Is reaching 90/90/90 enough to end AIDS? Lessons from Amsterdam

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REVIEW

Is reaching 90/90/90 enough to end AIDS? Lessons from Amsterdam

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Purpose of review
Although cities present opportunities for infectious pathogens such as HIV to spread, public health infrastructure within these cities also provides opportunities to design effective approaches to eliminate transmission of these pathogens. The HIV Transmission Elimination AMsterdam (H-TEAM) Initiative, a consortium of relevant stakeholders involved in HIV prevention and care, designed an integrated approach to curb the HIV epidemic in Amsterdam, including providing preexposure prophylaxis (PrEP), increasing awareness of acute HIV infection, offering same-day test and treat, and improving indicator disease-driven HIV testing.

Recent findings
In 2013, approximately 230 people in Amsterdam were newly diagnosed with HIV, largely belonging to one of two key affected populations, namely MSM and people with a migration background. Since the start of H-TEAM in 2014, a decrease in new diagnoses was observed (130 in 2017), with an increasing proportion of MSM who had been diagnosed with a recent infection.

Summary
The H-TEAM shows that a city-based concerted effort is feasible. However, major challenges remain, such as reducing the number of late HIV diagnoses, and identifying and providing appropriate services to a diminishing group of individuals who are likely the source of transmission.

Keywords
Amsterdam, epidemic, HIV

INTRODUCTION THE POTENTIAL OF CITY-CENTERED APPROACHES TO END THE HIV EPIDEMIC (MAX 2500>2495)

Worldwide, around eight million people living with HIV live in urban areas (http://www.unaids.org/en/resources/documents/2014/thecitiesreport), where social, economic and structural factors drive inequality in access to health services, thereby contributing to the propagation of an HIV epidemic in a city. At the same time, cities often have strong prevention and care infrastructures that could be used to curb the ongoing transmission of the virus. In addition, various interventions are currently available that individually target each of the potential drivers of HIV transmission. These interventions range from protection from infection through preexposure prophylaxis (PrEP), testing for, and diagnosis of, early HIV infection, and institution of immediate treatment to achieve rapid viral suppression, that in turn prevents ongoing viral transmission. The potential of such interventions in containing HIV epidemics in urban areas has been demonstrated in San Francisco and British Columbia. For example, in San Francisco, a reduction in

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KEY POINTS

- Despite having achieved and in fact surpassed the UNAIDS 90–90–90 goals, Amsterdam still faces a significant number of individuals who enter care at a late stage of infection.
- Our experience with the H-TEAM Initiative shows that a city-based combination prevention approach, involving all relevant stakeholders, offers novel opportunities by which to further curb the HIV epidemic in Amsterdam.
- The demonstration study on PrEP for MSM at high risk of HIV infection shows that offering PrEP assists in reaching out to a subgroup of MSM at very high risk of infection and, at least over the short term, does not lead to a significant increase in sexually transmitted infections.
- Early recognition, testing and immediate linkage to care for same day start of treatment of acute HIV infection is feasible and has potentially contributed to an increase in the proportion of early HIV diagnosis among MSM.

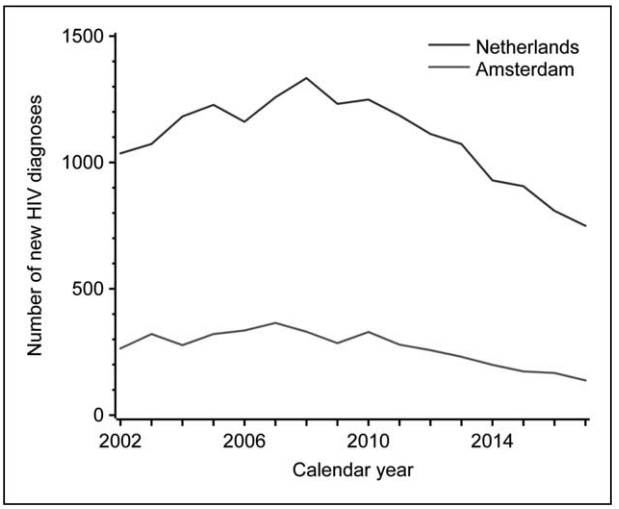

FIGURE 1. Trend in new HIV diagnoses in Amsterdam and the Netherlands. Number of new diagnoses in the Netherlands and Amsterdam since 2002 (data Stichting HIV Monitoring). *Source:* van Sighem AI, Boender TS, Wit FWNM, *et al.* Monitoring report 2018. HIV infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2018. Available online at www.hiv-monitoring.nl.

