PrEP in the Netherlands
The introduction of HIV pre-exposure prophylaxis
Hoornenborg, E.

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Chapter 1.1

Pre-exposure prophylaxis for men who have sex with men and transgender persons in early adopting countries

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ABSTRACT

Pre-exposure prophylaxis (PrEP) is a potent and underutilized HIV prevention tool. In this paper we review the state of knowledge regarding PrEP implementation for men who have sex with men and transgender persons in early adopting countries. We focus on implementation of PrEP in demonstration projects and clinical care, and describe the status of PrEP availability and uptake. We report on approaches to identifying appropriate PrEP candidates in real-world settings and on best practices for clinical monitoring. This includes the exclusion of undiagnosed HIV infection prior to PrEP initiation and longitudinal measurement of renal function, in light of safety data. Since adherence is the primary factor moderating the effectiveness of PrEP, we discuss effective adherence support interventions. Additionally, we review the evidence for risk compensation with PrEP use and opportunities to provide PrEP as part of comprehensive and inclusive preventive health programs. We summarize cost-effectiveness studies, including their variable conclusions because of differing underlying assumptions, and discuss the importance of budgetary impact for public health programs and health care insurers. Further, we emphasize a need for greater engagement of health care providers in PrEP to increase access. We conclude with recommendations for ways to improve future efforts at implementing PrEP.
INTRODUCTION

The use of antiretrovirals to prevent HIV infection as part of a comprehensive prevention package when used in conjunction with universal treatment of those who are infected offers an opportunity for epidemic control [1]. The efficacy of using tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP) to prevent HIV acquisition was established more than 7 years ago [2], but uptake has been relatively limited, given that there are still close to 2 million new HIV infections annually [3]. Even in the United States where PrEP was first approved for clinical use by the Food and Drug Administration in 2012, and more than one million Americans are considered to be appropriate candidates for PrEP [4], only about 10% of those at greatest risk have accessed PrEP [5]. Europe and other resource-rich countries are lagging behind the United States in implementing PrEP [6]. PrEP roll-out is a work in progress, with regulatory approvals for its use for HIV prevention completed in 15 countries, ranging from South Africa to Peru to Taiwan, and dossiers under review in multiple other countries [6].

The current paper reviews the state of knowledge regarding PrEP in men who have sex with men (MSM) and transgender persons, given that HIV continues to spread most rapidly in these populations in the developed world [7]. We focus on the experiences of the earliest adopters, recognizing that structural impediments common for at-risk heterosexuals and people who inject drugs, particularly in resource-constrained environments (e.g. poverty and limited health infrastructure) pose additional challenges to PrEP implementation.

REGIONAL AND NATIONAL EXPERIENCES WITH PREP IMPLEMENTATION

Pre-exposure prophylaxis in the United States

In 2012, the United States became the first nation where PrEP had been granted regulatory approval. PrEP uptake has been gradual in the United States, but studies have found that rates of new PrEP prescriptions have increased steeply in recent years [8, 9]. About 100,000 started PrEP in total in the United States. In Table 1, PrEP implementation in the United States as well as in Canada, Australia and Europe is summarized [4, 9-13, 14-22]. Of the 80,000 individuals who initiated PrEP in the United States from 2012 through 2015, about 75% were men and nearly 75% were white, which did not reflect the US epidemic, suggesting that racial and gender disparities in PrEP utilization remain [23, 24]. Addressing these disparities is an urgent priority given disproportionately high rates of new HIV infections in the United States among people of color [25, 26]. Although few data are available about PrEP use by transgender persons in the United States, the experience of a lesbian, gay,
bisexual, transgender (LGBT-)focused community health center in New York City illustrates the need for culturally-tailored services for this population [27]: after implementing a more inclusive healthcare environment for transgender people, their PrEP utilization increased substantially [27].

Within the United States, there is heterogeneity in PrEP utilization by region and state [9]. The states where providers are more aware of PrEP, and at-risk persons are more likely to use it, tend to have less discriminatory climates for sexual and gender minorities [28]. Interventions that can decrease disparities in insurance access, increase public financing of PrEP-related costs, and improve the social environment for cultural acceptance of sexual and gender minorities, are needed to facilitate more universal access to PrEP in the United States.

