PrEP in the Netherlands

The introduction of HIV pre-exposure prophylaxis

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Chapter 6

General Discussion
GENERAL DISCUSSION

In this thesis we addressed the outcomes of a demonstration project among MSM and transgender persons using PrEP according to a daily or event-driven regimen in the Netherlands. The choice of regimen was up to the user, after being informed about the two regimens. In addition, we assessed the attitudes of professionals towards the implementation of pre-exposure prophylaxis (PrEP) and we evaluated the adoption of an application for mobile phone for monitoring PrEP adherence and behavioural characteristics.

1. UPDATE ON THE IMPLEMENTATION OF PREP IN HIGH-INCOME COUNTRIES

A general description of the implementation of PrEP up to mid 2017 is provided in the introduction of this thesis. Here we present an update.

1.1 PrEP in the United States

In the United States, about 140,000 people ever started PrEP, and more than 70,000 people used PrEP in the fourth quarter of 2017 according to a study based on prescribing data [1, 2]. Of those 70,000 individuals, about 96% were men. Over the period 2012 to 2017, the annual prevalence of PrEP use increased; the increase was faster among men than among women, among 25- to 34-year olds compared to other age categories, and in the Northeast region compared to the South. Individuals aged less than or equal to 24 years and residents of the South had lower levels of PrEP use relative to epidemic needs [1].

1.2 PrEP in Europe

In Europe, the European Medicines Agency (EMA) granted a marketing authorisation for Truvada (TDF/FTC) for preventive use in July 2016 [3], followed by authorisation for several generic formulations of TDF/FTC. Some European countries started implementing PrEP, however, Europe and other resource-rich countries are still lagging behind the United States in implementing PrEP [4]. France was the first European country to start rolling out PrEP in January 2015, and reported an estimated number of 12,000 people using PrEP by end-2018 (personal communication J-M Molina). Since market autorisation by the European Commission for TDF/FTC, national regulatory agencies approved TDF/FTC for preventive use in France, Norway, Belgium, England, Wales, Scotland, Denmark, Czech Republic, Germany, Greece, Ireland, Italy, the Netherlands, Slovenia, Spain, Portugal and Sweden by April 2019 [3, 5]. The IMPACT trial in the UK, originally designed for 10,000 participants, increased its capacity because of high demands for PrEP from 10,000 to 26,000 [6, 7]. In addition, PrEP programmes at low or no costs for the user are currently in place in...
Belgium, Norway, Sweden and Portugal (small-scale early-access program), and planned to start in Ireland, the Netherlands and Germany in 2019 (table 1). As of November 2018, a PrEP roll-out plan is not yet in place for other European countries. The availability of generic PrEP by 2017 in several European countries, which is one of the measures to increase availability of PrEP, has led to an increase in uptake in some settings compared to the period when only the patented product was available [5, 8]. Generic PrEP has also been mentioned as a contributing factor to decreases in HIV infections as observed in London [9]. A more detailed overview of the current state of the availability of PrEP in Europe is presented in table 1 and figure 1, 2 and 3, and is available online [5].

1.3 PrEP in Australia

In Australia, the number of MSM using PrEP has increased rapidly since 2017. Recently, the Australian EPIC-NSW team reported on a decline in new HIV diagnoses in New South Wales from 295 in the 12 months before PrEP roll-out to 221 in the 12 months after roll-out, corresponding with a relative risk reduction of 25.1% (95% CI -4.5 to 36.6) [10]. This is one of the first studies reporting on the potential impact of PrEP, if combined with other interventions such as immediate treatment upon diagnosis, on the epidemic. In April 2018, PrEP was approved, thereby providing broader access to PrEP for Australian residents [11].

2. IMPLEMENTING PREP TO PREVENT HIV INFECTION: GETTING THERE

2.1 Starting the Amsterdam PrEP project

The efficacy of PrEP to prevent HIV infections among men who have sex with men (MSM) was established in 2010 by the landmark randomised controlled trial iPrEx and confirmed by additional research in 2014 (iPrEx OLE) and 2015 (Ipergay and Proud studies) [12-15]. In an editorial in the Lancet, the publication of the efficacy of HIV PrEP was called “a defining moment in the global AIDS response”, where treatment of all people living with HIV infection and prevention with antiretroviral medication for those at risk of an infection, together are very promising to change the course of the HIV epidemic [16].

By the start of research into PrEP around 2010, condoms had been promoted for decades, and although use had been high in the 80’s and early 90’s as response of the HIV epidemic [17], it decreased when effective treatment for HIV infection became generally available [18, 19]. Despite this, Dutch researchers stated in 2013 that only in exceptional situations use of PrEP would have added value in HIV prevention [20].
<table>
<thead>
<tr>
<th>Country</th>
<th>Guidance</th>
<th>Summary of indications for PrEP</th>
<th>Implementation status by November 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
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<tr>
<td>United States</td>
<td>United States Public Health Services (2014)</td>
<td>MSM, heterosexuals and PWID with additional risk factors for HIV infection</td>
<td>Implemented</td>
</tr>
<tr>
<td>Canada</td>
<td>Biomedical HIV Prevention Working Group of the Canadian HIV Trials Network (2017)</td>
<td>MSM and transgender women who report condomless anal sex and have any of: infectious syphilis or rectal bacterial STI, recurrent PEP, an HIV-infected partner with substantial risk of transmission, or a high-incidence risk index (HIRI)-MSM risk score ≥ 11</td>
<td>Implemented</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
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<tr>
<td>Australia</td>
<td>Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. Update April 2018</td>
<td>Men who have condomless sex with multiple partners; people who share injecting equipment; and individuals with HIV-infected partners who are not using antiretroviral treatment or who do not have an undetectable viral load</td>
<td>Implemented</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
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</tbody>
</table>
| Austria     | German-Austrian guideline for HIV-PrEP                                   | (1) MSM or transgender-people, who report condomless anal sex within the last 3-6 months and/or presumably within the next months OR an STI within the last 12 months  
(2) Serodiscordant couples with one HIV-positive viremic partner not on ART, on non-suppressive ART or in the early stages of ART  
(3) Other individual substantial risks (e.g. people who have condomless sex with partners who are likely to have an undiagnosed HIV-infection or PWID not using sterile injection equipment) | Implemented                          |
<table>
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<tr>
<td>Belgium</td>
<td>Rijksinstituut voor Ziekte- en Invaliditeitsvereniging (2017) [174]</td>
<td>MSM who reported condomless anal sex with 2 or more partners in preceding 6 months, or several episodes of STI or at least one PEP in preceding year, or having sex while using substances. People sharing needles. Sex workers who have condomless sex, other people with high risk of HIV. People with an HIV-positive partner with a detectable viral load.</td>
<td>Implemented in June 2017</td>
</tr>
<tr>
<td>Croatia</td>
<td>No formal guidelines. PrEP is given only in one hospital; there are local guidelines.</td>
<td>MSM with (1) inconsistent condom use, (2) STI in the last 12 months, (3) ever used PEP (4) had experience with chemsex, or (5) are worried about getting HIV which impairs their sex life, (6) have an HIV+ partner who is not taking ART.</td>
<td>Implemented in September 2018, fully reimbursed. Can be given to anybody with health insurance in Croatia and an indication.</td>
</tr>
<tr>
<td>France</td>
<td>ANRS (2018) and Haute santé de santé (2017) [175, 176]</td>
<td>MSM and transgender people who reported condomless anal sex with 2 or more partners in preceding 6 months, or several episodes of STI or PEP in preceding year, or having sex while using substances. People sharing needles. Sex workers who have condomless sex, other people with high risk of HIV.</td>
<td>Implemented in January 2016. In 2018: starting and one visit per year at hospital; renewal of prescriptions by GP or STI clinic</td>
</tr>
<tr>
<td>Germany</td>
<td>Deutsche AIDS Gesellschaft (2018) [173]</td>
<td>(1) MSM or transgender persons reporting anal sex without condom within the last 3-6 months and / or expected having anal sex without condoms in the next months or with a history of an STI in the last 12 months. (2) HIV serodiscordant constellations with a viremic HIV positive partner without ART, non-suppressive ART or in the initial phase of an ART (3) In addition, there can be a substantial individual risk justifying PrEP prescription, especially for people practicing sex without condom with partners for whom undiagnosed HIV infection is likely and PWID without use of or access to sterile injection equipment.</td>
<td>Available but not reimbursed; expected decision about reimbursement in July 2019</td>
</tr>
<tr>
<td>Greece</td>
<td>Not available</td>
<td></td>
<td>Not implemented, one pilot program</td>
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Table 1 (part 1). PrEP implementation in early adopting countries by November 2018. (continued)

<table>
<thead>
<tr>
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<th>Implementation status by November 2018</th>
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</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>National guidance has been developed but not yet published; PrEP is not yet reimbursed[177]</td>
<td>(1) MSM or transgender women having sex with men (2) HIV negative individuals having condomless sex with a HIV positive person who is not stably suppressed on antiretroviral therapy (3) Other HIV negative heterosexual men, heterosexual women and transgender men considered by a senior clinician specialising in HIV Medicine to be at substantial risk for sexual acquisition of HIV</td>
<td>Available (on a private prescription through community pharmacies) but not reimbursed; national implementation expected in 2019</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>No, refer to French guidelines</td>
<td>high risk of sexual transmission and also other modes of transmission, so it could be used for PWID or sex workers</td>
<td>Available at the National Service for Infectious Diseases as a pilot project (2017-2019)</td>
</tr>
<tr>
<td>Malta</td>
<td>No, refer to BHIVA/BASHH guidelines</td>
<td></td>
<td>2016: informal PrEP use; PrEP obtained abroad online</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>NVHB (2019)[53]</td>
<td>MSM or transgender person with one of the following in the preceding 6 months: condomless anal sex with a male partner with unknown HIV status or HIV-infected partner with a detectable viral load; a rectal STI or syphilis; or PEP</td>
<td>Both implementation projects and small-scale implementation; national implementation (for a 5-year study period) is expected in the third quarter of 2019</td>
</tr>
<tr>
<td>Norway</td>
<td>Norsk Forening for Infeksjonsmedicin[178]</td>
<td>MSM or transgender person having condomless anal sex with several partners in preceding 6 months and anticipated to continue; other additional indications are past use of PEP, recent STI, or sex while using substances/alcohol. Individuals with HIV-infected partners who are not using antiretroviral treatment or who do not have an undetectable viral load</td>
<td>Implemented (autumn 2017); from 2018 financing of HIV drugs from state to hospitals, so GPs can no longer prescribe PrEP, and PrEP users are transferred by GPs to the hospital</td>
</tr>
</tbody>
</table>
### Table 1 (part 1). PrEP implementation in early adopting countries by November 2018. (continued)