mean viral load and community viral load (defined as the sum of the most recent viral loads of all HIV-positive individuals in a community in the city) was accompanied by a decrease in new HIV diagnoses. This decline in new diagnoses correlated with increased combination antiretroviral therapy (cART) coverage and changes in regulation regarding HIV testing [1,2]. Moreover, over a 15-year period (1996–2009) in British Columbia, community viral load decreased as cART coverage increased [3]. Furthermore, in San Francisco, the early introduction of PrEP as an effective measure to prevent new infections among individuals at high risk for HIV infection, together with a roll out of testing coupled with immediate initiation of cART, has contributed to a further decline in new HIV diagnoses [4]. These studies indicate that a tailored and comprehensive combination intervention approach, in which prevention and treatment are combined with city-specific strategies to remove structural barriers for access to services, are potentially most successful to significantly reduce incident HIV infections [5].

SITUATION IN 2013–2014 AGAINST THE BACKGROUND OF STANDARD PREVENTION AND CARE AT THE TIME

In 2013–2014, the Netherlands faced around 1000 new HIV diagnoses each year [6]. Twenty-two percentage of these new HIV diagnoses occurred within the Amsterdam area (data National Institute for Public Health and the Environment). Today, an estimated 6000 individuals living with HIV reside in Amsterdam, with MSM being the largest key affected population (78% of new diagnoses). Of the remaining 22%, the majority is heterosexual with a migration background. Most likely due to the very early introduction and high coverage of harm reduction strategies in Amsterdam in the early years of the HIV epidemic, the proportion of individuals acquiring HIV through injection drug use has become extremely small (<1%). The number of new diagnoses in Amsterdam in 2013 was around 230 (Fig. 1). Several HIV test and treat strategies were in place at the time, including the introduction of opt-out testing for HIV at the large Amsterdam sexually transmitted infection (STI) clinic (introduced in 2007 [7]) and online test facilities for MSM (Man tot Man Testlab) (introduced in 2009), and the recommendation to already start cART during early HIV infection in 2012. However, despite all these 'standard' prevention and care measures, a rapid decline in new diagnoses was not yet being achieved. Of all people living with HIV in Amsterdam, an estimated 5% remained unaware of their infection in 2017 (Stichting HIV Monitoring, Amsterdam, The Netherlands). Within this group of individuals, MSM, especially those who have an acute or recent HIV infection, are particularly likely to be the main source of ongoing transmission [8]. At the same time, in 2017, an average of around 32% of newly diagnosed individuals presented for care

with a late stage of infection (i.e. with a $CD4^+$ cell count below 350 cells/ml or with an AIDS-defining illness). Although such late presentation is more common in women and men other than MSM (41%), the group of late presenters is quite diverse and also includes a substantial proportion of MSM (30%). In addition to MSM who are unaware of experiencing an acute infection, late presenting MSM may also be importantly contributing to ongoing transmission of HIV. It is therefore critical to obtain more granular insight into the characteristics of specific late presenter subgroups. Such insights would facilitate identification of those who contribute most importantly to onward HIV transmission and thereby enable improved and novel testing interventions. These considerations were the rationale behind the HIV Transmission Elimination AMsterdam (H-TEAM) Initiative that aims to deploy a city-based combination intervention strategy focused on all factors that maintain the epidemic. To accomplish these aims H-TEAM (www.hteam.nl) brought together all relevant stakeholders from public health, civil society, key affected communities, general practitioners (GPs) and HIV-treating physicians in Amsterdam, with the aim of designing and implementing a multidisciplinary and integrated approach. In the present article, we describe changes in the HIV epidemic in Amsterdam over time, covering the period of 2 years (2013–2014) before the start of the H-TEAM Initiative in 2015, until 2017. In addition, we briefly summarize the introduction of different interventions concerning prevention, testing and treatment uptake and how they may relate to observed trends in new diagnoses and stage of infection at time of diagnosis.

