offer patients with [IC]* an HIV test	Attitude	5-point Likert scale: Very negative - Very positive
HIV is common in patients in my specialty	Beliefs	5-point Likert scale: Definitely not - Definitely yes
Offering HIV testing in patients with [IC]* leads to better health outcomes	Beliefs	5-point Likert scale: Definitely not - Definitely yes
My colleagues find it important that we offer patients with [IC]* an HIV test	Professional norms	5-point Likert scale: Very unimportant - Very important
Patients with [IC]* expect me to/find it important that I offer them an HIV test	Professional norms	5-point Likert scale: Definitely not - Definitely yes
HIV testing in patients with [IC]* is discussed in my specialty	Professional norms	5-point Likert scale: Never - Very often
Offering HIV testing in patients with [IC]* is in our guidelines	Professional norms	5-point Likert scale: Definitely not - Definitely yes
I am comfortable offering patients with [IC]* an HIV test	Self-efficacy	5-point Likert scale: Very uncomfortable - Very comfortable

Supplementary Table 1: Content of online survey on determinants for indicator condition guided testing in a selection of seven indicator conditions managed by five medical specialties in the hospital setting (continued)

Question	TPB domain	Response options
I am capable of offering patients with [IC]* an HIV test	Self-efficacy	5-point Likert scale: Highly incapable - Highly capable
It is easy offering patients with [IC]* an HIV test	Self-efficacy	5-point Likert scale: Very hard - Very easy
Ordering HIV testing in patients with [IC]* is easily arranged	Self-efficacy	5-point Likert scale: Very difficult to arrange - very easily arranged

*Per specialty department, the relevant indicator condition(s) were displayed for each question in section 2. IC: indicator condition. n/a: not applicable. TPB: theory of planned behaviour.

Supplementary Table 2: Fit statistics of the Structural Equation Models on associations between determinants for behaviour and self-reported HIV testing behaviour in patients diagnosed with indicator conditions among 163 physicians in the hospital setting in the region of Amsterdam, the Netherlands, 2020

We developed a structural equation model (SEM) to determine which domains from the TPB model contributed to (1) self-reported HIV testing behaviour directly (i.e., direct model) and (2) intention to test for HIV as a mediator for self-reported HIV testing behaviour (i.e., intentional model).

The likelihood ratio (LR) test was used to compare goodness of fit of both models compared to models with perfectly fitting covariances. Additionally, we compared the Bayesian information criteria (BIC), the root mean squared error of approximation (RMSEA), the standardized root mean squared residual (SRMR) and the coefficient of determination (CD) between models to determine which model had the best fit.

Fit statistic	Model 1: Direct model	Model 2: Intentional model
Likelihood ratio	127.22	165.55
Bayesian information criteria	2635.48	2855.09
Root mean squared error of approximation	0.197	0.192
90% confidence interval of root-squared error of approximation	0.165 – 0.231	0.164 -0.221
Standardized root mean squared residual	0.177	0.179
Coefficient of determination	0.808	0.881

Supplementary Table 3: Associations between determinants for behaviour and self-reported HIV testing behaviour in structural equations models in patients diagnosed with indicator conditions among 163 physicians in the hospital setting in the region of Amsterdam, the Netherlands, 2020

	Parameter estimate β (95% CI)	P-value
Intentional model		
Testing behaviour		
Intention to test	0.44 (0.28 to 0.60)	<0.001
Guidelines	0.39 (0.22 to 0.55)	<0.001
Easily arranged	0.16 (0.05 to 0.27)	0.003
Intention to test		
Attitude	0.52 (0.40 to 0.65)	<0.001
Self-efficacy	-0.02 (-0.12 to 0.08)	0.669
Professional norms	0.59 (0.46 to 0.71)	<0.001
Professional norms		
Colleagues	0.65 (0.54 to 0.77)	<0.001
Patients	0.50 (0.35 to 0.64)	<0.001
Often discussed	0.74 (0.65 to 0.83)	<0.001
Self-efficacy		
Easily arranged	0.38 (0.23 to 0.52)	<0.001
Attitude		
Belief	0.56 (0.45 to 0.67)	<0.001
Guidelines		
Professional norms	0.89 (0.82 to 0.95)	<0.001
Direct model		
Testing behaviour		
Attitude	0.28 (0.12 to 0.43)	0.001
Professional norms	0.16 (-0.09 to 0.42)	0.208
Guidelines	0.46 (0.26 to 0.67)	<0.001
Self-efficacy	0.17 (0.03 to 0.30)	0.015
Easily arranged	0.11 (0.00 to 0.22)	0.061
Professional norms		
Colleagues	0.70 (0.59 to 0.81)	<0.001
Patients	0.51 (0.36 to 0.66)	<0.001
Often discussed	0.83 (0.74 to 0.92)	<0.001
Self-efficacy		
Easily arranged	0.38 (0.23 to 0.52)	<0.001
Attitude		
Belief	0.56 (0.45 to 0.67)	<0.001
Guidelines		
Professional norms	0.78 (0.69 to 0.87)	<0.001

The parameter estimates (β) represent the change in modelled outcomes per standardized unit increase of the determinant. CI: confidence interval.

Chapter 9

Improving indicator-condition guided testing for HIV in the hospital setting (PROTEST 2·0): A multicenter, interrupted time-series analysis

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SUMMARY

Background
Indicator-condition (IC) guided HIV testing is a feasible and cost-effective strategy to identify undiagnosed people living with HIV (PLHIV), but remains insufficiently implemented. We aimed to promote IC-guided HIV testing in seven ICs.

Methods
Relevant departments in five hospitals of the Amsterdam region participated. HIV testing among adult patients without known HIV infection but with an IC was assessed using electronic health records during pre-intervention (January 2015-June 2020) and intervention (July 2020-June 2021) periods. The multifaceted intervention included audit and feedback. The primary endpoint was HIV testing ≤3 months before or after IC diagnosis and the effect of the intervention was evaluated using segmented Poisson regression.

Findings
Data from 7,986 patients were included, of whom 6,730 (84·3%) were diagnosed with an IC in the pre-intervention period and 1,256 (15·7%) in the intervention period. The proportion HIV tested ≤3 months before or after IC diagnosis increased from 36·8% to 47·0% (adjusted risk ratio [RR]= 1·16, 95% CI=1·03-1·30, p=0·02). For individual ICs, we observed significant increases in HIV testing among patients with cervical cancer or intraepithelial neoplasia grade 3 (adjusted RR=3·62, 95% CI=1·93-6·79) and peripheral neuropathy (adjusted RR=2·27 95% CI=1·48-3·49), but not the other ICs. Eighteen of 3,068 tested patients were HIV positive (0·6%).

Interpretation
Overall IC-guided testing improved after the intervention, but not for all ICs. Variations in effect by IC may have been due to variations in implemented developments, but the effect of separate elements could not be assessed.

Funding
HIV Transmission Elimination Amsterdam (H-TEAM) initiative, Aidsfonds (grant number: P-42702).

RESEARCH IN CONTEXT

Evidence before this study

Prevention of HIV transmission through HIV diagnosis and treatment is key to end the HIV epidemic. A feasible and cost-effective strategy is to test for HIV in patients with indicator conditions (ICs), that are associated with HIV. However, this strategy is still insufficiently implemented in Western countries. Patients with ICs may present themselves across both infectious disease and non-infectious disease specialties in the hospital setting, but knowledge among healthcare professionals (HCP) of this testing strategy varies by specialty. We searched Ovid MEDLINE and Embase from inception up until April 29th, 2022, using various terms for 'indicator condition', 'HIV testing' and 'intervention' or 'educational' or 'improving' to identify studies aiming to improve IC-guided testing for HIV in the hospital setting. No language restrictions were used. Reference lists of included references were additionally searched. We identified 115 references of which 4 full-text articles and 9 short reports/conference abstracts reported on the effect of implemented interventions. The mean increase in HIV testing among eligible patients was 23% after implementation (range -6% to 60%). Interventions that were most effective at increasing HIV testing were those that employed a combination of an educational intervention for HCP including audit and feedback as well as structural changes such as routine/opt-out testing, changes to order-sets or guideline adaptations. Conversely, isolated educational interventions or implementation of routine testing alone were least effective.

Added value of this study

Our multicenter intervention study confirmed that using a multifaceted intervention including an educational intervention with audit and feedback, as well as structural changes including guideline adaptations, electronic prompts, reflex testing and visual prompts effectively increased IC-guided HIV testing in the hospital setting. However, the effect may depend on variations in implementation by setting. We also confirmed this testing strategy's cost-effectiveness to identify undiagnosed people living with HIV in a high-income setting, as the HIV positivity percentage observed exceeded the cost- effectiveness threshold.

Implications of all the available evidence

Multifaceted interventions employing a combination of educational interventions and structural solutions to support HIV testing effectively increase IC-guided HIV testing, which is a cost-effective strategy to identify undiagnosed people living with HIV.

INTRODUCTION

Timely HIV diagnosis is key to our efforts in ending the HIV epidemic. Earlier diagnosis is associated with numerous individual health benefits, such as decreased morbidity, hospital admissions, and mortality,[1-3] while also preventing onward HIV transmission.[4] One feasible and cost-effective strategy is to routinely test patients diagnosed with an HIV indicator condition (IC).[5-7] ICs are AIDS-defining illnesses and HIV-associated conditions in which ≥1 per 1000 individuals (≥0·1%) have undiagnosed HIV. They include conditions that share the same transmission route as HIV and conditions commonly seen with HIV-associated immunosuppression.[8] However, IC-guided HIV testing is still being insufficiently implemented in many Western countries a decade after its global introduction.[9] Adopting systematic IC-guided testing, and creating awareness of this strategy among involved specialties is an important first step in improving its implementation.[9]

Overall, 24,000 people were estimated to be living with HIV in the Netherlands in 2020, of which an estimated 1,640 (7%) remained undiagnosed. An estimated 6,420 people living with HIV resided in Amsterdam, including 300 (5%) undiagnosed individuals. It is estimated that 90% of HIV transmissions in the Netherlands come from persons with undiagnosed HIV.[10,11] More appropriate HIV testing strategies could therefore help to reach our goal of ending the HIV epidemic by 2030.[10] We introduced a multifaceted intervention in five hospitals of the Amsterdam region to promote IC-guided HIV testing.[12] Our objectives were to (1) generate awareness about ICs and the importance of IC-guided HIV testing amongst physicians working in hospitals, and (2) improve HIV testing in patients with ICs amongst different medical specialties in the hospital setting. In this study, we aimed to evaluate the effect of this intervention on HIV testing in patients diagnosed with ICs.

Study design and setting

We conducted a multicentre intervention study at two university hospitals, two non-academic teaching hospitals and one non-teaching hospital. The study protocol has been described elsewhere and registered with the Dutch Trial registry.[12] Reporting was done in accordance with the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) guidelines (Supplementary Table 1). During the pre-intervention phase, data on IC-guided HIV testing from January 2015 through June 2020 were collected. For all hospitals and departments, the intervention started on July 1, 2020. A repeat assessment of IC-guided HIV testing was performed in all settings from July 2020 through June 2021. We refer to this one-year period as the intervention period, which included the rollout of the interventions as well as the assessment of its effects. An *a priori* selection of seven ICs was included based on their relatively high incidence and the fact that they are managed by several medical specialties (i.e. pulmonology, gynaecology, haematology, gastroenterology and neurology) and were expected to vary in the proportion of patients that were tested for HIV prior to the intervention. These ICs were: tuberculosis (TB), cervical cancer or cervical intraepithelial neoplasia grade III (CC/CIN-3), vulvar cancer or vulvar intraepithelial neoplasia grade III (VC/VIN-3), malignant lymphoma (ML),

hepatitis B virus infection (HBV), hepatitis C virus infection (HCV) and peripheral neuropathy (PN).

Intervention strategy

The intervention primarily consisted of a tailored educational intervention session using audit and feedback, taking place at each relevant specialty in each participating hospital during the intervention period. The sessions were scheduled by local physicians and conducted live or through video-conferencing based on the department's preferences and in accordance with any locally implemented COVID-19 measures. Attendants were medical specialists, residents and interns. To optimize the efficacy of the intervention, we employed a multifaceted strategy consisting of various elements (Table 1).[12]

Patient eligibility

In each participating hospital, patients 18 years or over were identified using national disease billing codes. Patients without one of the selected definitive IC diagnoses, those with a known HIV infection prior to IC diagnosis, and those diagnosed and treated for their IC at another hospital were excluded by reviewing the patients' electronic health records (EHR). However, patients who were referred for a second opinion or transferred for treatment after IC diagnosis were included. Several IC-specific inclusion criteria were used (Supplementary Table 2). All eligible patients from university hospital 1 were included in the dataset. For all other hospitals, a random sample of 500 patients per IC was screened for eligibility if >500 patients were identified. This sampling was done to maintain a manageable workload as the added precision of more than 500 inclusions is negligible.[12]

METHODS

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Data collection
Data on patient demographics, diagnosed IC, and HIV testing (if any) were extracted from the EHRs of eligible patients, which contain integrated hospital laboratory data, using a standardized data collection form (Supplementary Table 3). For HIV testing, all laboratory records, scanned documents and patient notes were searched for evidence of any HIV test performed. If there was no evidence of HIV testing, reasons for not testing for HIV were sought and recorded if available. Female patients with a recorded pregnancy in the Netherlands after January 1, 2004 were assumed to have been tested for HIV by their midwife during antenatal care, as the number opting out of this universal screening method is negligible.[13] EHR reviews and data processing were performed by several junior researchers and a random sample of ≥10% per IC was checked for agreement by the primary research physician (SJB). All data were processed using Castor (Castor Electronic Data Capture, Amsterdam, the Netherlands).

Outcomes
The primary outcome was the proportion of patients diagnosed with an IC who were tested for HIV within 3 months before or after IC diagnosis. Secondary outcomes were the proportion of patients tested for HIV before initiating treatment for their

IC, the proportion of patients not tested within 3 months before or after IC diagnosis where a reason for not testing was reported, the percentage testing HIV positive within 3 months before or after IC diagnosis, the proportion of new HIV diagnoses that were late stage infections (defined as CD4 count <350 cells/mm^3 in this study), the proportion HIV tested within 6 months before or after IC diagnosis, and the proportion of patients diagnosed with an IC that were ever tested for HIV before or up to 6 months after IC diagnosis.

Table 1 – Elements of the multifaceted strategy to promote indicator condition-guided testing for HIV, Amsterdam region, the Netherlands, 2020

Pre-intervention: Assessment of barriers, facilitators and opportunities for improvement
Assessment of HIV testing recommendations in local and national IC specialty guidelines
Dissemination of an online questionnaire among medical specialists and residents from relevant specialties (pulmonology, gynaecology, haematology, gastroenterology and neurology) to assess barriers and facilitators for IC-guided HIV testing
Conduction of semi-structured interviews in a convenience sample of at least one physician per specialty to assess opportunities for improved HIV testing strategies
Intervention: Educational sessions and further implementation elements
Reporting of competitive feedback on HIV testing behaviour per specialty, compared to other hospitals: Reporting results of proportion of patients tested for HIV in the pre-intervention period for the relevant IC per specialty Reporting results from pre-intervention phase: barriers, facilitators and opportunities for improvement
Reporting evidence on IC-guided HIV testing and up-to-date information on HIV epidemiology, testing and treatment
Interactive discussion on strategies to further improve HIV testing in the department, such as: Adding HIV testing recommendations to specialty guidelines Adding HIV testing to the standard laboratory order sets for outpatients Implementing electronic prompts for HIV testing Implementing reflex testing for HIV in the case of IC diagnosis
Dissemination of materials (pocket cards and posters) on IC-guided HIV testing and specialty-specific information
Assisting in implementation of any structural solutions for routine or improved HIV testing that were proposed during the intervention phase
Dissemination of a newsletter including a summary of the information from the intervention phase, a discussion of the most commonly reported barriers for appropriate HIV testing, and a 3-minute educational video on HIV testing of patients with a relevant IC

IC: indicator condition.

Statistical analysis

Categorical data were summarised using frequencies and percentages, and continuous data as means and standard deviations (SD) or medians and interquartile ranges (IQR). Variable distributions were compared between patients diagnosed

with an IC in the pre-intervention versus intervention phase using unpaired *t*-tests or Mann-Whitney U tests for continuous data and X^2 or Fisher-exact tests for categorical data.

A binomial probability test was performed to compare the observed percentage HIV positive in our study to the 0.1% positivity that has been identified as the cost-effectiveness threshold for routine HIV testing in previous studies. We modelled the overall proportion tested for HIV as a function of calendar time (in quarter-year periods) and intervention period (pre-intervention versus intervention) using a segmented (i.e., interrupted) time-series Poisson regression model. We evaluated the effect of the intervention from the intervention period term, which represents the log relative change in proportion tested from the intervention versus pre-intervention periods. The null hypothesis of no change in proportion was tested using a Wald χ^2 test. We estimated this model for both the overall population, as well as each IC separately and each IC per hospital separately. An average number of 31 patients per IC per quarter-year was determined sufficient to reach >95% power to determine the anticipated 18-20% increase in HIV testing due to the intervention.[12] Patient characteristics that were deemed potential confounders (i.e., age, sex, socioeconomic status [SES] as derived from patient's 4-digit postal-code and stratified in low SES, intermediate SES and high SES based on national tertiles, and pregnant at IC diagnosis) were added to the regression model. The outcome was not over-dispersed (i.e. modeling the outcome with negative-binomial regression did not improve fit).

Additionally, a separate analysis including a random intercept for hospital was performed to account for the variation between hospitals. We performed two sensitivity analyses: (1) the proportion HIV tested within 3 months after IC diagnosis only was used as the endpoint to evaluate the effect of the intervention on HIV testing as a reflex to diagnosing an IC, and (2) patients who died within 3 months after IC diagnosis were excluded to evaluate the potential effect of immortality bias. A *p*-value of <0·05 was considered statistically significant. All analyses were performed using Stata (v15·1, StataCorp, College Station, TX, USA).

Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Ethical considerations

All eligible patients were given the opportunity to opt-out of the use of their data. The Medical Ethics Committee of the Amsterdam University Medical Centers location University of Amsterdam determined that this study did not meet the definition of medical research involving human subjects under Dutch law.

RESULTS

Study population

The EHRs of 23,764 patients were assessed for eligibility and data of 7,986 patients were included in the analysis, including 6,730 patients (84·3%) in the pre-intervention period and 1,256 (15·7%) in the intervention period (Figure 1). A mean of 44 patients per IC per quarter-year were included. More patients died within 3 months after IC diagnosis in the intervention period compared to the pre-intervention period, while other patient characteristics were comparable. However, additional differences in patient characteristics were observed when stratified by IC (Table 2).

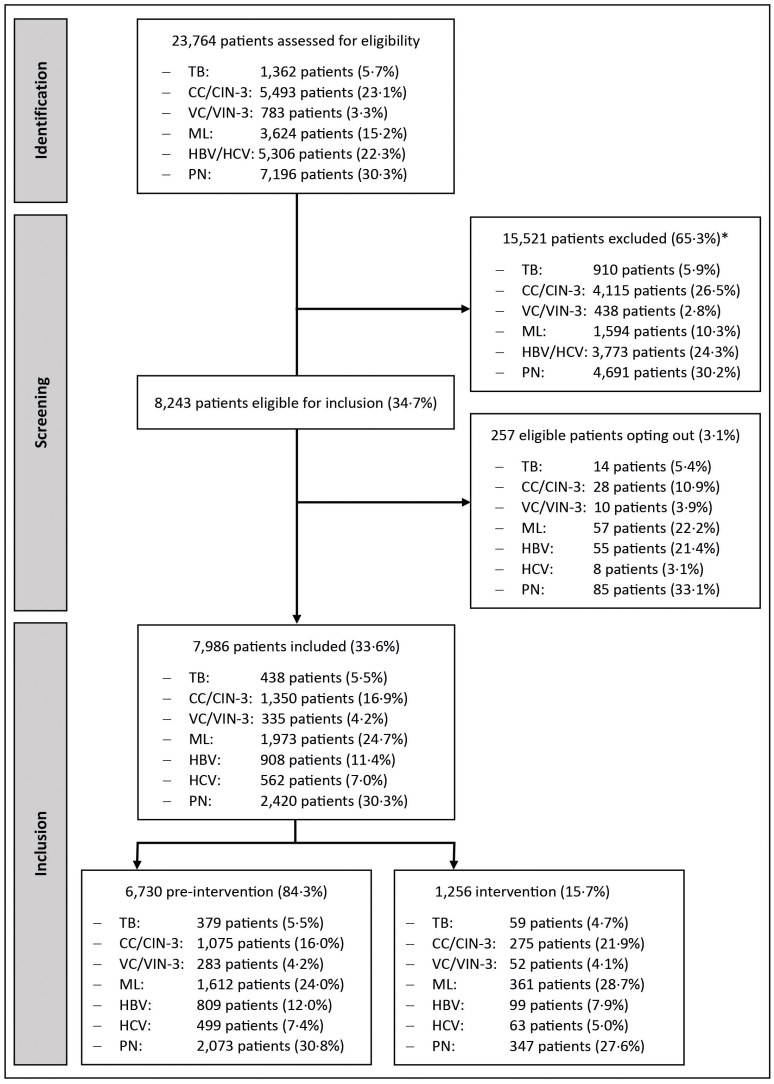
Intervention

Overall, 26 educational intervention sessions were conducted among the five different specialties in the five participating hospitals, and a total of 384 physicians attended. Median number of attendees per session was 13 (IQR 8-20). Additional developments to improve IC-guided HIV testing occurred as a result of the educational intervention in several hospitals and specialties (Table 3).

Proportion HIV tested within 3 months before or after IC diagnosis

Overall, 3,068/7,986 (38·4%) patients were tested within 3 months before or after IC diagnosis. The proportion HIV tested within 3 months before or after IC diagnosis increased from 2,478/6,730 (36·8%) in the pre-intervention period to 590/1,256 (47·0%) in the intervention period (unadjusted RR 1·13, 95% CI 1·01-1·27, p=0·04, Table 4; RR adjusted for patients' age, sex, SES and pregnant at IC diagnosis: 1·16, 95% CI 1·03-1·30, p=0·02, Figure 2, Table 4). For individual IC, significant increases in HIV testing were observed after the intervention among patients with CC/CIN-3 (aRR 3·62, 95% CI 1·93-6·79, p<0·001) and PN (aRR 2·27 95% CI 1·48-3·49, p=<0·001), but not the other ICs. Stratification by subtypes of ML revealed higher proportions HIV tested in high-grade subtypes compared to low-grade subtypes, but no significant increase in HIV testing using time-series analyses (Table 4). In sensitivity analysis using HIV testing within 3 months after IC diagnosis only, the proportion HIV tested increased from 1,506/6,730 (22·4%) to 367/1,256 (29·2%), aRR 1·33 95% CI 1·14-1·55, p=<0·001 (Supplementary Table 4). Results did not change in sensitivity analyses where patients who died within 3 months after IC diagnosis were excluded (overall aRR 1·15, 95% CI 1·02-1·29, p=0·02). Stratified by hospital and IC, we noted the same pattern as in the main analysis, except in TB and HCV, where we observed non-significant decreases in proportions tested in three hospitals (Supplementary Table 5). In an analysis where we allowed effects to vary by hospital (random effects model), the overall aRR was 1·16 (95% CI 1·03-1·31, p=0·01, Supplementary Table 6). For individual IC, the aRRs for CC/CIN-3 (aRR 3·76, 95% CI 2·01-7·04, p<0·001) and PN (aRR 2·33, 95% CI 1·52-3·59, p<0·001) were also slightly higher in this model.

Figure 1: Flowchart of identification, screening and inclusion of data of patients diagnosed with indicator conditions in 5 hospitals in the region of Amsterdam, 2015–2021.



*Reasons for exclusion were: no definitive indicator condition diagnosis (53.4%), indicator condition diagnosis outside study period (18.3%), indicator condition-specific exclusion criteria (18.0%), diagnosed and treated for the indicator condition at another hospital (6.6%), and known HIV infection prior to IC diagnosis (3.7%). HBV and HCV could not be reported separately in the identification and screening phase as they have a shared disease billing code. TB: tuberculosis, CC/CIN-3: cervical cancer or intraepithelial neoplasia grade III, VC/VIN-3: vulvar cancer or intraepithelial neoplasia grade III, ML: malignant lymphoma, HBV: hepatitis B virus infection, HCV: hepatitis C virus infection, PN: peripheral neuropathy.

Table 2: Characteristics of included patients diagnosed with indicator conditions in five hospitals in the region of Amsterdam before- and after intervention, overall and by indicator condition, 2015-2021

	Overall	Before intervention	After intervention	*p* value
Overall	**(n=7,986)**	**(n=6,730)**	**(n=1,256)**	
Sex				0·24
Female	4,488 (56·2%)	3,763 (55·9%)	725 (57·7%)	
Male	3,498 (43·8%)	2,967 (44·1%)	531 (42·3%)	
Pregnant at IC diagnosis*	150 (3·3%)	128 (3·4%)	22 (3·0%)	0·61
Age at IC diagnosis, y	56 (41-68)	56 (41-68)	58 (41-69)	0·18
Socio-economic status**				0·49
Low	2,897 (36·6%)	2,454 (36·8%)	443 (35·4%)	
Intermediate	1,833 (23·2%)	1,529 (22·9%)	304 (24·3%)	
High	3,189 (40·3%)	2,683 (40·3%)	506 (40·4%)	
Died ≤3 months after IC diagnosis	133 (1·7%)	103 (1·5%)	30 (2·4%)	0·03
Hospital of inclusion				<0·001
University hospital 1	3,306 (41·4%)	2,945 (43·8%)	361 (28·7%)	
University hospital 2	1,083 (13·6%)	919 (13·7%)	164 (13·1%)	
Teaching hospital 1	1,891 (23·7%)	1,531 (22·8%)	360 (28·7%)	
Teaching hospital 2	786 (9·8%)	612 (9·1%)	174 (13·9%)	
Non-teaching hospital 1	920 (11·5%)	723 (10·7%)	197 (15·7%)	
Tuberculosis	**(n=438)**	**(n=379)**	**(n=59)**	
Sex				0·40
Female	164 (37·4%)	139 (36·7%)	25 (42·4%)	
Male	274 (62·6%)	240 (63·3%)	34 (57·6%)	
Pregnant at IC diagnosis*	3 (1·8%)	3 (2·2%)	0 (0%)	0·46
Age at IC diagnosis, y	42 (31-58)	42 (31-58)	45 (32-57)	0·57
Socio-economic status**				0·66
Low	228 (53·2%)	200 (53·9%)	28 (48·3%)	
Intermediate	80 (18·7%)	67 (18·1%)	13 (22·4%)	
High	121 (28·2%)	104 (28·0%)	17 (29·3%)	
Died ≤3 months after IC diagnosis	9 (2·1%)	9 (2·4%)	0 (0%)	0·23
Cervical cancer or CIN-3	**(n=1,350)**	**(n=1,075)**	**(n=275)**	
Pregnant at IC diagnosis*	41 (3·0%)	34 (3·2%)	7 (2·6%)	0·59
Age at IC diagnosis, y	41 (32-52)	40 (32-51)	41 (32-56)	0·23
Socio-economic status**				0·33
Low	468 (34·9%)	368 (34·5%)	100 (36·4%)	
Intermediate	345 (25·7%)	268 (25·1%)	77 (28·0%)	
High	530 (39·5%)	432 (40·5%)	98 (35·6%)	
Died ≤3 months after IC diagnosis	15 (1·1%)	8 (0·7%)	7 (2·6%)	0·01

Table 2: Characteristics of included patients diagnosed with indicator conditions in five hospitals in the region of Amsterdam before- and after intervention, overall and by indicator condition, 2015-2021 (continued)

	Overall	Before intervention	After intervention	*p* value
Vulvar cancer or VIN-3	**(n=335)**	**(n=283)**	**(n=52)**	
Pregnant at IC diagnosis*	1 (0·3%)	1 (0·4%)	0 (0%)	0·67
Age at IC diagnosis, y	70 (59-79)	71 (59-80)	69 (59-76)	0·44
Socio-economic status**				0·48
Low	134 (40·1%)	117 (41·5%)	17 (32·7%)	
Intermediate	112 (33·5%)	93 (33·0%)	19 (36·5%)	
High	88 (26·4%)	72 (25·5%)	16 (30·8%)	
Died ≤3 months after IC diagnosis	6 (1·8%)	6 (2·1%)	0 (0%)	0·29
Malignant lymphoma	**(n=1,973)**	**(n=1,612)**	**(n=361)**	
Sex				0·71
Female	837 (42·4%)	687 (42·6%)	150 (41·6%)	
Male	1,136 (57·6%)	925 (57·4%)	211 (58·5%)	
Pregnant at IC diagnosis*	10 (1·2%)	7 (1·0%)	3 (2·0%)	0·32
Age at IC diagnosis, y	61 (50-71)	61 (49-71)	62 (50-70)	0·89
Socio-economic status**				0·55
Low	598 (30·6%)	494 (31·0%)	104 (28·9%)	
Intermediate	477 (24·4%)	392 (24·6%)	85 (23·6%)	
High	877 (44·9%)	706 (44·4%)	171 (47·5%)	
Died ≤3 months after IC diagnosis	89 (4·5%)	70 (4·3%)	19 (5·3%)	0·45
Hepatitis B virus infection	**(n=908)**	**(n=809)**	**(n=99)**	
Sex				0·53
Female	377 (41·5%)	333 (41·2%)	44 (44·4%)	
Male	531 (58·5%)	476 (58·8%)	55 (55·6%)	
Pregnant at IC diagnosis*	81 (21·5%)	72 (21·6%)	9 (20·5%)	0·86
Age at IC diagnosis, y	41 (33-52)	41 (33-52)	40 (32-52)	0·97
Socio-economic status**				0·19
Low	479 (53·1%)	422 (52·5%)	57 (57·6%)	
Intermediate	163 (18·1%)	142 (17·7%)	21 (21·2%)	
High	261 (28·9%)	240 (29·9%)	21 (21·2%)	
Died ≤3 months after IC diagnosis	3 (0·3%)	2 (0·3%)	1 (1·0%)	0·21
Hepatitis C virus infection	**(n=562)**	**(n=499)**	**(n=63)**	
Sex				0·10
Female	186 (33·1%)	171 (34·3%)	15 (23·8%)	
Male	376 (66·9%)	328 (65·7%)	48 (76·2%)	
Pregnant at IC diagnosis*	7 (3·8%)	6 (3·5%)	1 (6·7%)	0·54
Age at IC diagnosis, y	53 (43-60)	53 (44-60)	50 (38-59)	0·09
Socio-economic status**				0·02