Pre-exposure prophylaxis in Europe

In 2015, two landmark European studies, one of which was also conducted in Canada, reported high PrEP effectiveness in MSM when used on a daily [29] or event-driven basis [30]. Subsequently, France began rolling out PrEP in January 2015, after temporary regulatory approval, and reported having around 3400 people using PrEP by mid-2017 [10]. In August 2016, the European Commission officially granted marketing authorization for TDF/FTC in combination with safer-sex to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk, which led to national regulatory agencies providing access to PrEP in Norway, Belgium, Portugal, Wales and Scotland [20, 31]. In England, after the successful PROUD trial, PrEP has been temporarily made available by the National Health Service England for 10,000 people who are at risk for HIV infection [32]. However, no free-of-charge PrEP programs are currently in place in other European countries, and heterogeneity in PrEP access seems to be evolving, resulting in national heterogeneity. As a consequence of the lack of reimbursement of PrEP medication costs, in combination with the high retail price of TDF/FTC, informal PrEP use (i.e. use of generic PrEP obtained overseas, online, or from friends) has been reported [33, 34]. This may be contributing to decreases in HIV infections as observed in London [35].

Pre-exposure prophylaxis in Canada

One of the sites for the Ipergay study was in Quebec [30] but it was not until February 2016 that Health Canada approved the daily oral use of TDF/FTC in combination with safer sex practices, to reduce the risk of HIV transmission. However, PrEP funding is to be determined at the provincial level and not yet in place throughout Canada. Canada’s first PrEP demonstration project started in Toronto in October 2014 [36]. A clinic in Montreal has more than 1000 people on daily and event-driven PrEP [37].
Pre-exposure prophylaxis in Australia

Early efforts to implement PrEP in Australia have been MSM-focused. PrEP has not received full regulatory approval in Australia. Australia’s major demonstration projects have opened in several states: the Expanded PrEP Implementation in Communities in New South Wales program, in New South Wales [38], the pre-exposure prophylaxis expanded program in Victoria and South Australia [39]; and Queensland PrEP study program in Queensland [40]. These projects represent partnerships amongst research, medical, community and government organizations and include large-scale, rapid roll-out of PrEP in community settings and assessment of HIV incidence, using clinical data collection systems and over 12,000 people are enrolled in these projects by July 2017 [11]. If these projects are successful, they could provide a model for enacting a coordinated public health program for implementing PrEP in Australia and other countries.

EMERGING CHALLENGES

Identifying appropriate pre-exposure prophylaxis candidates

Because PrEP entails the use of medication in otherwise healthy individuals, which has costs and requires monitoring and adherence support, the identification of those who would most benefit from PrEP is of great importance, but poses many challenges. The societal benefit and cost-effectiveness of PrEP will be attenuated if individuals at low risk for HIV infection start PrEP, (“worried-well”), and if people at high risk are not interested in, or do not access, PrEP [41]. Eligibility criteria are needed to ensure that PrEP is implemented in an efficient way in order to not only minimize harms and maximize benefits for individuals but also to optimize public health impact and cost-effectiveness.

Most PrEP clinical trials, demonstration projects, and national guidelines have recommended PrEP for MSM and transgender persons who report condomless anal sex (CAS), recent sexually transmitted infection (STI), and/or use of post-exposure prophylaxis (PEP) after sexual exposures to HIV [42], however recommendations regarding number of partners, or recency of exposures have varied across studies/projects and guidelines. Some subpopulations are at particularly high risk for HIV because of the concentration of undiagnosed and untreated HIV within their sexual networks. For example, in the United States, black MSM represent a group at very high risk of acquiring HIV infection [26, 43, 44]; however, PrEP uptake has been disproportionately low compared to non-black MSM [45-47] which may be attributable to assortative mixing (preferentially choosing partners from within one’s ethnic group, thereby concentrating risk per contact) and limited social mobility, disparities in healthcare access, and distrust of culturally-insensitive healthcare systems [48, 49]. Some data suggest that 72% of the infections among migrant MSM in Eu-
rope occur after migration \[50\], but there is limited evidence \[51\] about PrEP uptake among specific racial and ethnic MSM subgroups in Europe and Australia. Transgender women also bear a disproportionate HIV burden. In the United States, estimated HIV prevalence among transgender women is 22% \[52\] and in Europe, limited studies among transgender sex workers also suggest increased HIV risk \[53, 54\]. However, the number of transgender persons in the major PrEP studies (0 to 29) \[2, 30, 55\] has been too small to draw definitive conclusions about PrEP efficacy for transgender people \[56, 57\]. Several PrEP studies focusing on transgender women are now underway; however, identifying and engaging MSM and transgender women at highest risk for HIV infection remains challenging. The PROUD study successfully engaged MSM at high risk by using sexual health clinics \[29\], and the Ipergay \[30\] and US PrEP Demo Project \[55\] attracted MSM at high risk through community and venue-based recruitment. These studies prove that identifying MSM at high risk is feasible, but the question is whether less supportive jurisdictions are capable of sustaining PrEP scale up and implementation.