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<thead>
<tr>
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<th>Implementation status by November 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>Polish AIDS Society(^{[179]})</td>
<td>MSN who have</td>
<td>Not nationally implemented, but available to those who want to use it and can pay for all costs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- sex with HIV+ partners either not treated or with detectable viral load</td>
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<tr>
<td></td>
<td></td>
<td>- sex with unknown partners</td>
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<td></td>
<td></td>
<td>- PEP or STI during last 12 months</td>
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<tr>
<td></td>
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<td>- sex under the influence of drugs/alcohol</td>
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<tr>
<td></td>
<td></td>
<td>People who inject drugs</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Sex workers</td>
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</tr>
<tr>
<td>Portugal</td>
<td>Departamento da Qualidade na Saúde(^{[180]})</td>
<td>MSM reporting condomless sex with a recent STI, a partner with an unknown HIV status, of who is HIV positive and not treated or with detectable viral load, use chemsex, PWID and have no access to clean injection equipment</td>
<td>A national early-access program for 200 people started in April 2018; hospital-based.</td>
</tr>
<tr>
<td>Sweden</td>
<td>Referensgruppen för AntiViral terapi (RAV)(^{[181]})</td>
<td>PrEP is primarily recommended for MSM who have sexual behavior that poses a significant risk of being infected with HIV and where other protection measures are considered insufficient. PrEP may also be considered for other persons where the risk of infection is considered significant</td>
<td>PrEP is implemented nation-wide (2018). All visits are free from costs. PrEP is prescribed within the framework of general healthcare insurance, including medication.</td>
</tr>
<tr>
<td>Spain</td>
<td>Dirección General de Salud Pública(^{[182]})</td>
<td>For MSM and transgender people: not infected with HIV AND at least TWO of the following (referring to last year): more than 10 sexual partners, condomless anal sex, engaging in chemsex, use of PEP more than once, diagnosis of STI.</td>
<td>Implementation studies (n=2), clinical trial (n=1) (Catalunya, Comunitat Valencia and Basque Country) and users who buy PrEP at own cost. PrEP monitoring is provided at NGO programs and public STI clinics free of charge.</td>
</tr>
<tr>
<td>Country</td>
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</tr>
<tr>
<td>Switzerland</td>
<td>Eidgenössische Kommission für sexuelle Gesundheit (EKSG) [183]</td>
<td>HIV-negative persons at high risk of HIV infection. High risk may be indicated by behavioural factors (high number of sexual partners, difficulties using condoms consistently for anal or vaginal sex), recently acquired infections such as syphilis or lymphogranuloma venereum, use of so-called chemsex drugs, or repeated use of HIV post-exposure prophylaxis.</td>
<td>TDF/FTC is not approved for the use of PrEP in Switzerland. It can therefore only be prescribed off-label</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
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</tr>
<tr>
<td>England</td>
<td>BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis [116]</td>
<td>MSM and transwomen who report condomless anal sex in previous 6 months and ongoing; individuals with HIV-infected partner with detectable viral load or less than 6 months on cART; other people considered to be at similar high risk</td>
<td>Three-year PrEP IMPACT trial for 26,000 participants, started September 2017</td>
</tr>
</tbody>
</table>
| Scotland         | PrEP Short Life Working Group [184]                                                                                                                                                                        | (1) Current sexual partners, irrespective of gender, of people who are HIV positive who have a detectable viral load.  
(2) Cis and transgender gay and bisexual men, other men who have sex with men, and transgender women with a documented bacterial rectal sexually transmitted infection in the last 12 months.  
(3) Cis and transgender gay, bisexual men and other men who have sex with men, and transgender women reporting condomless penetrative anal sex with two or more partners in the last 12 months and likely to do so again in the next three months.  
(4) Individuals, irrespective of gender, at an equivalent highest risk of HIV acquisition, as agreed with another specialist clinician | Implemented July 2017                                                                                                    |
<p>| Wales            | Public Health Wales [185]                                                                                                                                                                                  | MSM, transgender men and -women who are engaging in condomless anal sex; individuals with HIV-infected partner with detectable viral load; other people considered to be at similar high risk | Three-year study launched on July 17th, 2017; no limit on the number of participants                                    |</p>
<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated number of eligible persons*</th>
<th>Estimated number on PrEP* (November 2018)</th>
<th>Daily and/or event-driven PrEP</th>
<th>Co-payment</th>
<th>Generic drugs available</th>
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<tr>
<td><strong>North America</strong></td>
<td></td>
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</tr>
<tr>
<td>United States</td>
<td>1 in 4 sexually active MSM (492,000); 1 in 200 heterosexual adults (624,000); 1 in 5 persons who inject drugs (115,000)</td>
<td>Around 100,000[^5]</td>
<td>Daily</td>
<td>Depending on insurance</td>
<td>Yes</td>
</tr>
<tr>
<td>Canada</td>
<td>Not available</td>
<td>Not available</td>
<td>Daily, event-driven can be considered</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
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<tr>
<td>Australia</td>
<td>Around 30,000 (MSM only, no data on other groups)</td>
<td>Around 12,000 people</td>
<td>Daily</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
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</tr>
<tr>
<td>Austria</td>
<td>Not available</td>
<td>600</td>
<td>Daily, event-driven in exceptional situations</td>
<td>Yes, 50 to 60 euro per month</td>
<td>Yes (Jan 2018)</td>
</tr>
<tr>
<td>Belgium</td>
<td>Not available</td>
<td>2000 (personal communication)</td>
<td>Daily and event-driven, choice of user</td>
<td>Yes, 11.90 euro for 30 PrEP tablets, costs of testing if exceeding 2 tests/year</td>
<td>No</td>
</tr>
<tr>
<td>Croatia</td>
<td>970</td>
<td>30</td>
<td>Daily is recommended</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>France</td>
<td>Not available</td>
<td>12,000</td>
<td>Daily and event-driven, choice of user</td>
<td>Depends on location: in hospital small amount for consultation and testing; in STI clinics completely free</td>
<td>Yes (July 2017)</td>
</tr>
</tbody>
</table>
Table 1 (part 2). PrEP implementation in early adopting countries by November 2018. (continued)

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated number of eligible persons*</th>
<th>Estimated number on PrEP* (November 2018)</th>
<th>Daily and/or event-driven PrEP</th>
<th>Co-payment</th>
<th>Generic drugs available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Not available</td>
<td>5,000-8,000</td>
<td>Official recommendation is daily</td>
<td>Depends on location: tests are free at some VCT sites and some physicians would prescribe tests on health insurance cost, while other VCT sites and physicians would require out-of-pocket payment from the clients, costs of PrEP tablets paid by user</td>
<td>Yes (Oct 2017)</td>
</tr>
<tr>
<td>Greece</td>
<td>Not available</td>
<td>70 in pilot program</td>
<td>Daily and event-driven, choice of user</td>
<td>People need to purchase PrEP drugs themselves. Many public STI/HIV/ID clinics offer PrEP consultations, prescriptions and monitoring. In public clinics, all services are provided for free, including HIV/STI testing.</td>
<td>Yes</td>
</tr>
<tr>
<td>Ireland</td>
<td>Around 10,000[177]</td>
<td>As PrEP is only being accessed informally, these data are not available</td>
<td>Daily and event-driven, choice of user</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td>unknown</td>
<td>100</td>
<td>Daily and event-driven, choice of user</td>
<td>Fully reimbursed by social security</td>
<td>No</td>
</tr>
<tr>
<td>Malta</td>
<td>500</td>
<td>85</td>
<td>Daily and event-driven, choice of user</td>
<td>No reimbursement</td>
<td>No</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Around 5,200-13,100[186]</td>
<td>Around 1500-2000</td>
<td>Daily and event-driven, choice of user</td>
<td>Expected: 12 euro/30 tablets from 2019 onwards through national roll-out program. Alternatively: a proportion of GPs prescribes PrEP, in this case costs are for the generic PrEP (around 40 euro/30 tablets and STI/HIV test costs are covered by health insurance after the deductible is paid</td>
<td>Yes (2017)</td>
</tr>
<tr>
<td>Country</td>
<td>Estimated number of eligible persons*</td>
<td>Estimated number on PrEP* (November 2018)</td>
<td>Daily and/or event-driven PrEP</td>
<td>Co-payment</td>
<td>Generic drugs available</td>
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<tr>
<td>Norway</td>
<td>Not available</td>
<td>800-1000</td>
<td>Daily and event-driven, choice of user</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Poland</td>
<td>5,000-10,000</td>
<td>600-800</td>
<td>Daily and event-driven, choice of user</td>
<td>All costs paid by user (testing, consultation, PrEP tablets)</td>
<td>Yes (Oct 2017)</td>
</tr>
<tr>
<td>Portugal</td>
<td>Not available</td>
<td>228</td>
<td>Daily</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sweden</td>
<td>Approximately 500 MSM per year will be eligible if the national recommendation is followed. Probably more MSM will be eligible for PrEP as it is expected that anyone who wants PrEP will get it as long as no medical contraindications exist.</td>
<td>Approximately 1,100 (implementation studies, clinical trial and public STI clinics)</td>
<td>National guidelines recommend daily regimen</td>
<td>Testing is free in STI clinics; PrEP tablets at own cost</td>
<td>Yes (July 2018)</td>
</tr>
<tr>
<td>Spain</td>
<td>Not available</td>
<td>Approximately 1,100 (implementation studies, clinical trial and public STI clinics)</td>
<td>National guidelines recommend daily regimen</td>
<td>Testing is free in STI clinics; PrEP tablets at own cost</td>
<td>Yes, but officially they can be prescribed only for treatment</td>
</tr>
<tr>
<td>Switzerland</td>
<td>The Federal Commission of sexual health estimated that 1,000 people were eligible in 2016. Others believe that this may be a conservative estimate, and 4000 is more realistic.</td>
<td>No surveillance system is in place. A very rough estimation is about 1,000 to 1,500 users</td>
<td>Daily and event-driven are recommended</td>
<td>Co-payments for lab-tests and consultations are covered by the obligatory health insurance. However, some people have a high deductible to be paid before the health insurance will cover the costs. Costs for tablets are paid for by the user.</td>
<td>No</td>
</tr>
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<td>Country</td>
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<tr>
<td><strong>United Kingdom</strong></td>
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<tr>
<td>England</td>
<td>Around 20,000-100,000 MSM attending genitourinary clinics. Other populations uncertain.</td>
<td>Around 10,000 (IMPACT) and an unknown number that self-obtained PrEP</td>
<td>Daily and event-driven, choice of user</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>Previous estimate 1700 (range 1,500 to 1,900) has not been updated[^{124}]</td>
<td>More than 2,000</td>
<td>Daily and event-driven, choice of user</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>Around 560 (range 480-620)</td>
<td>313[^{137}]</td>
<td>Daily</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Data collected via personal communication unless mentioned otherwise