Table 2: Characteristics of included patients diagnosed with indicator conditions in five hospitals in the region of Amsterdam before- and after intervention, overall and by indicator condition, 2015-2021 (continued)

	Overall	Before intervention	After intervention	*p* value
Low	223 (40·7%)	206 (42·5%)	17 (27·0%)	
Intermediate	121 (22·1%)	100 (20·6%)	21 (33·3%)	
High	204 (37·2%)	179 (36·9%)	25 (39·7%)	
Died ≤3 months after IC diagnosis	1 (0·2%)	1 (0·2%)	0 (0%)	0·72
Peripheral neuropathy	**(n=2,420)**	**(n=2,073)**	**(n=347)**	
Sex				0·11
Female	1,239 (51·2%)	1,075 (51·9%)	164 (47·3%)	
Male	1,181 (48·8%)	998 (48·1%)	183 (52·7%)	
Pregnant at IC diagnosis*	7 (0·6%)	5 (0·5%)	2 (1·2%)	0·23
Age at IC diagnosis, y	64 (54-73)	64 (54-72)	66 (56-74)	0·01
Socio-economic status**				0·33
Low	767 (31·8%)	647 (31·4%)	120 (34·7%)	
Intermediate	535 (22·2%)	467 (22·6%)	68 (19·7%)	
High	1,108 (46·0%)	950 (46·0%)	158 (45·7%)	
Died ≤3 months after IC diagnosis	10 (0·4%)	7 (0·3%)	3 (0·9%)	0·16

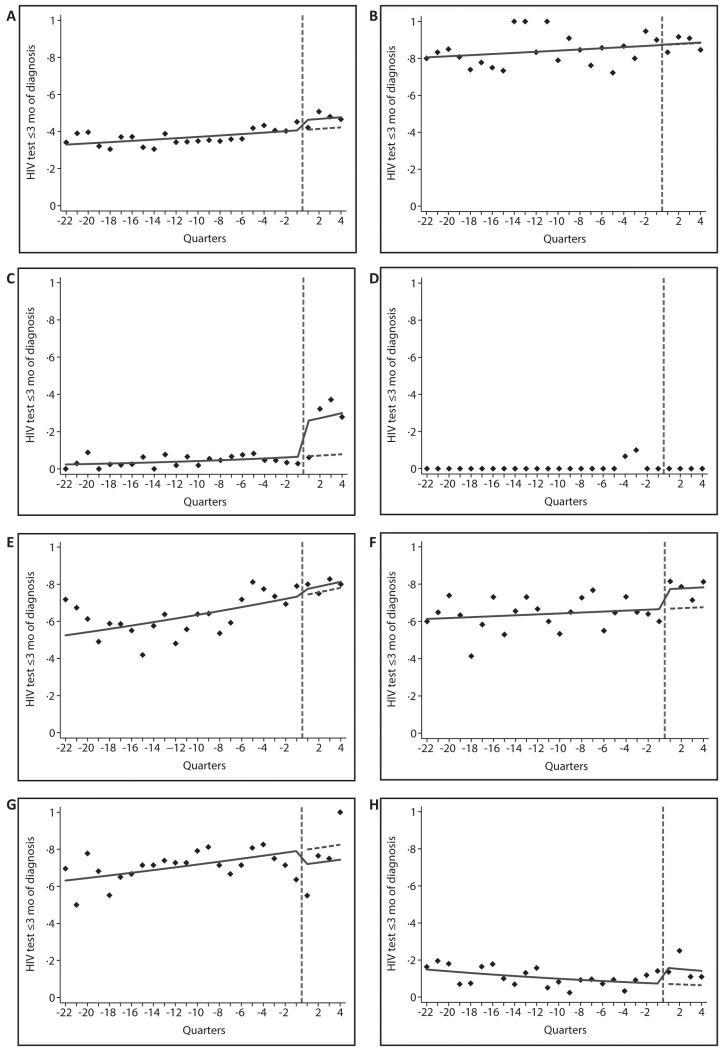
Data are depicted as n (%) or median (IQR). *Percentages are calculated using the number of female patients as denominator. **Overall, 67 patients had a missing socio-economic status value; 64 in the pre-intervention and 3 in the intervention period. CIN-3: Cervical intraepithelial neoplasia grade III. IC: Indicator condition. VIN-3: vulvar intraepithelial neoplasia grade III.

Table 3: Additional developments that occurred as a result of the educational intervention to promote indicator condition-guided testing for HIV, Amsterdam region, the Netherlands, 2020-2022

Development	Time of implementation
All participating hospitals	
Electronic prompts for HIV testing in electronic health records in the case of tuberculosis, hepatitis B virus infection and hepatitis C virus infection diagnoses	March 2021 for both university hospitals, March 2022 for both teaching hospitals and the non-teaching hospital*
University hospital 1	
Recommendation of HIV testing in local protocol for patients diagnosed with cervical carcinoma	December 2020
Reflex testing for HIV in the case of hepatitis B virus infection or hepatitis C virus infection	November 2021*
Addition of HIV testing as part of standard orders for newly diagnosed malignant lymphoma patients	September 2020
University hospital 2	
Addition of HIV testing as part of standard orders for newly diagnosed malignant lymphoma patients	September 2020
Teaching hospital 1	
Recommendation of HIV testing in the local protocol for patients diagnosed with cervical carcinoma	April 2021
Recommendation of HIV testing in the local protocol for patients diagnosed with peripheral neuropathy	January 2021
Teaching hospital 2	
Routine check of HIV testing before start of therapy in all malignant lymphoma patients by oncology nurse	December 2020

*Implementation occurred after the intervention's effect assessment was concluded, and their implementation is therefore not reflected in our findings.

Figure 2: Time-series analysis of the proportion HIV tested within 3 months before or after indicator condition diagnosis overall and by indicator condition.



Results are presented overall (Panel A) and by indicator condition: (Panel B) tuberculosis. (Panel C) cervical cancer or intraepithelial neoplasia grade III. (Panel D) vulvar cancer or intraepithelial neoplasia grade III. (Panel E) malignant lymphoma. (Panel F) hepatitis B virus infection. (Panel G) hepatitis C virus infection. (Panel H) peripheral neuropathy. The vertical dotted line represents the transition from the pre-intervention to the intervention period, which consists of a one-year period starting from the start date of the intervention. The diamonds represent the observed proportions tested for HIV within 3 months before or after indicator condition diagnosis by quarter-year period. The solid lines are the trend lines based on unadjusted time-series Poisson regression analysis. The horizontal dashed lines represent the expected trend in the intervention period based on the pre-intervention period. Trends and expected trends could not be obtained for vulvar cancer or intraepithelial neoplasia grade III (Panel D).

Table 4: Proportion of patients tested for HIV within 3 months before or after indicator condition diagnosis, and unadjusted and adjusted risk ratio's, overall and by indicator condition, Amsterdam region 2015-2021.

	Before intervention (n=6,730)	After intervention (n=1,256)	Unadjusted risk ratio (95% CI)	*p* value	Adjusted risk ratio* (95% CI)	*p* value
Overall	2,478/6,730 (36·8%)	590/1,256 (47·0%)	1·13 (1·01-1·27)	0·04	1·16 (1·03-1·30)	0·02
By indicator condition						
Tuberculosis	317/379 (83·6%)	52/59 (88·1%)	1·00 (0·69-1·45)	0·99	1·00 (0·68-1·45)	0·98
Cervical cancer or CIN-3	46/1,075 (4·3%)	77/275 (28·0%)	3·81 (2·04-7·11)	<0·001	3·62 (1·93-6·79)	<0·001
Vulvar cancer or VIN-3	2/283 (0·7%)	0/52 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	1,021/1,612 (63·3%)	286/361 (79·2%)	1·04 (0·88-1·24)	0·65	1·05 (0·88-1·25)	0·61
Hodgkin's lymphoma	158/228 (69·3%)	32/35 (91·4%)	1·12 (0·70-1·81)	0·64	1·14 (0·71-1·85)	0·58
T-cell lymphoma	111/173 (64·2%)	32/36 (88·9%)	1·16 (0·69-1·94)	0·57	1·13 (0·67-1·89)	0·64
Diffuse large B-cell lymphoma	393/536 (73·3%)	132/150 (88·0%)	1·05 (0·80-1·37)	0·72	1·04 (0·80-1·37)	0·76
Mantle cell lymphoma	65/90 (72·2%)	22/26 (84·6%)	1·11 (0·56-2·19)	0·76	1·21 (0·60-2·46)	0·59
Follicular lymphoma	121/234 (51·7%)	18/37 (48·7%)	0·67 (0·37-1·22)	0·19	0·68 (0·37-1·24)	0·21
Marginal zone/MALT lymphoma	58/133 (43·6%)	21/32 (65·6%)	1·00 (0·50-1·98)	0·99	1·07 (0·53-2·16)	0·85
Burkitt lymphoma	25/28 (89·3%)	4/4 (100·0%)	n/a	n/a	n/a	n/a
Lymphoplasmacytic lymphoma	4/16 (25·0%)	1/1 (100%)	n/a	n/a	n/a	n/a
Non-Hodgkin lymphoma, other	86/174 (49·4%)	24/40 (60·0%)	1·03 (0·57-1·88)	0·91	0·99 (0·54-1·82)	0·98
Hepatitis B virus infection	520/809 (64·3%)	77/99 (77·8%)	1·16 (0·87-1·54)	0·31	1·16 (0·87-1·54)	0·32
Hepatitis C virus infection	351/499 (70·3%)	46/63 (73·0%)	0·90 (0·62-1·31)	0·59	0·90 (0·61-1·33)	0·60
Peripheral neuropathy	221/2,073 (10·7%)	52/347 (15·0%)	2·22 (1·45-3·39)	<0·001	2·27 (1·48-3·49)	<0·001

*Analyses are performed using multivariable models adjusting for confounding patient characteristics sex, age, socio-economic status, and pregnant at time of indicator condition diagnosis. n/a: parameter estimates could not be obtained. CIN-3: Cervical intraepithelial neoplasia grade III. MALT: mucosa-associated lymphoid tissue. VIN-3: vulvar intraepithelial neoplasia grade III.

Of the 3,068 patients tested for HIV within 3 months before or after IC diagnosis, 93·4% had been tested in the hospital setting, 2·9% by their general practitioner, 2·7% during antenatal care services, 0·7% at a sexual health clinic, and 0·3% elsewhere. Of patients tested for HIV, 87·5% in the pre-intervention and 91·3% in the intervention period had been tested before initiating treatment for their IC (p=0·03). Compared to those not tested for HIV within 3 months before or after IC diagnosis, patients who had been tested were more often male, younger, were of a lower SES category, and more often deceased within 3 months after IC diagnosis (Supplementary Table 7).

Patients not tested for HIV within 3 months before or after IC diagnosis

In 92 (1·9%) of the 4,918 patients who did not receive HIV testing within 3 months before or after IC diagnosis, there was evidence of an HIV test being offered by the treating physician. In 55/92 (59·8%) of these cases, the patient agreed to receiving an HIV test, but the test was ultimately not performed by decision of the physician or patient. In 9/92 (9·8%) of these cases, the patient explicitly refused the HIV test. In the remaining 28/92 (30·4%) cases, it could not be determined whether the test was accepted or not. In 47/4,918 (1·0%) of patients who did not receive HIV testing within 3 months before or after IC diagnosis, the physician had explicitly noted the reason for not offering HIV testing in the EHR, which included negative HIV tests in the past (n=38), no perceived HIV risk (n=5), or transfer of care to another facility or primary care (n=4).

Percentage HIV positive

Overall, 18/3,068 (0·6%) patients tested HIV positive within 3 months before or after IC diagnosis: 17/2,478 (0·7%) in the pre-intervention period and 1/590 (0·2%) in the intervention period (p=0·23, Supplementary Table 8), exceeding the cost-effectiveness threshold for HIV screening of 0·1% (p<0·0001). Eight (44·4%) had TB, seven (38·9%) had ML, two (11·1%) had HBV and one (5·6%) had HCV. Of the seven with ML, five had diffuse large B-cell lymphoma, one had Burkitt's lymphoma and one had T-cell lymphoma. Fourteen (77·8%) of 18 patients were male, the median age was 45 years (IQR 34-54), and the majority lived in a low SES postal-code area (10 [55·6%] low, 3 [16·7%] intermediate, 5 [27·8%] high). Most patients (17/18; 94·4%) received their diagnosis at a late stage. Compared to patients testing HIV negative within 3 months before or after IC diagnosis, patients testing HIV positive were younger (mean age 45 years [IQR 34-54] vs. 52 [IQR 37-64] p=0·05), more often male (77·8% vs. 58·0% male, p=0·10) and more often of lower SES (55·6% vs. 39·6% low, 16·7% vs. 22·3% intermediate and 27·8% vs. 38·1% high SES, p=0·42, Supplementary Table 8).

Proportion HIV tested within 6 months before or after IC diagnosis and ever

Overall, 3,327/7,986 (41·7%) patients were tested within 6 months before or after IC diagnosis. The proportion HIV tested within 6 months before or after IC diagnosis increased from 2,707/6,730 (40·2%) in the pre-intervention period to 620/1,256 (49·4%) in the intervention period (aRR 1·15, 95% CI 1·02-1·28, p=0·02). The proportion of patients ever tested for HIV before or up to 6 months after IC diagnosis did not

increase significantly (from 3,355/6,730 [49·9%] to 761/1,256 [60·6%]; aRR 1·08, 95% CI 0·98-1·20, p=0·14).

DISCUSSION

This multifaceted intervention resulted in an overall 10·2% absolute increase in IC-guided HIV testing within 3 months before or after IC diagnosis. The overall proportion HIV tested within 3 months before or after IC diagnosis improved significantly following the intervention in this interrupted time-series analysis. The crude proportion HIV tested increased in all ICs except VC/VIN-3, and in all ML subtypes except follicular lymphoma. However, a significant increase in HIV testing was only observed in CC/CIN-3 and PN, the ICs with the lowest pre-intervention proportion HIV tested. HIV testing within 3 months before or after IC diagnosis was still only done in less than half of included patients following the intervention, highlighting persistent missed opportunities for HIV testing.

We observed large variation in HIV testing in the pre-intervention phase. HIV testing was already reasonably high among patients with TB, HCV and high-grade subtypes of ML (i.e., 84%, 70% and 64%-89% respectively), but considerable improvement was warranted among patients diagnosed with other ICs. A possible explanation is the lack of routine HIV testing recommendations in specialty guidelines for PN, CC/CIN-3, VC/VIN-3 and several ML subtypes, particularly lowgrade ones, while HIV testing is explicitly recommended in TB, HBV and HCV guidelines, as well as some ML subtype guidelines.[14-20] This difference in testing recommendations is reflected in our data, where we observed lower crude proportions HIV tested among patients diagnosed with follicular lymphoma and marginal zone lymphoma compared to other lymphomas. Additionally, physician beliefs of the importance of IC-guided HIV testing may have played a role, such as low perceived risk among women and older patients, which could explain the lower proportion tested for HIV in these groups. Patients with VC/VIN-3, the IC with the oldest population, were tested least.

Several specialty departments implemented additional changes at varying times triggered by the intervention, which may have influenced HIV testing (Table 3). While the design of the educational sessions was identical per hospital and specialty, it is therefore challenging to disentangle the direct effect of the intervention versus these varying intervention developments. For example, we saw the largest effect among patients diagnosed with CC/CIN-3, specifically at one university hospital. HIV testing recommendations had been lacking from CC/CIN-3 guidelines prior to the intervention; immediately following the educational meeting, it was added by gynaecologists at this hospital to their local guideline as well as the standard laboratory orders for new patients diagnosed with cervical carcinoma. In the one non-academic teaching hospital where this recommendation was also added to the local guideline, we observed an absolute increase in HIV testing of 10%. In that same hospital, neurologists added HIV testing recommendations to their local PN guidelines following the educational intervention meeting and HIV testing among

PN patients increased from 14% to 26%. Although these settings with guideline revisions demonstrated modest increases in HIV testing, such revisions alone might not be sufficient to have a substantial impact on HIV testing.[21,22] Possibly, additional intervention strategies to support guideline adaptations would have been more effective, such as adapting the laboratory orders to automatically include an HIV test. The absolute overall increase of 10% in IC-guided HIV testing within 3 months before or after IC diagnosis observed in our data is comparable to that in other multifaceted intervention programmes aiming to improve IC-guided testing for HIV in Europe,[23,24] as well as interventions aiming to improve appropriate treatment strategies for other infectious diseases.[25,26]

Previous studies have determined routine HIV screening is cost-effective in comparable settings where the undiagnosed HIV prevalence is >0·1%.[5,27,28] The percentage that tested HIV positive of 0·6% observed in our study was substantially above this cost-effectiveness threshold, indicating that this strategy to identify undiagnosed people living with HIV is indeed cost-effective. However, although the proportion tested increased, we observed a lower percentage positive after the intervention than before (0·2% vs. 0·7%, respectively), and a percentage positive of 0% in some ICs. Thus, the question arises when this routine HIV testing strategy is no longer cost-effective in our setting. We therefore believe that focusing on ICs with the largest undiagnosed HIV prevalence, including TB, ML and HBV, may be most efficient when working with limited resources for interventions. Additionally, nearly all newly diagnosed people living with HIV in this study received their diagnosis at a late stage, suggesting that while this strategy was cost-effective to identify undiagnosed individuals, it may not be an optimal strategy for early HIV diagnosis.

The low number of patients who explicitly refused HIV testing concurs with findings from other studies reporting that this approach is acceptable for patients diagnosed with ICs[6,7]; we do not expect that refusal of HIV testing when offered by the physician goes unrecorded in the EHRs. In the majority of cases where no HIV testing was done within 3 months before or after IC diagnosis, no reasoning was reported by the physician, while only in 1% of cases the physician had a justified reason for not testing. As it is likely that physicians will report any conscious deviation from recommended diagnostic approaches in patients' EHR, among cases where no reasoning was reported, explicit deliberation on HIV testing was probably not done.

The main strength of this study is the large number of included patients per IC, the participation of various types of hospitals (i.e., university, teaching and non-teaching), which increases the generalizability of our findings to other settings in the Netherlands and other low-prevalence, high-income settings. Additionally, using time-series regression to estimate the effect of our intervention allowed us to correct for trends in HIV testing that would have otherwise been disregarded in a study design comparing outcomes before and after a given intervention, possibly leading to an overestimation of the intervention's effect.[29] Third, we employed feasible, low-cost elements in our local interventions that were tailored to hospital and specialty department. Additional opportunities for implementation were identified during

discussion at several educational meetings. Physicians were actively involved in the local development of strategies and implementation. Consequently, we ensured that the intervention was appropriate and relevant for each setting specifically, and therefore more likely to be impactful.[30]

A considerable limitation of our study is the short follow-up time after the intervention. While the intervention phase launched in all sites on the same date, implementation of various site-specific intervention developments was more outspread, and the effect of some developments might therefore not be apparent in our data if their implementation was finalised towards the end of the phase. Due to the short follow-up time, we can also not report on the sustainability of the effect of our interventions. However, it is likely that structural intervention developments, such as adding HIV testing to orders, are likely to yield sustained improvement in HIV testing.[9] Second, as we collected our data from patient EHRs, certain data such as migration background was unavailable and could not be accounted for in analyses. Additionally, reporting bias might have occurred if patients were tested for HIV outside of the hospital setting and this was not reported in the EHR. However, as physicians are expected to report any reasoning for deliberately deviating from recommended practice in patient EHRs, we would then have expected to find more reports of HIV tests done elsewhere in this case, but only 7% of tests took place outside the hospital setting. Finally, The COVID-19 pandemic may have negatively impacted the effect of our intervention. As the intervention phase was conducted during this pandemic, while restrictions were imposed by the Dutch government, several educational meetings were conducted through videoconferencing. This, and the increased strain on healthcare workers during this time, might have reduced the effect of the meetings. However, attendance at the meetings was not impacted as educational meetings were still routinely attended during this period.

CONCLUSION

The multifaceted intervention increased IC-guided HIV testing, but its effect varied by IC, possibly due to variations in implemented developments as well as a short follow-up period. Our study confirmed the cost-effectiveness of this testing strategy to identify undiagnosed people living with HIV, underlining its importance in contributing to end HIV transmission.

Contributors
SJB, MFSL, JEAMB and SEG designed the study. SEG and JEAMB acquired funding. SJB recruited patients, collected data, supervised the junior researchers collecting data, and wrote the first and final draft of the manuscript. MFSL and AB collaborated in the statistical analysis. SJB performed all data cleaning and analyses, which was all subsequently checked by MFSL. UD was involved in the design of the questionnaire. KB, KS, JB, NB and SEG supported local implementation of the intervention and data collection. All authors had access to the data used in this study. All authors interpreted the data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Data sharing statement
Data collected for this study will be made available upon reasonable request directed to the principal investigator, Prof Suzanne E. Geerlings (s.e.geerlings@amsterdamumc.nl) after completing a data sharing agreement.

Declaration of interests
Dr. Bogers has nothing to disclose. Dr. Schim van der Loeff has nothing to disclose. Dr. Boyd reports grants or contracts: ANRS, ZonMW and Participation on the Data Safety Monitoring Board or Advisory Board: Amsterdam University Medical Centers, Inserm. Dr. Davidovich has nothing to disclose. Dr. van der Valk reports grants or contracts: ViiV Healthcare, Gilead Sciences and Participation on the Data Safety Monitoring Board or Advisory Board: Viiv Healthcare, Gilead Sciences, MSD. Reimbursement paid to institution, and Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Member EACS ART and comorbidities guideline committee. Dr. Brinkman has nothing to disclose. Dr. Sigaloff has nothing to disclose. Dr. Branger has nothing to disclose. Dr. Bokhizzou has nothing to disclose. Dr. de Bree has nothing to disclose. Dr. Reiss reports grants or contracts: Gilead Sciences; ViiV Healthcare; Merck: Investigator-initiated study grants to institution and Participation on the Data Safety Monitoring Board or Advisory Board: Gilead Sciences; ViiV Healthcare; Merck: Honoraria for scientific advisory board participation paid to institution. Dr. van Bergen has nothing to disclose. Dr. Geerlings has nothing to disclose.

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REFERENCES

1. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med* 2015;**373(9)**:795-807.
2. Rutstein SE, Ananworanich J, Fidler S, et al. Clinical and public health implications of acute and early HIV detection and treatment: a scoping review. *J Int AIDS Soc* 2017;**20(1)**:21579.
3. Temprano Anrs Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015;**373(9)**:808-22.
4. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med* 2016;**375(9)**:830-9.
5. Bert F, Gualano MR, Biancone P, et al. Cost-effectiveness of HIV screening in high-income countries: A systematic review. *Health Policy* 2018;**122(5)**:533-47.
6. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.
7. Scognamiglio P, Chiaradia G, De Carli G, et al. The potential impact of routine testing of individuals with HIV indicator diseases in order to prevent late HIV diagnosis. BMC Infect Dis 2013;13:473.
8. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. Available online at https://www.eurotest.org/Projects-Collaborations/Indicator-Condition-Guided-HIV-Testing-HIDES/Guidance-HIV-Indicator-Conditions. Accessed 25 Feb 2022.
9. Bogers SJ, Hulstein SH, Schim van der Loeff MF, et al. Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis. EClinicalMedicine 2021;35:100877.
10. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2021. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2021. Available online at www.hiv-monitoring.nl.
11. Ratmann O, van Sighem A, Bezemer D, et al. Sources of HIV infection among men having sex with men and implications for prevention. Sci Transl Med 2016;8(320):320ra2.
12. Bogers SJ, Schim van der Loeff MF, Davidovich U, et al. Promoting HIV indicator condition-guided testing in hospital settings (PROTEST 2.0): study protocol for a multicentre interventional study. BMC Infect Dis 2021;21(1):519.
13. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Prenatale Screening, Infectieziekten en Erytrocytenimmunisatie (PSIE) procesmonitor 2019 (Dutch). 2019. Available online at https://www.pns.nl/documenten/proces-monitor-psie. Accessed 25 Feb 2022.
14. Nederlandse Vereniging voor Neurologie. Richtlijn Polyneuropathie (Dutch). In: Federatie van Medisch Specialisten, editor. 2019. Available online at https://richtlijnendatabase.nl/richtlijn/polyneuropathie/startpagina_-_polyneuropathie.html. Accessed 15 May 2022.
15. Nederlandse Vereniging van Obstetrie en Gynaecologie (NVOG). Richtlijn Cervixcarcinoom (Dutch). In: Federatie van Medisch Specialisten, editor. 2022. Available online at https://richtlijnendatabase.nl/richtlijn/cervixcarcinoom/startpagina_-_cervixcarcinoom.html. Accessed 15 May 2022.

16. Nederlandse Vereniging van Obstetrie en Gynaecologie (NVOG). Richtlijn Vulvacarcinoom (Dutch). In: Federatie van Medisch Specialisten, editor. 2021. Available online at https://richtlijnendatabase.nl/richtlijn/vulvacarcinoom/startpagina_-_vulvacarcinoom.html. Accessed 15 May 2022.

17. Nederlandse Vereniging voor Hematologie. Richtlijn voor de diagnostiek, behandeling en follow-up van het folliculair lymfoom (Dutch). 2017. Available online at https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Lymphoma/FL-richtlijn_revisie2019.pdf. Accessed 15 May 2022.

18. Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose. Richtlijn Medicamenteuze behandeling van tuberculose (Dutch). 2014. Available online at https://www.nvalt.nl/kwaliteit/richtlijnen/infectieziekten//Infectieziekten/Richtlijn-medicamenteuze-behandeling-van-TBC%20Oktober%202014.pdf. Accessed 15 May 2022.

19. AASLD/ISDA. Recommendations for Testing, Managing and Treating Hepatitis C. 2020. Available online at https://www.hcvguidelines.org/. Accessed 15 May 2022.

20. Nederlandse Vereniging voor Hematologie. Richtlijn diffuus grootcellig B-cel non-Hodgkin lymfoom (Dutch). 2021. Available online at https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Lymphoma/Richtlijn-DLBCL-_NVvH_2021.pdf. Accessed 15 May 2022.

21. Darling KE, Hugli O, Mamin R, et al. HIV testing practices by clinical service before and after revised testing guidelines in a Swiss University Hospital. *PLoS One* 2012;**7(6)**:e39299.

22. Elmahdi R, Gerver SM, Gomez Guillen G, Fidler S, Cooke G, Ward H. Low levels of HIV test coverage in clinical settings in the U.K.: a systematic review of adherence to 2008 guidelines. *Sex Transm Infect* 2014;**90(2)**:119-24.

23. Desai S, Tavoschi L, Sullivan AK, et al. HIV testing strategies employed in health care settings in the European Union/European Economic Area (EU/EEA): evidence from a systematic review. *HIV Med* 2020;**21(3)**:163-79.

24. Sokhi DS, Oxenham C, Coates R, Forbes M, Gupta NK, Blackburn DJ. Four-Stage Audit Demonstrating Increased Uptake of HIV Testing in Acute Neurology Admissions Using Staged Practical Interventions. *PLoS One* 2015;**10(9)**:e0134574.

25. Spoorenberg V, Hulscher ME, Geskus RB, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. *PLoS One* 2015;**10(12)**:e0142672.

26. van Daalen FV, Prins JM, Opmeer BC, et al. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. *Clin Microbiol Infect* 2017;**23(7)**:485 e1- e8.

27. Walensky RP, Weinstein MC, Kimmel AD, et al. Routine human immunodeficiency virus testing: an economic evaluation of current guidelines. *Am J Med* 2005;**118(3)**:292-300.

28. Yazdanpanah Y, Sloan CE, Charlois-Ou C, et al. Routine HIV screening in France: clinical impact and cost-effectiveness. *PLoS One* 2010;**5(10)**:e13132.

29. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015;**350**:h2750.

30. Baker R, Camosso-Stefinovic J, Gillies C, et al. Tailored interventions to address determinants of practice. *Cochrane Database Syst Rev* 2015**(4)**:CD005470.

Supplementary Table 1: Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2·0) checklist

Text Section and Item Name	Section or Item Description	Page reported
Title and Abstract		
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)	1
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	2
Introduction	*Why did you start?*	
3. Problem Description	Nature and significance of the local problem	4
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies	4
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	4
6. Specific aims	Purpose of the project and of this report	4-5
Methods	*What did you do?*	
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	5-6
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	5, tables 1 & 3
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	6-8

Supplementary Table 1: Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2·0) checklist (continued)

Text Section and Item Name	Section or Item Description	Page reported
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	6-7, supplementary tables 2-3
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	7-8
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	8
Results	*What did you find?*	
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	9-11, Tables 1-4, supplementary tables 4-8

Supplementary Table 1: Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2·0) checklist (continued)

Text Section and Item Name	Section or Item Description	Page reported
Discussion	*What does it mean?*	
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	12-14
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs	12-15
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations	14-15
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps	15, 16-17
Other information		
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	8

Supplementary Table 2: Indicator-condition specific inclusion and exclusion criteria

Tuberculosis	Patients with latent *M. tuberculosis* infection, but no tuberculosis disease, were excluded.
Cervical cancer or CIN-3	Patients without biopsy-confirmed grade III intraepithelial neoplasia or carcinoma (invasive or non-invasive) were excluded.
Vulvar cancer or VIN-3	Patients without biopsy-confirmed grade III intraepithelial neoplasia or carcinoma (invasive or non-invasive) were excluded.
Malignant lymphoma	All types of malignant lymphoma, including all subtypes of Hodgkin's lymphoma and non-Hodgkin lymphoma were included.
Hepatitis B virus infection	Both acute and chronic, and active and inactive hepatitis B virus infection cases were included. Hepatitis B virus infection cases with and without detectable serum replication were included.
Hepatitis C virus infection	Both acute and chronic, and active and inactive hepatitis C virus infection cases were included.
Peripheral neuropathy	Patients with known diabetes mellitus before presentation and patients for whom no diagnostic laboratory workup was indicated/performed were excluded.