To support busy clinicians in readily identifying PrEP candidates, the U.S. Centers for Disease Control and prevention (CDC) developed an MSM risk-index score, based on age, sexual risk behavior and substance use, to estimate risk for HIV infection \[58\] and subsequent eligibility for PrEP \[59\]. Some providers have applied this score in their clinical practice \[60\], but use of this and other risk assessment tools is not widespread. Other international guidelines do not utilize a risk score, but provide criteria to identify which MSM and transgender women are at greatest risk \[61, 62\].

**Clinical Monitoring**

After many thousands of person-years of experience with PrEP, side effects are common (39% in the Preexposure Prophylaxis Initiative (iPrEPX) Open Label Extension study), generally mild, and tend to peak in the first month of PrEP use, with gastrointestinal symptoms and headache being most prevalent \[63\]. Clinical trials and a systematic review found that most adverse events did not significantly differ among individuals using TDF-based PrEP versus placebo \[2, 64-67\]. Because TDF can cause small, albeit reversible, reductions in estimated glomerular filtration rate (eGFR) \[2, 64, 65\], creatinine clearance should be monitored every 6 months for younger people, but more frequent monitoring may be indicated for older persons, and those with predisposing conditions. Clinically insignificant loss of bone mineral density has been reported in association with TDF use \[68, 69\]; routine bone mineral densiometry is not recommended for PrEP users, although may be indicated in patients with pre-existing osteoporosis and/or osteopenia.

The emergence of viral resistance in PrEP users with incident HIV infection is another safety concern. As PrEP involves only two antiretroviral agents, resistance may be selected
Table 1. Countries in North America, Australia or Europe where PrEP implementation or demonstration projects are active

<table>
<thead>
<tr>
<th>Country</th>
<th>Guidance</th>
<th>Summary of indications for PrEP</th>
<th>Implementation underway vs. demonstration projects only</th>
<th>Estimated numbers of eligible persons</th>
<th>Estimated number on PrEP$^3$</th>
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<tbody>
<tr>
<td>North America</td>
<td></td>
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<tr>
<td>United States</td>
<td>US Public Health Services (2014) $^{[132]}$</td>
<td>MSM, heterosexuals and PWID with additional risk factors for HIV infection</td>
<td>Implemented</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) $^{[4]}$</td>
<td>Around 100,000 $^{[3]}$</td>
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<tr>
<td>Canada$^2$</td>
<td>Under development</td>
<td>Not available</td>
<td>Patchy implementation, not in all provinces</td>
<td>Not available</td>
<td>Not available</td>
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<td>Australia</td>
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<tr>
<td>Australia$^3$</td>
<td>Yes $^{[133]}$</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>Large-scale demonstration projects only</td>
<td>Around 30,000 (MSM only, no data on other groups)</td>
<td>around 12,000 people $^{[22]}$</td>
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<tr>
<td>Europe</td>
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<tr>
<td>Belgium$^4$</td>
<td>Breach 2017 $^{[18]}$</td>
<td>MSM or transgender persons, members of sub-Saharan populations, or individuals with an HIV-infected sexual partner who has not been on effective therapy for at least 6 months, AND any of the following: condomless anal or vaginal intercourse in the past 6 months, past use of PEP, multiple concurrent sex partners, history of multiple STI, use of drugs when having sex, or transactional sex</td>
<td>Implemented</td>
<td>500-1500 (expected to start PrEP)</td>
<td>Not applicable</td>
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<td>Country</td>
<td>Guidance</td>
<td>Summary of indications for PrEP</td>
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<td>France</td>
<td>ANRS (2015)</td>
<td>MSM with condomless anal sex with 2 or more partners in preceding 6 months, or several episodes of STI or PEP in preceding year, or sex while using substances. People sharing needles. For other groups consider on a case by case basis.</td>
<td>Implemented</td>
<td>Not available</td>
<td>Around 3,400 on PrEP[^10]</td>
</tr>
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<td>The Netherlands[^5]</td>
<td>NVHB (2016) [^19]</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 PEP</td>
<td>Demonstration project only[^12, 17]</td>
<td>Around 5,200-13,100 (rough estimate)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Norway[^6]</td>
<td>Norsk Forening for Infeksjonsmedicin [^16]</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</td>
<td>Not available</td>
<td>Largest center has 200 persons on PrEP</td>
</tr>
<tr>
<td>Portugal[^7]</td>
<td>Under development</td>
<td>Not available</td>
<td>Implementation underway, a national program has been announced on May 29, 2017</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Country</td>
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<tr>
<td>England</td>
<td>BHIVA statement (2012, updated in 2016)- Guidelines to be released Q4/2017</td>
<td>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</td>
<td>PrEP Impact trial for 10,000 participants to start September 2017</td>
<td>Around 20,000-100,000 MSM attending genitourinary clinics. Other populations uncertain.</td>
<td>Not applicable</td>
</tr>
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<td>Scotland</td>
<td>PrEP Short Life Working Group [21]</td>
<td>MSM or transgender person with a rectal STI in preceding 12 months or reporting condomless penetrative anal sex with 2 or more partners in preceding 12 months and anticipated to continue, individuals with HIV-infected partner with detectable viral load or those at high risk of HIV infection as deemed by specialist clinician</td>
<td>Implemented summer 2017</td>
<td>1,700 (range 1,500 to 1,900) [20]</td>
<td>Not available</td>
</tr>
<tr>
<td>Wales</td>
<td>Guidelines by Public Health Wales (not yet available online)</td>
<td>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</td>
<td>Three-year study launched on July 17th, 2017; no limit on the number of participants</td>
<td>Around 560 (range 480-620)</td>
<td>Not available</td>
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</tbody>
</table>