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Figure 1. Status of formal HIV PrEP implementation in Europe, by November 2018
Green: PrEP nationally available, costs are (largely) reimbursed; light green: ongoing pilot or research project; very light green: generics available, but PrEP costs not reimbursed; red: PrEP not implemented or available. Overlap is possible, e.g., in the Netherlands, generics are available and a research project is ongoing. For Spain, regional variations in implementation status are illustrated.
Courtesy of Teymur Noori, ECDC

Figure 2. Implementation of daily only and both daily and event-driven PrEP at choice of the user
Daily only (yellow) versus a choice of daily or event-driven PrEP (blue), according to national guidelines or common practice
In 2013, dr. Han Fennema, medical director of the Public Health Service of Amsterdam (GGD Amsterdam) requested Prof. dr. F. van Griensven to perform a consultancy on how to reduce HIV transmission in Amsterdam. One of the key recommendations of the report was to start “a demonstration or experimental project in which publicly funded state-of-the-art HIV exposure prophylaxis is made available to high-risk MSM for the prevention of HIV infection” [21]. In line with this report, the Public Health Service of Amsterdam reasoned that additional interventions were dearly needed to stop HIV from spreading, and PrEP, as part of comprehensive preventive care, could have an additional impact on the epidemic. In that period the annual number of new HIV infections among MSM did not substantially decrease in the Netherlands.

Our approach to PrEP research was pragmatic (“Additional interventions are needed to stop further spread of HIV”) and research-based (“Considering the outcomes of the Ipergay and Proud trials, we can study the uptake, acceptability and outcomes of daily and event-driven PrEP at choice of the participant”). This aim was the basis of the Amsterdam PrEP (AMPPrEP) demonstration project, which started in 2015, preceding European marketing authorization of PrEP [22]. Although earlier studies had showed the efficacy (i.e., to which extent an intervention produces the desired effect under perfect circumstances) of PrEP to prevent HIV infection, much less was known about the effectiveness (i.e., the degree of beneficial effect under “real-world” clinical settings) and about potential undesired effects of PrEP, e.g., decreases in condom use and increases in incidence or prevalence of sexually transmitted infections (STI).
We were in close contact with a community group established for this project, which provided input for the design, management, and communication strategies of the project (see also paragraph 2.6). Moreover, AMPrEP was embedded in the broader approach to stop the epidemic in Amsterdam, the HIV Transmission Elimination Amsterdam initiative (H-TEAM) [23]. The H-TEAM represents a city-focused approach to the HIV epidemic and combines various innovative interventions to prevent transmission of the virus by promoting prevention, earlier HIV testing and immediate treatment (see also paragraph 4.2). Being part of this comprehensive approach to the epidemic illustrated to funders, media, communities and the general public that we did not see PrEP as the silver bullet, but rather as an intervention that may have an additional effect on reaching epidemic control [14].

2.2 Other PrEP-related activities and policy making in the Netherlands

A Dutch national working group on PrEP, “Prepared”, started in June 2015, with the aim to develop a comprehensive approach to PrEP implementation, including models for service delivery in the Netherlands [24, 25]. The non-governmental organisation Soa Aids Nederland chaired this working group, and was very active in the national lobby for PrEP. In 2018, an additional working group “We are Prepared: PrEP care in the Netherlands” started working on preparing framework conditions for implementation of PrEP in the country [26]. Meanwhile, starting in 2016, a community initiative was initiated: PrEPnu [27]. PrEPnu is a grassroots initiative started in 2015 with the aim of making PrEP and PrEP care available to all those who need PrEP in the Netherlands. It was founded by a group of committed gay men who strive to inform key populations about PrEP and who started a lobby to make PrEP available.

In 2017, several STI clinics started medical care programmes for those who obtained PrEP informally or requested a prescription to buy PrEP at their own costs in a pharmacy; by the end of 2018, around 11 (out of 24) public STI clinics had prescribed PrEP (personal communication Noëmi Nijsten) [28, 29]. The latter occurred mainly after generic TDF/FTC appeared on the Dutch market, in November 2017, and costs of PrEP were substantially reduced. Some general practitioners also started prescribing PrEP and providing medical care [30]. In some regions, specialised professionals in hospitals provided PrEP care including PrEP prescriptions for those who could not access care elsewhere (personal communication Marc van der Valk).

In October 2017, following the European marketing authorization in July 2016, Minster Schippers, former Minister of Health, Welfare and Sport, asked the Health Council to advise on the public benefits of providing PrEP, key groups and expected other outcomes, e.g., changes in HIV resistance and in the prevalence STI other than HIV. On March 27th, 2018, the Health Council provided the advisory report to the new minister for Medical Care, Minister Bruins [31] and recommended to start a PrEP programme for MSM who have a high risk for HIV infection, to provide good medical support, and to start this programme.
urgently to prevent non-supervised PrEP use, to monitor PrEP use and to re-evaluate the program after five years.

Subsequently, on July 10th 2018, two weeks before the start of the 22nd International AIDS Conference in Amsterdam, Minister Bruins informed the House of Representatives about his decision to provide PrEP for a period of 5 years to MSM with an increased risk for acquisition of HIV, and to other groups at substantial risk for HIV, through public health services. The national programme is currently being prepared and expected to start in the third quarter of 2019.

2.3 Opinions about PrEP in the media in the Netherlands

Our work in the Netherlands did not remain unnoticed and, next to many neutral and positive items in magazines, papers, and on national television, various concerns were heard. For example, at the Amsterdam broadcasting channel AT5 an activist voiced the concern that by spending money on PrEP in Europe, more people with an HIV infection in African countries would be left without ART. In the weekly magazine for all Dutch doctors Medisch Contact, a columnist stated that “PrEP will lead to more sex in darkrooms and saunas, as men will feel protected. At the end of the day this will result in more HIV infections and many more other STI, such as syphilis. Sex without love will cause damage to your body, either with or without PrEP.” A letter in the daily newspaper het Parool stated that “Costs of our healthcare system cannot be contained; that is why our parents live in care homes and use incontinence pads while the urine is running down their pants. So do not provide PrEP at our costs.” A research group from Rotterdam stated in Lancet HIV that clarification of normative considerations, e.g., own responsibility to use a condom and the relevance of being free from fear for acquiring HIV is needed before nation-wide implementation of PrEP. Internationally, the AIDS Healthcare Foundation voiced their concerns about implementation of PrEP. These concerns included healthcare barriers that would limit implementation of PrEP, low efficacy because of poor adherence, increases in risky sexual behaviour (labeled by the authors “a potentially damaging culture change”) and increased transmission of other STI. Other researchers commented on the comparison between PrEP and other preventive interventions, e.g., contraceptives and condoms. Such remarks were often followed by the comment that contraceptives and condoms are not provided free-of-charge, hence it would be inconsistent if PrEP costs were reimbursed. However, one could draw a comparison with hepatitis B vaccination for MSM to prevent sexual transmission of hepatitis B, which is provided free-of-charge in the Netherlands and is a cost-effective prevention intervention for this group. The use of contraceptives by women revoked many judgmental remarks (e.g., “contraception allows people (even married people) to have sex purely for enjoyment”) in the early years after its availability, before they became widely accepted. Would it just take time for PrEP to be embraced?
2.4 Attitudes of health care providers and intentions to start PrEP among MSM

Effective scale-up of PrEP will require the engagement of a large number of healthcare providers. However, clinicians may have barriers to prescribing PrEP, for example regarding the efficacy, safety, and cost of PrEP. Among health care professionals working at public health STI clinics in the Netherlands, one measurement of attitudes towards PrEP was done, which showed a moderate acceptability (just above neutral) towards the use of PrEP in 2015 (Chapter 2 of this thesis). In the Netherlands, the previously mentioned nationwide We are Prepared PrEP educational program funded by the AIDSfonds, made use of the information about barriers to PrEP use and facilitating factors found in this project [26]. This project reached general practitioners and public health professionals from all regions in the Netherlands and improved knowledge about, and possibly also acceptability of providing PrEP, although no formal assessment of knowledge and acceptability was done [25]. In 2016 a survey conducted in Belgium found an accepting attitude towards PrEP in the majority of the participating HIV specialists and primary care providers [44].

How acceptable is the use of PrEP among the most relevant key group in the Netherlands, MSM? In the Amsterdam Cohort study on HIV (ACS), the intention to start PrEP was assessed in 2012/2013 and in 2015 [45, 46]. Intention increased from 13% to 30% and intention was higher among those who were eligible for PrEP. These findings support the hypothesis that, as awareness and knowledge about PrEP increase, its use becomes more acceptable as a preventive measure against HIV.