CIN-3: Cervical intraepithelial neoplasia grade III. IC: Indicator condition. VIN-3: vulvar intraepithelial neoplasia grade III.

Supplementary Table 3: Content of the data collection form used for the collection of data from the electronic health records of eligible patients

	Form question	Options	Quality check
	Inclusion		
1.1	Is the patient diagnosed with one of the selected IC?	Yes/no	Exclusion message appears when 'no' is selected
1.2	Is the patient aged ≥18 years at diagnosis of selected IC?	Yes/no	Exclusion message appears when 'no' is selected
1.3	Is the patient known HIV positive prior to the diagnostic process for selected IC (i.e. fist presentation with/for the selected IC)?	Yes/no	Exclusion message appears when 'no' is selected
	Patient characteristics		
2.1	Patient year of birth	4-digit field	Lower/upper limit: 1900 - 2004
2.2	Year of IC diagnosis	4-digit field	Lower/upper limit: 2015 - 2021
2.3	Patient sex	Male/Female/Other	n/a
2.4	Is patient pregnant at IC diagnosis?	Yes/No	Shown if 2.3 = female
2.5	Socio-economic status of postal-code area of patient	3-digit field	Values ranging from -7.78 to 2.82 based on patient's 4-digit postal-code. Values were subsequently recoded into low/intermediate or high socio-economic status based on national tertile segments.
2.6	Is the patient deceased?	Yes/No	n/a
2.7	Date of passing	Date field	Shown if 2.6 = Yes

Supplementary Table 3: Content of the data collection form used for the collection of data from the electronic health records of eligible patients (continued)

	Form question	Options	Quality check
	Indicator condition		
3.1	Indicator condition diagnosed	Tuberculosis Cervical carcinoma/CIN-3 Vulvar carcinoma/VIN-3 Malignant lymphoma Hepatitis B virus infection Hepatitis C virus infection Peripheral neuropathy	n/a
3.2	Date of IC diagnosis	Date field	n/a
3.3	Type of lymphoma	Text field	Shown if 3.1 = malignant lymphoma
3.4	Is the patient newly diagnosed?	Yes/No	Shown if 3.1 = malignant lymphoma
3.5	Newly diagnosed lymphoma	Requiring immediate treatment Required delayed treatment Not requiring treatment	Shown if 3.4 = Yes
3.6	Not newly diagnosed lymphoma	Progressive, requiring treatment Recurrent, after remission Second opinion Transfer from another hospital	Shown if 3.4 = No
3.7	Is the patient treated for the IC?	Yes/No	n/a
3.8	Date of IC treatment initiation	Date field	Shown if 3.7 = Yes
3.9	Date of IC treatment abstention (i.e. no treatment was initiated)	Date field	Shown if 3.7 = No
3.10	Remarks on treatment abstention	Text field	Shown if 3.7 = No

Supplementary Table 3: Content of the data collection form used for the collection of data from the electronic health records of eligible patients (continued)

	Form question	Options	Quality check
	HIV testing		
4.1	Was an HIV test ever performed?	Yes/Yes, as screening during pregnancy/No	n/a
4.2	Was an HIV test performed within 3 months before or after IC diagnosis?	Yes/Yes, as screening during pregnancy/No	Shown if 4.1 = Yes
4.3	When was this test done?	Date field	Shown if 4.2 = Yes
4.4	Where was this test done?	Hospital/General practitioner/sexual health clinic/Midwife/Self-test/Community testing/ Other	Shown if 4.2 = Yes
4.5	What was the HIV test result?	Positive/Negative	Shown if 4.2 = Yes
4.6	Was a CD4 count determined after HIV diagnosis	Yes/No	Shown if 4.5 = Positive
4.7	Date of CD4 count determined	Date field	Shown if 3.6 = Yes
4.8	Value of CD4 count determined (unit cells/ mm^3)	4-digit field	Shown if 3.6 = Yes; Lower/upper limit: 0-1000
4.9	Was an HIV test performed more than 3 months, but less than 6 months before or after IC diagnosis?	Yes/Yes, as screening during pregnancy/No	Shown if 4.1 = Yes
4.10	When was this test done?	Date field	Shown if 4.9 = Yes
4.11	Where was this test done?	Hospital/General practitioner/sexual health clinic/Midwife/Self-test/Community testing/ Other	Shown if 4.9 = Yes
4.12	What was the HIV test result?	Positive/Negative	Shown if 4.9 = Yes
4.13	Was a CD4 count determined after HIV diagnosis	Yes/No	Shown if 4.12 = Positive

Supplementary Table 3: Content of the data collection form used for the collection of data from the electronic health records of eligible patients (continued)

	Form question	Options	Quality check
4.14	Date of CD4 count determined	Date field	Shown if 3.13 = Yes
4.15	Value of CD4 count determined (unit cells/ mm^3)	4-digit field	Shown if 3.13 = Yes; Lower/upper limit: 0-1000
4.16	Was an HIV test performed >6 months before or after IC diagnosis?	Yes/Yes, as screening during pregnancy/No	Shown if 4.1 = Yes
4.17	When was this test done?	Date field	Shown if 4.16 = Yes
4.18	Where was this test done?	Hospital/General practitioner/sexual health clinic/Midwife/Self-test/Community testing/ Other	Shown if 4.16 = Yes
4.19	What was the HIV test result?	Positive/Negative	Shown if 4.16 = Yes
4.20	Was a CD4 count determined after HIV diagnosis	Yes/No	Shown if 4.19 = Positive
4.21	Date of CD4 count determined	Date field	Shown if 3.20 = Yes
4.22	Value of CD4 count determined (unit cells/ mm^3)	4-digit field	Shown if 3.20 = Yes; Upper/lower limit: 0-1000
4.23	Was an HIV test offered by the physician at IC diagnosis?	Yes/No	Shown if 4.1, or 4.2 and 4.9 = No
4.24	Did the patient agree to the HIV test?	Yes/No	Shown if 4.23 = Yes
4.25	Comment on not testing	Text field	Shown if 4.23 = Yes
4.26	Was a reason for not offering HIV testing reported by the physician?	Yes/No	Shown if 4.23 = No
4.27	Comment on not offering	Text field	Shown if 4.23 = No
4.28	Other remarks	Text field	n/a

CIN-3: cervical intraepithelial neoplasia grade 3. IC: indicator condition. n/a: not applicable. VIN-3: vulvar intraepithelial neoplasia grade 3.

Supplementary Table 4: Proportion of patients tested for HIV within 3 months after indicator condition diagnosis, and unadjusted and adjusted risk ratio's, overall and by indicator condition, Amsterdam region 2015-2021.

	Before intervention (n=6,730)	After intervention (n=1,256)	Unadjusted risk ratio (95% CI)	*p* value	Adjusted risk ratio* (95% CI)	*p* value
Overall	1,506/6,730 (22·4%)	367/1,256 (29·2%)	1·32 (1·13-1·53)	<0·001	1·33 (1·14-1·55)	<0·001
By indicator condition						
Tuberculosis	183/379 (48·3%)	32/59 (54·2%)	1·12 (0·69-1·81)	0·65	1·06 (0·65-1·73)	0·82
Cervical cancer or CIN-3	36/1,075 (3·4%)	66/275 (24·0%)	4·35 (2·15-8·79)	<0·001	4·09 (2·01-8·29)	<0·001
Vulvar cancer or VIN-3	1/283 (0·4%)	0/52 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	632/1,612 (39·2%)	190/361 (52·6%)	1·03 (0·83-1·28)	0·80	1·03 (0·83-1·28)	0·80
Hodgkin's lymphoma	76/228 (33·3%)	19/35 (54·3%)	1·21 (0·63-2·31)	0·56	1·19 (0·62-2·30)	0·60
T-cell lymphoma	75/173 (43·4%)	19/36 (52·8%)	0·84 (0·45-1·59)	0·60	0·83 (0·44-1·56)	0·56
Diffuse large B-cell lymphoma	271/536 (50·6%)	94/150 (62·7%)	1·07 (0·78-1·47)	0·68	1·07 (0·77-1·48)	0·69
Mantle cell lymphoma	53/90 (58·9%)	15/26 (57·7%)	0·79 (0·37-1·71)	0·55	0·87 (0·39-1·95)	0·74
Follicular lymphoma	66/234 (28·2%)	12/37 (32·4%)	0·70 (0·33-1·48)	0·35	0·69 (0·32-1·46)	0·33
Marginal zone/MALT lymphoma	33/133 (24·8%)	17/32 (53·1%)	1·62 (0·68-3·87)	0·28	1·62 (0·67-3·91)	0·28
Burkitt lymphoma	18/28 (64·3%)	2/4 (50·0%)	0·98 (0·18-5·41)	0·98	0·85 (0·15-4·73)	0·85
Lymphoplasmacytic lymphoma	2/16 (12·5%)	0/1 (0·0%)	n/a	n/a	n/a	n/a
Non-Hodgkin lymphoma, other	38/174 (21·8%)	12/40 (30·0%)	0·90 (0·38-2·13)	0·81	0·84 (0·35-2·02)	0·70
Hepatitis B virus infection	267/809 (33·0%)	23/99 (23·2%)	1·10 (0·67-1·79)	0·71	1·11 (0·68-1·81)	0·68
Hepatitis C virus infection	231/499 (46·3%)	18/63 (28·6%)	0·77 (0·44-1·34)	0·35	0·76 (0·43-1·35)	0·35
Peripheral neuropathy	156/2,073 (7·5%)	38/347 (11·0%)	2·39 (1·44-3·96)	0·001	2·43 (1·46-4·05)	0·001

*Analyses are performed using multivariable models adjusting for confounding patient characteristics sex, age, socio-economic status, and pregnant at time of indicator condition diagnosis. CIN-3: Cervical intraepithelial neoplasia grade III. n/a: parameter estimates could not be obtained. MALT: mucosa-associated lymphoid tissue. VIN-3: vulvar intraepithelial neoplasia grade III.

Supplementary Table 5: Proportions of patients tested for HIV within 3 months before or after indicator condition diagnosis, and unadjusted and adjusted risk ratio's, by hospital and indicator condition, Amsterdam region 2015-2021.

	Before intervention	After intervention	Unadjusted risk ratio* (95% CI)	*p* value	Adjusted risk ratio** (95% CI)	*p* value
University hospital 1	**n= 2,945**	**n=361**				
Tuberculosis	46/61 (75·4%)	6/9 (66·7%)	0·96 (0·35-2·65)	0·94	n/a	n/a
Cervical cancer or CIN-3	34/596 (5·7%)	65/114 (57·0%)	4·32 (2·11-8·86)	<0·001	4·29 (2·10-8·80)	<0·001
Vulvar cancer or VIN-3	1/226 (0·4%)	0/38 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	297/473 (62·8%)	54/69 (78·3%)	1·09 (0·76-1·58)	0·63	1·15 (0·79-1·66)	0·47
Hepatitis B virus infection	155/217 (71·4%)	11/13 (84·6%)	1·01 (0·51-2·04)	0·97	1·03 (0·51-2·07)	0·94
Hepatitis C virus infection	109/155 (70·3%)	6/6 (100·0%)	n/a	n/a	n/a	n/a
Peripheral neuropathy	157/1,217 (12·9%)	16/112 (14·3%)	2·00 (1·04-3·86)	0·04	2·17 (1·12-4·21)	0·02
University hospital 2	**n=919**	**n=164**				
Tuberculosis	40/51 (78·4%)	5/5 (100·0%)	1·08 (0·34-3·43)	0·90	n/a	n/a
Cervical cancer or CIN-3	1/52 (1·9%)	0/1 (0·0%)	n/a	n/a	n/a	n/a
Vulvar cancer or VIN-3	0/3 (0·0%)	0/0 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	293/471 (62·2%)	92/111 (82·9%)	0·96 (0·70-1·31)	0·80	0·96 (0·70-1·31)	0·79
Hepatitis B virus infection	83/131 (63·4%)	11/12 (91·7%)	1·90 (0·85-4·21)	0·12	1·82 (0·81-4·10)	0·15
Hepatitis C virus infection	50/77 (64·9%)	5/8 (62·5%)	1·06 (0·36-3·12)	0·92	n/a	n/a
Peripheral neuropathy	6/134 (4·5%)	4/27 (14·8%)	4·72 (0·55-40·53)	0·16	n/a	n/a
Teaching hospital 1	**n=1,531**	**n=360**				
Tuberculosis	178/205 (86·8%)	26/28 (92·9%)	0·93 (0·56-1·56)	0·79	n/a	n/a
Cervical cancer or CIN-3	4/172 (2·3%)	5/43 (11·6%)	0·69 (0·08-6·11)	0·74	n/a	n/a
Vulvar cancer or VIN-3	1/27 (3·7%)	0/9 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	259/352 (73·6%)	83/109 (76·1%)	0·92 (0·66-1·28)	0·63	0·92 (0·66-1·29)	0·64
Hepatitis B virus infection	208/321 (64·8%)	47/62 (75·8%)	0·98 (0·67-1·43)	0·92	0·96 (0·65-1·41)	0·84

Supplementary Table 5: Proportions of patients tested for HIV within 3 months before or after indicator condition diagnosis, and unadjusted and adjusted risk ratio's, by hospital and indicator condition, Amsterdam region 2015-2021. (continued)

	Before intervention	After intervention	Unadjusted risk ratio* (95% CI)	*p* value	Adjusted risk ratio** (95% CI)	*p* value
Hepatitis C virus infection	152/210 (72·4%)	32/43 (74·4%)	0·88 (0·54-1·44)	0·61	0·94 (0·55-1·59)	0·81
Peripheral neuropathy	33/244 (13·5%)	17/66 (25·8%)	1·49 (0·65-3·42)	0·35	1·54 (0·64-3·70)	0·33
Teaching hospital 2	**n=723**	**n=197**				
Tuberculosis	27/35 (77·1%)	5/7 (71·4%)	1·18 (0·33-4·31)	0·80	n/a	n/a
Cervical cancer or CIN-3	4/97 (4·1%)	5/55 (9·1%)	1·20 (0·14-10·06)	0·87	n/a	n/a
Vulvar cancer or VIN-3	0/16 (0·0%)	0/4 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	99/203 (48·8%)	40/52 (76·9%)	1·44 (0·86-2·40)	0·17	1·47 (0·86-2·51)	0·16
Hepatitis B virus infection	57/112 (50·9%)	3/5 (60·0%)	1·46 (0·41-5·18)	0·56	1·76 (0·48-6·47)	0·40
Hepatitis C virus infection	35/47 (74·5%)	3/6 (50·0%)	0·68 (0·15-3·00)	0·61	n/a	n/a
Peripheral neuropathy	14/213 (6·6%)	8/68 (11·8%)	1·34 (0·42-4·28)	0·62	n/a	n/a
Non-teaching hospital 1	**n=612**	**n=174**				
Tuberculosis	26/27 (96·3%)	10/10 (100·0%)	1·09 (0·39-3·02)	0·87	n/a	n/a
Cervical cancer or CIN-3	3/158 (1·9%)	2/62 (3·2%)	2·15 (0·13-35·42)	0·59	n/a	n/a
Vulvar cancer or VIN-3	0/11 (0·0%)	0/1 (0·0%)	n/a	n/a	n/a	n/a
Malignant lymphoma	73/113 (64·6%)	17/20 (85·0%)	1·13 (0·56-2·28)	0·73	n/a	n/a
Hepatitis B virus infection	17/28 (60·7%)	5/7 (71·4%)	1·17 (0·33-4·16)	0·81	n/a	n/a
Hepatitis C virus infection	5/10 (50·0%)	0/0 (0·0%)	n/a	n/a	n/a	n/a
Peripheral neuropathy	11/265 (4·2%)	7/74 (9·5%)	7·69 (1·30-45·30)	0·02	n/a	n/a

*Analyses are performed using segmented time-series models not correcting for patient characteristics. ** Analyses are performed using multivariable models adjusting for confounding patient characteristics sex, age, socio-economic status, and pregnant at time of indicator condition diagnosis. CIN-3: Cervical intraepithelial neoplasia grade III. n/a: parameter estimates could not be obtained. VIN-3: vulvar intraepithelial neoplasia grade III.

Supplementary Table 6: Proportions tested for HIV within 3 months before or after indicator condition diagnosis, and risk ratio, overall and by indicator condition - Random effects model accounting for variability by hospital. Amsterdam region, 2015-2021.

	Before intervention (n=6,730)	After intervention (n=1,256)	Adjusted risk ratio (95% CI)*	p value
Overall	2,478/6,730 (36·8%)	590/1,256 (47·0%)	1·16 (1·03-1·31)	0·01
By indicator condition				
Tuberculosis	317/379 (83·6%)	52/59 (88·1%)	n/a	n/a
Cervical cancer or CIN-3	46/1,075 (4·3%)	77/275 (28·0%)	3·76 (2·01-7·04)	<0·001
Vulvar cancer or VIN-3	2/283 (0·7%)	0/52 (0·0%)	n/a	n/a
Malignant lymphoma	1,021/1,612 (63·3%)	286/361 (79·2%)	1·04 (0·88-1·24)	0·64
Hodgkin's lymphoma	158/228 (69·3%)	32/35 (91·4%)	n/a	n/a
T-cell lymphoma	111/173 (64·2%)	32/36 (88·9%)	n/a	n/a
Diffuse large B-cell lymphoma	393/536 (73·3%)	132/150 (88·0%)	n/a	n/a
Mantle cell lymphoma	65/90 (72·2%)	22/26 (84·6%)	n/a	n/a
Follicular lymphoma	121/234 (51·7%)	18/37 (48·7%)	0·67 (0·37-1·22)	0·19
Marginal zone/MALT lymphoma	58/133 (43·6%)	21/32 (65·6%)	1·12 (0·56-2·26)	0·75
Burkitt lymphoma	25/28 (89·3%)	4/4 (100·0%)	n/a	n/a
Lymphoplasmacytic lymphoma	4/16 (25·0%)	1/1 (100%)	n/a	n/a
Non-Hodgkin lymphoma, other	86/174 (49·4%)	24/40 (60·0%)	n/a	n/a
Hepatitis B virus infection	520/809 (64·3%)	77/99 (77·8%)	n/a	n/a
Hepatitis C virus infection	351/499 (70·3%)	46/63 (73·0%)	n/a	n/a
Peripheral neuropathy	221/2,073 (10·7%)	52/347 (15·0%)	2·33 (1·52-3·59)	<0·001

*Analyses are performed using multivariable models correcting for relevant patient characteristics sex, age, socio-economic status, and pregnant at time of indicator condition diagnosis. CIN-3: Cervical intraepithelial neoplasia grade III. n/a: parameter estimates could not be obtained. MALT: mucosa-associated lymphoid tissue. VIN-3: vulvar intraepithelial neoplasia grade III.

Supplementary Table 7: Characteristics of patients tested and not tested for HIV within 3 months before or after indicator condition diagnosis in five hospitals in the region of Amsterdam, 2015-2021

	Tested for HIV (n=3,068)	Not tested for HIV (n=4,918)	*p* value
Sex			<0·001
Female	1,285 (41·9%)	3,203 (65·1%)	
Male	1,783 (58·1%)	1,715 (34·9%)	
Pregnant at IC diagnosis*	98 (7·6%)	52 (1·6%)	<0·001
Age at IC diagnosis, y	52 (37-64)	59 (43-71)	<0·001
Socio-economic status**			<0·001
Low	1,204 (39·7%)	1,693 (34·7%)	
Intermediate	676 (22·3%)	1,157 (23·7%)	
High	1,156 (38·1%)	2,033 (41·6%)	
Deceased ≤180 days after IC diagnosis	131 (4·3%)	113 (2·3%)	<0·001

Data are depicted as n (%) or median (IQR). *Percentages are calculated using the number of female patients as denominator. **Overall, 67 patients had a missing socio-economic status value; 32 in the tested and 35 in the not-tested group.

Supplementary Table 8: Characteristics of patients testing HIV positive versus HIV negative within 3 months before or after indicator condition diagnosis in five hospitals in the region of Amsterdam, 2015-2021

	HIV positive (n=18)	HIV negative (n=3,050)	*p* value
Study period			0·23
Pre-intervention	17 (0·7%)	2,461 (99·3%)	
Post-intervention	1 (0·2%)	589 (99·8%)	
Sex			0·10
Female	4 (0·3%)	1,281 (99·7%)	
Male	14 (0·8%)	1,769 (99·2%)	
Pregnant at IC diagnosis*	0 (0·0%)	98 (100%)	1·00
Age at IC diagnosis, y	45 (34-54)	52 (37-64)	0·05
Socio-economic status**			0·42
Low	10 (0·8%)	1,194 (99·2%)	
Intermediate	3 (0·4%)	673 (99·6%)	
High	5 (0·4%)	1,151 (99·6%)	
Indicator condition			0·02
Tuberculosis	8 (2·2%)	361 (97·8%)	
Cervical cancer or CIN-3	0 (0·0%)	123 (100%)	
Vulvar cancer or VIN-3	0 (0·0%)	2 (100%)	
Malignant lymphoma	7 (0·5%)	1,300 (99·5%)	0·36
Hodgkin's lymphoma	0 (0·0%)	190 (100%)	
T-cell lymphoma	1 (0·7%)	142 (99·3%)	
Diffuse large B-cell lymphoma	5 (1·0%)	520 (99·0%)	
Mantle cell lymphoma	0 (0·0%)	87 (100%)	
Follicular lymphoma	0 (0·0%)	139 (100%)	
Marginal zone/MALT lymphoma	0 (0·0%)	79 (100%)	
Burkitt lymphoma	1 (3·5%)	28 (96·6%)	
Lymphoplasmacytic lymphoma	0 (0·0%)	5 (100%)	
Non-Hodgkin lymphoma, other	0 (0·0%)	110 (100%)	
Hepatitis B virus infection	2 (0·4%)	595 (99·7%)	
Hepatitis C virus infection	1 (0·3%)	396 (99·8%)	
Peripheral neuropathy	0 (0·0%)	273 (100%)	
Hospital of inclusion			0·25
University hospital 1	4 (0·4%)	953 (99·6%)	
University hospital 2	5 (0·9%)	585 (99·2%)	
Teaching hospital 1	5 (0·5%)	1,040 (99·5%)	
Teaching hospital 2	1 (0·3%)	299 (99·7%)	
Non-teaching hospital 1	3 (1·7%)	173 (98·3%)	
Died ≤3 months after IC diagnosis	2 (2·9%)	68 (97·1%)	0·01

Supplementary Table 8: Characteristics of patients testing HIV positive versus HIV negative within 3 months before or after indicator condition diagnosis in five hospitals in the region of Amsterdam, 2015-2021 (continued)

	HIV positive (n=18)	HIV negative (n=3,050)	*p* value
CD4 count at HIV diagnosis, cells/mm³	97 (50-130)	n/a	
CD4 count <350 cells/mm³ at HIV diagnosis	17 (94·4%)	n/a	

Data are depicted as n (%) or median (IQR). *Percentages are calculated using the number of female patients as denominator. **Overall, 67 patients had a missing socio-economic status value; 32 in the tested and 35 in the not-tested group. CIN-3: Cervical intraepithelial neoplasia grade III. MALT: mucosa-associated lymphoid tissue. n/a: not applicable. VIN-3: vulvar intraepithelial neoplasia grade III.

Chapter 10

Mapping hematologists' HIV testing behavior among lymphoma patients – A mixed-methods study

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ABSTRACT

Background
HIV testing among patients with malignant lymphoma (PWML) is variably implemented. We evaluated HIV testing among PWML, and mapped factors influencing hematologists' testing behavior.

Materials
We conducted a mixed-methods study assessing HIV testing among PWML, factors influencing HIV testing and opportunities for improvement in five hospitals in the region of Amsterdam, the Netherlands. The proportion of PWML tested for HIV within 3 months before or after lymphoma diagnosis and percentage positive were assessed from January 2015 through June 2020. Questionnaires on intention, behavior and psychosocial determinants for HIV testing were conducted among hematologists. Through twelve semi-structured interviews among hematologists and authors of hematology guidelines, we further explored influencing factors and opportunities for improvement.

Findings
Overall, 1,612 PWML were included for analysis, including 976 patients newly diagnosed and 636 patients who were referred or with progressive/relapsed lymphoma. Seventy percent (678/976) of patients newly diagnosed and 54% (343/636) of patients with known lymphoma were tested for HIV. Overall, 7/1,021 (0.7%) PWML tested HIV positive, exceeding the 0.1% cost-effectiveness threshold. Questionnaires were completed by 40/77 invited hematologists, and 85% reported intention to test PWML for HIV. In the interviews, hematologists reported varying HIV testing strategies, including testing all PWML or only when lymphoma treatment is required. Recommendations for improved HIV testing included guideline adaptations, providing electronic reminders and monitoring and increasing awareness.

Conclusions
Missed opportunities for HIV testing among PWML occurred and HIV test strategies varied among hematologists. Efforts to improve HIV testing among PWML should include a combination of approaches.

INTRODUCTION

In 2020, an estimated 2.6 million people were living with HIV in the European region and an estimated 170,000 people became newly infected[1]. Meanwhile, an estimated 33% were unaware of their HIV status, underlining the urgent need for optimal HIV testing[1].

A cost-effective strategy for HIV testing is indicator condition (IC)-guided testing[2-5]. ICs are conditions that are associated with an undiagnosed HIV prevalence of >0.1%, the established cost-effectiveness threshold for HIV screening, that are AIDS-defining, or conditions where failure to identify an HIV infection may have significant adverse implications[6-9]. Even though IC-guided HIV testing is now widely recommended, it is still not a routine practice in the European hospital setting[10-12].

Malignant lymphoma, including both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), is one of the currently recognized ICs[9]. The risk of developing NHL or HL is markedly increased in people living with HIV (PLHIV) compared to HIV-negative persons[13,14]. The cumulative incidence of NHL and HL among PLHIV by the age of 75 years is 4.5% and 0.9%, compared to 0.7% and 0.1% among HIV-negative people, respectively[15]. In the Netherlands, NHL is the first occurring AIDS-defining event in 6% of PLHIV, and HL is one of the most common non-AIDS-defining malignancies[16]. HIV testing in patients diagnosed with malignant lymphoma (PWML) may therefore be an important strategy to identify undiagnosed PLHIV, and routine HIV testing at diagnosis is recommended in the guidelines of several lymphoma subtypes[17-19].

We designed a multicenter intervention study (PROTEST 2.0) to assess and subsequently improve IC-guided testing in a selection of ICs, including malignant lymphoma[20,21]. We found that prior to the intervention, 63% of PWML were tested for HIV within 3 months before or 3 months after lymphoma diagnosis. Stratification by lymphoma type revealed significant variation in HIV testing, with the highest proportions of PWML tested among patients with aggressive types of lymphoma including Burkitt's lymphoma (89%), diffuse large B-cell lymphoma (DLBCL; 73%), mantle cell lymphoma (72%), HL (69%), and T-cell lymphoma (64%), while lowest testing proportions were observed among patients with low-grade types of lymphoma, including lymphoplasmacytic lymphoma (25%), marginal zone or mucosa-associated lymphoid tissue lymphoma (44%), and follicular lymphoma (52%)[21].

As it is unknown which factors influence IC-guided testing for HIV among PWML, in this study, we aimed to assess HIV testing among PWML in more detail, and map factors influencing hematologists' HIV testing behavior among PWML.

MATERIAL AND METHODS

Study design and setting

This study is part of the PROTEST 2.0 study, which was conducted at two university hospitals, two teaching hospitals and one non-teaching hospital[20]. We performed a mixed-methods study using retrospective data on HIV testing from PWML, and questionnaires and semistructured interviews among hematologists in the region of Amsterdam, the Netherlands. Data on HIV testing among PWML overall and by subtype have previously been reported in the context of the PROTEST 2.0 study results[21]. Here we report on HIV testing among PWML by diagnosis and treatment status.

Patient eligibility and assessment of HIV testing

Data from all eligible patients diagnosed with any type of malignant lymphoma in the five participating hospitals from January 2015 through June 2020 were collected. Patients ≥18 years, diagnosed with lymphoma or referred for a second opinion or treatment after lymphoma diagnosis were eligible. Patients without a pathology-confirmed lymphoma diagnosis, those with a known HIV infection prior to lymphoma work-up and diagnosis, and those diagnosed and treated for lymphoma at another hospital were excluded. The primary outcome was the proportion of patients who were tested for HIV within 3 months before or after lymphoma diagnosis. Secondary outcomes were the proportion of patients tested for HIV before initiating lymphoma treatment, the proportion HIV positive, and the proportion of patients who had a CD4 count <350 cells/mm^3 at diagnosis (i.e. late-stage HIV infection).

Questionnaire design and recruitment

Online questionnaires on HIV testing in PWML were conducted anonymously among hematologists in June 2020. All hematology attending physicians and residents in the five hospitals were invited to participate in the questionnaire study by email, and the response ratio was recorded. The questionnaire was based on the Attitude, Social influence and self-Efficacy (ASE) model derived from the Theory of Planned Behavior (TPB)[22,23]. The final questionnaire contained fifteen 5-point Likert scale questions (1 = most negative response, 5 = most positive response), including one on self-reported HIV testing in PWML, two on intention to test, and twelve on attitudes, norms and self-efficacy regarding HIV testing in PWML (Supplemental Table 1).