PREVENTION OF NEW INFECTIONS: THE IMPLEMENTATION AND EVALUATION OF PREEXPOSURE PROPHYLAXIS IN AMSTERDAM

PrEP is currently recommended for individuals at substantial risk for HIV infection, namely MSM, transgender persons and heterosexual serodiscordant couples at substantial risk for HIV [9]. After the efficacy of PrEP had been demonstrated in large clinical trials [10–12], it remained unclear how PrEP would preferably be used in practice (that is daily or event-driven), how it would affect sexual risk-taking behavior, and whether longer term PrEP use would change the incidence of STIs. Therefore, in 2015, the Amsterdam PrEP demonstration project (AMPrEP) was initiated to study the uptake, acceptability and usability of the choice between daily or event-driven PrEP for MSM and transgender persons ($n = 367$) at high risk of acquiring HIV infection. The majority of individuals (73%) chose daily PrEP, and the baseline analysis showed a remarkably high prevalence of common STIs (17%) and an unexpectedly high prevalence of hepatitis C virus (HCV) (4.8% compared with 1% among HIV-negative MSM not on PrEP visiting the STI clinic in Amsterdam) [13–16]. Very similar to what was observed in the PROUD [11] and Ipergay studies [12], these data suggest that offering PrEP assists in reaching MSM at particularly high risk for HIV infection. An ongoing concern is whether offering PrEP may induce risk compensation and could result in an increase in STI incidence. In the AMPrEP study, the number of condomless anal sex acts with casual partners increased, but the STI incidence did not increase statistically significantly during the first 24 months after enrollment [17▪]. We did observe one case of incident wild-type HIV infection in an individual with a very high frequency of receptive condomless anal intercourse, in spite of adequate and sustained adherence to PrEP [18]. The initial results of the AMPrEP study, together with those from other PrEP studies and the ongoing international experience with PrEP, importantly informed the advice issued by the Dutch National Health Council to the Ministry of Health to support the implementation of PrEP in the Netherlands. The high STI prevalence in the population likely to access PrEP underscores the need for careful implementation, with regular screening for STIs, including for HIV and HCV. The expected increase in PrEP uptake in the near future will hopefully result in a steeper reduction in incident HIV infection among MSM than has been observed in previous years.

PREVENTION OF NEW INFECTIONS: IMMEDIATE 'TEST AND TREAT' FOR ACUTE HIV INFECTION

As indicated previously, individuals with acute HIV infection (AHI), who are generally characterized by having very high viral load levels, have a particularly high likelihood of transmitting HIV [19–21]. According to a recent study on HIV transmission that combined viral phylogenetics and detailed clinical and demographic data, 70% of all forward transmissions in MSM in the Netherlands were estimated to have occurred during the early stage of infection (defined as 3 months post infection) [8]. The challenge, however, is that AHI may easily be missed because individuals are unaware of their infection. This is primarily due to a lack of knowledge of AHI and its symptoms, and/or failure to recognize or link symptoms to recent risk behavior [22,23]. Other factors contributing to this unawareness of infection include an underestimation of one''s own risk

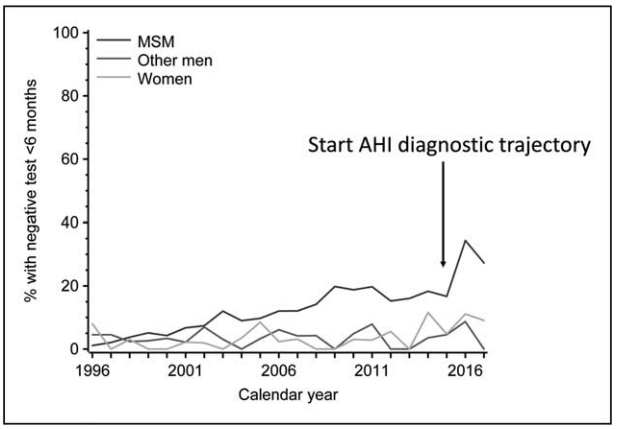

FIGURE 2. Increase in proportion of recent HIV diagnoses. Proportion of all newly diagnosed MSM (blue), other men (red) and women (gray) in Amsterdam with documented evidence of recent HIV infection. A recent infection is defined as a known negative HIV test within the 6 months preceding diagnosis. *Source:* van Sighem AI, Boender TS, Wit FWNM, *et al.* Monitoring report 2018. HIV infection in the Netherlands. Amsterdam: Stichting HIV Monitoring; 2018. Available online at www.hiv-monitoring.nl.