2.5 Moving forward to PrEP implementation

No matter what the public opinion was, or the acceptability among professionals, the willingness to participate in AMPPrEP largely exceeded capacity of 370 participants (Chapter 3.1). When designing the project in 2014/2015, the initial end date of the project was set at 1 June 2018, with the expectation that PrEP would be available in standard public or primary health care by mid 2018. However, as mentioned in paragraph 2.2, policy makers on the national level took a long time to decide about making PrEP available to the larger group that can benefit from it. In Amsterdam, the city council partly filled this gap by providing resources for providing PrEP-related care to another 250 MSM and transgender persons who obtained their PrEP informally (InPrEP project) in 2017 [28, 47]. Rightly, the deputy mayor mentioned that this is not a topic to be solved by local politicians, and a nationwide solution was dearly needed [48]. In conjunction, several activities from multiple stakeholders directed to the Ministry of Health, Welfare and Sport were undertaken to lobby for a rapid implementation of PrEP [49-51]. The delay in nationwide PrEP provision, next to research questions on long-term use of PrEP, prompted us to try to prolong the AMPPrEP project until 2020.
Guidelines on the use of PrEP initially existed only in the United States of America \cite{52}. As a growing interest in, and various questions about PrEP from health professionals and clients were noted in the Netherlands, a writing group was established by the Dutch Association of HIV-treating Physicians (NVHB) to develop a multidisciplinary professional guideline on the use of PrEP in 2016 \cite{53}. Input from several research projects including AMPrEP and from international guidelines was used. When the first version of the national guideline was published in September 2016, PrEP was not yet implemented and not available through a national reimbursement programme, nor were generic products. However, some people used the websites prepster.info and Iwantprepnow.co.uk or the Dutch advocacy group PrEPnu (PrEPnu.nl) to obtain PrEP. The guideline enabled them and their health care providers to get the necessary information regarding PrEP use and monitoring, including testing. Health policy makers have referred to the professional guideline, e.g., in their recommendations about prioritization of key groups for PrEP and testing during use of PrEP \cite{31}.

With the availability of generic PrEP by the end of 2017 and the publication of the guideline, several public health services and general practitioners started to provide PrEP care and prescribe PrEP, resulting in 3,000 people who had been prescribed PrEP at least once by the end of 2018, according to data from Dutch pharmacies; participants of PrEP studies are not included in this number \cite{54}. Of those prescriptions, 73% were by general practitioners (personal communication, J. Lukaart, Stichting Farmaceutische kengetallen, to J. van Bergen).

The Dutch national PrEP guideline was updated in April 2019 \cite{53}.

### 2.6 Community engagement and activism

Good participatory practice in biomedical prevention studies is advocated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the AIDS Vaccine Advocacy Coalition (AVAC), and helps ensure the ethical and scientific quality of research, as well as its relevance to the community \cite{55, 56}. In addition, the involvement of participants in trials is known to improve enrolment \cite{57}.

In 2015, we established an AMPrEP community group consisting of key figures from the Amsterdam gay party and sex scene. The group consisted of persons using PrEP, those with the intention to start PrEP and persons not planning to initiate PrEP. The community group functioned as a think tank and a sounding board between the participants and the researchers. Ideas and experiences were shared, as well as research questions and outcomes, resulting in new/improved research questions, a better management of the project, and effective communication to the study group as a whole.
In parallel, several community efforts started with the aim of promoting knowledge about, and to advocate for implementation of PrEP. One of the most active ones in the Netherlands is PrEPnu (figure 4 and paragraph 2.2). An example of the synergy between community, advocates, researchers, clinicians, and policy makers was seen during the first PrEP in Europe summit in Amsterdam in 2018 [58]. Also, a combined lobby for implementation of PrEP in the Netherlands by several stakeholders, including COC Nederland, Hiv Vereniging, Soa Aids Nederland, the Dutch Association of HIV-treating Physicians (NVHB), which involved letters to Minister Bruins and other activities, was undertaken [59].

Figure 4. Website of the Dutch advocacy group PrEPnu, courtesy of team PrEPnu
2.7 Early PrEP adopters

For PrEP to have an impact on the epidemic, those with a substantial risk of HIV infection need to use PrEP. The participants of AMPrEP, selected on sexual behaviour characteristics, history of STI and use of HIV Post-exposure Prophylaxis, were “early adopters”: they were among the first to adopt the innovation of HIV protection with a pill. Considering the reported sexual behaviour characteristics at baseline and the high STI prevalence (chapters 3.1 and 3.2), we indeed, after random selection of all who applied for participation, included participants that were at considerable risk of HIV and could benefit from PrEP. Data on sexual behaviour while using PrEP and incidence of STI (chapter 5.3 and 5.4) further provide support for this conclusion.

According to the theory of innovation, early adopters will be followed by the early majority, late majority, and laggards [60]. An important question is whether this shift in groups using PrEP will affect outcomes of PrEP. The societal benefits and cost-effectiveness of PrEP will be attenuated if individuals at low risk of HIV, e.g., those who consistently use condoms, have few sexual partners, and who are not involved in chemsex (i.e., the use of drugs around sex) or group sex, will start PrEP. The same applies to situations where HIV risk decreases while an individual continues using PrEP.

Despite efforts to inform all PrEP-eligible populations, only very few transgender persons were included in AMPrEP. This was also the case in other PrEP studies from Europe and elsewhere [12, 13, 15, 61, 62]. Specific efforts need to be undertaken to find early adopters for PrEP among transgender populations, who subsequently may be followed by early and late majorities.

New groups at considerable risk that are not initially reached may be engaged in PrEP care at a later stage. They may seem to be late majority but in fact be early adopters within their larger community group. Similarly, young people who start to become sexually active will enter the group eligible for PrEP. Early adopters in these groups may inform their peers. As long as HIV transmission is ongoing, each new generation will need its own early adopters and champions.

Some time in the future, when very little HIV transmission is taking place or vaccination is available, the debate about the need for continued PrEP in the Netherlands will have to start. Cost-effective analyses can provide input for continuation of PrEP programmes.

2.8 Event-driven use of PrEP

AMPrEP is the first project worldwide to offer a choice of daily and event-driven PrEP to its participants. We were able to do so because of the results from the Ipergay study that
reported the high efficacy of event-driven PrEP \cite{12}. A few months after the initiation of AMPrEP, the Belgium Be-PrEP-ared study (Institute of Tropical Medicine, Antwerp, Belgium), with a similar design of offering two regimens, started \cite{63}. Event-driven PrEP is also offered in several other European countries and in Canada (figure 2, table 1). The proportions of event-driven PrEP users in AMPrEP (chapter 3.2) and in most other, subsequently started PrEP demonstration studies or implementation projects where a choice of daily and event-driven PrEP is offered, are relatively small (14-34%), resulting in lower numbers and limited power to draw conclusions\cite{63-65}. The exception is France, where around three-quarter chose for event-driven PrEP use \cite{12, 66}.

Some interesting observations regarding event-driven PrEP use were made in AMPrEP. No HIV infections were diagnosed during event-driven PrEP use among AMPrEP participants. The number of sexual partners, acts and condomless anal sex acts with casual partners was lower during event-driven PrEP use, and the number of PrEP tablets used during event-driven PrEP was about half of the number used during daily PrEP. Other studies that include event-driven PrEP have not yet reported follow-up outcomes, or did not stratify outcomes to PrEP regimen\cite{63, 64, 66}. In AMPrEP, switching between regimens occurred frequently in both directions: from daily to event-driven and from event-driven to daily \cite{67}.

These data show that there is a clear interest in taking event-driven PrEP at least in some periods by a significant proportion. Motives for choosing a regimen were assessed using quantitative (chapter 3.1) and qualitative methods \cite{68}. The latter showed that a wide array of motives was reported, and that choices for a PrEP regimen can be addressed as a continuum of flexible and changing options over time. Future joint analyses combining data from several studies will result in more power and provide a better substantiation of conclusions and recommendations, especially concerning event-driven PrEP use \cite{69}.

2.9 Hepatitis C prevalence

An unexpected finding from the AMPrEP project was the high baseline prevalence of hepatitis C virus (HCV) infections (4.8%), likely sexually acquired \cite{70}. Previously, HCV prevalence was low (0.6%) among HIV-negative MSM visiting our STI clinic\cite{71}, and more recent data confirmed this low prevalence \cite{72}. The findings from both studies suggest that the HCV epidemic is confined to relatively small groups of HIV-negative MSM and has not yet spread to the larger HIV-negative MSM community. Phylogenetic analysis showed that HCV sequences of HIV-negative MSM starting PrEP were highly interspersed with HCV sequences obtained from HIV-positive MSM, suggesting that sexual transmission is occurring between these groups.
General Discussion

What gets measured gets done. Systemic testing of HCV among participants of AMPReP resulted not only in one of the earlier reports about high HCV prevalence among HIV negative MSM starting with PrEP (chapter 3.2) but also contributed to the worldwide attention for HCV among HIV negative MSM [73-76]. We urged for vigilance and HCV testing in all MSM PrEP cohorts and PrEP implementation programmes. We increased frequency of HCV testing in AMPReP after we became aware of the high baseline prevalence. From 2017 onwards, several international PrEP guidelines included HCV testing in their recommendations for MSM (see table 2) [77-80].

3. OUTCOMES OF PREP

3.1 Behavioural outcomes

Condoms are the cornerstone of effective protection against STI, including HIV. Although in theory condoms could offer 100% protection against HIV, in real life, among MSM, this is around 70-91%, as condoms may break, slip off or not been used when needed [81-84]. In recent years, especially after the availability of antiretroviral therapy (ART), condom use decreased among MSM [18, 19, 85-87].

In addition, the landmark HPTN052 and PARTNER studies [88-91], which showed that HIV-positive persons with an undetectable viral load cannot transmit HIV sexually (“Undetectable is Untransmissible, “U=U”), most likely contributed to this decrease. PrEP may also play a role in the decrease in condom use: as people have increasing confidence in PrEP, condoms may more often be omitted. Some voiced that this decrease in condom use seems to reflect a change in community norms, either predating widespread use of PrEP [86], or accompanying the increasing uptake [85, 87]. Disentangling the role of PrEP and U=U versus other reasons for the observed decrease in condom use is complex. Moreover, standardised reporting of a minimum set of behavioural data is scarce, resulting in the lack comparability between studies.