Interview design and recruitment

Semi-structured interviews were conducted among hematologists and authors of hematology guidelines in the five hospitals from August 2020 through April 2021. Authors were identified using author lists of currently published national hematology guidelines. The TPB model was used in the design of the interview guide for hematologists[22]. The five domains were knowledge, attitudes, norms, self-efficacy and perceived barriers (Supplemental Table 2). The translational research model developed from Rogers' diffusion of innovations model was used in the design of the interview guide for authors of hematology guidelines[24,25]. The three domains were guideline characteristics (i.e. what is recommended in regards to HIV testing,

and who and how is this recommended), communication, and normative systems (Supplemental Table 3). All interview participants were additionally requested to suggest opportunities to improve HIV testing in PWML. Convenience sampling was used for participant recruitment. Questionnaire respondents were invited to participate in the interviews at the end of the questionnaire. Additionally, interview participants were recruited through personal invitation by email in all five hospitals, regardless of whether they had completed the questionnaire.

Data collection

Eligible patients were given the opportunity to opt-out of the use of their data. From the electronic health records (EHR) of included PWML, data on patient demographics, lymphoma diagnosis, and HIV testing were collected using Castor (Castor EDC, Amsterdam, the Netherlands)[20]. Scanned referral letters and other archived documents in patients' EHRs were searched for any evidence of HIV testing done in other settings. LimeSurvey was used for collection of questionnaire data (LimeSurvey GmbH, Hamburg, Germany). As interviews took place during the COVID-19 pandemic, all interviews were conducted through Zoom (Zoom Video Communications Inc., San Jose, California, USA) by AD. The duration of the interviews ranged from 9 to 30 minutes. Audio recordings were made using a secured recording device. No personal identifiers were recorded during the interviews. Interviews were transcribed verbatim by SJB and AD.

Data analysis

Categorical data collected from EHR of eligible PWML were summarized using frequencies and percentages, and continuous data as means and standard deviations (SD) or medians and interquartile ranges (IQR). Variable distributions were compared between patient groups using unpaired t-tests or Mann-Whitney U tests for continuous data and X^2 or Fisher-exact tests for categorical data. Data on questionnaire participant characteristics and factors influencing HIV testing among PWML were summarized descriptively. All quantitative data analyses were performed using Stata 15 (StataCorp LLC, College Station, Texas, USA). AD and SJB coded all transcribed interview data and completed an initial coding system following thematic analysis methods by Braun and Clarke[26]. Subsequently, HZ checked a random sample of 50% for agreement. The final coding system was completed after consensus discussion by SJB and HZ. All qualitative data analyses were performed using MaxQDA 2022 (VERBI Software, Berlin, Germany).

Ethics statement

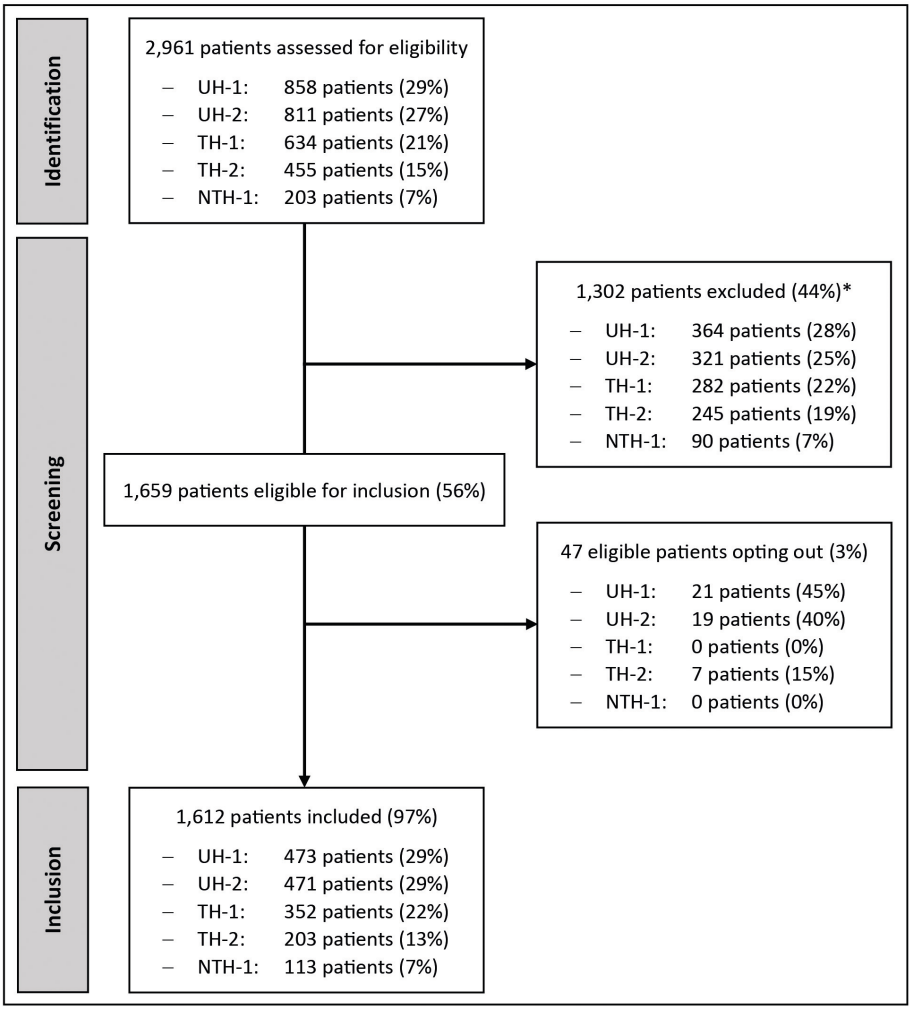
All eligible patients were given the opportunity to opt-out of their data being used through written correspondence. All questionnaire and interview participants provided written consent to participation. The Medical Ethics Committee of the Amsterdam UMC, location AMC (METC AMC) determined that this study does not meet the definition of medical research involving human subjects under Dutch law (file no. A1 20.076, 24 February 2020).

RESULTS

HIV testing results

A total of 2,961 patient EHRs were screened for eligibility and data of 1,612 patients were included (Figure 1).

Figure 1: Flowchart of identification, screening and inclusion of data of patients diagnosed with malignant lymphoma in five hospitals in the region of Amsterdam, 2015-2020.



*Reasons for exclusion were: no definitive lymphoma diagnosis (20%), lymphoma diagnosis and treatment prior completely took place before the study period (57%), diagnosed and treated for lymphoma all took place at another hospital (20%), and known HIV infection prior to lymphoma work-up and diagnosis (3%). NTH: Non-teaching hospital. TH: Teaching hospital. UH: University hospital.

Table 1. Characteristics of included patients with malignant lymphoma in five hospitals in the region of Amsterdam, overall and by HIV testing within 3 months before and after malignant lymphoma diagnosis, treatment or work-up, 2015-2020

	Overall (column %) (n= 1,612)	Tested for HIV (row %) (n=1,021)	Not tested for HIV (row %) (n=591)	*p* value
Sex				<0.001
Female	687 (42.6%)	398 (57.9%)	289 (42.1%)	
Male	925 (57.4%)	623 (67.4%)	302 (32.7%)	
Age at lymphoma diagnosis (y)	61 (49-71)	59 (47-69)	64 (53-74)	<0.001
Socio-economic status*				0.870
Low	494 (31.0%)	317 (64.2%)	177 (35.8%)	
Intermediate	392 (24.6%)	250 (63.8%)	142 (36.2%)	
High	706 (44.4%)	443 (62.8%)	263 (37.3%)	
Hospital of inclusion				<0.001
University hospital 1	473 (29.3%)	297 (62.8%)	176 (37.2%)	
University hospital 2	471 (29.2%)	293 (62.2%)	178 (37.8%)	
Teaching hospital 1	352 (21.8%)	259 (73.6%)	93 (26.4%)	
Teaching hospital 2	203 (12.6%)	99 (48.8%)	104 (51.2%)	
Non-teaching hospital 1	113 (7.0%)	73 (64.6%)	40 (35.4%)	
Lymphoma diagnosis				<0.001
Newly diagnosed at study site	976 (60.6%)	678 (69.5%)	298 (30.5%)	<0.001
Requiring immediate treatment	832 (85.3%)	614 (73.8%)	218 (26.2%)	
Requiring treatment later	44 (4.5%)	24 (54.6%)	20 (45.5%)	
Not requiring treatment	100 (10.3%)	40 (40.0%)	60 (60.0%)	
Known lymphoma diagnosis at presentation	636 (39.5%)	343 (53.9%)	293 (46.1%)	<0.001
Progressive, requiring treatment	26 (4.1%)	8 (30.8%)	18 (69.2%)	
Relapsed lymphoma	171 (26.9%)	82 (48.0%)	89 (52.1%)	
Second opinion	117 (18.4%)	20 (17.1%)	97 (82.9%)	
Transfer from another hospital	322 (50.6%)	233 (72.4%)	89 (27.6%)	

Data are depicted as n (%) or median (IQR). *Twenty patients had a missing socio-economic status.

Overall, 976 patients (61%) had a new lymphoma diagnosis, and 636 (40%) had a known lymphoma diagnosis but newly entered into care at one of the study sites due to transfer of care, relapsed or progressive disease, or a second opinion. Overall, 1,021 patients (63%) were tested for HIV within 3 months before or after diagnosis[21]; 678/976 (70%) of patients newly diagnosed and 343/636 (54%) of patients who newly entered care. The proportion of patients tested was higher among males than females and higher in younger patients, but did not differ by socio-economic status (Table 1). The proportion of patients tested for HIV varied significantly by hospital (Table 1). By type of lymphoma, significant differences in proportion of patients tested by hospital were observed among patients with Hodgkin's lymphoma (p=0.007), DLBCL (p=0.037), mantle cell lymphoma (p=0.029), follicular lymphoma (p=0.001) and marginal zone or mucosa-associated lymphoid tissue lymphoma (p<0.001), but not among patients with T-cell lymphoma (p=0.364), Burkitt lymphoma (p=0.891), LPL (p=0.504), and other NHL types (p=0.095).

Of 1,306 patients who received treatment for their lymphoma, 928 (71%) were tested for HIV within 3 months before or after diagnosis, of whom 838 (90%) were tested before or on the first day of lymphoma treatment. However, 242/1,306 (19%) of patients who received treatment had no evidence of ever being tested for HIV in their EHR. The remaining 136/1,306 (10%) were tested more than 3 months before or after lymphoma diagnosis. Among patients without any evidence of HIV testing, 139/242 (57%) had a new lymphoma diagnosis requiring immediate treatment.

Of 1,021 patients who were tested for HIV within 3 months before or after diagnosis, seven (0.7%) were HIV positive, all of whom had a CD4 count <350 cells/mm^3 at diagnosis (median 97 cells/mm^3, IQR 60-130). Of these, five (71%) had DLBCL, one (14%) had Burkitt's lymphoma and one (14%) had T-cell lymphoma. All patients were male and median age at diagnosis was 51 years (IQR 35-57).

Questionnaire results

The overall response ratio to the hematologists' questionnaire was 40/77 (52%), including 21/40 (53%) in the two university hospitals, 5/21 (24%) in the two teaching hospitals and 14/16 (88%) in the non-teaching hospital. Of respondents, 15 (38%) were attending physicians and 25 (63%) were residents. Median length of work experience in hematology was 4 years (IQR 1-10). Respondents answered all questions. While 27/40 (68%) of respondents reported that they had tested PWML for HIV in the last year, 34/40 (85%) reported intention to test in the future (Figure 2). By hospital, self-reported testing in the last year varied significantly (p=0.032) and was lowest in the non-teaching hospital (mean Likert score 2.8, SD 1.7), followed by the university hospitals (mean 4.3, SD 0.9), while it was highest in the teaching hospitals (mean 4.4, SD 0.9). Intention to test in the future did not differ significantly (mean Likert scores of 4.6, SD=0.6 in the university hospitals, 4.6, SD=0.9 in the teaching hospitals, and 4.1, SD=4.1 in the non-teaching hospital, p=0.480). Overall, average statement scores were similar across the attitudes, norms and self-efficacy domains. The statements "PWML expect me to test them for HIV" (norms), "HIV testing in PWML is discussed in my department" (norms) and "I'm comfortable

offering PWML an HIV test" (self-efficacy) scored lowest on a 5-point Likert scale. The statements "Testing PWML for HIV is in our lymphoma guidelines" (norms), "Ordering an HIV test for PWML is easily arranged" (self-efficacy), and "I'm capable of testing PWML for HIV" (self-efficacy) scored highest (Figure 2).

Interview results

Ten hematologists and two authors of hematology guidelines were interviewed. Median age of respondents was 42 years (IQR 40-46 years). Nine (75%) worked at a university hospital and 3 (25%) at a teaching hospital. No hematologists from the non-teaching hospital could be recruited.

Interviews with hematologists

From the interviews with the hematologists, seven themes emerged, including **testing strategy**, **timing**, **reasons**, **knowledge**, **norms**, **ways of informing patients**, **patient's responses**, **self-efficacy**, **barriers** and **facilitators** (Table 2).

Several HIV **testing strategies** were identified, including testing as part of the diagnostic work-up for lymph node swelling, when recommended by lymphoma guidelines, testing all new lymphoma patients, and only testing when lymphoma treatment was indicated:

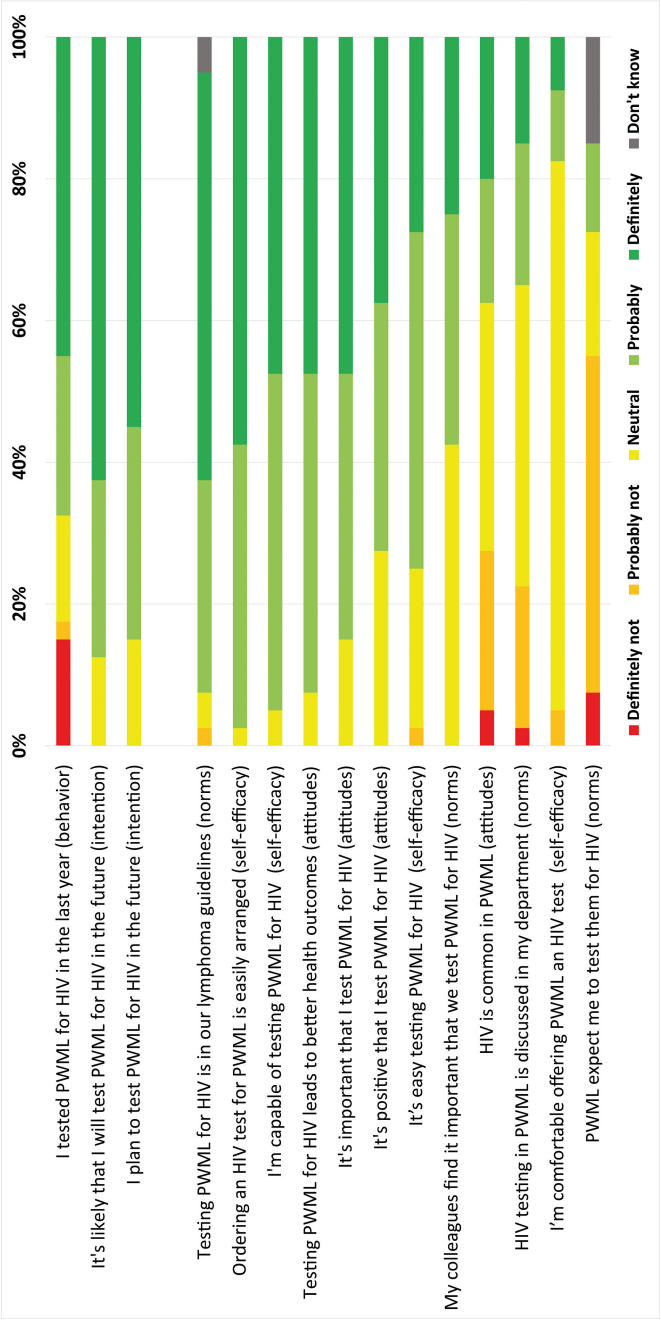
"*It has more to do with the immunosuppressive therapy I am giving them. If they have HIV, I want to know of course*." (university hospital hematologist, female, 39 years)

Accordingly, the **timing of testing** varied among respondents, with some reporting to test immediately at lymphoma diagnosis, while others test before/at the start of lymphoma treatment. One hematologist reported that timing of testing may vary:

"*The timing of the testing may be different because in patients with chronic lymphocytic leukemia for example I do it at diagnosis but some people only do it when they start the treatment*." (university hospital hematologist, female, 42 years)

Reasons for HIV testing among PWML included clinical relevance for patients and provider: HIV being a risk factor for lymphoma, HIV negatively affecting the lymphoma treatment outcome, and to protect staff from occupational infection. Hematologists reported that they gained their **knowledge** on HIV testing recommendations from national and local guidelines, as well as educational sessions. However, the majority (n=7) reported not knowing the exact guideline recommendations on HIV testing, while others (n=5) reported that the guidelines do recommend HIV testing. Regarding **norms**, several hematologists reported that they were reminded of HIV testing when colleagues mentioned it, while one reported routinely mentioning HIV testing to remind others. No hematologists reported that patients' beliefs or attitudes regarding HIV testing influenced their own HIV testing behavior.

Figure 2: Questionnaire responses on barriers and facilitators for HIV testing among patients with malignant lymphoma by 40 hematology physicians from 5 hospitals in the region of Amsterdam, 2020, ranked by statement score.



PWML: patients with malignant lymphoma.

Table 2: Themes identified from semi-structured interviews with hematologists on their HIV testing behavior among lymphoma patients, and influencing factors

HIV testing strategy
Test every new lymphoma patient *(n=8)*
Test lymphoma patients only when treating *(n=5)*
Test as part of lymph node swelling/ diagnostic work-up *(n=3)*
Follow the guideline *(n=2)*
Timing
Test at/before start of treatment *(n=8)*
Test at lymphoma diagnosis *(n=3)*
Timing may vary by lymphoma type *(n=1)*
Reasons for testing for HIV among lymphoma patients: Clinical relevance for patient and provider
HIV is a risk factor for lymphoma *(n=6)*
HIV negatively influences lymphoma treatment/outcomes *(n=2)*
Important to test to protect staff *(n=1)*
Knowledge about HIV testing recommendations in guidelines
Sources of information
National and local guideline *(n=2)*
Educational sessions *(n=2)*
Type of information
Not sure about the exact guideline recommendation *(n=7)*
Guidelines recommend HIV testing *(n=5)*
Malignant lymphoma is an indicator condition *(n=2)*
Don't use of guideline *(n=1)*
Perception of guidelines
It feels safe to have HIV testing recommended in guidelines *(n=1)*
Norms on testing for HIV among lymphoma patients
Colleagues
Colleagues' mentioning HIV testing reminds me *(n=4)*
Disagree with colleagues not routinely testing for HIV *(n=1)*
I bring it up/test more to remind others *(n=1)*
Not influenced by colleagues *(n=1)*
Patients
Not influenced if patients have low perceived risk *(n=1)*
Not influenced if patients are afraid *(n=1)*
Ways of informing patients
Inform it's part of routine work-up *(n=8)*
Do not ask permission, only inform *(n=6)*
Inform on clinical relevance for treatment plan/outcomes *(n=5)*
Ask for permission *(n=2)*
It's more effort to inform patients not in the risk category *(n=2)*
Stress confidentiality *(n=1)*

Table 2: Themes identified from semi-structured interviews with hematologists on their HIV testing behavior among lymphoma patients, and influencing factors (continued)

Lymphoma patient responses to HIV test offering
Patients rarely/never do not agree *(n=9)*
Patients perceived discrimination because of sexual orientation *(n=2)*
Surprised response by patients *(n=2)*
Patients need for more information before agreeing *(n=1)*
Hematologists' perceived self-efficacy to test for HIV
Good self-perceived efficacy *(n=4)*
Good perceived self-efficacy to deliver positive test result
Positive tests are rare *(n=3)*
Like telling them they have lymphoma/also bad news *(n=2)*
I am able to do that *(n=2)*
Low perceived self-efficacy in counseling/referral for counsel *(n=5)*
Barriers to HIV testing
Provider level - related to patients' characteristics
Done less in older patients *(n=3)*
When patients are accompanied *(n=2)*
Anticipated patient feeling stigmatized *(n=1)*
Provider level - general
Testing might have been done in referring hospital *(n=5)*
Forget if you didn't do it right away *(n=1)*
Don't re-test in recurrent lymphoma *(n=1)*
System level
Lack of awareness on guideline *(n=2)*
Not in standard order set *(n=1)*
IC guided testing not implemented well enough in general *(n=1)*
Contextual level
Not a clear association of HIV with all lymphoma types *(n=5)*
HIV is not common *(n=1)*
Facilitators for HIV testing
Working environment
Low threshold in Amsterdam because it's more common *(n=3)*
Training/working in HIV treatment center, more routine *(n=2)*
It is routine/part of the work-up
Because it is included in the routine test/order set *(n=4)*
Because it's in the guidelines *(n=1)*
No longer a big taboo like in the past *(n=2)*
Readily available *(n=1)*
If a patient asks for an HIV test it is easy *(n=1)*
You no longer have to ask for elaborate informed consent *(n=1)*

On **ways of informing patients**, the majority (n=8) of hematologists reported that they inform the patient that it is part of a routine workup for lymphoma, and six hematologists added that they do not explicitly ask for permission to test for HIV, while two reported explicitly asking for permission. Five reported they inform the patient on the clinical relevance of HIV testing for the treatment and outcome of their lymphoma, and two mentioned that they found informing their patient of HIV testing to require more effort when patients did not belong to HIV key groups:

"If you have a 23 year old student with a lymphoma, I will explain that to them that we test for viral associations. It's something that we mention, but it doesn't change our practice. But it takes more effort to explain why you're testing that." (teaching hospital hematologist, male, 42 years)

On **patients' responses** to being offered an HIV test, nearly all respondents (n=9) reported that patients rarely or never refuse an HIV test, although some reported that patients may sometimes respond surprised, need more information before agreeing, or perceive discrimination when offered HIV testing because of their sexual orientation. No hematologists reported that they have low perceived **self-efficacy** to test for HIV. However, while two reported that they are well-trained at delivering news of a positive HIV test result as it is just like informing patients of a cancer diagnosis, five reported low perceived self-efficacy in counselling patients with newly diagnosed HIV, and will refer them to an HIV specialist for this.

Contextual level, provider level, and system level **barriers** to HIV testing among PWML were identified (Table 2). Contextual level barriers included HIV not being common, and a lack of a clear association between HIV and incidence of some types of lymphoma:

"For Hodgkin lymphoma I understand that you do not test it immediately because the association with HIV is not that clear as with DLBCL." (university hospital hematologist, female, 39 years)

General provider level barriers included testing having been done in the referring hospital, and forgetting to test when it's not done right away:

"Sometimes you think we've already performed a test, because in a lot of patients when I see them first, I already do the HIV testing. And it could be that sometimes you forget, and then later on, you think you've done it already, and you don't look back." (teaching hospital hematologist, female, 41 years)

Provider level barriers specifically related to patients' characteristics included older age, where hematologist's mentioned low perceived risk in older patients, anticipating patients feeling stigmatized, and patients being accompanied:

"*I think it's easier to talk about it when people are not sitting here with their whole family. That's a barrier. Also when it's a heterosexual relationship, I might feel that it's*

more difficult to talk about it than if it's a homosexual relationship." (teaching hospital hematologist, female, 41 years)

Identified **facilitators** for HIV testing included it no longer being a big taboo and informed consent no longer being required, making it easier and less time-consuming to discuss, and HIV testing being part of a routine or guideline and readily available:

"It's a package with hepatitis B and C, everything is in it. You don't have to think about it." (university hospital hematologist, female, 39 years)

"*The test is easy, available and just part of the workup. So, I don't have any barriers*." (university hospital hematologist, male, 47 years)

Additionally, HIV being relatively common in Amsterdam, as well as working in an HIV treatment center where HIV testing is more routinely done were identified facilitators for HIV testing.

"I worked in [HIV treatment center] for a while where I learned to do the testing, because there they talk easily about it because they have so many patients with HIV that it's a normal thing." (university hospital hematologist, female, 42 years)

Interviews with authors of hematology guidelines

From the interviews with authors of hematology guidelines, themes on the reason and evidence for HIV testing recommendations in lymphoma guidelines, and themes on guideline development and communication on guidelines with end-users emerged. The guideline authors mentioned that HIV testing recommendations are included in lymphoma guidelines because an HIV infection would influence the treatment plan, because lymphoma is more common among PLHIV and might be a presenting symptom of HIV, and because it is important to have a uniform HIV testing recommendation for PWML. On the evidence for HIV testing among PWML, respondents stated that there is no extensively researched recommendation for HIV testing in the lymphoma guidelines, because they thought it is already common practice and not a matter of debate when developing the guidelines. However, one respondent clarified that the evidence for HIV testing likely varies by lymphoma type. On guideline development and communication, the authors mentioned that the target audience for the guidelines, i.e. hematologists, are actively invited by email to respond to concept guidelines for approval and feedback, and updated guidelines are disseminated and presented at hematology meetings, in the Dutch hematology journal, and through the Dutch hematology society's website and electronic mailings, assuring that all involved may give feedback and are informed on guidelines. However, one respondent added that local implementation of guideline recommendations including routine HIV testing in PWML is not monitored.

Reflections and recommendations on observed proportions of patients HIV tested
All twelve interview participants reflected on the measured proportions of patients HIV tested among PWML and were asked for recommendations for improvement. Most hematologists had expected higher proportions of patients tested based on their own HIV testing behavior and acknowledged a need for improvement (Table 3). Ten respondents recommended increasing awareness among hematologists on the need for HIV testing among PWML. Examples for increased awareness included electronic solutions such as prompts in the EHR of PWML, presenting HIV testing recommendations at conferences or in hematology journals and receiving audit and feedback on HIV testing. Additionally, some respondents recommended adding HIV testing recommendations to all lymphoma guidelines and checking whether any opportunities for HIV diagnosis were previously missed among PWML. Conversely, one respondent pointed out that HIV testing might not need improving in all PWML patients due to low HIV prevalence, such as among elderly patients with low-grade lymphoma (Table 3).

DISCUSSION

We assessed HIV testing by hematologists among PWML and mapped factors influencing hematologists' testing behavior. Overall, 63% of all PWML[21], and 70% of newly diagnosed PWML were tested for HIV within 3 months before or after lymphoma diagnosis. While 71% of patients who received treatment for lymphoma had been tested for HIV within 3 months, 10% was tested less recently, and 19% had no evidence of ever having been tested, revealing opportunities for improvement. The observed HIV positivity percentage of 0.7% among PWML exceeded the previously established cost-effectiveness threshold for HIV screening of 0.1%[9]. However, as newly diagnosed patients had either DLBCL, Burkitt lymphoma, or T-cell lymphoma, cost-effectiveness of this testing strategy among other types of malignant lymphoma could not be verified in this study.

In the questionnaires and interviews, hematologists reported that their intention to test for HIV among PWML is high, although some reported that this varies by lymphoma type, patient characteristics such as age, and whether lymphoma treatment is required. This is reflected in our observed proportions of patients tested for HIV, which were highest among patients diagnosed with types of lymphoma requiring immediate treatment, and among younger male patients. We observed that there is disagreement among hematologists as to whether patients with all types of lymphoma should be tested for HIV or not, and guideline authors mentioned that the evidence supporting HIV testing may vary by lymphoma type.

Table 3. Hematologists' reflections on HIV testing among patients with malignant lymphoma and recommendations for improvement

Theme	Example
Expected/should be higher (at my hospital) *(n=10)*	
Expected higher proportions of patients HIV tested (n=5)	"I didn't really believe it, I said I test all my patients, and we actually checked if it weren't my patients but we were actually kind of shocked by the result." (teaching hospital hematologist, female, 41)
If you don't test for HIV you should have a good reason *(n=1)*	"If there is a very good reason not to do it, I mean if somebody is already known HIV positive we don't need to do it again but if you don't know the HIV status, at least you should write down in your file why you don't do the test." (university hospital hematologist, male, 47)
It's a missed opportunity not to test for HIV *(n=1)*	"I think it's a missed opportunity. We should educate our people better." (university hospital hematologist, male, 47)
We need more awareness on HIV testing recommendations *(n=10)*	
We need a system to remind us of HIV testing *(n=5)*	"We could be helped by the system. So the computer system could for example pop up and say well, you entered a new diagnosis of lymphoma, did you do an HIV test, do you want to do it right now? That could be really good." (university hospital hematologist, male, 39)
Hematologists should be reminded of the guidelines *(n=3)*	"I think because the guidelines are quite clear I think some people should be reminded this is part of the routine testing specially certain types of lymphoma." (university hospital hematologist, female, 37)
Present HIV testing recommendation and evidence at conference/in national hematology journal *(n=3)*	"I think it would help to put this issue with lack of HIV testing in the Dutch hematology conference or something like that. I think that would help." (teaching hospital hematologist, female, 40)
Audit and feedback HIV testing implementation *(n=2)*	"I think it's just showing the numbers and making people see the importance of it I think by giving a presentation, making people aware of these numbers I think it can help." (university hospital hematologist, female, 39)
Mention HIV testing every day when there are new patients *(n=2)*	"We have these meetings where we discuss new lymphoma patients. One of us should be asking always what about HIV." (university hospital hematologist, female, 58)
Add HIV testing to all lymphoma guidelines *(n=4)*	"I think it would be most feasible as an implementation strategy if you basically say lymphoma equals HIV test." (university hospital hematologist, male, 39)
Would be good to check if we missed any HIV diagnoses *(n=1)*	"It would be good to do an HIV test in these patients who didn't receive an HIV test to see if it's the case if we've missed any HIV patient." (university hospital hematologist, female, 39)
Likely no need to improve it in all lymphoma types *(n=1)*	"If it's definitely not indicated, if you're 70+ and you're diagnosed with a low-grade lymphoma, and in the past 5 years, nobody with those characteristics has ever been tested positive for HIV, then you might also consider not testing that group, you know." (teaching hospital hematologist, male, 42)

Research showed that in the era of effective antiretroviral therapy for HIV, the risk of NHL is elevated 11-fold among PLHIV compared to the general population, but this risk varies substantially by type of NHL, and is not increased among some types, with a standardized incidence ratio of 1.0 (95% CI 0.4-2.3) for mantle cell lymphoma, and 0.8 (95% CI 0.5-1.2) for chronic lymphocytic leukemia/small lymphocytic lymphoma[21]. Not routinely testing for HIV among some types of (indolent) lymphoma may therefore be justified. However, while only 25% of patients with lymphoplasmacytic lymphoma (LPL) in the PROTEST 2.0 study was tested for HIV within 3 months[21], the previously identified standardized incidence ratio of LPL among PLHIV was 3.6 (95% CI 2.0-6.0)[27], highlighting likely missed opportunities for HIV diagnosis among patients with low-grade NHL subtypes.