behavior and lack of awareness regarding the benefits of early treatment initiation during AHI [19,24]. The clinical importance of early cART initiation became evident from recent studies which revealed that starting cART during the acute phase of infection improved prognosis [24–26]. These insights prompted us to design a specific acute HIV diagnostic pathway to which people can self-refer through an online AHI awareness tool (www.hebikhiv.nl) or be referred by their GP or the general STI clinic in Amsterdam. Using a symptom recognition score, adopted to fit the characteristics of individuals with AHI [27], which is obtained through the website symptom checker tool, together with point of care HIV RNA testing, we have tested 431 individuals since August 2015 (data until March 2019). Of these individuals, 25 turned out to have AHI (5.8%) and four had chronic HIV infection. All these individuals were referred to a treatment center in Amsterdam for same day start of cART [28]. These data resemble those from a similar approach in San Francisco [29], both demonstrating that targeted screening for AHI and immediate referral for start of treatment is feasible. We evaluated the effectiveness of the

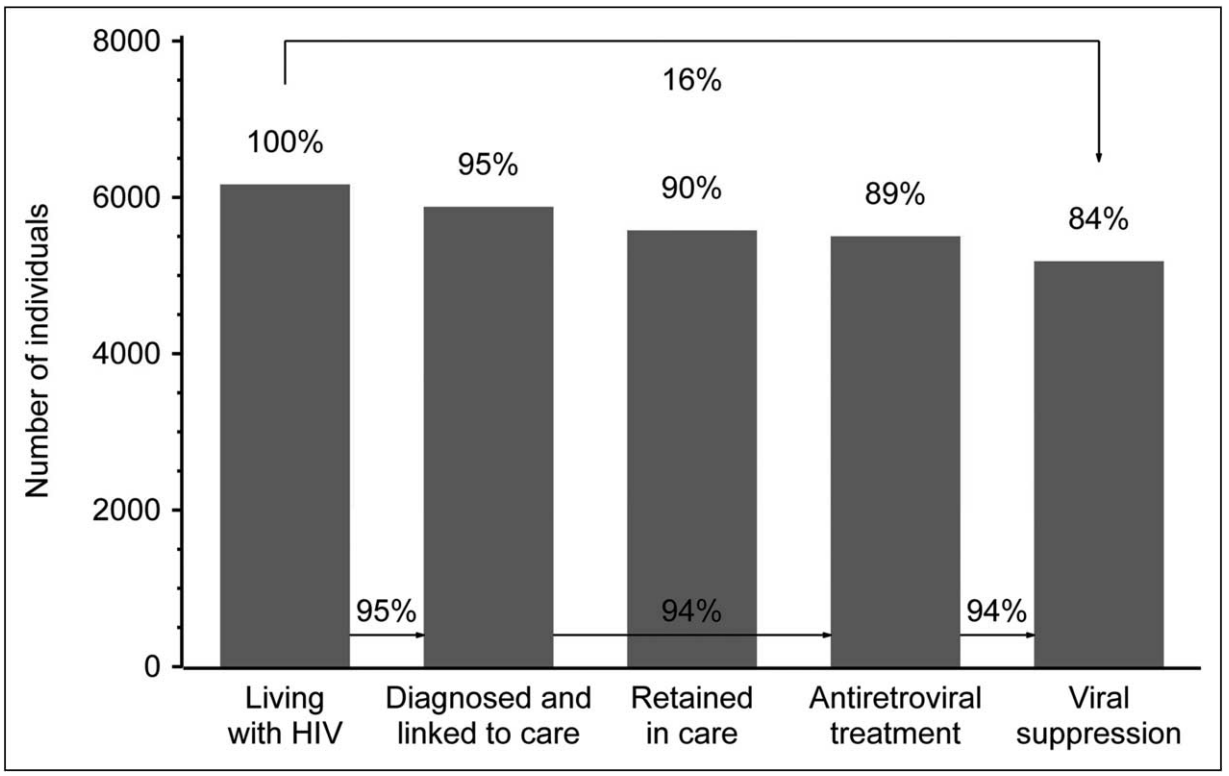

FIGURE 3. Continuum of care for the total estimated HIV-positive population in Amsterdam by the end of 2017. The percentages at the top of the bars are calculated relative to the number living with HIV, while percentages at the bottom correspond to UNAIDS' 90–90–90 targets. Individuals were considered to be retained in care if they had at least one HIV RNA or $CD4^+$ cell count measurement or a clinic visit in 2017. Viral suppression was defined as a most recent HIV RNA measurement in 2017 below 200 copies/ml.