In the AMPReP study we found that condom use decreased six months after the initiation of PrEP compared to baseline (chapter 5.2). However, not all participants changed their behaviour: 39% of participants reported an increase in sexual risk behaviour (i.e., an increase in the number of receptive condomless anal sex acts with casual partners) from baseline to six months after initiation of PrEP. The short time-line suggests an effect of initiating PrEP, but this observation included only one follow-up time-point. Data from the first two years of PrEP use confirmed these findings: condoms use with casual partners decreased. However, the number of partners and sex acts were stable over time (chapter 5.3). In the absence of a control group, it remains uncertain which part of the observed
changes is due to PrEP. Our findings correspond with those from most other studies (reviewed by Traeger et al), reporting decreases in condom use among PrEP users [92]. These outcomes indicate that, while respecting individual decisions about sexual expression, a new and effective condom narrative is needed.

| Table 2. (Inter)national testing guidelines for sexually transmitted infections and hepatitis C virus in HIV negative MSM who start and use PrEP |
|-----------------------------|----------------|----------------|----------------|
| **Guideline** | **Year** | **STI testing recommendation** | **Frequency of STI testing** | **HCV testing recommendation** | **Frequency of HCV testing** |
| WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection, Module 1[79] | 2017 | According to local guidelines | When starting PrEP and 3- or 6-monthly according to local guidelines | HCV antibody | When starting PrEP and annually |
| CDC Pre-exposure prophylaxis for the prevention of HIV infection in the United States[170] | 2017 | NG, CT, syphilis pharyngeal, rectal, urine | When starting PrEP and 6-monthly | HCV, not specified | When starting PrEP; annual retesting for persons with ongoing risk of HCV can be considered |
| BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis[110] | 2018 | NG, CT, syphilis pharyngeal, rectal, urine | When starting PrEP and 3-monthly | HCV, not specified | When starting PrEP and 3-monthly |
| Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults. Recommendations of the International Antiviral Society–USA Panel[115] | 2018 | Not specified which STI, pharyngeal, rectal, urine | 3-monthly | HCV antibody | Annually, more frequently in case of elevated transaminase levels or in individuals at high risk |
| Dutch HIV PrEP guideline[53] | 2019 | NG, CT, syphilis pharyngeal, rectal, urine | When starting PrEP and 3-monthly | HCV antibody; if positive: HCV RNA and/or ALT | 3-monthly; if HCV antibody positive 6-monthly |

3.2 eHealth tools

Monitoring sexual behaviour via an app for daily data collection can provide better insight into (short-term) pattern of sexual activity compared to quarterly, aggregated data. However, it was previously unknown whether it would be feasible and acceptable to collect daily data on PrEP use and sexual behaviour through an app. Evidence of the validity of this app-based data collection was also lacking. We reported in chapter 4 about the specifically designed AMPrEP app for smartphone that aimed to support adherence to PrEP and collect daily data (Supplementary figures 1 and 2 in chapter 4). Data were reported on a daily base by the majority of participants after twelve months of study participation, indicating that such a data collection instrument is acceptable, at least in a research setting. The sexual behaviour data collected via the app were comparable to data collected by 3-monthly questionnaires. These results paved the road for more research studies to use apps for daily data collection. However, caution is needed to prevent a tsunami of new apps in the research and/or sexual health field [93-99]. It may be wise to focus on the development of one overarching, national app for sexual health in the Netherlands.

Three studies reported on the use of an eHealth intervention to improve PrEP adherence. In a randomised controlled substudy of the PrEP Brasil study, weekly interactive text messaging was associated with increased odds of achieving protective drug concentrations (OR 2.13, 95% CI 1.02–4.47) at week 48 from initiation of PrEP among people aged 18-24 years [100]. Another study from California among MSM and transgender persons found that near-perfect adherence was higher in the intervention arm using individual texting to improve adherence (51.0% vs 37.4%; P = 0.02) vs. the control arm after 48 weeks [95]. Finally, Liu et al reported about a randomised controlled trial using a bidirectional text messaging-based PrEP support intervention among people aged 18-29 years in Chicago. They reported that users of the intervention were more likely to have tenofovir-diphosphate levels consistent with ≥4 doses/week (72% vs. 57%, OR=2.05, 95%CI 1.06-3.94) compared to young persons initiating PrEP and not using the intervention [93]. The use of app-based interventions (as opposed to text-based interventions) to improve adherence has not yet been reported and warrants further research.

In a few settings (e.g., San Francisco and Bangkok) PrEP is now also provided through an online service for those who prefer this delivery method [96, 98]. We expect that more countries will look at opportunities for online PrEP provision, with the aim to increase capacity of programmes, to make services more cost-effective and to improve accessibility for those who experience barriers to visit a health care provider [101].
3.3 PrEP effectiveness and breakthrough infections

Studies showed that PrEP has 86% effectiveness to prevent HIV among MSM \[12, 15\]. In subgroup analyses among those with high adherence, effectiveness was even higher than 95% \[13\]. We reported in chapter 5.3 that in AMPPrEP the incidence of HIV was low among MSM over the first two years of participation (n=2, incidence 0.30/100 person-years, 95% CI 0.07-1.19).

Objectively measuring long-term adherence to PrEP is possible by assessing tenofovir diphosphate levels in dried blood spots. However, only few laboratories perform this analysis, limiting its use in daily practice. In research projects, outcomes of drug levels have been informative to distinguish between infection during non-adherence and PrEP failure (i.e., acquisition of HIV despite well-documented long-term adherence to PrEP) in breakthrough infections. Currently, little is known about the phenomenon of PrEP failure worldwide. Seven well-documented cases of breakthrough infections despite documented good adherence have been reported \[102-108\]. Six were infections with a multiresistant virus strain, and the only case of wild-type virus infection was observed in our study (chapter 5.1). In all seven cases, as well as in an additional case reported in 2008 in a person who was infected during use of PrEP as PEP \[109\], low-level viremia and delayed antibody formation were found. Infections were missed when only third generation antibody tests were used \[110\]. The unusual HIV test results in the context of antiretroviral medication were the topic of a recent expert meeting of the World Health Organization (WHO). One of the recommendations from this meeting was to prioritise research into establishing an HIV diagnosis in cases of repeated discrepant results of HIV serological and virological tests in a current or former PrEP user \[111\].

The PrEP failure case reported by our group gave rise to a discussion in Lancet HIV. One group worried about risk compensation behaviour by PrEP users because of perceived high effectiveness of PrEP over time \[112\]. Another group remarked that, as we did not find any HIV proviruses in peripheral blood mononuclear cells, the infection was probably mucosally contained, and not starting ART was, in retrospect, a missed opportunity because a very early start of treatment is associated with favourable outcomes such as a low or even absent immune activation \[113\]. We replied that starting ART indeed was considered \[114\]. However, the case was complex and unprecedented, with a very unusual seroconversion pattern. The HIV infection was suspected, as the 4th generation ELISA test was positive, but the diagnosis could not be confirmed at antibody seroconversion, in spite of extensive diagnostic efforts. Still, evidence is limited about how to handle cases of PrEP failure.

In case of a suspected HIV infection while on PrEP, the IAS-USA guideline advises to stop PrEP and use other prevention methods until HIV infection is confirmed \[115\]. However, the
same guideline states that if HIV infection is strongly suspected (not further explained) or confirmed, fully suppressive ART should be administered immediately. The BHIVA/BASHH guidelines from the United Kingdom recommend that the current best practice is to intensify ART while investigations are ongoing if a seroconversion event is suspected on PrEP \(^{(116)}\). Other guidelines do not give specific recommendations, or advise to consult an expert for atypical cases \(^{(53, 78)}\). In conclusion, while waiting for more evidence, one might decide on the best approach on a case-by-case basis, and the advantages of an early start of ART after diagnosis need to be weighted against starting ART while a diagnosis has not been fully established.

3.4 STI

The era of PrEP resulted in decoupling trends of HIV and STI: where HIV incidence has been very low in several PrEP demonstration projects, STI prevalence and incidence were high, especially among MSM \(^{(62, 66, 100, 117)}\). A high incidence and prevalence of STI were not only observed among those using PrEP, but also in the larger MSM population of both HIV positive and HIV negative MSM in the Netherlands and globally \(^{(118, 119)}\). The availability of PrEP is urging clinicians, researchers and communities to focus on STI, which may result in creative approaches to the integration of HIV and STI research and programmes. This way, PrEP might even act as a gateway to enhanced STI surveillance through more frequent testing, to improved community education about both PrEP and STI, and be an accelerator for STI prevention research. The Ipergay PrEP trial sub-study of doxycycline for the prevention of syphilis is an example of how a PrEP project can facilitate STI prevention research \(^{(120)}\).

Over the first two years of follow-up in AMPPrEP, we diagnosed and treated more than 700 STI, and 253/367 (69%) participants were treated at least once for a STI; the incidence of STI did not increase over time (chapter 5.3). While we stated that “In the first two years after initiation of daily or event-driven PrEP (...) STI incidence was high”, one could question how to interpret the indication “high”.

It is important to note that in our study we did not have a control group or a good comparator “before-PrEP” observation period, because data on STI in the period before enrollment were not systemically collected. Some studies did compare STI rates before and after PrEP retrospectively. Nguyen et al showed, after adjusting for differences in frequency of testing to account for detection bias, a small, non-significant increase in STI comparing the year before and after initiation of PrEP \(^{(121)}\). However, as was pointed out in a letter to the editor by another research group, the authors did not adjust for temporal changes in STI unrelated to PrEP, which could have explained part of the increase \(^{(122)}\). Another study using a case- crossover design showed an increase in rectal chlamydia and syphilis...
diagnoses, but not in other STI, when comparing the period before and after initiation of PrEP \[123\]. Interestingly, they found that increases in STI were detected in only 28\% of participants. Traeger at al found an increase of 12\% in STI in the year after initiation of PrEP compared with the year before, after adjusting for testing frequency \[117\]. In this study, the majority of STI (76\%) were diagnosed in only 25\% of the participants. In these two studies, no adjustments for temporal changes were made either. An additional methodological flaw was observed and commented on by our group \[124\].

The STI incidence rates in AMPrEP were not high in comparison to other PrEP demonstration and implementation projects \[62, 66, 100, 117\], although methods to assess incidence varied across studies. Can we compare these rates with STI rates in other MSM groups in the Netherlands to help putting these numbers into perspective?

(1) Among clients visiting STI clinics, we do not have good incidence data to compare, as people often attend clinic services only when there is a reason, e.g., experiencing symptoms suggestive for an STI, having received a partner notification, or a sense of having been at risk for an STI. Frequent testing, defined as 6-monthly testing, is relatively uncommon (18.5\%) \[125\]. Moreover, at many public STI clinics clients can test anonymously, limiting longitudinal analyses.