Several hematologists stated that they do not routinely test in patients not requiring treatment for their lymphoma, and the observed proportions HIV tested among patients not requiring treatment was 40%, versus 74% among patients requiring immediate treatment. A possible explanation is that hematologists may not have reduction of undiagnosed HIV as their primary goal, but are more focused on mitigating adverse outcomes of lymphoma treatment, potentially leading to missed opportunities for HIV diagnosis. Additionally, the proportion tested among patients who required treatment later on due to progressive disease was only 31%, indicating missed opportunities for HIV testing in cases where testing is not performed among patients not requiring (immediate) treatment. This is reflected in the interviews, during which hematologists mentioned they do not re-test for HIV in relapsed lymphoma and may forget to test when it is not done right away.

We identified several additional factors influencing hematologists' routine HIV testing behavior among PWML. Provider level barriers related to patients' characteristics included older age, discomfort discussing HIV testing when patients are accompanied, and anticipation of patients feeling stigmatized. These findings highlight the importance of communication skills when offering an HIV test, as well as education on HIV epidemiology among hematologists, as 26% of individuals newly diagnosed with HIV in 2020 were 50 years or older[16].

Identified facilitators for HIV testing included adding routine HIV testing to guidelines and standard laboratory order sets, while recommendations for improvement included implementing electronic prompts in EHRs. Such prompts may be especially helpful to prevent missed testing opportunities in cases where testing was not done right away. Previous research showed that electronic prompts may increase HIV testing, although their effect is often lost when deactivated[28]. Additionally, guideline recommendations are often not adhered to without additional efforts to increase awareness of, and agreement on such recommendations[29-31]. Likewise, in our study hematologists recommended increasing awareness of HIV testing recommendations and guidelines through presentations at national conferences or in hematology journals, educational sessions, discussion of HIV testing during patient review meetings and audit and feedback. These examples all highlight that making HIV testing a routine procedure, and communicating it as such with patients, helps

implement HIV testing practices. A combination approach of guideline adaptations, electronic prompt systems, educational interventions and routine reminders is likely to be most effective in improving routine HIV testing among PWML.

Strengths and limitations

A strength of this study is the mixed-methods approach used to evaluate both actual HIV testing, and factors influencing hematologists' HIV testing behavior among PWML. To our knowledge, this is the first study aiming to understand hematologists' HIV testing behavior. Including questionnaires and interviews with hematologists provided deeper insight into determinants for HIV testing, in addition to assessing proportions of patients who were tested for HIV. The considerable range in duration of interviews may suggest that the interviewed participants formed a heterogeneous group in terms of subject engagement. However, some limitations should be noted. While we attained a relatively high response ratio to the questionnaire, only a small number of hematologists, and none from the non-teaching hospital could be recruited for an interview, possibly leading to response bias and limited generalizability. Additionally, we did not include the patient's perspective in our study. Interviewing this stakeholder group, or conducting focus groups involving all stakeholders, may have led to additional insights in factors influencing HIV testing as well as opportunities for improvement. Finally, as some of the findings in this study are specific to the Dutch setting, generalization of our findings to other settings should only be done with caution.

CONCLUSIONS

This study provided insight into the implementation of routine HIV testing among PWML and factors influencing hematologists' testing behavior. HIV testing was done in a relatively small majority of PWML. Missed opportunities for testing occurred, likely due to lack of HIV testing recommendations in guidelines for some lymphoma types, and conflicting testing strategies among hematologists. The overall HIV positivity percentage confirmed the cost-effectiveness of routine testing among PWML. Efforts to improve its implementation should entail a combination of approaches, including increasing awareness and fortifying rationales for testing, guideline adaptations, providing electronic reminders and monitoring, and increasing institutional and normative support for this testing strategy.

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Competing interests
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REFERENCES

1. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Geneva 2021. Available online at https://www.who.int/publications/i/item/9789240027077. Accessed 5 December 2022.
2. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.
3. Raben D, Sullivan AK, Mocroft A, et al. Improving the evidence for indicator condition guided HIV testing in Europe: Results from the HIDES II Study - 2012 - 2015. *PLoS One* 2019;**14(8)**:e0220108.
4. Omland LH, Legarth R, Ahlstrom MG, Sorensen HT, Obel N. Five-year risk of HIV diagnosis subsequent to 147 hospital-based indicator diseases: a Danish nationwide population-based cohort study. *Clin Epidemiol* 2016;**8**:333-40.
5. Scognamiglio P, Chiaradia G, De Carli G, et al. The potential impact of routine testing of individuals with HIV indicator diseases in order to prevent late HIV diagnosis. *BMC Infect Dis* 2013;**13**:473.
6. Bert F, Gualano MR, Biancone P, et al. Cost-effectiveness of HIV screening in high-income countries: A systematic review. *Health Policy* 2018;**122(5)**:533-47.
7. Walensky RP, Weinstein MC, Kimmel AD, et al. Routine human immunodeficiency virus testing: an economic evaluation of current guidelines. *Am J Med* 2005;**118(3)**:292-300.
8. Yazdanpanah Y, Sloan CE, Charlois-Ou C, et al. Routine HIV screening in France: clinical impact and cost-effectiveness. *PLoS One* 2010;**5(10)**:e13132.
9. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. Available online at https://www.eurotest.org/Projects-Collaborations/Indicator-Condition-Guided-HIV-Testing-HIDES/Guidance-HIV-Indicator-Conditions. Accessed 5 December 2022. Accessed 25 Feb 2022.
10. Bogers SJ, Hulstein SH, Schim van der Loeff MF, et al. Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis. *EClinicalMedicine* 2021;**35**:100877.
11. Tominski D, Katchanov J, Driesch D, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. *HIV Med* 2017;**18(2)**:125-32.
12. Wohlgemut J, Lawes T, Laing RB. Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study. *BMC Infect Dis* 2012;**12**:72.
13. Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. *J Clin Pathol* 2007;**60(12)**:1365-72.
14. Spina M, Carbone A, Gloghini A, Serraino D, Berretta M, Tirelli U. Hodgkin's Disease in Patients with HIV Infection. *Adv Hematol* 2011;**2011**.
15. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. *Ann Intern Med* 2015;**163(7)**:507-18.
16. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2021. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2021. Available online at www.hiv-monitoring.nl.

17. Nederlandse Vereniging voor Hematologie. Richtlijn voor de diagnostiek, behandeling en follow-up van het folliculair lymfoom (Dutch). 2017. Available online at https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Lymphoma/FL-richtlijn_revisie2019.pdf. Accessed 5 December 2022.

18. Nederlandse Vereniging voor Hematologie. Richtlijn diffuus grootcellig B-cel non-Hodgkin lymfoom (Dutch). 2021. Available online at https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Lymphoma/Richtlijn-DLBCL-_NVvH_2021.pdf. Accessed 5 December 2022.

19. Nederlandse Vereniging voor Hematologie. Richtlijn voor de diagnostiek, behandeling en follow-up van het Hodgkin lymfoom (Dutch). 2019. Available online at https://hovon.nl/_asset/_public/TreatmentGuidelines/TreatmentGuidelines_Lymphoma/richtlijn_hodgkin_lymfoom_hovon_2019_v1.pdf. Accessed 5 December 2022.

20. Bogers SJ, Schim van der Loeff MF, Davidovich U, et al. Promoting HIV indicator condition-guided testing in hospital settings (PROTEST 2.0): study protocol for a multicentre interventional study. *BMC Infect Dis* 2021;**21(1)**:519.

21. Bogers SJ, Schim van der Loeff MF, Boyd A, et al. Improving indicator-condition guided testing for HIV in the hospital setting (PROTEST 2.0): A multicenter, interrupted time-series analysis. *Lancet Reg Health Eur* 2022;**23**:100515.

22. Ajzen I. The theory of planned behavior. *Organizational Behavior and Human Decision Processes* 1991;**50(2)**:179-211.

23. de Vries H, Dijkstra M, Kuhlman P. Self-efficacy: the third factor besides attitude and subjective norm as a predictor of behavioural intentions. *Health Education Research* 1988;**3(3)**:273-82.

24. Rogers EM. Diffusion of innovations. New York: Free Press; 2003.

25. Titler MG, Everett LQ. Translating research into practice. Considerations for critical care investigators. *Crit Care Nurs Clin North Am* 2001;**13(4)**:587-604.

26. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology* 2006;**3(2)**:77-101.

27. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. *AIDS* 2014;**28(15)**:2313-8.

28. Smit M, Jordans CCE, Reinhard JM, et al. Clinical decision support systems to guide healthcare providers on HIV testing. *AIDS* 2022;**36(8)**:1083-93.

29. Darling KE, Hugli O, Mamin R, et al. HIV testing practices by clinical service before and after revised testing guidelines in a Swiss University Hospital. *PLoS One* 2012;**7(6)**:e39299.

30. Desai S, Tavoschi L, Sullivan AK, et al. HIV testing strategies employed in health care settings in the European Union/European Economic Area (EU/EEA): evidence from a systematic review. *HIV Med* 2020;**21(3)**:163-79.

31. Elmahdi R, Gerver SM, Gomez Guillen G, Fidler S, Cooke G, Ward H. Low levels of HIV test coverage in clinical settings in the U.K.: a systematic review of adherence to 2008 guidelines. *Sex Transm Infect* 2014;**90(2)**:119-24.

Supplemental Table 1. Content of online questionnaire on barriers and facilitators for HIV testing among patients with malignant lymphoma

	Question	Response options
Section 1: Respondent characteristics		
1.1	Sex of respondent	Male/Female
1.2	Age of respondent (in years)	2-digit field
1.3	Specialty department of respondent	Pulmonology/gastroenterology/ gynecology/neurology/hematology/ other, i.e....
1.4	Job description of respondent	Resident/intern/attending/other, namely...
1.5	Number of years work experience in this specialty	2-digit field
1.6	Type of hospital of respondent	University hospital/teaching hospital/non-teaching hospital/ other, i.e....
Section 2: HIV testing behavior		
2.1	HIV is common in patients in patients with malignant lymphoma	5-point Likert scale: Definitely not - Definitely yes
2.2	I tested patients with malignant lymphoma for HIV in the last year	5-point Likert scale: Never - Very often
2.3	When I see patients with malignant lymphoma, I plan to test them for HIV	5-point Likert scale: Strongly disagree - Strongly agree
2.4	It is likely that I will test patients with malignant lymphoma for HIV in the future	5-point Likert scale: Very unlikely – Very likely
2.5	It's important that I test patients with malignant lymphoma for HIV	5-point Likert scale: Very unimportant - Very important
2.6	It's positive that I test patients with malignant lymphoma for HIV	5-point Likert scale: Very negative - Very positive
2.7	I'm comfortable offering patients with malignant lymphoma an HIV test	5-point Likert scale: Very uncomfortable - Very comfortable
2.8	I'm capable of testing patients with malignant lymphoma for HIV	5-point Likert scale: Highly incapable - Highly capable
2.9	It's easy testing patients with malignant lymphoma for HIV	5-point Likert scale: Very hard - Very easy
2.10	My colleagues find it important that we test patients with malignant lymphoma for HIV	5-point Likert scale: Very unimportant - Very important
2.11	Patients with malignant lymphoma expect me to test them for HIV	5-point Likert scale: Definitely not - Definitely yes

Supplemental Table 1. Content of online questionnaire on barriers and facilitators for HIV testing among patients with malignant lymphoma (continued)

	Question	Response options
2.12	HIV testing in patients with malignant lymphoma is discussed in my specialty	5-point Likert scale: Never - Very often
2.13	HIV testing in patients with malignant lymphoma is in our guidelines	5-point Likert scale: Definitely not - Definitely yes
2.14	Ordering an HIV test in patients with malignant lymphoma is easily arranged	5-point Likert scale: Very difficult to arrange - very easily arranged
2.15	HIV testing in patients with malignant lymphoma leads to better health outcomes	5-point Likert scale: Definitely not - Definitely yes

Supplemental Table 2. Interview guide for semi-structured interviews with hematologists working in the region of Amsterdam on factors influencing HIV testing behavior among malignant lymphoma patients

Part 1: Knowledge on HIV testing recommendations among malignant lymphoma patients
What do you know about HIV testing guidelines/recommendations in malignant lymphoma patients?
What source(s) have you used to get the information?
Part 2: Attitudes and behavior regarding HIV testing among malignant lymphoma patients
What is your attitude/strategy regarding HIV testing in malignant lymphoma patients?
Why do you adopt this approach?
Do you test for HIV among malignant lymphoma patients presenting with all types of lymphoma?
Part 3: Norms regarding HIV testing among malignant lymphoma patients
How do your colleagues' attitudes regarding HIV testing in malignant lymphoma patients influence your approach?
How do malignant lymphoma patients' beliefs on HIV testing influence your attitudes?
Part 4: Self-efficacy regarding HIV testing among malignant lymphoma patients
How would you judge your ability to successfully perform HIV testing in malignant lymphoma patients?
How would you judge your ability to successfully deliver a positive HIV test result to malignant lymphoma patients?
Part 5: Perceived barriers regarding HIV testing among malignant lymphoma patients
What are your perceived barriers for HIV testing in malignant lymphoma patients?

Supplemental Table 3. Interview guide for semi-structured interviews with authors of hematology guidelines working in the region of Amsterdam on the extent of and reasons for HIV testing recommendations in malignant lymphoma guidelines

Part 1: Characteristics of HIV testing recommendations in malignant lymphoma guidelines
Why is HIV testing included in the malignant lymphoma guidelines?
To what extent is HIV testing included in the malignant lymphoma guidelines?
What is the evidence for this HIV testing recommendation in the malignant lymphoma guidelines?
What are the main characteristics of HIV testing recommendations in malignant lymphoma patients, in terms of clarity, specificity, strength of evidence?
What is the process of making the malignant lymphoma guidelines (who made the guidelines, how were they approved and by whom)
Part 2: Communication and dissemination of malignant lymphoma guidelines
What kind of communication strategies did you use for the dissemination and implementation of these malignant lymphoma guidelines?
Part 3: Social system involved in malignant lymphoma guidelines
How did you identify malignant lymphoma guideline users?
What kind of targeted user strategies such as feedback did you use to assess the implementation of these malignant lymphoma guidelines?

Part

IV

Conclusions

Chapter 11

General discussion

GENERAL DISCUSSION

HIV transmission can be effectively prevented through biomedical interventions such as the use of Pre-Exposure Prophylaxis (PrEP) by individuals without HIV, and by adequate use of antiretroviral treatment (ART) by people living with HIV[1-3], thereby making the elimination of the HIV epidemic an attainable goal. In the Netherlands, the Ministry of Health formulated a plan to improve sexual health and the care for HIV and sexually transmitted infections (STI) in 2018[4]. This plan included goals to decrease the number of new HIV diagnoses by 50% compared to 2015, to have 95% of people living with HIV know their status, 95% of those diagnosed accessing treatment, 95% of those accessing treatment to have suppressed viral loads, and, finally, to reach zero acquired immunodeficiency syndrome (AIDS)-related deaths by the year 2022. In 2020, the first goal was already attained, and the second goal was within reach by achieving a score of 93%-94%-95%. However, completing the goal of zero AIDS-related deaths is hampered by the large proportion of individuals that are still diagnosed at a late stage of HIV infection, leading to a stable number of AIDS-related deaths over the past years[5]. These figures underline the importance of optimal HIV testing strategies to facilitate early diagnosis. The national action plan therefore listed proactive HIV testing in healthcare settings as one of their approaches to reach these goals[4]. In order to improve the HIV testing and care cascade on a city-level in Amsterdam, the HIV Transmission Elimination AMsterdam (H-TEAM) consortium was founded in 2014[6]. The consortium's efforts were backed by the City Council of Amsterdam, who published a policy paper on reaching zero new HIV infections in Amsterdam by 2026. In this policy paper, the City Council recognized the need for expanded HIV testing availability as a key focal point[7]. In line with this statement, the final objectives of the studies in this thesis were to improve provider-initiated HIV testing and care (PITC) in the primary care and hospital setting in the region of Amsterdam through educational interventions among healthcare providers. In this chapter, we provide an overview of the findings from these studies, and we reflect on these findings given the current evidence on this topic. Finally, we discuss our findings' implications as well as suggestions for future directions.

MAIN FINDINGS

Comparing HIV testing practices in primary care

In the Netherlands, general practitioners (GPs) provide the majority of sexual health consultations and diagnose about a third of HIV infections, but limited data were available on HIV testing practices in primary care[8]. In contrast, extensive data are available on HIV testing by sexual health centers (SHCs), which offer opt-out HIV testing for key groups[8]. We therefore studied HIV testing practices by GPs compared to SHCs in various regions of the Netherlands. We found a large regional variation in the annual number of HIV tests per 10,000 residents ordered by general practitioners (GPs), with higher HIV test rates in highly urbanised regions, compared to more rural areas (**chapter 2**). The highest positivity percentages were also reported in highly urbanised regions. Compared to SHCs, GPs conducted fewer

HIV tests overall, while by region GPs tested less in some regions, and comparably in other regions. In none of the studied regions did GPs' testing rates significantly exceed the SHCs' rates. The positivity percentages were comparable between GPs and the SHC in all regions except Amsterdam, where positivity was higher among people tested by GPs. Considering that in Amsterdam, the GPs' HIV test rate per 10,000 residents was less than half that of the SHC, the higher positivity percentage among GPs from Amsterdam suggests more selective testing and possibly missed opportunities for earlier HIV diagnosis. When examining trends in HIV testing by GPs in Amsterdam from 2011 to 2017, we observed a decline in testing from 2011 to 2014 that was most pronounced among women and patients aged 20-49 years (**chapter 3**). From 2015 to 2020, overall HIV testing increased by 10%, from 123 to 135 per 10,000 residents.

Evaluating indicator condition guided testing in various healthcare settings

The World Health Organization recommends provider-initiated testing in patients presenting with conditions that could indicate an HIV infection, to decrease the number of people living with undiagnosed HIV[9]. Through a systematic review of existing literature, we assessed the proportion of patients diagnosed with such HIV indicator conditions (ICs) that were tested for HIV in various healthcare settings in Western countries, including primary care and hospital settings (**chapter 6**). We found that this testing strategy is insufficiently implemented, suggesting that opportunities for HIV diagnosis are being missed. We observed a large variation in the proportions tested for HIV by IC, with the highest proportions tested observed among patients with tuberculosis, while proportions were lowest among patients with cervical carcinoma or cervical intraepithelial neoplasia grade 2+. Additionally, we observed differences in HIV testing by healthcare setting (e.g. HIV test ratios among patients with malignant lymphoma being lower in the primary care setting compared to the hospital setting), and by testing strategy (e.g. HIV test ratios were higher in settings that implemented an opt-out testing strategy, compared to settings that did not). When we evaluated the change in HIV test ratios reported in intervention studies aiming to increase IC-guided testing, we found that while some studies reported increased HIV testing, other studies found no increase and some even reported decreased HIV testing. From these results, we concluded that educational efforts among healthcare providers alone may not be sufficient to improve HIV testing, and a combination of interventions including educational efforts, guideline adaptations and opt-out HIV testing strategies may be needed to yield positive effects.

Barriers and facilitators for HIV testing in the primary care and hospital setting

Primary care setting

Several barriers to optimal HIV testing in primary care have been previously described, including personal discomfort among healthcare providers, fear of offending or stigmatizing the patient, limited knowledge on benefits of early HIV diagnosis, and time restraints[10,11]. We performed a mixed-methods study using

questionnaires and semi-structured interviews on HIV testing behavior among GPs who participated in our educational intervention. GPs reported barriers to optimal HIV testing that can be categorized as patient-level, provider-level and system-level barriers (**chapter 5**). Examples were fear of offending or stigmatizing the patient, cultural differences, lack of training on sexual health and HIV, GPs feeling less motivated to test for HIV due to the decreasing HIV prevalence, the financial burden on the patient when ordering an HIV test, and the STI consultation guideline being too extensive for easy adherence. Conversely, reported facilitators for HIV testing included easy discussion of HIV testing with key groups including men who have sex with men (MSM), routine testing in the case of ICs, publications on appropriate testing strategies in national medical journals for primary care, the introduction of PrEP leading to increased per protocol testing and formal written informed consent no longer being mandatory for HIV testing. These findings inform on further opportunities for improved HIV testing in primary care.

Hospital setting

We assessed pathways toward adopting IC-guided testing for HIV in the hospital setting through a questionnaire among physicians from five medical specialties in five hospitals in the region of Amsterdam. Physicians reported a higher intention to apply IC-guided testing, than actual self-reported testing behavior (**chapter 8**). A structural equations model assessing the association between determinants and actual testing behavior directly had a better fit than a model assessing the association between determinants and intention to test as the most proximal determinant of behavior, as has been suggested in the Theory of Planned Behavior model. This suggests that there may be factors hampering the transition from intention to test to testing behavior. The most important determinants for behavior were guideline recommendations for HIV testing, physicians' attitudes and physicians' self-efficacy, and these should therefore be focused on when designing interventions to improve IC-guided testing in the hospital setting (**chapter 8**). Among hematologists specifically, 85% reported intention to test for HIV, while 68% reported having applied testing in the last year. Self-efficacy to test for HIV and hematologists' attitudes towards IC-guided testing scored highest of all determinants, and hematologists reported HIV testing is generally recommended in malignant lymphoma guidelines (**chapter 10**). In semi-structured interviews among ten hematologists from university hospitals and teaching hospitals, several barriers to routine HIV testing in patients with malignant lymphoma were identified. These included lack of awareness, lack of routine, and fear of stigmatization. Additionally, we found that applied HIV testing strategies varied by hematologists, with some only testing for HIV among patients who receive chemotherapeutic treatment for their lymphoma, while others tested all patients newly diagnosed with lymphoma. This discrepancy in testing strategies is likely due to the fact that not all types of lymphoma have a guideline recommending HIV testing, and not all types of lymphoma are equally associated with HIV. For example, the risk of some low-grade subtypes of non-Hodgkin lymphoma is not markedly increased among people living with HIV (PLHIV)[12]. When assessing the electronic health records of patients with malignant lymphoma, we found that 37% of patients with malignant lymphoma

overall, and 21% of patients who received treatment for malignant lymphoma were not tested for HIV within 3 months before or after lymphoma diagnosis. In the semi-structured interviews with hematologists, most acknowledged the need to increase these HIV testing rates to prevent missed opportunities for HIV diagnosis. Suggestions to improve HIV testing made by hematologists included increasing awareness, adapting guidelines and implementing electronic solutions to support routine testing (**chapter 10**).

Effect of interventions

Primary care setting
The implementation of a multifaceted educational intervention to improve testing for HIV and other STI among GPs in Amsterdam yielded a modest but significant increase in HIV testing (**chapter 4**). The educational intervention also increased chlamydia testing, with the largest increase in anorectal testing. Conversely, we observed a decrease in urogenital gonorrhea testing among GPs who participated, while there was an increase in anorectal gonorrhea testing, likely reflecting the lack of an indication for urogenital gonorrhea testing in patients presenting for a sexual health consultation without symptoms or risk-factors for STI[13]. To further assess whether and how the quality of GPs' HIV and STI testing strategies changed following the intervention, we performed a mixed-methods study using questionnaires and interviews among participating GPs. Most GPs reported the intervention had changed their HIV and STI testing knowledge, attitude and behavior, and that they had increased their HIV testing frequency (**chapter 5**). Interviewed participants reported specific examples of improved HIV testing, including more proactive HIV testing and increased IC-guided testing, but also less frequent HIV testing in low-risk patients. Additionally, interviewed participants reported having gained more skills and knowledge on appropriate patient interview techniques and testing for HIV and STI during sexual health consultations. In an evaluation of the program, interviewees reported that using already established training structures for continuing medical education (CME) and using competitive audit and feedback helped increase the impact of the intervention as they invoked intrinsic motivation to improve HIV and STI testing behavior. This, in addition to using repeat sessions in the design of the program likely improved the sustainability of the improvements. This was supported by the fact that, in the evaluation of changes in actual HIV testing behavior using laboratory data, the effect among GPs after participation did not wane over time (**chapter 4**).

True quality of testing behavior is complex to assess as it may depend on several factors including the patient's risk-profile, symptoms and any findings during physical or laboratory examination. This was illustrated by the discrepancy between the rather moderate increases in HIV testing assessed from laboratory data (**chapter 4**) and the more considerate self-reported improvements in HIV testing knowledge, attitude and behavior (**chapter 5**). This discrepancy may have been a reflection of an overestimation of quality by respondents, of appropriate intentional decreases in testing among low-risk patients, or of a discrepancy between GPs' intention to

apply proactive HIV testing strategies, versus their actual behavior, as had been observed through questionnaires in the hospital setting.

Hospital setting
An educational intervention to improve IC-guided testing among physicians working at five medical specialties in five hospitals in the region of Amsterdam significantly increased the overall proportion of patients with ICs tested for HIV within 3 months before or after IC diagnosis from 37% to 47% (**chapter 9**). The effect varied by IC, and was only significant among two of the IC that had the lowest HIV test ratio at baseline (i.e. cervical cancer or intraepithelial neoplasia grade III and peripheral neuropathy). It is commonly observed that interventions yield the largest effect when baseline performance is poorest[14,15]. However, after our intervention, the proportions of patients who were still NOT tested for HIV within 3 months before or after IC diagnosis were still 12%, 21%, 22% and 27% among patients with tuberculosis, malignant lymphoma, and hepatitis B and C virus infection, respectively. These findings highlight persistent missed opportunities for HIV diagnosis among these groups. Overall, patients who were tested for HIV within 3 months before or after IC diagnosis were significantly more often male, younger, were of a lower socio-economic status category, and more often deceased within 3 months after IC diagnosis. In only 1% (47/4,918) of patients who did not receive HIV testing within 3 months before or after IC diagnosis, an explicit reason for not testing for HIV was noted in their electronic health record by their physician, while only nine cases (0.2%) were identified where the patient was offered an HIV test, but refused. This suggests that while IC-guided testing is an acceptable strategy for patients, cases where HIV testing was not performed are likely missed opportunities rather than deliberate diagnostic choices. In our study, we observed an HIV positivity percentage of 0.7%, exceeding the established cost-effectiveness threshold for HIV screening of 0.1%[16]. The observed positivity percentage varied by IC and was highest among patients with tuberculosis (2.2%), but was 0% among patients with cervical cancer or intraepithelial neoplasia grade III, vulvar cancer or intraepithelial neoplasia grade III and peripheral neuropathy. While we observed an overall increase in HIV testing following the intervention, the overall positivity percentage remained stable.

REFLECTION ON FINDINGS

Implementing and evaluating effective interventions

In our educational interventions, several evidence-based elements for implementation programs and behavioral change among healthcare professionals were used[15,17-19]. For example, the interventions in both the primary care and the hospital setting included interactive graphical audit and feedback, as well as educational materials including posters, pocket cards and digital newsletters with further reading[19-22]. Additionally, tailored elements were implemented per group of GPs and per specialty and hospital. These elements addressed specific opportunities for improvement that were identified during the educational sessions by groups of participating GPs (i.e. quality improvement plans) or by specialty

departments (e.g. guideline adaptations, HIV test prompts, adaption of standard diagnostic order sets). Implementation of such setting-specific elements is likely to increase the effectiveness of interventions, as it ensures relevance for target audiences[23]. However, a downside to the use of tailored elements per participant group in educational interventions is that it complicates assessing the effect of the intervention overall versus the effect of these varying elements. This was especially the case in the hospital setting, where additional tailored elements in some specialty departments and hospitals included impactful interventions such as reflex testing (i.e. automated testing for HIV in the case of a positive hepatitis B or C virus test result), and guideline adaptations.

Another challenge in assessing the true effect of our interventions was that we could not correct for all contextual factors that may have influenced HIV testing during the intervention periods, as has been observed in other studies evaluating the impact of CME[15]. For example, in the period that the educational intervention in primary care was conducted, GPs in Amsterdam were also exposed to other interventions aiming to improve HIV testing such as the HIV test week and an update of the STI consultation guideline for GPs[13,24], as well as other developments including the introduction of PrEP, an increase in the national compulsory annual deductible for patients' healthcare costs, and the implementation of a ceiling on government funding for SHCs. Similarly, healthcare professionals in the hospital setting may have been exposed to HIV awareness campaigns as well as workflow changes impacting HIV testing strategies during our intervention in the hospital setting. Therefore, confounding may have occurred. We aimed to mitigate this by adjusting for year of testing in our analysis and comparing testing behavior between providers before- and after the intervention (in the primary care setting), and by using time-series regression analysis correcting for year of testing (in the hospital setting).

We encountered some challenges in the implementation of our interventions in both settings that may have hampered their potential effectiveness. In the primary care setting, the roll-out of the educational intervention program took longer than anticipated, as enrolling groups of GPs was effortful due to the workload and time constraints of GPs. Consequently, while the overall participation to this program was good, only a third of participating GPs attended both sessions, likely due to time-constraints among GPs, as well as a large offer of other CME sessions. In the hospital setting, scheduling the educational sessions in each of the five specialty departments in the five participating hospitals was also challenging, as the intervention period took place during the first wave of the COVID-19 pandemic, while restrictions were imposed by the Dutch government[25]. This led to difficulties in motivating healthcare workers to participate in educational meetings, or to complete questionnaires assessing barriers and facilitators for IC-guided testing. While physicians from all departments ultimately participated in the intervention, and 43% responded to the questionnaire, the increased strain on healthcare workers during this time may have also reduced their motivation to change their HIV testing behavior following the meetings.