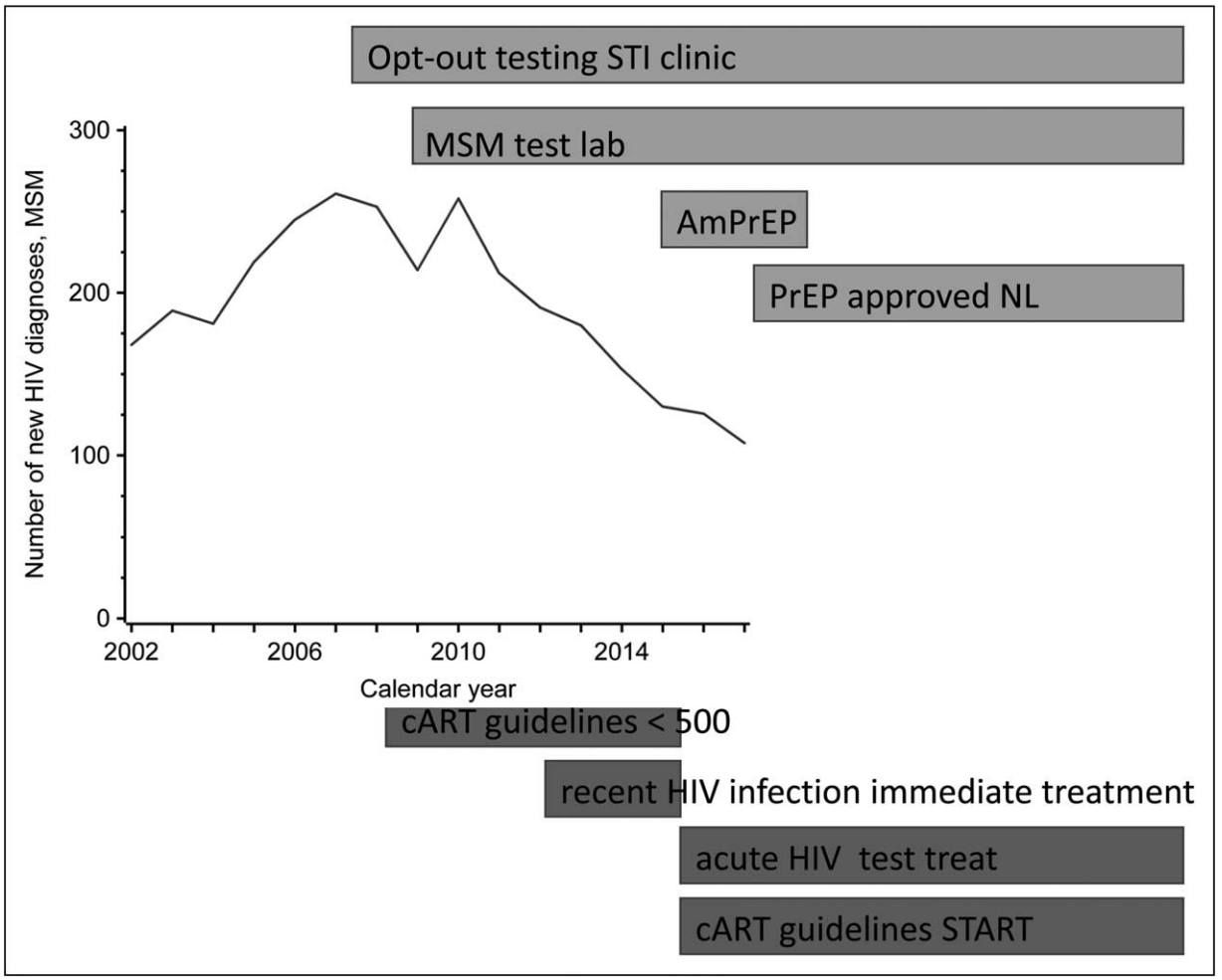

FIGURE 4. Decreasing number of new diagnoses in Amsterdam. The trend in new diagnoses is depicted against the different prevention and treatment interventions over the years 2002 until 2017. The *y* axis shows the number of new diagnoses among MSM in Amsterdam. *Source:* Stichting HIV Monitoring, Amsterdam, The Netherlands.

Amsterdam AHI trajectory by comparing the time between diagnosis and viral suppression for MSM diagnosed through this pathway and for those diagnosed through the routine testing facility at the STI clinic. For all MSM diagnosed with HIV (chronic as well as acute infection) at the STI clinic in Amsterdam, the median time between diagnosis and achieving viral suppression on treatment decreased from 228 days (median) [interrquartile range (IQR) 129–435] in the period 2012–2015 to 95 days (median) in 2015–2017 (IQR 63–136). In comparison, MSM who were diagnosed through the AHI trajectory between 2015 and 2017 ($n = 19$) achieved an undetectable viral load a median of 55 (IQR 31–74) days after diagnosis [28]. Finally, potentially following implementation of this approach, a sharp increase was observed in the proportion of MSM in Amsterdam diagnosed with HIV with evidence of recent infection (Fig. 2).