(2) The STI incidence among MSM participating in the Amsterdam Cohort studies on HIV (ACS) was 19.6/100 PY (95\%-CI 16.2-23.7) in 2016, which is considerably lower than among AMPrEP participants (90.4/100 PY) \[126\]. However, the ACS cohort is not comparable to the AMPrEP cohort, as ACS is an open longitudinal cohort study among MSM living in the Amsterdam area who reported to have had sex with other men in the preceding 6 months, whereas AMPrEP inclusion criteria allow only enrollment of those with higher levels of risk behaviour. Despite this, an international meta-analysis on STI among MSM on PrEP did use data from the ACS and comparable cohorts of MSM to investigate associations of PrEP with STI rates \[127\]. Considering the differences between eligibility for the observational cohorts of MSM such as the ACS and PrEP cohorts, it was not surprising that the authors found much higher STI rates among MSM using PrEP. However, their recommendations were well stated: to offer frequent STI testing among MSM using PrEP and provide comprehensive preventive services, including partner services.

In conclusion, STI rates were high among AMPrEP participants, as has been observed in other cohorts of MSM using PrEP. Interpreting these rates is not an easy task, because PrEP usually was started for a reason (e.g., having or desiring to start sexual activities that put one at risk of HIV) and inclusion criteria restricted participation in studies to MSM with higher levels of sexual behaviour. Participants of a PrEP study may thus not be rep-
resentative of the wider population of MSM. Whether STI increases are associated with the initiation of PrEP is still unclear, as STI increases predated the introduction of PrEP[119]. In addition, high rates or increases of STI are reported in subsets of MSM participating in PrEP studies, rather than in the group at large [117], suggesting that testing frequencies and prevention interventions may be tailored based upon behavioural profiles. In AMPPrEP, a large proportion of STI were diagnosed during non-scheduled visits in-between study visits (chapter 5.3); this finding provides additional support for tailoring testing to a clinical or behavioural indication.

3.5 HCV
Sexually acquired HCV is known to occur predominantly among HIV positive MSM[128, 129]. However, high incidence rates have been reported among HIV negative MSM using PrEP in the Netherlands (chapter 5.4) and France[73, 74, 130]. HCV re-infection rates among HIV negative MSM were only reported for our AMPPrEP study and were remarkably higher than primary rates (chapter 5.4), possibly resulting from both behavioural and sexual network characteristics. Interestingly, recent studies from the UK and France reported that of all new HCV diagnoses among MSM, 40% and 45% in 2017, respectively, were in those who were HIV-negative [130, 131]. These outcomes should urge clinicians to offer frequent HCV testing among both HIV positive and HIV negative MSM eligible for, starting with and using PrEP.

Since the introduction of direct-acting antivirals (DAAs), the elimination of HCV as a public health threat is considered feasible [132-134]. However, similarly to PrEP not being the silver bullet in elimination of HIV, up scaling of DAAs is not the one and only solution to stop the HCV epidemic. Modelling studies revealed that a comprehensive package of prevention, screening, behavioural and treatment interventions is needed for a significant impact on the epidemic [135-137]. In table 2 the current HCV test recommendations for MSM starting with or using PrEP are summarised. Because most guidelines on PrEP for MSM advice to test for HCV, PrEP may be a gateway to HCV diagnosis and treatment in those who otherwise would not have been tested and treated. However, prevention interventions for HCV (re-)infection, especially targeting behaviour, and affordable tests to diagnose HCV re-infection are much needed.

3.6 STI testing challenges
Effective testing strategies should incorporate characteristics of the person who is tested (e.g., pre- and post-test probability of the presence of a disease), test characteristics (e.g., sensitivity, specificity, costs, turn-around time, and invasiveness), and cost-effectiveness of testing programmes [138]. In the early days of PrEP, risk compensation (i.e., a decrease in condom use due to an anticipated lower risk of HIV) after initiation of PrEP was feared [139].
To detect possible increases in STI rates, which would be an undesired effect of a PrEP programme, frequent testing of STI has been part of the PrEP trials, demonstration studies and guidelines since. However, the more you look, the more you find, and the relevance of diagnosing and treating asymptomatic Chlamydia trachomatis (CT) and Neisseria gonorhoeae (NG) is debatable. Most PrEP guidelines for MSM advise STI testing regardless of symptoms at 3-month intervals (table 2). In AMPrEP, about 90% of the STI (CT, NG, and syphilis) diagnosed during 3-month study visits were asymptomatic. In contrast, of the STI diagnosed at additional, non-study visits (e.g., for STI-related complaints or after receiving a partner notification), 40% were asymptomatic (chapter 5.3). Several of those asymptomatic STI might have remained unnoticed without a PrEP programme, as 3-month testing is not generally advised outside of PrEP programmes, not even for sexually active MSM.\textsuperscript{[140]}

Testing and treatment of those asymptomatic STI put pressure on the services provided by sexual health clinics, not only in the Netherlands but also in several other countries \textsuperscript{[101]}. Another possible negative consequence of treating asymptomatic infections is the emergence of antimicrobial resistance \textsuperscript{[141]}. WHO took the lead and organised an expert meeting to determine which STI services are needed and how they can be optimised in PrEP programmes, given potential unintended consequences, in March 2019. Preliminary action points from this meeting include to drive advocacy (e.g., convene partners on the HIV/STI syndemic, and investigate how PrEP can serve as a gateway to STI services), to advocate for funding (e.g., for STI services in PrEP programmes), to assess the landscape of the current and future diagnostics pipeline (e.g., need for cheaper, better STI testing) and to pursue innovations in service delivery (e.g., home delivery of STI testing kits and self-testing) (personal communication Teodora Wi, WHO; report in preparation).

Detection of HCV re-infections is challenging as antibody tests cannot be used and HCV RNA tests come at a much higher costs compared with HCV antibody tests. For this reason, Alanine Aminotransferase (ALT) levels have been used to guide HCV RNA testing, a strategy which is known to be less sensitive to diagnose re-infections in HIV positive MSM\textsuperscript{[142, 143]}. Another alternative is testing for the hepatitis C core antigen, which is less expensive than viral-load testing, and slightly less sensitive compared to HCV RNA\textsuperscript{[144]}. It is remarkable that in some countries including France and the Netherlands, it is now recommended to test for HCV more often in HIV negative MSM on PrEP than in HIV positive MSM\textsuperscript{[53, 130]}. In addition, in the Dutch PrEP guidelines, the recommended testing frequency is higher for individuals without a previous HCV infection compared to those with a previous HCV infection\textsuperscript{[53]}, whereas higher incidence rates of reinfections than rates of primary infection were found in our study (see chapter 5.4), as well as in studies among HIV positive MSM\textsuperscript{[143, 145, 146]}. The fact that the Dutch PrEP guideline advises less frequent testing among those with a history of HCV compared to those without may seem wise.
from a cost perspective, as HCV RNA testing is costly, but foolish from a public health perspective (table 2).

4. STRIVING FOR EPIDEMIC CONTROL

4.1 Lessons learned
What have we learned from AMPREb about the potential of PrEP in contributing to stop the epidemic? We learned that the wish to start PrEP among Dutch MSM largely exceeded the capacity of our project, and that people were looking for alternative ways to get PrEP, including buying it abroad and using it without adequate monitoring/testing and without being properly counseled\textsuperscript{147, 148}. Besides Dutch MSM aged about 30 to 50 years, it was hard to serve all key groups, including transgender people, bisexual men, young MSM and migrant MSM. It became clear that both daily and event-driven regimens should be offered, and many people switched regimens over time. We observed the, generally positive, experiences of participants with PrEP\textsuperscript{68} and a tremendous commitment to the project, both for individual benefits but also to contribute to the availability of PrEP for a group beyond the early adopters in AMPREb.

We added data to existing evidence that PrEP is effective and safe. And although we diagnosed and treated many STI, the incidence of STI did not increase over time on PrEP. A new group that is at risk of HCV infection was identified, and this group should be tested regularly.

We translated some of our lessons learned into ten recommendations for a successful, sustained implementation of PrEP (see boxed text).

4.2 City-based approach to the epidemic
More than half the world’s population lives in cities and it is projected that this will further increase to 60% by 2030\textsuperscript{149}. As dynamic hubs for economic activities, education, and positive social change, cities can be incubators for innovation and drivers of sustainable development. Cities also have inherent advantages in accelerating responses and in delivering services to all inhabitants in an equitable and efficient way. Collaborations, including meetings and events for stakeholders and key groups are relatively easy established if all are based in the confinement of a city. Travel time will be limited and public transport (or the bicycle, if based in Amsterdam) can be used to travel to meetings. The Fast-Track Cities network, launched by the International Association of Providers of AIDS Care (IAPAC), The Joint United Nations Programme on HIV/AIDS (UNAIDS), the United Nations Human Settlements Programme (UN-Habitat) and the City of Paris, serves to provide support to
Ten points for a successful, sustained implementation of PrEP

We are at the verge of a new era in the Netherlands: in the coming five years we will be providing PrEP to MSM and others at considerable risk of HIV. How are we going to ensure that PrEP will become a success?

1. Be inclusive, in the set-up of clinics, in language, in a non-judgmental attitude towards gender and sexual expression, in welcoming and providing services to all key groups. Provide continued education for health care providers, both on PrEP and on motivational interviewing and inclusive communication.

2. Reduce PrEP stigma and its negative impact on the HIV epidemic. A multilevel approach to reduce stigma is necessary to ensure PrEP can be utilised by all individuals who can benefit from it.

3. Do not hesitate to provide PrEP. Although prescribing ART is new for many primary care and public health doctors and nurses, resulting in feelings of uncertainty, PrEP is a safe, effective and much valued prevention strategy that allows users to take the responsibility to stay safe, and use PrEP at a well-chosen moment of the day.

4. Allocate resources to reach all PrEP key groups, including young MSM, transgender persons, migrant MSM, sex workers, and people who inject drugs; create demand for PrEP beyond the groups currently enrolled in PrEP care, e.g., using information campaigns and role models.

5. Do not restrict the number of participants in the national PrEP programme; if this number is not sufficient, this restriction will create inequity, as marginalized and hard to serve populations will likely present later for PrEP care than other groups, risking to be turned away, lose faith in public health services and acquire HIV.

6. Offer tailored care. Sexual behaviour may vary over time as a result of changes in relationships, life events and milestones such as moving to another city or starting a new job. These changes demand tailored prevention. In addition, different people have different beliefs, attitudes and preferences. Providing a choice, e.g., for daily or event-driven PrEP use, an opportunity to switch and stop over time, and information about safely starting and stopping PrEP may increase uptake and adherence.