An important difference in the design of both interventions is that GPs attended interventions in small groups of GPs regularly attending CME sessions together, while in the hospital setting, the sessions were delivered to entire departments at once. The small-scale setup for GPs has been proven effective in the past[15,19], and was positively evaluated by interviewed participants, who explicitly mentioned that it is important to be able to ask awkward questions and be vulnerable during discussion because of the safe setting (**chapter 5**). While we did not evaluate how the effectiveness of the educational sessions in the hospital was perceived by participants, the larger scale setup of the sessions may have inhibited some participants from taking part in critical discussion on the proposed HIV testing strategy. This may have hampered the intervention's potential. Another important difference between the two interventions was that while in the primary care setting, the promoted strategies for HIV testing were already recommended in the STI consultation guideline for GPs[13], IC-guided HIV testing was not recommended in all specialty guidelines in the hospital setting[26]. While we established that guideline recommendations are an important determinant for behavior (**chapter 8**), we did not manage to adapt all relevant guidelines during the course of our intervention program, as adapting protocols is generally a lengthy process.

Our final aim was to create a sustainable improvement in provider-initiated HIV testing in the primary care and hospital setting. In the primary care setting, the effect on testing among participants did not wane over time, while a decrease in effect over time has been observed in other studies[27,28]. As established from interviews with participants this may have been the result of the design including repeat sessions, with audit and feedback and custom quality improvement plans, which created intrinsic motivation for improvement. In contrast, in the hospital setting, we could not assess the degree of sustained effect due to a short follow-up time. However, as we implemented several structural changes that support sustained improved HIV testing including guideline changes and reflex testing, ongoing effect of the intervention is likely in this setting as well.

Effect of changes in HIV testing on the number of new HIV diagnoses

We observed an increase in HIV testing in both the primary care setting and the hospital setting following the implementation of our educational interventions. In primary care, this increase was highest among populations that were tested least at baseline, including women and patients ≤19 years old and 50-64 years old. This suggests that there was a shift in testing practices among GPs after participation in the educational intervention. Meanwhile, the observed HIV positivity percentage did not differ significantly between GPs before and after participation. Given the observed increase in testing frequencies and the decreasing HIV prevalence in the Netherlands[5], this suggests that testing may have become more targeted, as it did not lead to a dilution of HIV-positive results. Therefore, the educational intervention has likely led to improved HIV testing in the primary care setting. Moreover, the observed shift in testing practices is favorable, as it increased HIV testing among populations that are more commonly diagnosed at a late-stage HIV infection, and who therefore may benefit from increased provider-initiated testing[5]. While SHCs

are a major provider for routine HIV testing among selected key groups, GPs hold the unique position of providing healthcare consultations for the whole population, including patients who do not belong to or identify with such key groups. GPs may recognize symptoms of acute HIV infection, diagnose ICs, and provide sexual health consultations, all leading to HIV testing indications. The improved HIV testing strategies among GPs therefore likely help to reduce the number of undiagnosed PLHIV.

In the hospital setting, we observed that HIV testing was most commonly done among male and younger patients, suggesting that some risk stratification among patients with ICs occurred. While IC-guided testing guidelines recommend no additional risk-stratification and HIV testing should be done on the basis of an IC diagnosis only, in practice healthcare providers may have chosen to test for HIV less often among patients not fitting typical characteristics associated with an HIV infection, including native heterosexual individuals, women and older patients. However, as such individuals are most commonly diagnosed at a late stage of HIV infection[5], this approach may lead to missed opportunities for earlier diagnosis. Therefore, we recommend that healthcare providers do not apply any risk-stratification when performing IC-guided testing, as long as routine testing in that IC exceeds the cost-effectiveness threshold. However, as the HIV incidence has been steadily declining in the Netherlands, continuous re-evaluation of the cost-effectiveness and appropriateness of recommended HIV testing strategies per IC is needed. While previous research determined that routine HIV testing in all currently recognized IC meets the cost-effectiveness threshold[16,29,30], it is likely, and even desirable, that in the Dutch healthcare setting, several ICs will no longer meet this threshold in the future. Therefore, routinely monitoring HIV positivity among patients with IC is an important strategy to determine which IC will still meet cost-effectiveness criteria moving forward.

Barriers and facilitators for provider-initiated HIV testing

The barriers to optimal HIV testing strategies experienced by healthcare providers identified in our studies, including HIV-related stigma, fear of offending the patient, time and financial constraints, lack of guidelines or training, and low perceived risk of HIV all hamper timely HIV diagnosis, and therefore the effective elimination of HIV transmission. Unfortunately, PLHIV who completed a survey in 2020 reported to experience more HIV-related stigma when accessing healthcare services, compared to PLHIV who completed a survey in 2007, although not all demographic characteristics were comparable between the two respondent groups[31]. The increase in HIV-related stigma was especially prevalent in the hospital setting, where over a third of PLHIV reportedly experienced stigma. Manifestations included increased physical distance, excessive preventive measures, awkward social interactions and avoidance or unnecessary referrals by healthcare providers, indicating that healthcare providers disproportionally fear occupational infection[31]. This suggests that the message of Undetectable = Untransmittable (U=U), i.e. people living with HIV who have an undetectable level of virus in their blood due to treatment are unable to transmit the virus to others[3], is insufficiently known among healthcare providers.

This was also observed in interviews among hematologists, where a hematologist reported that one reason to routinely test for HIV was to protect hospital staff from occupational infection (**chapter 10**). The increase in perceived HIV-related stigma in healthcare settings is particularly harmful, as it is associated with poor medication adherence, avoidance of health care, and decreased HIV testing and PrEP uptake, which are all essential factors in the prevention of HIV transmission[31-33]. For example, while nearly all PLHIV who participated in a survey reported healthcare usage in the Netherlands in the two years preceding HIV diagnosis, HIV testing was rarely discussed, and in interviews, PLHIV who were diagnosed late reported that they had avoided discussing HIV with their GP due to acceptance concerns[34,35]. It is therefore crucial that healthcare providers are properly trained to have sufficient knowledge on HIV and awareness about behaviors perceived as stigmatizing by PLHIV.

Effectiveness of a city-based approach

The interventions to improve HIV testing in the primary care and hospital setting were part of a larger initiative to eliminate HIV transmission and reach zero new infections in the city of Amsterdam, as designed by the H-TEAM initiative[6]. A city-based approach has the advantage that it builds on existing community, organizational, and healthcare structures[6,36,37]. As HIV incidence and prevalence are concentrated in urban areas, with the highest rates observed in Amsterdam, it seemed likely that such a city-based approach would have a substantial impact on ending the HIV epidemic in the Netherlands[5,38]. Additional advantages of this approach were that while we implemented the educational interventions among healthcare providers, they were also exposed to several other H-TEAM initiatives aiming to increase HIV awareness, prevention and testing, including public campaigns, HIV testing weeks, partner notification projects, PrEP pilots and primary care newsletters[6,24,39-41], likely increasing momentum and effectiveness of our interventions. Meanwhile, the H-TEAM also worked on improving the implementation of effective strategies to treat newly diagnosed people with HIV at the earliest opportunity, decreasing the time between diagnosis, treatment initiation and reaching viral suppression[42,43]. We think that the H-TEAM's city-based approach, which focuses on all aspects of the HIV cascade of care, from prevention and diagnosis to retention in care and viral suppression, is more effective to eliminate HIV transmission than individual initiatives alone would be.

Our educational interventions were designed for GPs and specialty departments in hospitals in the region of Amsterdam specifically, but they can readily be transferred to other settings in the Netherlands or beyond, while taking the local context into account[10,32,33,44-50]. For example, we used evidence-based elements in our interventions that were validated in various international settings including as multifaceted designs, multimedia materials and audit and feedback[15,17-19,21,23]. However, assessing setting-specific barriers and opportunities for optimal HIV testing strategies prior to implementation of any interventions is warranted. Characteristics of key populations, available resources, availability of guidelines and perceived barriers among healthcare providers and key populations may vary, and will likely strongly affect any intervention's implementation and impact, even within

countries. For example, when comparing HIV testing practices of GPs and SHCs in five regions of the Netherlands, we found large variation, possibly due to variation in HIV-related perceptions and HIV prevalence as well as available resources (e.g. governmental funding of the SHCs varies by region; in more rural regions the distance to the nearest SHC may be considerable). Therefore, transferring our city-based approach to other settings without adjusting for local circumstances would likely diminish its effectiveness.

Implications for practice: Lessons learned

We aimed to improve provider-initiated testing in the primary care and hospital setting through educational interventions. Even though only a moderate increase of 7% was observed in primary care, HIV testing knowledge and behavior likely improved. The proportion of patients with ICs that were tested increased by 10% in the hospital setting, and testing did not improve in each individual IC, but the overall positivity rate exceeded the cost-effectiveness threshold. Ultimately, an optimal HIV testing strategy by healthcare providers is one of the key components to end the HIV epidemic. Our lessons learned are:

1. Optimal HIV testing strategies need continuous addressing

Previous research on implementation in clinical care showed that repeat educational sessions are more effective than only one session in creating behavioral change among healthcare providers[15,19]. Similarly, healthcare providers in both the primary care and hospital setting acknowledged that repeatedly addressing HIV testing is desirable to attain sustainably improved HIV testing behavior. This is especially important as a shrinking HIV epidemic will likely lead to a decrease in both patients' and healthcare providers' perceived risk of HIV in the future. Repeatedly addressing HIV testing may for example be done by routine discussion of HIV testing during patient review meetings, through medical conferences or media-outlets aimed at healthcare professionals, or through CME sessions. In the design of CME sessions, creators should ensure that attendance is rewarding by delivering tailored information or integrating HIV topics with other topics, and accrediting attendance. Additionally, session coordinators should aim to create a sense of importance and urgency for timely HIV testing and educate healthcare providers on the message of U=U, as CME is most effective when it is focused on outcomes that are considered important by physicians[11,15]. Members of the national expert group on sexual health in primary care (SeksHAG), HIV nurse practitioners, and HIV medicine specialists may take the lead in addressing HIV testing, as they are well-informed on best practices in HIV care and the experiences of PLHIV and can therefore effectively act as advocates.

2. Auditing HIV testing increases motivation and evaluates practice

The use of audit and (competitive) feedback is highly effective in both informing healthcare providers of their behavior and in creating motivation for improvement[15,21,22,51,52]. When evaluating the use of audit and feedback in the educational sessions for GPs, interviewees reported that it helped establish intrinsic motivation to improve HIV/STI testing behavior. Audit and feedback is most effective when it is up-to-date and specific for the individual or setting. We found that HIV testing is not routinely audited in the hospital setting, and hematologists reported that receiving such audit and feedback would be desirable to increase awareness and implementation of HIV testing. We therefore recommend the use of up-to-date individual audit and feedback in efforts to promote provider-initiated HIV testing. Moreover, collected audit and feedback may be used to evaluate the effectiveness of routine HIV testing to identify undiagnosed PLHIV, and to assess whether the implemented strategies still meet cost-effectiveness thresholds. This way, audit and feedback may help to continuously assess which strategies should be maintained moving forward.

3. Interventions should focus on improving behavior rather than intention

It has been previously described that physicians may overestimate the quality of their behavior, and that they sometimes do not perceive that there is a major need for improvement in their own behavior[53-55]. Both in the primary care and hospital setting, we observed discrepancies in self-reported quality of behavior, or intention to apply HIV testing, and actual HIV testing behavior. Moreover, actual behavior was better predicted by determinants for testing directly, than indirectly though determinants for intention to apply IC-guided HIV testing. This suggests that errors in judgment of quality and other factors obstructing the transition from intention to behavior may hamper optimal testing behavior. Although we established that evaluating and quantifying improvement in applied testing behavior is complex, we recommend that interventions focus on improving behavior rather than intention, as we found that determinants for the two, and therefore the design of interventions, may differ.

4. Facilitating testing will improve self-efficacy and decrease barriers to testing

Previously, time-constraints and complicated or elaborate guidelines for HIV testing have been identified as barriers for appropriate HIV testing by GPs[10,11,50]. These findings highlight the need for concise, practical tools that support proactive HIV testing practices. Similarly, in the hospital setting, missed opportunities for HIV testing persisted despite clear guideline recommendations. Making routine testing as easy as possible in settings where it is already recommended and thereby improving self-efficacy and eliminating the barrier of time-constraints, is key to improve HIV testing. We therefore implemented several initiatives to facilitate routine HIV testing. Examples were including HIV testing in standard order sets, laboratory prompts, and reflex testing. GPs and medical specialists should be encouraged to further facilitate routine testing solutions such as reflex testing (i.e. automatically testing for HIV when an IC is diagnosed using the same blood sample)[56,57]. While in the past, a formal

written informed consent was needed to order HIV testing, this is no longer the case. Instead, giving the patient the opportunity to object, just as in any other diagnostic or therapeutic procedure, is required under the Dutch Medical Treatment Contracts Act[58]. Approaching HIV testing as a routine procedure, such as through reflex testing, decreases HIV related taboo and stigma, and this strategy may ensure that most opportunities for IC-guided testing are utilized in the future[59,60].

5. Further reduction of HIV-related stigma in healthcare is needed

Finally, persistent HIV-related stigma among both the public and healthcare providers will continue to hamper optimal HIV test offering and uptake[31,35]. Opportunities to reduce stigma that should be considered include improving discussion of sexual health and knowledge on HIV through vocational training and educating healthcare professionals on U=U to prevent fear of occupational infection. Only when HIV-related stigma among healthcare providers is eliminated, can proactive provider-initiated testing be fully engrained in all healthcare settings. Ultimately, we must realize healthcare settings in which HIV is a natural part of the differential diagnosis in all relevant conditions, routinely addressed in clinical rounds and other clinical meetings, and no longer an exceptional or unusual topic of discussion.

Future directions

Future steps to improve HIV testing in both the primary care and hospital setting should address the barriers identified in our studies. Besides addressing the barriers mentioned in our lessons learned, including facilitation and structural implementation of HIV testing, further training of healthcare providers on optimal communication skills during sexual health consultations, sufficient knowledge on HIV, and awareness about behaviors perceived as stigmatizing by PLHIV is needed. Furthermore, additional steps can be taken to ensure optimal HIV testing in the primary care and hospital setting:

Involving other conditions, specialties and healthcare providers

We addressed only a selection of seven ICs in our educational intervention for hospital physicians. However, healthcare providers may encounter other ICs in daily practice that we did not specifically address. Therefore, expanding awareness campaigns to other conditions and healthcare workers may be needed in the future. For example, we only addressed HIV testing among malignant lymphoma patients with hematologists, while they also commonly encounter patients with ICs such as thrombotic thrombocytopenic purpura or unexplained thrombocytopenia. Likewise, we only addressed HIV testing among peripheral neuropathy patients with neurologists, while they also commonly encounter patients with cerebral toxoplasmosis, Guillain-Barre syndrome and subcortical dementia. Moreover, while we primarily focused on GPs and medical specialists from five different departments in the hospital setting in our interventions, the impact on provider-initiated HIV testing may be further increased by involving other healthcare providers that

commonly encounter individuals presenting with ICs. These may involve medical specialists from other departments including dermatology, ophthalmology, and even dentistry[61-63]. Additionally, involving nurses and physician assistants in both the primary care and hospital setting may further improve proactive HIV testing. In the primary care setting, nurses are commonly involved in routine STI consultations, and should therefore receive proper training on risk assessment and recognizing indications for HIV testing[64,65]. In the hospital setting, nurses and physician assistants working with PLHIV may be encouraged to take on leadership roles and advocate for the reduction of HIV-related stigma among their peers in other healthcare settings, as they are most commonly involved in the experiences of PLHIV.

Adapting specialty guidelines

National specialty guidelines on the diagnosis and treatment of ICs should be adapted to include HIV where lacking. However, given the decline in HIV prevalence, current evidence on cost-effectiveness and appropriateness for routine testing should be assessed per IC through an up-to-date literature review before adding such recommendations to guidelines to ensure support among end users. For example, we started a collaboration with colleagues from the #Aware.HIV study group from Rotterdam[66,67] and are currently working on a literature review to support the recommendation for HIV testing in the diagnostic guideline for cervical carcinoma. Other medical specialists should be encouraged to take similar steps for other ICs.

Removing financial barriers to HIV testing

Empowering patients to seek HIV testing will help prevent missed opportunities for HIV testing, especially in the primary care setting. An important facilitator would be to remove the mandatory deductible for HIV/STI testing that has to be paid by patients in the primary care setting[68-70]. While the Amsterdam city council proposed this strategy to lower barriers to HIV testing[7], this would entail policy change on the national level, and additional campaigns lobbying for this approach are currently needed.

Encourage self-testing services

Finally, while we aimed to improve provider-initiated HIV testing in the primary care and hospital setting, the use of commercial self-testing and self-sampling HIV testing services is increasing[8]. The uptake of these testing strategies is not monitored and thus data on the numbers tested are not available currently. Individuals, especially key groups, should be encouraged to use these testing services in addition to traditional services, to further decrease barriers to HIV testing that they may perceive. However, when applying this strategy, optimal counselling, connection to care and partner notification should be ensured in case of positive HIV test results[71-73].

Moving beyond borders

While Amsterdam and the Netherlands are well on their way to curb the HIV epidemic and effectively end HIV transmission, more work still needs to be done

beyond borders. In Western Europe, key statistics on the current state of the HIV epidemic are comparable to those of the Netherlands[74]. However, the number of new HIV infections in Eastern Europe continues to rise at an alarming rate[74]. Lack of access to testing and care, as well as HIV related stigma and criminalization of sex work, drug use and non-disclosure of HIV are key drivers that hamper any effective public health interventions to change this tide[74]. Additionally, political conflict further frustrates delivery of HIV prevention and care in Eastern Europe[74-76]. European healthcare and policy leaders should therefore continue to collaborate in aiding countries that have not sufficiently advanced interventions to end HIV transmission and AIDS related illness and mortality.

The Netherlands should also continue to invest in assisting partnering and constituent countries including the Dutch Caribbean and Suriname in their HIV testing strategies. For example, in Suriname, only an estimated 52% of PLHIV in 2018 knew their HIV status, and a third of diagnosed PLHIV reached viral load suppression[77,78]. In Curaçao, a constituent country of the Netherlands and part of the Dutch Caribbean, an estimated 89% of PLHIV knew their status in 2020, and 64% were diagnosed at a late-stage HIV infection[5]. These figures highlight the need for improved HIV testing in these settings. We therefore connected with local HIV experts to assess whether the approaches used in our studies would be useful for implementation locally. We learned that in the Dutch Antilles, improving provider-initiated testing in the primary care setting is already being addressed, while promoting IC-guided testing in the hospital setting is not likely to be an urgently needed strategy, as the majority of undiagnosed PLHIV do not regularly attend non-emergency hospital care. In contrast, in Suriname, it is likely that a significant proportion of undiagnosed PLHIV are presenting with ICs in the hospital setting. An intervention to improve IC-guided testing in various medical departments is therefore highly relevant to improve the country's HIV testing and care cascade. To support these efforts, we are sharing the lessons learned in Amsterdam, and supporting our colleagues in adapting our projects for tailored, local implementation of interventions to improve IC-guided testing in the hospital setting in Paramaribo, Suriname.

Conclusion

We implemented two educational interventions, which yielded modest but statistically significant increases in HIV testing in the primary care and hospital setting. Lessons learned on determinants for HIV testing as well as identified persistent barriers and HIV-related stigma among patients and healthcare providers should be addressed in our efforts to improve HIV testing in healthcare settings moving forward. Ultimately, this will contribute to a reduction of the proportion of PLHIV who remain undiagnosed and the proportion diagnosed at a late-stage HIV infection, thereby improving individual's health outcomes, and preventing onward transmission of HIV.

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med* 2016;**375(9)**:830-9.
2. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016;**387(10013)**:53-60.
3. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet* 2019;**393(10189)**:2428-38.
4. David S, van Benthem B, Deug F, van Haastrecht P. Nationaal Actieplan soa, hiv en seksuele gezondheid 2017-2022. National Institute for Public Health and the Environment (RIVM). 2018. Availabe at https://www.rivm.nl/bibliotheek/rapporten/2018-0034.pdf. Last accessed 9 January 2023.
5. van Sighem AI, Wit FWNM, Boyd A, Smit C, Matser A, van der Valk M. Monitoring Report 2022. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2022. Available from www.hiv-monitoring.nl.
6. de Bree GJ, van Sighem A, Zuilhof W, et al. Is reaching 90-90-90 enough to end AIDS? Lessons from Amsterdam. *Curr Opin HIV AIDS* 2019;**14(6)**:455-63.
7. Amsterdam City Council. Aiming for zero new HIV infections in Amsterdam by 2026. Amsterdam 2020. Available at: https://www.fast-trackcities.org/sites/default/files/Aiming%20for%20zero%20new%20HIV%20infections%20in%20Amsterdam%20by%202026_final.pdf. Last accessed 9 January 2023.
8. Staritsky LE, Visser M, Aar Fv, et al. Sexually transmitted infections in the Netherlands in 2020. National Institute for Public Health and the Environment (RIVM). Bilthoven 2021. Available at: https://www.rivm.nl/bibliotheek/rapporten/2021-0052.pdf. Last accessed 9 January 2023.
9. World Health Organization. Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva, Switzerland; 2007. Report No.: ISBN 978 92 4 159556 8.
10. Apers H, Nostlinger C, Van Beckhoven D, et al. Identifying key elements to inform HIV-testing interventions for primary care in Belgium. *Health Promot Int* 2020;**35(2)**:301-11.
11. Joore IK, van Roosmalen SL, van Bergen JE, van Dijk N. General practitioners' barriers and facilitators towards new provider-initiated HIV testing strategies: a qualitative study. *Int J STD AIDS* 2017;**28(5)**:459-66.
12. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. *AIDS* 2014;**28(15)**:2313-8.
13. AB E, Bruggeling NM, Donker GA, et al. NHG-Standaard Het soa-consult (Versie 2.1) (Dutch). *Nederlands Huisartsen Genootschap* 2022. Available from www.nhg.org.
14. Laan BJ, Maaskant JM, Spijkerman IJB, et al. De-implementation strategy to reduce inappropriate use of intravenous and urinary catheters (RICAT): a multicentre, prospective, interrupted time-series and before and after study. *Lancet Infect Dis* 2020;**20(7)**:864-72.

15. Cervero RM, Gaines JK. The impact of CME on physician performance and patient health outcomes: an updated synthesis of systematic reviews. *J Contin Educ Health Prof* 2015;**35(2)**:131-8.

16. HIV Indicator Conditions: Guidance for Implementing HIV Testing in Adults in Health Care Settings. Copenhagen, Denmark: HIV in Europe; 2014. Available at https://www.eurotest.org/Projects-Collaborations/Indicator-Condition-Guided-HIV-Testing-HIDES/Guidance-HIV-Indicator-Conditions. Last accessed 9 January 2023.

17. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. *Implement Sci* 2013;**8**:35.

18. Fleuren MA, Paulussen TG, Van Dommelen P, Van Buuren S. Towards a measurement instrument for determinants of innovations. *Int J Qual Health Care* 2014;**26(5)**:501-10.

19. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;**362(9391)**:1225-30.

20. Wensing M, Grol R. Implementatie. Effectieve verbetering van de patiëntenzorg. Houten: Bohn Stafleu van Loghum; 2017.

21. Ivers NM, Grimshaw JM, Jamtvedt G, et al. Growing literature, stagnant science? Systematic review, meta-regression and cumulative analysis of audit and feedback interventions in health care. *J Gen Intern Med* 2014;**29(11)**:1534-41.

22. Spoorenberg V, Hulscher ME, Geskus RB, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. *PLoS One* 2015;**10(12)**:e0142672.

23. Baker R, Camosso-Stefinovic J, Gillies C, et al. Tailored interventions to address determinants of practice. *Cochrane Database Syst Rev* 2015**(4)**:CD005470.

24. Bartelsman M, Joore IK, van Bergen JE, et al. HIV testing week 2015: lowering barriers for HIV testing among high-risk groups in Amsterdam. *BMC Infect Dis* 2017;**17(1)**:529.

25. Ministerie van Onderwijs Cultuur en Wetenschap, Ministerie van Veiligheid en Justitie, Ministerie van Volksgezondheid Welzijn en Sport. Nieuwe maatregelen tegen verspreiding coronavirus in Nederland - Nieuwsbericht - Rijksoverheid.nl. 2020. Available at https://www.rijksoverheid.nl/actueel/nieuws/2020/03/12/nieuwe-maatregelen-tegen-verspreiding-coronavirus-in-nederland. Last accessed 9 January 2023.

26. Jordans CCE, Vasylyev M, Rae C, et al. National medical specialty guidelines of HIV indicator conditions in Europe lack adequate HIV testing recommendations: a systematic guideline review. *Eurosurveillance* 2022;**27(48)**:2200338.

27. Davies CF, Kesten JM, Gompels M, et al. Evaluation of an educational intervention to increase HIV-testing in high HIV prevalence general practices: a pilot feasibility stepped-wedged randomised controlled trial. *BMC Fam Pract* 2018;**19(1)**:195.

28. Town K, McNulty CA, Ricketts EJ, et al. Service evaluation of an educational intervention to improve sexual health services in primary care implemented using a step-wedge design: analysis of chlamydia testing and diagnosis rate changes. *BMC Public Health* 2016;**16**:686.

29. Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One* 2013;**8(1)**:e52845.

30. Raben D, Sullivan AK, Mocroft A, et al. Improving the evidence for indicator condition guided HIV testing in Europe: Results from the HIDES II Study - 2012 - 2015. *PLoS One* 2019;**14(8)**:e0220108.

31. Stutterheim SE, Kuijpers KJR, Walden MI, Finkenflugel RNN, Brokx PAR, Bos AER. Trends in HIV Stigma Experienced by People Living With HIV in the Netherlands: A Comparison of Cross-Sectional Surveys Over Time. *AIDS Educ Prev* 2022;**34(1)**:33-52.

32. Geter A, Herron AR, Sutton MY. HIV-Related Stigma by Healthcare Providers in the United States: A Systematic Review. *AIDS Patient Care STDS* 2018;**32(10)**:418-24.

33. Gagnon M. Re-thinking HIV-Related Stigma in Health Care Settings: A Qualitative Study. *J Assoc Nurses AIDS Care* 2015;**26(6)**:703-19.

34. van Bilsen WPH, Bil JP, Prins JM, et al. Testing and healthcare seeking behavior preceding HIV diagnosis among migrant and non-migrant individuals living in the Netherlands: Directions for early-case finding. *PLoS One* 2022;**17(3)**:e0264435.

35. Bedert M, Davidovich U, de Bree G, et al. Understanding Reasons for HIV Late Diagnosis: A Qualitative Study Among HIV-Positive Individuals in Amsterdam, The Netherlands. *AIDS Behav* 2021;**25(9)**:2898-906.

36. UNAIDS: Joint United Nations Programme on HIV/AIDS. The cities report. UNAIDS Outlook 2014. Geneva, Switzerland 2014. Available at: https://www.unaids.org/sites/default/files/media_asset/JC2687_TheCitiesReport_en.pdf. Last accessed 9 January 2023.

37. Jones A, Cremin I, Abdullah F, et al. Transformation of HIV from pandemic to low-endemic levels: a public health approach to combination prevention. *Lancet* 2014;**384(9939)**:272-9.

38. Blenkinsop A, Monod M, van Sighem A, et al. Estimating the potential to prevent locally acquired HIV infections in a UNAIDS Fast-Track City, Amsterdam. *Elife* 2022;**3(11)**:e76487.

39. den Daas C, Meddens EM, van Bergen J, et al. Increasing awareness and prompting HIV testing: Contributions of Amsterdam HIV Testing Week 2016. *Int J STD AIDS* 2018;**29(11)**:1057-65.

40. Hoornenborg E, Coyer L, van Laarhoven A, et al. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. *AIDS* 2018;**32(11)**:1527-32.

41. Hoornenborg E, Coyer L, Achterbergh RCA, et al. Sexual behaviour and incidence of HIV and sexually transmitted infections among men who have sex with men using daily and event-driven pre-exposure prophylaxis in AMPrEP: 2 year results from a demonstration study. *Lancet HIV* 2019;**6(7)**:e447-e55.

42. Dijkstra M, de Bree GJ, Stolte IG, et al. Development and validation of a risk score to assist screening for acute HIV-1 infection among men who have sex with men. *BMC Infect Dis* 2017;**17(1)**:425.

43. Dijkstra M, van Rooijen MS, Hillebregt MM, et al. Decreased Time to Viral Suppression After Implementation of Targeted Testing and Immediate Initiation of Treatment of Acute Human Immunodeficiency Virus Infection Among Men Who Have Sex With Men in Amsterdam. *Clin Infect Dis* 2021;**72(11)**:1952-60.

44. Desai S, Tavoschi L, Sullivan AK, et al. HIV testing strategies employed in health care settings in the European Union/European Economic Area (EU/EEA): evidence from a systematic review. *HIV Med* 2020;**21(3)**:163-79.

45. Justice AC, Goetz MB, Stewart CN, et al. Delayed presentation of HIV among older individuals: a growing problem. *Lancet HIV* 2022;**9(4)**:e269-e80.

46. Levy I, Maor Y, Mahroum N, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. *BMJ Open* 2016;**6(11)**:e012721.

47. Lin YD, Eades L, Nair A, Korman TM, Woolley I. Review of HIV testing recommendations in Australian specialty guidelines for HIV indicator conditions: a missed opportunity for recommending testing? *Intern Med J* 2020;**50(3)**:293-8.

48. Lin YD, Garner SE, Lau JSY, Korman TM, Woolley IJ. Prevalence of HIV indicator conditions in late presenting patients with HIV: a missed opportunity for diagnosis? *QJM* 2019;**112(1)**:17-21.