FINE-TUNING OUR INSIGHT INTO THE HIV EPIDEMIC ACROSS THE CITY: TARGETING INTERVENTIONS TO REDUCE LATE PRESENTATION FOR CARE

Immediate test and treat is critical in reducing onward transmission [30,31]. Recently, the final results of the PARTNER study confirmed the absence of a risk of linked transmission in serodiscordant gay couples in whom the seropositive partner was on suppressive ART [32▪▪]. These data provided the final scientific grounds for the 2016 Prevention Access Campaign 'U=U' statement [33] and will hopefully also contribute to a reduction in HIV-associated stigma and criminalization. In Amsterdam, the policy of test and treat was implemented city-wide in 2016 and the city almost reached the UNAIDS 95–95–95 goals in 2017 (Fig. 3). Nonetheless, despite the decline in new HIV diagnoses in Amsterdam over the past years (from 230 in 2013 to 130 in

2017) (Fig. 4), one of the remaining challenges is to reduce the proportion of individuals who are diagnosed at a late stage of infection. Recent numbers show that around 32% of all newly diagnosed individuals in Amsterdam are diagnosed at a late stage [6]. Of the total number of individuals diagnosed late in 2017 ($n = 51$), 35 were MSM and 12 were non-MSM born abroad. To tackle this issue of late diagnosis, we are currently developing multiple simultaneous strategies to gain more detailed insight into the distribution of late presenters across the city and improve targeted testing practices. This approach involves the application of geospatial information system mapping that uses postal code level data on new HIV diagnoses and late presentation. Such data can be combined with sociodemographic data and data regarding other relevant health issues (e.g. data regarding cardiovascular comorbidity), thereby providing further insight into which areas in the city may be prioritized for improved targeted testing for HIV combined with other health prevention efforts. In addition, the approach involves efforts to improve testing based on HIV indicator diseases in both general practices and hospitals. In the Netherlands, the GP provides primary care and therefore the general practice setting provides an especially important opportunity to further expand testing, including for migrants from HIV endemic countries [34]. GPs in the Netherlands perform an estimated 50–70% of STI consultations and diagnose roughly one-third of HIV infections [35]. However, recent data show that GPs may overlook opportunities to test for HIV, including opportunities within the MSM population [35,36]. For example, a recent study among individuals newly diagnosed with HIV showed that in the 5 years prior to HIV diagnosis, 60% had visited their GP with an HIV indicator illness without the visit resulting in an HIV test being carried out [37,38]. Therefore, to improve testing and recognition of a possible HIV infection, specific training sessions for GPs that include direct personalized feedback on HIV tests requested, have been developed and rolled out as part of the H-TEAM effort.

Since 2015, 21% of new HIV diagnoses in Amsterdam have been made in hospital, 73% of which involved late presenters [6]. Several studies have demonstrated that, despite European guideline recommendations, testing for HIV in the presence of an HIV indicator disease is still not routine practice in hospitals, and, as such, opportunities for earlier diagnoses are frequently missed [39,40]. To clarify the extent to which this also occurs in Amsterdam hospitals, we are currently undertaking a study to analyze compliance with such HIV indicator disease-based testing guidelines in Amsterdam hospitals.

CONCLUSION

To date, our collective experience with the H-TEAM Initiative shows that a city-centered effort, addressing multiple aspects across the HIV prevention and care continuum, is a feasible approach and may contribute to optimize epidemic control. In the context of an epidemic that has reached a phase in which only a relatively limited number of new annual diagnoses occurs, the most important insight is that HIV transmission likely continues to occur in communities at risk within the small geography of a city. These communities are potentially heterogeneous and apparently insufficiently manage to access existing medical and public health services. Key remaining challenges include identifying and reaching out to the relatively small group of individuals who are not accessing testing in a timely manner, which include those who continue to sustain onward transmission. Within such a context continuing to only provide services according to existing city and nationwide policies proves to be an insufficient and too blunt of a tool. Making use of more granular demographic, socioeconomic, behavioral and additional data, and close collaboration with each relevant affected community, will be essential when designing novel ways of ensuring access to the optimal mix of services for all of those remaining in need.

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Conflicts of interest

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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