7. Look beyond the five years of the national programme. Start planning for the period after the national programme sooner rather than later.

8. With scaling-up of PrEP use and immediate treatment of newly diagnosed HIV infections to prevent onward transmission, the end of the epidemic is close in some countries. However, the last mile is the most difficult. Continued political, organizational and financial support will be needed for many more years if we want to reach the goal of ending the epidemic.

9. Integrate PrEP care with comprehensive sexual health care, which includes motivational interviewing about sexual behaviour and condom use, STI and HCV testing and prompt treatment according to professional standards, PEP if needed, rapid testing trajectories for acute HIV testing and linking to care, partner notification and treatment.

10. Monitor PrEP care on the national level, including uptake related to expected uptake and outcomes (e.g., STI incidence), stratified by key groups.
cities to fast-track their HIV responses and to end the AIDS epidemic by 2030 [150]. The network was launched on 1 December 2014. Amsterdam was among the first cities to sign the Paris declaration [151], indicating the city’s commitment to attain the UNAIDS 90-90-90 targets by 2020: 90% of all people living with HIV will know their HIV status; 90% of all HIV-positive people will receive ART, and 90% of all HIV-positive people receiving ART will achieve viral suppression, and there is zero stigma. Amsterdam is currently part of the cohort of champion cities that have reached 90-90-90 and now move towards 95-95-95 and zero new infections. More than 300 cities and municipalities had joined the network by the end of 2018.

In Amsterdam, the H-TEAM, initiated in 2014 by the late dr. Joep Lange, embodies the city-based approach to the epidemic through an innovative integrated approach on HIV care, involving both prevention and treatment [23]. The H-TEAM consists of people working for NGOs, general practitioners, professionals from hospitals, and the Public Health Service of Amsterdam, and representatives of community groups. Interventions developed and evaluated in H-TEAM include, next to those studied in the AMPrEP project, innovative HIV testing including an acute HIV test and link-to-care project, several activities to promote HIV testing by general practitioners and an HIV test week [152-154]. In addition, barriers to test and treat strategies were studied [23]. The successful development, evaluation and finally implementation of activities after a successful pilot, incorporating cross-links between the projects, are ensured through multi- and interdisciplinary collaboration between all stakeholders.

Other successful city-based approaches are the “Getting to Zero initiative” in San Francisco and the “End the Epidemic project” in New York, USA [155, 156].

4.3 Estimating the impact of PrEP on the HIV epidemic

What do we know about the impact of PrEP on public health, in relation to decreases in condom use and increases in STI on the one hand, and getting closer to reaching epidemic control for HIV on the other hand?

A study from Australia reported on population level changes in condom use coinciding with a large increase in PrEP use from 2013 to 2017 [85]. In this study an increase occurred in the proportion of men using PrEP that reported condomless anal sex with casual partners. The proportion of men not on PrEP reporting consistent condom use with casual partners did not change, suggesting that mostly men on PrEP changed their behaviour. The authors suggested that monitoring of the behavioural effect of PrEP at a population level (i.e., not only in PrEP users) is justified to anticipate and detect changes in existing prevention practices at a population level. However, in the ACS, we found a decrease in
condom use among study participants, of which the majority was not using PrEP (WPH van Bilsen et al, manuscript submitted).

An HIV-negative person who has condomless anal sex with a person who is HIV-positive with an undetectable viral load or with a person who states to be on PrEP might feel protected against HIV, resulting in population-wide decreases in condom use. Although herd immunity (e.g., a growing proportion of the population cannot acquire or pass on HIV) may indeed offer protection beyond those using PrEP, surveillance is needed for early detection of population-wide changes in the use of preventive interventions.

Large reductions in the number of new HIV diagnoses have been reported from jurisdictions with a large uptake of PrEP. In the state New South Wales in Australia, the annual number of HIV diagnoses in MSM declined (relative risk reduction of 25·1%) in the year after PrEP was rolled-out to 3700 people [10]. In London, HIV diagnoses in MSM visiting selected sexual health clinics fell by 32% in one year in a period when PrEP was purchased online by an unknown but presumed large number of MSM [9]. It is unclear to what extent this decrease is associated with more testing, rapid initiation of treatment on HIV diagnosis and an increase in PrEP use. However, this remarkable decrease suggests that controlling the epidemic may be achievable if several interventions are combined and implemented at a larger scale. In San Francisco, community-based surveys estimated that the proportion of HIV negative MSM reporting current PrEP use increased about fourfold between 2014 to 2017, while the number of new HIV diagnoses showed a decreasing trend from 458 in 2012 to 221 in 2017 [157]. However, in other jurisdictions, no changes in number of new HIV diagnoses have been recorded, regardless of uptake of PrEP. In the United States as a whole, for example, the number of new HIV diagnoses remained stable between 2012 and 2016 whereas PrEP uptake increased [158, 159]. In the European Union/European Economic Area (EU/EEA) there is evidence of a decline in the rate of new HIV diagnoses; nevertheless, HIV rates continue to increase in one-third of EU/EEA countries [160]. The decrease seems to be driven by a decrease in HIV diagnoses among MSM in Belgium, Greece, the Netherlands, Spain and the United Kingdom. Interestingly, PrEP has not been implemented at large scale in Greece, Spain and the Netherlands, and only recently in Belgium and the UK, suggesting that the decrease is largely due to interventions other than PrEP, of which immediate treatment after diagnosis (“U=U”) [91] is probably the most important. Moreover, in France, which was the first country in the EU where PrEP was nationally implemented, in 2016 [161], 12,000 people were on PrEP by end-2018 (personal communication J-M Molina), but no decline in the annual number of HIV diagnoses has been noted [160]. A full explanation is lacking, but the facts that France is a country where (1) heterosexual transmission is the most commonly reported mode of HIV transmission among newly diagnosed cases, (2) more than half of those diagnoses are among migrants
originating from countries with generalised HIV epidemics, and (3) the uptake of PrEP is almost exclusively by MSM, may partly explain this finding. This clearly indicates the need for information campaigns and demand creation for PrEP among the non-MSM population at risk of HIV when implementing PrEP, not only in France but also in other countries where heterosexual transmission is an important factor in sustaining the epidemic.

4.4 Impact on the HIV epidemic in the Netherlands

This thesis has not covered the impact of PrEP on the population-level in the Netherlands. The annual number of new HIV diagnoses has steadily been decreasing in the Netherlands since 2008 [162]. In 2008, 1236 new diagnoses were made (870 among MSM), and in 2017 this number was 692 (516 among MSM). At public health STI clinics, 393 new diagnoses in 2008 (320 among MSM) and 249 in 2018 (224 among MSM) were made [118, 162, 163]. In the same period, HIV testing has increased [118], late diagnosis has decreased, mostly among MSM, and treatment is started sooner after diagnosis [162]. In the UN Global AIDS update 2018, the Netherlands is mentioned as one of just six countries worldwide that have reached the 90-90-90 target [164]. The effect of each of the individual interventions on these outcomes is uncertain. In 2015 and 2016 PrEP was started by MSM participating in AMPrEP, followed by MSM participating in the InPrEP study in 2017 and 2018, and through purchasing PrEP online or through local pharmacies with a prescription from a general practitioner or public health service from 2017 onwards. Considering that the decrease in new HIV diagnoses started well before enrolment in AMPrEP and InPrEP was completed, and before the availability of generic PrEP in 2017, it is unlikely that PrEP has already had a large effect on the HIV epidemic in the Netherlands. Possibly, the effects of PrEP have added to the effect of improvements in HIV testing, early diagnosis and prompt treatment on the epidemic. Future data, stratified by risk group, on uptake of PrEP, HIV testing and proportions testing positive, number of new HIV diagnoses, proportions with acute HIV infection and proportions presenting late for care may provide further insights. Data from the ACS and other cohort as well cross-sectional studies on HIV will provide further insights in HIV incidence and prevalence, on uptake of PrEP by key groups, and on possible additive population effects of PrEP on the HIV epidemic.

4.5 The prevention cascade

The 90-90-90 target set by UNAIDS in 2014 has been a major advocacy tool and has stimulated governments and programmes to ensure that all HIV-positive people are offered treatment. The UNAIDS target is based on a cascade, starting with people living with HIV, followed by the proportion diagnosed among those living with HIV, the proportion that started treatment among those diagnosed, and the proportion having an undetectable viral load among those that started treatment. If targets are reached, this improves the health of people living with HIV and renders them no longer infectious. Such a simple,
clear strategy is less well applicable to the HIV prevention field considering the diversity of priority populations and interventions. Recently, a generic prevention cascade was proposed in *Lancet HIV*, consisting of three domains of motivation, access, and effective use (e.g., PrEP adherence during periods at risk of HIV) in a priority population that is eligible for PrEP (figure 5) \[165\]. Methods for measuring the domains of the cascade must be developed and validated. HIV prevention cascades can improve implementation of programmes by identifying gaps in motivation, access, and effective use, and by using them as advocacy tools. Cascades per key population can provide further insights in the most important gaps for each group, informing prevention programmes.

In the Netherlands, data on the motivation to use PrEP by MSM, the first step of the prevention cascade for MSM, are available \[45, 46\]. However, data about access, the second step, are lacking as the national PrEP programme has not yet started. Effective use (i.e. adherence, the third step) is currently being evaluated among the AMPPrEP participants, which will be partly informative for a larger group of MSM using PrEP. However, to evaluate effective use of event-driven PrEP is complicated as use needs to be assessed related to episodes of risk. Data collection instruments that are easy to use, e.g., apps, need to be developed, evaluated and improved together with the community.

### 5. RECOMMENDATIONS

#### 5.1 Monitoring and surveillance

Monitoring systems are needed to measure uptake of PrEP, stratified by key population, ethnicity, and age. Monitoring the uptake among groups that need specific attention is particularly important. These groups include young MSM, transgender persons, migrant MSM, sex workers, and people who inject drugs. Denominators, i.e., numbers eligible for PrEP, for these groups are needed to adequately assess PrEP coverage. Next to uptake, use of daily versus event-driven PrEP regimens and its determinants, switching between those regimens, PrEP persistence (i.e., continuing the use of PrEP while at risk for HIV infection) adherence, reasons for stopping (or not starting), and use of other preventive measures should be assessed. These data will enable us to fine-tune our campaigns, to evaluate whether programmes reach vulnerable groups, and to estimate the impact of PrEP on the epidemic and the cost-effectiveness of PrEP programmes.