49. Lord E, Stockdale AJ, Malek R, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. *HIV Med* 2017;**18(4)**:300-4.

50. Tan K, Black BP. A Systematic Review of Health Care Provider-Perceived Barriers and Facilitators to Routine HIV Testing in Primary Care Settings in the Southeastern United States. *J Assoc Nurses AIDS Care* 2018;**29(3)**:357-70.

51. van Braak M, Visser M, Holtrop M, Statius Muller I, Bont J, van Dijk N. What motivates general practitioners to change practice behaviour? A qualitative study of audit and feedback group sessions in Dutch general practice. *BMJ Open* 2019;**9(5)**:e025286.

52. Takada T, Heus P, van Doorn S, et al. Strategies to reduce the use of low-value medical tests in primary care: a systematic review. *Br J Gen Pract* 2020;**70(701)**:e858-e65.

53. Abbo L, Sinkowitz-Cochran R, Smith L, et al. Faculty and resident physicians' attitudes, perceptions, and knowledge about antimicrobial use and resistance. *Infect Control Hosp Epidemiol* 2011;**32(7)**:714-8.

54. Davis DA, Mazmanian PE, Fordis M, Van Harrison R, Thorpe KE, Perrier L. Accuracy of physician self-assessment compared with observed measures of competence: a systematic review. *JAMA* 2006;**296(9)**:1094-102.

55. Ludikhuize J, Dongelmans DA, Smorenburg SM, Gans-Langelaar M, de Jonge E, de Rooij SE. How nurses and physicians judge their own quality of care for deteriorating patients on medical wards: self-assessment of quality of care is suboptimal*. *Crit Care Med* 2012;**40(11)**:2982-6.

56. Srivastava R, Bartlett WA, Kennedy IM, Hiney A, Fletcher C, Murphy MJ. Reflex and reflective testing: efficiency and effectiveness of adding on laboratory tests. *Ann Clin Biochem* 2010;**47(Pt 3)**:223-7.

57. Murphy MJ. Reflex and reflective testing: progress, but much still to be done. *Ann Clin Biochem* 2021;**58(2)**:75-7.

58. Gevers JK. [Evaluation of the Dutch Medical Treatment Act (WGBO)]. *Ned Tijdschr Geneeskd* 2001;**145(11)**:509-12.

59. Brinkman K, van Bergen JE. [Earlier implementation of HIV testing]. *Ned Tijdschr Geneeskd* 2013;**157(15)**:A6120.

60. Young SD, Monin B, Owens D. Opt-out testing for stigmatized diseases: a social psychological approach to understanding the potential effect of recommendations for routine HIV testing. *Health Psychol* 2009;**28(6)**:675-81.

61. MacKenzie AI, Holme SA. HIV testing in Scottish dermatology, a national audit. *Clin Exp Dermatol* 2013;**38(3)**:313-4.

62. Wadood AC, Dhillon B, McIlwaine G, Brettle RP. Delayed diagnosis of HIV infection in ophthalmic practice. *Eye (Lond)* 2004;**18(3)**:293-8.

63. Santella AJ, Conway DI, Watt RG. The potential role of dentists in HIV screening. *Br Dent J* 2016;**220(5)**:229-33.

64. Leber W, Panovska-Griffiths J, Martin P, et al. Evaluating the impact of post-trial implementation of RHIVA nurse-led HIV screening on HIV testing, diagnosis and earlier diagnosis in general practice in London, UK. *EClinicalMedicine* 2020;**19**:100229.

65. Anaya HD, Hoang T, Golden JF, et al. Improving HIV screening and receipt of results by nurse-initiated streamlined counseling and rapid testing. *J Gen Intern Med* 2008;**23(6)**:800-7.

66. Hensley KS, Jordans CCE, van Kampen JJA, et al. Significant Impact of Coronavirus Disease 2019 (COVID-19) on Human Immunodeficiency Virus (HIV) Care in Hospitals Affecting the First Pillar of the HIV Care Continuum. *Clin Infect Dis* 2022;**74(3)**:521-4.

67. Bogers SJ, Jordans CCE, Rokx C. [Towards zero new HIV infections in the Netherlands: proactive testing in case of indicator conditions]. *Ned Tijdschr Geneeskd* 2021;**165**.

68. Blondell SJ, Kitter B, Griffin MP, Durham J. Barriers and Facilitators to HIV Testing in Migrants in High-Income Countries: A Systematic Review. *AIDS Behav* 2015;**19(11)**:2012-24.

69. Bender SS, Fulbright YK. Content analysis: a review of perceived barriers to sexual and reproductive health services by young people. *Eur J Contracept Reprod Health Care* 2013;**18(3)**:159-67.

70. Denison HJ, Bromhead C, Grainger R, Dennison EM, Jutel A. Barriers to sexually transmitted infection testing in New Zealand: a qualitative study. *Aust N Z J Public Health* 2017;**41(4)**:432-7.

71. Krabbenborg N, Spijker R, Zakowicz AM, de Moraes M, Heijman T, de Coul EO. Community-based HIV testing in The Netherlands: experiences of lay providers and end users at a rapid HIV test checkpoint. *AIDS Res Ther* 2021;**18(1)**:34.

72. Nash S, Kall M, Enayat Q, Newbigging-Lister A, Delpech V, Public health England. 2021. HIV self-testing and self-sampling in Europe: Situation Report to January 2021. Availabe at: https://eurotest.org/Portals/0/Integrate%20JA/Tools/INTEGRATE_HIV_selftesting_and_selfsampling_in_Europe_final.pdf. Last accessed 9 January 2023.

73. Kelly DV, Kielly J, Hughes C, et al. Expanding access to HIV testing through Canadian community pharmacies: findings from the APPROACH study. *BMC Public Health* 2020;**20(1)**:639.

74. UNAIDS: Joint United Nations Programme on HIV/AIDS. Geneva 2022. IN DANGER: UNAIDS Global AIDS Update 2022. Available at https://www.unaids.org/en/resources/documents/2022/in-danger-global-aids-update. Last accessed 9 January 2023.

75. Maggioni A, Gonzales-Zamora JA, Maggioni A, et al. Cascading Risks for Preventable Infectious Diseases in Children and Adolescents during the 2022 Invasion of Ukraine. *Int J Environ Res Public Health* 2022;**19(12)**.

76. Essar MY, Matiashova L, Tsagkaris C, Vladychuk V, Head M. Infectious diseases amidst a humanitarian crisis in Ukraine: A rising concern. *Ann Med Surg (Lond)* 2022;**78**:103950.

77. UNAIDS: Joint United Nations Programme on HIV/AIDS. Geneva 2019. UNAIDS data 2019. Available at https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data. Last accessed 9 January 2023.

78. Stijnberg D, Kee MM, Bergs J, Adhin MR, Schrooten W. The continuum of care for people living with HIV in Suriname: identifying factors influencing the care delivery process. *IJQHC Communications* 2022;**2(2)**.

Chapter 12

Summary in English

SUMMARY IN ENGLISH

Eliminating HIV transmission and therefore ending the HIV epidemic is a feasible goal for 2030, if interventions to prevent HIV transmission are optimally applied. Diagnosing individuals living with HIV is one of the key prerequisites to prevent HIV transmission. Additionally, timely diagnosis and treatment of HIV lead to reduced mortality, morbidity, hospitalizations and healthcare costs, as well as improved response to antiretroviral therapy. Therefore, (timely) HIV diagnosis improves both individuals' and population health.

While the Netherlands is at the forefront of the HIV response, further improvements are needed to end HIV by 2030. Importantly, half of newly diagnosed individuals since 2018 were diagnosed with late-stage HIV infection (i.e. a CD4-count <350 cells/mm3), likely leading to poorer health outcomes as well as onward transmission. The proportion with late-stage infection was higher among patients diagnosed in the primary care and hospital setting compared to individuals diagnosed at sexual health centers (SHCs). While routine opt-out HIV testing among key populations is already applied in SHCs, healthcare providers in the primary care and hospital setting may contribute to reducing the proportion of people with undiagnosed HIV by implementing proactive, provider-initiated testing strategies.

Part I – Introduction
In **Chapter 1**, we introduce the topic addressed in this thesis, i.e. projects to improve provider-initiated testing for HIV in the primary care and hospital setting. We address the state of the HIV epidemic, and the evolution of the HIV epidemic in the Netherlands from an emerging public health threat to the current challenges in eliminating HIV transmission in the Netherlands. Next, we discuss the rationale for a city-based combination intervention approach to improve all facets of the HIV testing and care continuum. Then, we elaborate on the various HIV testing strategies that are available in the Netherlands, including resources for provider-initiated HIV testing and counseling (PITC). Finally, we discuss the role of primary care physicians and hospital physicians in provider-initiated HIV testing, and the concept of indicator condition-guided testing for HIV. We conclude this chapter with an outline of this thesis.

Part II – Primary care setting
In **Chapter 2**, we report on a retrospective observational study that compared HIV testing and positivity by general practitioners (GPs) versus SHCs in five Dutch regions with different levels of urbanization from 2011 to 2018. The included regions were Amsterdam, Rotterdam, Maastricht, Twente and North Netherlands. We collected data from laboratories performing diagnostics for GPs and SHCs in these regions and calculated mean and annual HIV testing rates per 10,000 residents. We additionally compared HIV testing rates between GPs and SHCs by calculating rate ratios (RR). Overall, we analyzed 505,167 HIV tests. The majority of HIV tests were performed by providers in the very highly urbanised regions of Amsterdam (59% of tests) and Rotterdam (19% of tests). SHCs performed more tests (64%) compared

to GPs (36%). By region, GPs' testing rates were lower than SHCs' in Amsterdam, Maastricht and Twente, while they were comparable in Rotterdam and North Netherlands. The highest positivity percentages were reported in Amsterdam (GP 0.7%, SHC 0.3%) and Rotterdam (GP 0.5%, SHC 0.5%). In Amsterdam, the positivity percentages were significantly higher among people tested by GPs compared with those tested by SHCs ($p<0.001$), while they were comparable in the other regions. We concluded that GPs play a significant role in HIV testing and diagnosis, but that their testing behavior varies considerably between regions.

In **Chapter 3**, we describe the rationale, design and implementation of an educational intervention program to improve HIV testing by GPs in Amsterdam, and report trends in HIV, chlamydia and gonorrhea testing by GPs in Amsterdam from 2011 to 2017. We describe how the program was designed, how participants were recruited, and how the program was evaluated. We additionally describe the content of the educational sessions, and the evidence for the effectiveness of elements used in their design. We collected data from laboratories performing diagnostics for GPs to analyze the initial results of the intervention and trends in testing. In this interim analysis, we report that 41% of all GPs in Amsterdam in 2017 (220/534) participated in the program, which was rated 8.4/10 in evaluations. We also discuss the topics commonly addressed in participating GPs' quality improvement plans for their practice. Finally, we describe that HIV testing rates by GPs in Amsterdam per 10,000 person years declined from 2011 to 2014 (from 175 to 116 per 10,000 person years, IRR 0.69), after which it stabilized (from 116 to 123, IRR 1.06), coinciding with the start of our intervention in 2015. Trends in chlamydia and gonorrhea testing in women showed a similar pattern as HIV testing trends, while in men, they remained stable over time. We concluded that the first results from this educational intervention showed a stabilization in HIV testing coinciding with the start of our intervention, although no inference on causality could be made.

In **Chapter 4**, we evaluated the effect of the educational intervention on HIV, chlamydia and gonorrhea testing by GPs in Amsterdam using laboratory data from 2011 to 2020. We compared testing by GPs before and after participation and estimated the effect of the intervention over time after participation. We observed a 7% increase in HIV testing among GPs after participation, compared to before participation (ratio 1.07, 95%CI 1.04-1.09, $p<0.001$). By patient sex, this increase was 6% among men and 8% among women and was largest among patients aged ≤19 and 50-64 years old. No significant change was observed in the proportion of positive HIV tests. We also observed an increase in urogenital chlamydia testing while urogenital gonorrhea testing decreased, likely reflecting better adherence to the sexual health consultation guideline, as it recommends gonorrhea testing only when selected risk factors are present. Extragenital chlamydia and gonorrhea testing both increased, likely reflecting increased awareness of extragenital testing indications that may have been overlooked in the past. The effect of the intervention did not wane over time, as we observed a slight increase in HIV testing over time since participation (adjusted RR 1.02 per quarter, 95% CI 1.01-1.02, $p<0.001$). We

therefore concluded that the intervention was associated with a modest, sustainable increase in HIV testing among GPs who participated.

In **Chapter 5**, we performed a mixed-methods study to gain a deeper understanding whether and how the quality of GPs' HIV, chlamydia and gonorrhea testing knowledge, attitude and behavior changed following the intervention, and what determinants for testing are. To this end, we evaluated 101 questionnaires that were completed by GPs during the second educational session and interviewed eight GPs that had participated. Overall, 69% of questionnaire respondents reported that they had learned new information (i.e. "eye-openers"), 72% reported that they had changed their testing behavior and 82% reported that they had implemented the quality improvement plans for their practice. The majority of respondents planned to further improve their testing in the future. In the interviews, some GPs reported less frequent HIV testing in low-risk patients, while others reported more frequent HIV testing, even in low-risk patients. Additionally, interviewees reported that they expected that their improvements in testing behavior would be sustainable, as they became intrinsically motivated by the audit and feedback reported during the sessions. However, some persistent barriers to testing were identified. These included HIV-related stigma, lack of training on sexual health, GPs feeling less motivated to test for HIV due to decreasing HIV prevalence in the Netherlands, and financial barriers, as testing by GPs must be paid out-of-pocket by patients when they have not yet depleted their annual mandatory deductible. We observed a discrepancy between the rather moderate increases in HIV testing assessed from laboratory data and the more considerable self-reported improvements in HIV testing knowledge, attitude and behavior, which may have been a reflection of "wishful thinking" or an overestimation of quality by respondents, or of appropriate intentional decreases in testing among low-risk patients. We concluded that self-reported testing behavior improved, but that barriers to optimal testing strategies still persist. Therefore, continually addressing proactive HIV testing to keep GPs actively engaged, will be a key contributor to end the HIV epidemic in the Netherlands.

Part III – Hospital setting

In **Chapter 6**, we assessed the implementation of indicator condition (IC)-guided testing in a selection of ICs in various healthcare settings, including primary care and the hospital setting, in Western countries. The selected ICs were: tuberculosis, cervical cancer or cervical intraepithelial neoplasia grade 2+, vulvar cancer or vulvar intraepithelial neoplasia grade 2+, malignant lymphoma, hepatitis B, hepatitis C, and peripheral neuropathy. We performed a systematic review and meta-analysis of available literature and included 57 publications. We found that there is a large variation in the implementation of IC-guided testing, with overall low HIV test ratios. Implementation was highest among patients with tuberculosis, hepatitis B, hepatitis C and malignant lymphoma, among whom HIV testing is generally recommended in guidelines, while it was low among patients with other ICs. When comparing different implementation strategies, routine HIV testing policies were more successful compared to risk-based testing. A combination intervention strategy

including guideline adaptations, creating awareness, and implementing routine testing solutions is therefore likely most effective to improve the implementation of IC-guided testing.

In **Chapter 7**, we present the study protocol for the PROmoting HIV indicator condition-guided TESTing in hospital settings (PROTEST 2.0) study. We consider that (timely) HIV diagnosis is crucial to end HIV transmission and therefore end the epidemic, and that IC-guided testing is variably and insufficiently implemented in Western countries. The aim of the intervention study is therefore to generate awareness about ICs and the importance of IC-guided HIV testing amongst physicians working in hospitals and improve implementation of IC-guided testing in hospitals in the region of Amsterdam, the Netherlands. Two university hospitals, two non-academic teaching hospitals and one non-teaching hospital are included in the study, which focuses on a selection of seven ICs generally managed by five different specialties. The selected ICs were tuberculosis, cervical cancer or high-grade cervical dysplasia, vulvar cancer or high-grade vulvar dysplasia, malignant lymphoma, hepatitis B, hepatitis C and peripheral neuropathy. The intervention strategy was multifaceted, and tailored by specialty and hospital, based on local opportunities for improvement. Elements included were educational meetings, presentation of graphical audit and feedback, interactive discussion on opportunities to improve HIV testing, handout of materials, and implementation of additional solutions to improve routine testing. The primary outcome was the HIV test ratio (i.e. the proportion of patients with an IC who were tested for HIV) within 3 months before to 3 months after IC diagnosis.

In **Chapter 8**, we evaluated the adoption of IC-guided testing in the hospital setting and its determinants through a survey study among 163 physicians working in five hospitals in the region of Amsterdam, the Netherlands. The survey was designed based on the Theory of Planned Behavior (TPB), and assessed self-reported IC-guided testing behavior, and intention to apply IC-guided testing in the future (behavioral intention), as determined by three domains: the respondents' attitude regarding the need for IC-guided testing, the professional norms of the respondent's environment, including colleagues and patients, and the respondent's self-efficacy, or their confidence in their ability to successfully apply IC-guided testing. We examined pathways involved in IC-guided testing behavior based on questionnaire responses using structural equation models. We found that reported behavior was lower than intention, and the observed association between intention and behavior was smaller than expected. This may be because healthcare providers have the perception that they should provide high-quality care, resulting in a high intention to apply IC-guided testing, but barriers to HIV testing might keep them from actually applying this strategy. We therefore examined an additional structural equations model in which the domains from the TPB model directly contributed to self-reported HIV testing behavior, while excluding intention from the model, and found that it had a better fit than the classical intentional model. Guideline recommendations, physician's attitudes and self-efficacy were the most important determinants for IC-guided HIV testing behavior in this direct model. We therefore

concluded that in order to increase adoption of IC-guided testing in the hospital setting, interventions should include implementation of guideline recommendations where these are lacking, followed by improving physicians' beliefs towards IC-guided HIV testing and self-efficacy.

In **Chapter 9**, we report the results of the PROTEST 2.0 study to improve IC-guided testing for HIV in the hospital setting. During the pre-intervention phase, data on IC-guided HIV testing from January 2015 through June 2020 were collected. For all hospitals and departments, the intervention started on July 1, 2020. A repeat assessment of IC-guided HIV testing was performed in all settings from July 2020 through June 2021. During the intervention phase, 26 educational intervention sessions were conducted in which 384 physicians participated. Additional developments to improve IC-guided HIV testing that occurred as a result of the educational intervention varied by setting and included guideline adaptations, revising diagnostic order sets, implementing reflex HIV testing, and electronic prompts for HIV testing. Overall, 23,764 patients were assessed for eligibility, and 7,986 patients were included for analysis, including 6,730 patients in the pre-intervention phase and 1,256 patients in the intervention phase. The intervention increased IC-guided testing from 37% before the intervention to 47% after the intervention (adjusted RR 1.16, 95% CI 1.03-1.30, p=0.02). By IC, we observed increases in HIV test ratios in all conditions except vulvar cancer or high-grade dysplasia, but these increases were only statistically significant in cervical cancer or high-grade dysplasia and peripheral neuropathy. Overall, we observed that 0.6% of all tested patients were HIV positive, which significantly exceeded the established cost-effectiveness threshold for HIV screening of 0.1% (p<0.0001). There was no difference in the percentage positive between pre-intervention and post-intervention phases (p=0.23). We concluded that the intervention was successful at increasing HIV testing, and positivity exceeded the previously established cost-effectiveness threshold, but that the effect varied by IC and setting, possibly due to variations in implemented developments as well as short follow-up.

In **Chapter 10**, we report on a substudy of the PROTEST 2.0 study assessing the implementation of HIV testing among patients with malignant lymphoma and map factors influencing hematologists' HIV testing behavior through a mixed-methods approach. We evaluated pre-intervention HIV test ratio among 1,612 patients with lymphoma by diagnosis and treatment status, questionnaires based on the Theory of Planned Behavior model completed by 40 hematologists, and semi-structured interviews among ten hematologists and two authors of hematology guidelines. We found that 70% of patients newly diagnosed with lymphoma and 54% of patients with a known lymphoma diagnosis but who newly entered into care at one of the study sites were tested for HIV within 3 months before or after lymphoma diagnosis. Among patients who were treated for lymphoma, 71% were tested within 3 months. Of the remaining 29%, 10% were tested more than 3 months before or after diagnosis, and 19% had no evidence of ever being tested for HIV. Overall, 0.7% of patients tested within 3 months were HIV positive. In questionnaires, 68% of hematologists reported having tested lymphoma patients

for HIV in the past, while 85% reported intention to test. From the interviews, we concluded that hematologists apply varying testing strategies, including testing in all lymphoma patients, or only at treatment initiation, and that awareness is lacking. Most hematologists reported that they address HIV testing to their patients as being a routine procedure, that patients rarely refuse testing, and that perceived self-efficacy to offer testing was high. Identified barriers to testing included low HIV prevalence, lack of a clear association between HIV and some lymphoma subtypes, forgetting to test when it is not done right away, HIV-related stigma, and low perceived risk among some patient groups. An important facilitator was HIV testing being part of a routine or guideline and it being easy to apply. We concluded that missed opportunities for HIV testing among patients with lymphoma were not uncommon, likely due to lack of HIV testing recommendations in guidelines for some lymphoma types, and due to conflicting testing strategies among hematologists. Efforts for improvement should entail a combination of approaches addressing determinants, barriers and facilitators identified in this study.

Part IV – Conclusions

In **Chapter 11**, we discuss the findings of the studies in this thesis and delve further into the meaning and importance of these results. We then summarize the lessons learned from these projects. Finally, we provide recommendations for future steps to improve HIV testing in both the primary care and hospital setting, to help reach the goals of ending HIV transmission, and the epidemic overall, in the Netherlands and beyond.

Chapter 13

Summary in Dutch

NEDERLANDSE SAMENVATTING

Het voorkomen van hiv-transmissie, en daarmee het beëindigen van de hiv-epidemie, is een haalbaar doel voor 2030, mits interventies die hiv-transmissie voorkomen optimaal worden ingezet. Het diagnosticeren van personen met hiv is een van de belangrijkste voorwaarden om hiv-transmissie te voorkomen. Daarnaast zorgt tijdige diagnose van hiv voor een reductie van mortaliteit, morbiditeit, ziekenhuisopname en zorgkosten, en een betere reactie op antiretrovirale behandeling. Het (tijdig) stellen van een hiv-diagnose leidt daarom tot verbetering van de gezondheid van het individu, én van de volksgezondheid.

Hoewel Nederland vooroploopt in het bestrijden van de hiv-epidemie, zijn er aanvullende maatregelen nodig om deze te beëindigen voor 2030. Van de mensen die sinds 2018 met hiv zijn gediagnosticeerd, is bij de helft sprake van diagnose in een laat stadium van hiv-infectie (met een CD4-getal <350 cellen/mm^3), wat kan leiden tot slechtere gezondheidsuitkomsten en verdere transmissie van hiv. Het aandeel mensen met een laat stadium hiv-infectie was hoger onder mensen die hun diagnose kregen in de huisartsenpraktijk en het ziekenhuis, vergeleken met mensen die hun diagnose kregen in een centrum voor seksuele gezondheid (CSG). Terwijl er al een geenbezwaarprocedure wordt gehanteerd in het testen van risicogroepen op hiv in CSG's, kunnen zorgverleners in de huisartsenpraktijk en het ziekenhuis nog meer bijdragen aan een verkleining van het aandeel mensen met ongediagnosticeerde hiv, door een proactieve hiv-teststrategie te hanteren.

Deel I – Introductie
In **Hoofdstuk 1** introduceren we de onderwerpen die in dit proefschrift aan bod komen: projecten ter verbetering van zorgverlener-geïnitieerd testen op hiv in de huisartsenpraktijk en het ziekenhuis. We bespreken de huidige staat van de hiv-epidemie, en de evolutie van de hiv-epidemie in Nederland van een opkomende bedreiging voor de volksgezondheid naar de huidige uitdagingen die het voorkomen van hiv-transmissie in de weg staan. Vervolgens bespreken we de motivatie voor, en voordelen van een gecombineerde aanpak op stadsniveau in het verbeteren van alle facetten van hiv-diagnostiek en -zorg. Daarna gaan we in op de verschillende hiv-testvoorzieningen die in Nederland beschikbaar zijn, waaronder voorzieningen voor zorgverlener-geïnitieerd testen en counselen. Ten slotte bespreken we de rol van huisartsen en ziekenhuisartsen in zorgverlener-geïnitieerd testen op hiv, en het principe van indicatoraandoening-geleid testen op hiv. We eindigen het hoofdstuk met een overzicht van de inhoud van dit proefschrift.

Deel II – Eerste lijn
In **Hoofdstuk 2** rapporteren we de bevindingen van een retrospectieve observationele studie, waarin het aantal hiv-testen en het aandeel positieve testen werd vergeleken tussen huisartsen en CSG's in vijf verschillende Nederlandse regio's met verschillende stedelijkheidsniveaus, van 2011 tot 2018. De regio's die werden gestudeerd waren: Amsterdam, Rotterdam, Maastricht, Twente en Noord-Nederland. We onderzochten aan de hand van laboratoriumgegevens de

gemiddelde en jaarlijkse aantallen hiv-testen per 10.000 inwoners, en we vergeleken de verhouding van deze aantallen tussen huisartsen en CSG's. In totaal analyseerden we gegevens van 505.167 hiv-testen. De meerderheid van deze testen was uitgevoerd door zorgverleners in de hoogstedelijke regio's Amsterdam (59% van de testen) en Rotterdam (19% van de testen). CSG's voerden gemiddeld meer testen uit dan huisartsen (64% versus 36%, respectievelijk). Gekeken per regio testten huisartsen minder dan CSG's in Amsterdam, Maastricht en Twente, terwijl dit ongeveer gelijk was in Rotterdam en Noord-Nederland. De hoogste percentages positieve testen werden gezien in Amsterdam (0,7% door huisartsen en 0,3% door het CSG) en in Rotterdam (0,5% door huisartsen en 0,5% door het CSG). In Amsterdam was het percentage positieve hiv-testen significant hoger onder personen getest door huisartsen in vergelijking met personen getest door het CSG ($p<0,001$), terwijl deze percentages vergelijkbaar waren tussen de twee groepen in de andere regio's. We concludeerden dat huisartsen een belangrijke rol spelen in het aanbieden van hiv-testen en stellen van hiv-diagnoses, maar dat hun hiv-testgedrag sterk varieert tussen regio's.

In **Hoofdstuk 3** beschrijven we de rationale, de opzet en de implementatie van een educatief interventieprogramma ter verbetering van hiv-testgedrag door huisartsen in Amsterdam. Ook rapporteren we trends in hiv-, chlamydia- en gonorroe-testen door huisartsen in Amsterdam van 2011 tot 2017. We beschrijven hoe het programma opgezet werd, hoe deelnemers werden geworven, en hoe het werd geëvalueerd. Ook beschrijven we de inhoud van de educatieve sessies, en het wetenschappelijk bewijs voor de effectiviteit van de elementen die werden gebruikt in het ontwerp van de sessies. We analyseerden de eerste resultaten van de interventie en trends in testen aan de hand van data van laboratoria die diagnostiek voor de eerste lijn verzorgen. Uit deze interim analyse bleek dat 41% van alle huisartsen in Amsterdam in 2017 (220/534) had deelgenomen aan het programma, dat in evaluaties gemiddeld werd beoordeeld met een 8,4/10. We bespreken ook de onderwerpen die het meest aan bod kwamen in de praktijkverbeterplannen die deelnemende huisartsen hadden opgesteld. Ten slotte beschrijven we dat het aantal hiv-testen per 10.000 inwoners door Amsterdamse huisartsen daalde van 2011 tot 2014 (van 175 naar 116 per 10.000 persoonsjaren, IRR 0,69), waarna een stabilisatie werd gezien (van 116 naar 123, IRR 1,06), die samenviel met de start van de interventie in 2015. Trends in het aantal chlamydia- en gonorroe-testen onder vrouwen lieten eenzelfde patroon zien als de trends in hiv-testen, terwijl het aantal testen onder mannen stabiel bleef gedurende deze periode. We concludeerden dat de eerste resultaten van deze educatieve interventie een stabilisatie in hiv-testgedrag liet zien, die samenviel met de start van de interventie. Een causaal verband kon in deze studie echter niet worden aangetoond.

In **Hoofdstuk 4** evalueerden we het effect van de interventie op aantallen hiv-, chlamydia- en gonorroe-testen door Amsterdamse huisartsen met behulp van laboratoriumdata van 2011 tot 2020. We vergeleken het aantal testen door huisartsen voor en na deelname en berekenden het effect van de interventie over de tijd na deelname. We zagen een stijging van 7% in hiv-testen onder huisartsen

die hadden deelgenomen in vergelijking met huisartsen voor deelname (ratio 1,07, 95% betrouwbaarheidsinterval 1,04-1,09, p<0,001). Die stijging was 6% onder mannelijke patiënten, en 8% onder vrouwelijke patiënten, en was het grootst onder patiënten met een leeftijd van ≤19 en 50-65 jaar. We zagen geen significante verandering in de proportie positieve testen. Wel zagen we een stijging in het aantal urogenitale chlamydia-testen, terwijl het aantal urogenitale gonorroe-testen daalde, waarschijnlijk door betere navolging van de richtlijn "Het soa-consult", waarin wordt aanbevolen om alleen op gonorroe te testen indien er sprake is van bepaalde risicofactoren. Het aantal extragenitale testen steeg voor zowel chlamydia als gonorroe, waarschijnlijk als gevolg van meer bewustwording rondom indicaties voor extragenitaal testen die eerder werden gemist. Het effect van de interventie nam niet af gedurende deze periode. In plaats daarvan zagen we een lichte stijging in het aantal hiv-testen sinds deelname aan het programma (ratio 1,02 per kwartaal sinds deelname, 95% betrouwbaarheidsinterval 1,01-1,02, p<0,001). We concludeerden daarom dat de interventie geassocieerd was met een bescheiden, duurzame stijging in het aantal hiv-testen onder huisartsen die hadden deelgenomen.