Collecting data beyond the official programme may be undertaken using an app or another eHealth-based application for PrEP users. Such data collection instruments would facilitate to collect additional data from the wider real-life setting, e.g., also from informal
motivation and access are requirements for effective prevention methods. Without motivation, so we propose that motivation is the first step. Access can be considered irrelevant in the absence of motivation. HIV prevention methods, including PrEP daily, to use condoms in particular sexual partnerships, or to use VMMC services, and is generally requires individual motivation to engage in these behaviours, although exceptions can occur. Behavioural intent and resonates strongly with the so-called COM-B model of behaviour change in which motivation, the cognitive processes that result in wanting to use a prevention method, is aligned with behavioural intent. The proposed model clearly identifies the priority population that could benefit from the prevention method (figure 1). The complete cascade that includes the gaps at each step is shown in figure 5.

**Figure 5.** Generic and unifying HIV prevention cascade framework. A. The core steps of the prevention method cascade. B. The complete cascade. Reprinted from The Lancet HIV, Vol. 6, January 2019. Robin Schaefer, Simon Gregson, Elizabeth Fearon, Bernadette Hensen, Timothy B Hallett, James R Hargreaves: HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades, Pages No 60-66., Copyright (2019), reprinted with permission from Elsevier.
PrEP users and those who use PrEP via general practitioner practices, where surveillance systems are generally not in place.

Considering the high incidence of STI among PrEP users, and awaiting further research on optimal testing frequency, we recommend 3-monthly testing of STI (CT and NG in pharynx, rectum and urine, and syphilis) among MSM who use PrEP. HCV should be tested bi-annually for those who never had an HCV infection; 3-monthly testing should be considered for those who had a previous HCV infection, as re-infection incidence rates are high.

Management of HIV breakthrough infections in a PrEP users should be determined on a case-by-case basis. Expert advice can be sought if an infection occurs during presumed good adherence, in which case a dried blood spot sample should be collected for assessing long-term adherence by measuring tenofovir diphosphate levels. Expert advice can also be helpful if a 4th generation ELISA test is positive in combination with an undetectable serum HIV RNA, in such cases diagnosis is not straightforward and highly sensitive viral load tests, measuring integrated HIV DNA, or testing samples from other locations (e.g., sigmoid biopsies) should be considered.

In addition, immunological studies among PrEP users are needed to increase our understanding of PrEP failures.

During consultations, beliefs and attitudes of the PrEP user rather than those of the health care provider should be taken as a starting point. We recommend to explicitly respect individual decisions about sexual expression, and use non-judgmental language; motivational interviewing techniques should be used when speaking about (changing one’s) sexual behaviour. The guideline “Motivational interviewing in the context of PrEP” may be used for background information and practical information \[166\]. As mental health problems and the use of drugs around sex (chemsex) are common among MSM using PrEP, these topics should also be discussed, and referral for appropriate specialised care should be offered if needed.

### 5.2 PrEP implementation for maximum impact

With the long-awaited start of the national PrEP programme in the Netherlands (planned for the third quarter of 2019), we need to think ahead about how to ensure that PrEP will be widely available and accessible in the next 5 years. For those who are young not yet aware that they need PrEP for better protection and those who need to overcome barriers to enter PrEP care, good access to PrEP is important. Denying access to PrEP to underserved or marginalised populations because the maximum number of the programme is reached, would be unacceptable. If the maximum capacity of 6,500 people is reached before the
end of the 5-year programme, expanding the programme is needed to continue to meet the needs of all key groups and provide truly comprehensive HIV preventive care. The process of establishing national policies about a biomedical HIV prevention intervention has proven to be fairly difficult and slow in the Netherlands (and elsewhere in Europe). Realizing this, it seems wise to start sooner rather than later to formulate strategies for future, sustainable PrEP implementation in the Netherlands after 2024.

Access to PrEP, as part of comprehensive preventive services, should be accessible, affordable and equitable. Services should be lesbian, homosexual, trans, intersex, and queer (LHBTIQ)-friendly, and be culturally, financially and geographically accessible for all those who may benefit from PrEP. Currently, several groups at risk of HIV may not feel that they can benefit from PrEP, or do not consider PrEP as a valuable and important option for them, and creation of demand is needed. The involvement of peers and communities can contribute to this.

Offering PrEP at various types of health care settings (e.g., public and private clinics for sexual health, and general practitioners) improves accessibility and should be considered. To ensure affordability of PrEP care, and keeping in mind that those using PrEP are often healthy people and not patients, hospital-based care is not the preferred type of care, except for those with co-morbidities warranting the involvement of specialised health care professionals. Task-shifting, e.g., from doctors to nurses (which is already the case in many Dutch sexual health clinics) or non-medical personnel, should be explored. In addition, innovative and differentiated delivery models for the provision of PrEP may improve uptake and warrant further evaluation.

People want options so they can make choices. We recommend offering a choice of daily and event-driven PrEP and providing information on safely starting and stopping PrEP. When new PrEP formulations or regimens that have a potential to create demand among underserved populations enter the market, their added value should be assessed either in demonstration projects or routine care.

It is of great importance that PrEP roll-out does not compete with other sexual health services such as counseling and testing for women and contraceptive services. The risk of decreased access to sexual health care for certain groups due to service pressure related to PrEP care is not inconceivable: the proportion of consultations offered to MSM at the Amsterdam STI clinic increased from 25% in 2014 to 40% in 2018 (personal communication Martijn van Rooijen). Ensuring accessibility of services for all populations in need is crucial, and resources should be sufficient to cover additional costs related to PrEP care. Co-payments in public health are uncommon in the Netherlands, but in the national PrEP
programme an unprecedented system of co-payment for the PrEP medication will be implemented. Whereas co-payments may be experienced as fair in the case of preventing HIV\cite{31} and could improve sustainability of programmes for all key groups, the accessibility of the services should not be at stake, and waivers for certain groups may be needed.

### 5.3 Future research

Data on event-driven PrEP use are limited. Event-driven use of PrEP is not offered in many countries, and if offered, the proportions opting for this regimen have generally been smaller than for daily PrEP. Adherence to event-driven regimens is more difficult to assess than for daily PrEP, as precise data on moments of HIV risk in conjunction with use of PrEP are needed. In addition, people may alternately use event-driven and daily PrEP. More research is needed to better characterize periods of event-driven PrEP use, and related characteristics. To increase power, pooling data from settings where a choice between daily and event-driven regimens are offered, should be considered.

The optimal frequency of testing for STI and HIV during PrEP use is not known. Quarterly testing is used in many settings, mostly because this was the testing frequency in many of the earlier PrEP trials and demonstration studies. Further research is needed to investigate whether testing frequency can be reduced or should be increased, both overall and for certain subgroups, depending on behavioural characteristics. Such studies should incorporate the potential negative outcomes for the individual (e.g., complications of untreated STI), public health (e.g., more onward transmission, viral and antimicrobial resistance), and cost-effectiveness.

Further cost-effectiveness analyses of programmes offering a choice of daily and event-driven PrEP could provide important input for implementing PrEP. Costs for monitoring and testing currently exceed medication costs in setting where generics are available, and variations in monitoring and testing could be incorporated in these analyses for improved insights.

People want options and programmes tailored to their needs; therefore, research into innovative and differentiated delivery PrEP models is needed. Online PrEP provision, with or without web-based consultation with a health care provider (ePrEP pathways) could improve uptake and continued use among certain groups, e.g., those experiencing stigma when visiting health care facilities, young people, or those with demanding jobs. Home-based self-sampling tests (i.e., the self-collected samples are sent to a certified laboratory for testing), and, when available, good quality self-tests (i.e. the sample is a self-collected and the test is performed by the client at home) for STI, warrant further assessment, with special attention for counseling and clinical follow-up when testing positive.
New PrEP formulations/regimens are needed to increase options. Several new products are currently being investigated in preclinical and clinical settings [167]. We advocate for the continuation of this research, including assessing the efficacy of innovative products such as implants, films, fast-dissolving inserts, or multipurpose products that may protect individuals not only from HIV but also other STI or pregnancy. Advocates and health care policy makers will need to ensure that new products are priced in a way that ensures access for all at risk of HIV.

Current tests for STI, especially NAAT-based tests for NG and CT, need advanced laboratory facilities, have a turn-around time of hours to days, and are costly. Innovations in laboratory testing of STI are long awaited, to meet the needs for affordable point-of-care tests.

Considering the high STI incidence rates, PrEP cohorts are well-placed for research into STI prevention, e.g., gonorrhoea vaccination or treatment trials, PrEP with doxycycline to prevent syphilis [120], or behavioural intervention studies. We recommend developing effective interventions to prevent and detect early HCV (re-+) infections.

This thesis is not about PrEP for women. However, in many countries, (young) women are at very high risk for HIV [168]. Not mentioning women at all in this thesis would be a missed opportunity, and research on optimal PrEP programmes for women is needed. Likewise, especially in jurisdictions where harm reduction measures are not in place, people who inject drugs may be at risk of HIV infection. We recommend leaving no one behind, and to focus on the development and implementation of effective PrEP products and programmes for women, and implement comprehensive harm reduction programmes including provision of PrEP for people who inject drugs.

The prevalence of HIV and STI among unselected populations of transgender persons is unknown. We did not succeed in reaching transgender populations at risk of HIV in our project. Assessment of their needs, characteristics, and preferred methods of receiving gender-affirmative care is much needed.

Data on long-term adherence outcomes, especially using an objective adherence measure such as tenofovir diphosphate in dried blood spots, are rare. Effective interventions to improve adherence to PrEP are scarce; further research on such interventions is needed, because adherence to PrEP is the key determinant of the efficacy to prevent HIV. Especially eHealth-based strategies are promising and require further research.

We provided insight on a population-level into behaviour and incidence of STI in MSM using PrEP. Nevertheless, there could be substantial variation between individuals with
respect to trajectories of behaviour and acquisition of STI\textsuperscript{[169]}. Insights into this variation and determinants of longitudinal patterns of STI risk could provide opportunities for improved tailoring of care.
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