In **Hoofdstuk 5** rapporteren we over een *mixed-methods*-studie, welke we uitvoerden om meer inzicht te krijgen in of, en hoe de kwaliteit van kennis, houding en gedrag van huisartsen op het gebied van hiv, chlamydia en gonorroe diagnostiek veranderde na de interventie, en waardoor dit werd bepaald. Hiertoe evalueerden we 101 vragenlijsten ingevuld door huisartsen tijdens de tweede nascholingssessie, en interviewden we acht huisartsen die hadden deelgenomen. In totaal rapporteerde 69% van de deelnemers aan de vragenlijst dat zij nieuwe, inzichtgevende informatie hadden geleerd, 72% rapporteerde dat ze hun teststrategie hadden gewijzigd en 82% rapporteerde dat zij hun praktijkverbeterplannen hadden geïmplementeerd. De meerderheid van de respondenten rapporteerde van plan te zijn hun testgedrag verder te verbeteren in de toekomst. In de interviews gaven enkele huisartsen aan minder frequent op hiv te testen onder patiënten met een laag hiv-risico, terwijl anderen aangaven meer te zijn gaan testen, ook in laagrisicopatiënten. Geïnterviewde huisartsen gaven tevens aan dat zij verwachtten dat de verbeteringen in testgedrag duurzaam zouden zijn, omdat zij intrinsiek gemotiveerd waren verbeteringen toe te passen door de spiegelinformatie die werd gegeven tijdens de sessies. Er werden ook barrières voor optimaal testgedrag geïdentificeerd. Voorbeelden waren hivgerelateerd stigma, onvoldoende training in onderwerpen omtrent seksuele gezondheid, lagere motivatie om op hiv te testen vanwege de krimpende epidemie in Nederland, en financiële barrières, omdat patiënten die hun eigen risico nog niet verbruikt hebben huisartsendiagnostiek zelf moeten betalen. We zagen een discrepantie tussen de bescheiden stijging in het aantal hiv-testen gemeten met laboratoriumdata en de aanzienlijkere zelfgerapporteerde verbeteringen in kennis, houding en gedrag omtrent hiv-diagnostiek, wat een uiting kan zijn van "*wishful thinking*" of een overschatting van de kwaliteit door respondenten, of van een terechte, intentionele afname in diagnostiek onder laagrisicopatiënten. We concludeerden dat zelfgerapporteerd testgedrag verbeterde, maar dat er nog steeds barrières zijn die optimaal testgedrag in de weg zitten. Het is daarom nodig dat er voortdurend en herhaald aandacht wordt besteed aan proactief testen op hiv door

huisartsen om hen gemotiveerd en betrokken te houden. Dit zal een belangrijke bijdrage leveren aan het beëindigen van de hiv-epidemie in Nederland.

Deel III – Ziekenhuissetting

In **Hoofdstuk 6** onderzochten we de mate van implementatie van indicatoraandoening-geleid testen op hiv in een selectie van indicatoraandoeningen in verschillende zorgsettings, waaronder de huisartsenpraktijk en het ziekenhuis, in westerse landen. De geselecteerde aandoeningen waren tuberculose, cervixcarcinoom of intra-epitheliale neoplasie graad 2+, vulvacarcinoom of intra-epitheliale neoplasie graad 2+, maligne lymfoom, hepatitis B, hepatitis C en perifere neuropathie. We voerden een literatuuronderzoek en meta-analyse uit en includeerden 57 publicaties. We stelden vast dat er grote variatie zit in de mate waarin indicatoraandoening-geleid testen is geïmplementeerd, met over het algemeen lage testratio's. De teststrategie was het meest geïmplementeerd onder patiënten met de aandoeningen tuberculose, hepatitis B, hepatitis C en maligne lymfoom, waarbij testen op hiv algemeen wordt aanbevolen in de richtlijnen. De teststrategie was slecht geïmplementeerd onder patiënten met de overige aandoeningen. Vergeleken met testen op hiv op basis van risicostratificatie, was een implementatiestrategie waarbij routinematig op hiv werd getest meer succesvol. Een gecombineerde interventiestrategie waarbij richtlijnen worden gereviseerd, bewustwording wordt gecreëerd onder zorgverleners, en oplossingen voor routinematig testen worden ingezet, is daarmee waarschijnlijk het meest effectief in het verbeteren van de implementatie van indicatoraandoening-geleid testen.

In **Hoofdstuk 7** presenteren wij het studieprotocol van de *PROmoting HIV indicator condition-guided TESTing in hospital settings (PROTEST 2.0)*-studie. We overwegen dat (tijdig) diagnosticeren van een hiv-infectie cruciaal is om hiv-transmissie, en daarmee de epidemie, te beëindigen, en dat indicatoraandoening-geleid testen wisselend en onvoldoende is geïmplementeerd in westerse landen. Het doel van deze interventiestudie is daarom om bewustwording omtrent indicatoraandoeningen, en het belang van deze teststrategie te vergroten onder ziekenhuisartsen, en om de implementatie van deze strategie te verbeteren in ziekenhuizen in de omgeving van Amsterdam. Twee universitaire ziekenhuizen, twee opleidingsziekenhuizen en één niet-opleidingsziekenhuis namen deel aan de studie die zich richtte op een selectie van zeven indicatoraandoeningen die over het algemeen worden gediagnosticeerd en behandeld door vijf specialismen. De geselecteerde aandoeningen waren tuberculose, cervixcarcinoom of hooggradige cervixdysplasie, vulvacarcinoom of hooggradige vulvadysplasie, maligne lymfoom, hepatitis B, hepatitis C en perifere neuropathie. De interventie bestond uit meerdere elementen en was per specialisme en ziekenhuis aangepast afhankelijk van lokale kansen voor verbetering. De elementen betroffen onder andere educatieve bijeenkomsten, presentatie van spiegelinformatie, interactieve discussie over mogelijkheden voor verbetering van hiv-teststrategieën, uitdelen van informatieve materialen, en implementeren van aanvullende oplossingen ter verbetering van routinematig testen op hiv. De primaire uitkomstmaat was de hiv-testratio; het aandeel patiënten gediagnosticeerd met

een indicatoraandoening dat werd getest op hiv binnen drie maanden vóór tot drie maanden na die diagnose.

In **Hoofdstuk 8** evalueerden we de uitvoering en determinanten van indicatoraandoening-geleid testen in ziekenhuizen door middel van een vragenlijstonderzoek onder 163 artsen uit vijf ziekenhuizen in de omgeving van Amsterdam. De vragenlijst was gebaseerd op de theorie van gepland gedrag, en onderzocht zelfgerapporteerd indicatoraandoening-geleid testgedrag, intentie om indicatoraandoening-geleid testen toe te passen in de toekomst (gedragsintentie), en de invloed van drie domeinen. Deze domeinen waren: de attitude van de respondent omtrent de noodzaak van indicatoraandoening-geleid testen, de professionele normen van de omgeving van de respondent inclusief collega's en patiënten, en de eigen kunde en bekwaamheid of het zelfvertrouwen van de respondent in zijn eigen vermogen om indicatoraandoening-geleid testen toe te passen. We maakten gebruik van structurele vergelijkingsmodellen om te onderzoeken welke relaties leiden tot indicatoraandoening-geleid testen. We vonden dat zelfgerapporteerd testgedrag lager was dan gedragsintentie, en de geobserveerde relatie tussen intentie en gedrag was kleiner dan verwacht. Een verklaring zou kunnen zijn dat zorgverleners vinden dat zij hoogwaardige zorg zouden moeten leveren, wat leidt tot hoge gedragsintentie, terwijl barrières voor hiv-diagnostiek daadwerkelijke implementatie van indicatoraandoening-geleid testen in de weg staan. We onderzochten daarom een aanvullend structureel vergelijkingsmodel waarin we de directe relatie tussen de domeinen uit de theorie van gepland gedrag en gedrag beoordeelden, zonder tussenkomst van gedragsintentie, en concludeerden dat dit model de uitkomsten beter voorspelde dan het klassieke intentionele model. Aanbevelingen in richtlijnen, de attitudes van artsen en hun eigen kunde en bekwaamheid om indicatoraandoening-geleid testen toe te passen waren de belangrijkste determinanten voor indicatoraandoening-geleid testgedrag in dit directe model. We concludeerden daarom dat om de implementatie van indicatoraandoening-geleid testen in het ziekenhuis te vergroten, interventies zich moeten richten op het toevoegen van aanbevelingen voor hiv-diagnostiek in richtlijnen, gevolgd door het verbeteren van de attitudes van artsen omtrent indicatoraandoening-geleid testen en hun kunde en bekwaamheid om indicatoraandoening-geleid testen toe te passen.

In **Hoofdstuk 9** rapporteren we de resultaten van de PROTEST 2.0-studie ter verbetering van indicatoraandoening-geleid testen op hiv in de ziekenhuissetting. In de fase vóór de interventie werden gegevens van patiënten die waren gediagnosticeerd met een indicatoraandoening van januari 2015 tot en met juni 2020 verzameld. De interventie startte in alle ziekenhuizen en specialismen op 1 juli 2020. Vervolgens werden gegevens van patiënten die waren gediagnosticeerd met een indicatoraandoening van juli 2020 tot en met juni 2021 verzameld. Tijdens de interventiefase werden 26 educatieve bijeenkomsten gehouden, waaraan in totaal 384 artsen deelnamen. Aanvullende maatregelen die als gevolg van de interventie werden geïmplementeerd om indicatoraandoening-geleid testen te verbeteren varieerden per afdeling. Voorbeelden van deze maatregelen waren aanpassing van

lokale richtlijnen, aanpassing van diagnostische orderpakketten, implementatie van reflexdiagnostiek, en elektronische herinneringen voor hiv-diagnostiek op indicatie. In totaal werden de elektronische dossiers van 23.764 patiënten beoordeeld op geschiktheid voor inclusie in de studie, en werden gegevens van 7.986 patiënten geïncludeerd, waarvan 6.730 uit de fase vóór de interventie en 1.256 uit de interventiefase. Door de interventie steeg het indicatoraandoening-geleid testen van 37% voor de interventie naar 47% na de interventie (gecorrigeerde RR 1,16, 95% betrouwbaarheidsinterval 1,03-1,30, p=0,02). Uitgesplitst per indicatoraandoening observeerden we een stijging in de hiv-testratio onder alle aandoeningen behalve vulvacarcinoom of hooggradige vulvadysplasie, maar de stijging was alleen statistisch significant in de aandoeningen cervixcarcinoom of hooggradige cervixdysplasie en perifere neuropathie. In totaal was 0,6% van de geteste patiënten hiv-positief. Dit percentage was significant hoger dan de in de literatuur vastgestelde kosteneffectiviteitsdrempel voor hiv-screening van 0,1% (p<0,0001). Er was geen significant verschil in het percentage positief geteste patiënten tussen de fase vóór de interventie en erna (p=0,23). We concludeerden dat de interventie succesvol was in het verbeteren van indicatoraandoening-geleid testen, en dat het percentage positief de eerder vastgestelde kosteneffectiviteitsdrempel oversteeg. Het effect van de interventie varieerde per indicatoraandoening en setting, waarschijnlijk vanwege verschillen in geïmplementeerde maatregelen en een korte follow-upperiode.

In **Hoofdstuk 10** rapporteren we de resultaten van een substudie van PROTEST 2.0, waarin we middels een *mixed-methods*-aanpak hebben gekeken naar de implementatie van testen op hiv in patiënten met maligne lymfoom, en waarin we factoren in kaart hebben gebracht die het hiv-testgedrag van hematologen beïnvloeden. We evalueerden de hiv-testratio onder 1.612 patiënten met lymfoom in de fase vóór de interventie, uitgesplitst per diagnose en behandelingsstatus. Daarnaast evalueerden we 40 vragenlijsten gebaseerd op de theorie van gepland gedrag die waren ingevuld door hematologen, en de uitkomsten van semigestructureerde interviews met tien hematologen en twee auteurs van hematologische richtlijnen. We observeerden dat 70% van de patiënten met een nieuwe maligne lymfoomdiagnose, en 54% van de patiënten met een bekende lymfoomdiagnose, maar die nieuw in zorg waren gekomen in een van de studiecentra op hiv was getest binnen 3 maanden voor of na lymfoomdiagnose. Van de patiënten die werden behandeld voor hun lymfoom was 71% getest op hiv binnen 3 maanden. Van de overige 29% was 10% meer dan 3 maanden voor of na de lymfoomdiagnose op hiv getest, terwijl bij 19% geen aanwijzing in het elektronisch patiëntendossier te vinden was dat zij ooit op hiv waren getest. In totaal bleek 0,7% van patiënten die getest waren binnen 3 maanden hiv-positief. In de vragenlijsten rapporteerde 68% van de hematologen dat zij lymfoompatiënten op hiv testten, terwijl 85% rapporteerde de intentie te hebben om deze patiënten te testen. Uit de interviews concludeerden we dat hematologen wisselende teststrategieën hanteren, waaronder testen van alle lymfoompatiënten of alleen wanneer zij starten met behandeling, en dat kennis over de aanbevelingen rondom hiv-diagnostiek bij lymfoompatiënten onvoldoende is. De meerderheid van geïnterviewde hematologen gaf aan dat zij testen op hiv bij hun patiënten aankaarten als een routineprocedure,

dat patiënten zelden een hiv-test weigeren, en dat de eigen kunde en bekwaamheid om een hiv-test aan te bieden hoog was. We identificeerden verscheidene barrières die testen in de weg staan, waaronder een lage hiv-prevalentie, het ontbreken van een duidelijke associatie tussen hiv en sommige subtypen lymfoom, het vergeten te testen wanneer dat niet onmiddellijk wordt gedaan, hivgerelateerd stigma, en een lage hiv-risicoperceptie door hematologen onder sommige patiëntengroepen. Belangrijke bevorderaren voor testen op hiv waren wanneer het onderdeel was van een routine of een richtlijn, en wanneer de praktische uitvoering gemakkelijk was. We concludeerden dat gemiste kansen om patiënten met maligne lymfoom op hiv te testen niet zelden voorkwamen, waarschijnlijk als gevolg van het ontbreken van aanbevelingen in richtlijnen van sommige lymfoomtypen, en als gevolg van tegenstrijdige hiv-teststrategieën onder hematologen. Initiatieven voor verbetering kunnen het best een combinatie van benaderingen toepassen, met inachtneming van de determinanten, barrières en bevorderaren geïdentificeerd in deze studie.

Deel IV – Conclusies

In **Hoofdstuk 11** bespreken we de bevindingen uit de studies in dit proefschrift en gaan we dieper in op hun implicaties. We vatten vervolgens de geleerde lessen samen. Ten slotte geven we aanbevelingen voor vervolgstappen ter verbetering van testen op hiv in de huisartsenpraktijk en het ziekenhuis, om zo bij te dragen aan het stoppen van hiv-transmissie, en het einde van de hiv-epidemie in Nederland en daarbuiten.

Part

V

Appendices

APPENDIX 1 – LIST OF PUBLICATIONS

Saskia J Bogers, Sebastiaan H Hulstein, Maarten F Schim van der Loeff, Godelieve J de Bree, Peter Reiss, Jan EAM van Bergen, Suzanne E Geerlings, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Current evidence on the adoption of indicator condition guided testing for HIV in western countries: A systematic review and meta-analysis. EClinicalMedicine. 2021 May 8;35:100877. doi: 10.1016/j.eclinm.2021.100877. PMID: 34027336; PMCID: PMC8129933.

Saskia J Bogers, Maarten F Schim van der Loeff, Udi Davidovich, Anders Boyd, Marc van der Valk, Kees Brinkman, Godelieve J de Bree, Peter Reiss, Jan EAM van Bergen, Suzanne E Geerlings, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Promoting HIV indicator condition-guided testing in hospital settings (PROTEST 2.0): study protocol for a multicentre interventional study. BMC Infect Dis. 2021 Jun 2;21(1):519. doi: 10.1186/s12879-021-06183-8. PMID: 34078315; PMCID: PMC8173796.

Saskia J Bogers, Maarten F Schim van der Loeff, Nynke van Dijk, Karlijn Groen, Marije L Groot Bruinderink, Godelieve J de Bree, Peter Reiss, Suzanne E Geerlings, Jan EAM van Bergen, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Rationale, design and initial results of an educational intervention to improve provider-initiated HIV testing in primary care. Fam Pract. 2021 Jul 28;38(4):441-447. doi: 10.1093/fampra/cmaa139. PMID: 33367646; PMCID: PMC8317217.

Saskia J Bogers*, Denise E Twisk*, Loes M Beckers, Hannelore M Götz, Bram Meima, Michelle Kroone, Elske Hoornenborg, Alewijn Ott, Marleen N Luning-Koster, Nicole HTM Dukers-Muijrers, Christian JPA Hoebe, Carlijn JG Kampman, Froukje Bosma, Maarten F Schim van der Loeff, Suzanne E Geerlings, Jan EAM van Bergen. Who is providing HIV diagnostic testing? Comparing HIV testing by general practitioners and sexual health centres in five regions in the Netherlands, 2011-2018. Sex Transm Infect. 2022 Jun;98(4):262-268. doi: 10.1136/sextrans-2021-055109. Epub 2021 Jul 27. PMID: 34315804; PMCID: PMC9120378.

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Saskia J Bogers, Maarten F Schim van der Loeff, Anders Boyd, Udi Davidovich, Marc van der Valk, Kees Brinkman, Kim Sigaloff, Judith Branger, Nejma Bokhizzou, Godelieve J de Bree, Peter Reiss, Jan EAM van Bergen, Suzanne E Geerlings, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Initiative. Improving indicator-condition guided testing for HIV in the hospital setting (PROTEST 2·0): a multicenter, interrupted time-series analysis. Lancet Reg Health Eur. 2022 Oct 7;23:100515. doi: 10.1016/j.lanepe.2022.100515. PMID: 36246146; PMCID: PMC9558045.

Saskia J Bogers, Hanne Zimmermann, Amie Ndong, Udi Davidovich, Marie José Kersten, Peter Reiss, Maarten Schim van der Loeff and Suzanne Geerlings, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Mapping hematologists' HIV testing behavior among lymphoma patients – A mixed-methods study. PLoS One. 2023 Jan 3;18(1):e0279958. doi: 10.1371/journal.pone.0279958. PMID: 36595516.

Saskia J Bogers, Maarten F Schim van der Loeff, Anders Boyd, Nynke van Dijk, Suzanne E Geerlings, Jan EAM van Bergen, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Improving provider-initiated testing for HIV and other STI in the primary care setting in Amsterdam, the Netherlands: results from a multifaceted, educational intervention programme. PLoS One. 2023 Mar 6;18(3):e0282607. doi: 10.1371/journal.pone.0282607. PMID: 36877664; PMCID: PMC9987818.

Submitted for publication

Saskia J Bogers, Pythia Nieuwkerk, Nynke van Dijk, Maarten F Schim van der Loeff, Suzanne E Geerlings, Jan EAM van Bergen, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Initiative. Understanding the effect of an educational intervention to optimize HIV testing strategies in primary care in Amsterdam – Results of a mixed-methods study.

Saskia J Bogers, Anders Boyd, Maarten Schim van der Loeff, Suzanne Geerlings and Udi Davidovich, on behalf of the HIV Transmission Elimination AMsterdam (H-TEAM) Consortium. Opportunities for improved indicator-based HIV testing in the hospital setting: A structural equation model analysis.

Other publications

Saskia J Bogers, Carlijn CE Jordans, Casper Rokx. Nederland naar nul nieuwe hiv-infecties. Ned Tijdschr Geneeskd. 2021 Nov 18;165:D6177. PMID: 35138722.

Saskia J Bogers*, Denise E Twisk*, Hannelore M Götz, Jan EAM van Bergen. Op weg naar 0 nieuwe hiv-infecties door proactief testen. Huisarts en wetenschap 2022;65(4):24 - 7. doi: 10.1007/s12445-022-1413-2. ISSN 0018-7070.

**These authors contributed equally to this work*

Carlijn CE Jordans, **Saskia J Bogers**, Jan van Beek, Marion Vriesde, Natasja van Holten, Willemien Dorama, Maarten F Schim van der Loeff, Suzanne E Geerlings, Casper Rokx. Nederland naar nul nieuwe hiv-infecties. De kracht van hiv-indicatoraandoening gericht testen. Dé Verpleegkundig Specialist 2023 Maart; 18(1), 6-11.

APPENDIX 2 – CONTRIBUTING AUTHORS

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APPENDIX 3 – PHD PORTFOLIO

Name PhD student: Saskia J. Bogers

PhD period: January 2019 – September 2022

PhD supervisors: prof. dr. Suzanne E. Geerlings, prof. dr. Maarten F. Schim van der Loeff, em. prof. dr. Jan E.A.M. van Bergen

General courses	**Year**	**ECTS**
BROK	2019	1.0
STATA for beginners	2019	0.4
Practical biostatistics	2019	1.1
Expert management of medical literature: EndNote + Searching for a systematic review	2019	0.2
Research data management	2019	0.5
Clinical epidemiology: Systematic review	2019	0.7
Clinical epidemiology: Observational epidemiology	2020	0.6
Getting Published	2022	1.0
Didactical skills	2022	0.4

Specific courses	**Year**	**ECTS**
NIHES Epidemiology of Infectious Diseases	2019	2.0
NIHES Logistic regression	2019	1.4
Infectious Diseases	2019	1.3
Advanced Topics in Biostatistics	2021	2.1

(Inter)national conferences, symposia and seminars	**Year**	**ECTS**
European Congress of Clinical Microbiology and Infectious diseases (ECCMID), Amsterdam, the Netherlands	2019	1.0
Soa onder Amsterdammers, GGD symposium, Amsterdam, the Netherlands	2019	0.25
Fast Track Cities conference, London, UK	2019	1.0
National Conference Soa Aids Nederland 2019-2021, Amsterdam, the Netherlands	2019-2021	0.75
Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment (NCHIV) 2019-2021	2019-2021	0.75
Infectious Diseases Symposium Amsterdam (IDSA) XXIV-XXVI	2019-2021	0.75
Infectieavonden: soa, tuberculose, vaccinaties	2020-2021	0.75
HIV op de agenda seminar	2020	0.25
Soa Aids Nederland: Nederland naar 0!-dag	2020	0.25
Weekly PhD Infectious Disease research meetings	2021-2022	0.5
APH Spring sessions – Implementation research	2021	0.75
Doen of Laten seminar	2021	0.2
Fast Track Cities conference, Lissabon, Portugal	2021	1.0

STI & HIV 2021 World Congress, ISSTDR, Amsterdam, the Netherlands	2021	1.0
Internistendagen 2021, NIV, Maastricht, the Netherlands	2021	1.0
Gepaste Zorg seminar	2022	0.2
Spinozalezing prof. dr. Steinert: "New trends and developments in Faculty Development"	2022	0.1
The 24th International AIDS Conference, Montreal, Canada	2022	1.0

Oral presentations	**Year**	**ECTS**
Proactive provider-initiated HIV testing, Global health minor lecture	2019	0.5
First results of an H-TEAM intervention to increase provider-initiated HIV testing in primary care, NVHB zomervergadering	2019	0.5
First results of an H-TEAM intervention to increase provider-initiated HIV testing in primary care, Fast Track Cities conference, London, UK	2019	0.5
Promoting indicator condition-guided testing for HIV in the hospital setting: Baseline results of a multicentre intervention study, NCHIV, Amsterdam, the Netherlands	2020	0.5
Het Diagnostisch Toets Overleg 'hiv en soa testen in de eerste lijn' NHG wetenschapdag, Amsterdam, the Netherlands	2021	0.5
Diagnostisch Toets Overleg (DTO) en het belang voor de soa/hiv-bestrijding door de huisarts, Afscheidssymposium Jan van Bergen	2021	0.5
Wie test op hiv? Een vergelijking van hiv diagnostiek door huisartsen versus centra seksuele gezondheid in vijf Nederlandse regio's, NVHB zomervergadering	2021	0.5
Talkshow panelist: Access to HIV testing/care for diverse communities, ISSDTR conference	2021	0.5
PROTEST 2.0: Studieresultaten en lessen geleerd, NIV dagen, Maastricht, the Netherlands	2021	0.5
Nederland naar nul nieuwe hiv-infecties: Landelijke disseminatie hiv-diagnostiek bij hiv-indicatoraandoeningen V&VN ALV, Utrecht, the Netherlands	2022	0.5

Poster presentations	**Year**	**ECTS**
First results of an H-TEAM intervention to increase provider-initiated HIV testing in primary care, NCHIV, Amsterdam, the Netherlands	2019	0.5
Diagnosing HIV in the Netherlands: comparing HIV testing by general practitioners and sexual health centres in five regions, NCHIV, Amsterdam, the Netherlands	2020	0.5
Assessing indicator condition-guided HIV testing in the hospital setting, ISSDTR conference	2021	0.5

A mixed-method approach to mapping hematologists' HIV testing behavior in lymphoma patients at the Amsterdam University Medical Centers, ISSDTR conference	2021	0.5
Lessons learned from an educational intervention to improve HIV testing by GPs in Amsterdam, the Netherlands, ISSDTR conference	2021	0.5
Diagnosing HIV in the Netherlands: comparing HIV testing by general practitioners and sexual health centres in five regions, ISSDTR conference	2021	0.5
Optimising provider-initiated indicator condition guided testing for HIV to identify undiagnosed individuals: Preliminary results of a multifaceted, multicenter intervention study, AIDS 2022, Montreal, Canada	2022	0.5
Improving HIV testing in the primary care setting: Results from a multifaceted, educational intervention study in Amsterdam, the Netherlands, AIDSS2022, Montreal, Canada	2022	0.5

Student supervision	**Year**	**ECTS**
Marcel van Dijk (*Medicine*) Master thesis: Promoting indicator-guided testing for HIV in the hospital setting and evaluating multifaceted group training to improve HIV/STI testing in primary care	2020	1.0
Amie Ndong (*Global Health*) Master thesis: Promoting indicator condition-guided testing for hiv in the hospital setting: a transdisciplinary approach to mapping hematologists' hiv testing behavior in lymphoma patients at the Amsterdam university medical centers	2020	1.0
Floris Sintenie (*Medicine*) Master thesis: The relation between current HIV epidemiology in Amsterdam and the characteristics and spread of general practitioners that attended the H-TEAM's educational intervention on HIV testing in primary care	2020	1.0
Tjiemen Ahmad (*Medicine*) Master thesis: PROTEST 2.0: difference in HIV Indicator Condition guided testing behavior after tailored multifaceted intervention strategies in a hospital setting	2021	1.0
Jip Korenblik (*Medicine*) Master thesis: Outcomes of cervical cancer screening in women living with HIV	2022	1.0

APPENDIX 4 – ABOUT THE AUTHOR

Saskia Jirina Bogers was born on 11 January 1989 in Wageningen, the Netherlands, where she grew up with her parents, her older sister Mirjam and her twin brother Daan. She attended primary school at the Montessorischool, and completed high school at the Pantarijn Scholengemeenschap in Wageningen in 2007. After graduation, she first wanted to explore some of the world and deferred university for one year to do volunteer work in Kathmandu and Nirmal Pokhari, a small village south of Pokhara, before backpacking through Southeast Asia. Thereafter, she returned to attend medical school at the University of Amsterdam.

Saskia completed her bachelor's degree in 2014, during which time she was a national board member of the international Federation of Medical Students Associations, and worked in a general practice as a doctor's assistant. During her master's degree, she completed elective internships in emergency medicine, geriatrics, internal medicine and medical service delivery for undocumented persons. She completed her scientific internship on delivery of HIV care among migrants at the Public Health Service of Amsterdam. In October 2017, Saskia obtained her medical degree with honors, after which she worked as a resident at the Internal Medicine department of the Flevoziekenhuis in Almere.

In 2019, she started her PhD trajectory in the department of Internal Medicine, under the supervision of prof. dr. S.E. Geerlings, prof. dr. M.F. Schim van der Loeff and em. prof. dr. J.E.A.M. van Bergen. Saskia worked for three years and nine months on projects aiming to improve provider-initiated HIV testing in the primary care and hospital setting, of which the results are presented in this thesis. During this time, she implemented weekly scientific education meetings for PhD students in infectious diseases. In February 2023, Saskia started the Internal Medicine residency program at the Amsterdam UMC.

APPENDIX 5 – ACKNOWLEDGEMENTS

Voordat ik begon aan dit promotietraject had ik eerlijk gezegd geen idee waar ik aan ging beginnen. Ik hoorde spannende verhalen over dat het een karakterproef zou zijn, met veel uitdagingen en ontzettend hard werken. Nu ik aan de andere kant sta kan ik concluderen dat promoveren een beproeving kan zijn, maar kijk ik ook terug op de leukste jaren uit mijn loopbaan tot nu toe. Ik kan iedereen van harte aanbevelen om te promoveren, en dan vooral op een onderwerp wat je aan het hart gaat. Ik heb veel geleerd, ben gegroeid, en ik had het voor geen goud willen missen. En hiervoor wil ik een aantal mensen heel erg bedanken. Te beginnen met mijn promotoren.

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Jan, toen ik net was begonnen aan de projecten liepen de DTO sessies nog, en gingen we deze samen af. Een paar keer zijn we na afloop wat gaan drinken, en spraken we over het project, over hobby's, en over ambities. Ik raakte enorm geïnspireerd van jouw verhalen. Jouw passie voor de projecten was aanstekelijk. Toen wekelijks een uur afspreken na het eerste jaar niet meer nodig was spraken we vaak af voor een kop koffie, wat uiteindelijk vaak ruim een uur (of nog langer) duurde, waarin we op een hoger niveau over de projecten praatten. Jij daagde me elke keer uit om mijn eigen mening te vormen en uit te spreken, en bleef doorvragen over hoe ik dacht dat het moest of zat. Hoewel ik het soms lastig vond, heeft dit me ontzettend veel geleerd en ben ik er zelfstandiger, kritischer, en een beter onderbouwde onderzoeker van geworden. Ik kijk ook met heel veel plezier terug op die vrijdag dat Suzanne, Maarten en ik naar Limburg afreisden om een dag samen dit promotietraject af te sluiten. Wat had je lekker gekookt en wat was het een memorabele afsluiter. Dankjewel dat je mij, ondanks je pensioen, nog tot dit laatste moment wilde begeleiden met je kritische opmerkingen en vragen.

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