1 as of July 2017, unless indicated otherwise; 2 personal communication Darrell Tan; 3 personal communication Edwina Wright, Iryna Zablotska-Manos, Andrew Grulich; 4 personal communication Bea Vuylsteke; 5 personal communication Anouk Urbanus and Silke David; 6 personal communication Michelle Hanlon; 7 personal communication Sofia Ribeiro; 8 personal communication Sheena McCormack, John Saunders, analysis of eligible population done by Sarika Desai; 9 personal communication with the Scottish National PrEP Implementation and Monitoring Group; 10 personal communication Adam Jones.

for in the setting of incident HIV infection with associated high-level viremia, particularly in partially adherent persons. However, this risk appears to be low: in a meta-analysis, resistance mainly occurred in those starting PrEP during acute (unrecognized) HIV infection [42], underscoring the importance excluding those who are viremic prior to the initiation of PrEP. Excluding those who started PrEP during acute infection, mutations were detected among five of 160 (3.1%) seroconvertors assigned to TDF/FTC in five studies, using standard genotyping, and all were M184I/V mutations. Only one of these five cases was likely to have selected the mutation due to PrEP use; the other four cases had no detectable drug levels at seroconversion [70]. Among those starting PrEP during acute infection (n=17 in five studies), mutations were detected in eight persons (47%). Moreover, data suggest that the vast majority of HIV infections that occur in PrEP users are due to medication nonadherence, and newly diagnosed patients found to have a drug-resistant strain, may have been infected with a resistant virus, or have selected drug-resistance by using PrEP after infection. However, there are three case reports of acute HIV infections among PrEP users who had protective TDF/FTC levels at the time they became infected [71-73]. In two of the cases, drug-resistant virus was transmitted, but in the third case, a sexually active MSM became infected with pan-sensitive virus. These data suggest that in rare cases, PrEP alone may not be 100% protective, though efficacy in those using the medication consistently has exceeded 90% for all populations studied in clinical trials.

Adherence

Adherence is the primary factor moderating the impact of PrEP on HIV acquisition [42]. Hence, maintenance of consistent adherence has an impact on the cost per infection averted [74, 75]. The pharmacology of TDF/FTC suggests that there may be more “forgiveness” (efficacy in the setting of occasional missed doses) for MSM and transgender women whose HIV exposure mode is via anal intercourse, because of increased TDF/FTC rectal mucosal concentrations, compared to women exposed heterosexually [76]. A post-hoc analysis of the iPREX study found that none of the individuals whose tenofovir-diphosphate concentrations in dried blood spots were consistent with using the medication at least four times a week became HIV-infected [77, 78]. However, in the real world retention in PrEP care may be a challenge. One study of PrEP utilization in clinics in three mid-sized US cities found that retention in PrEP care was suboptimal, with only 57% of patients retained in PrEP care at 6 months after initiation. Among those patients retained in care at 6 months, the proportion of patients with optimal adherence for the prior month ranged from 33 to 77%, suggesting a need for interventions to support adherence in real-world clinical settings [79].

It is possible that tailored PrEP use modalities improve adherence. Event-driven PrEP (two pills within 24 hours of an exposure and a pill a day for the 2 days following) was highly
effective in the Ipergay study for MSM [30], and was preferred by 27% of participants when offered the choice between daily and event-driven use [80]. This approach might improve cost-effectiveness as compared to daily PrEP, as fewer pills would generally be needed [75]. More data on the effectiveness of event-driven PrEP are needed, because the Ipergay study is the sole efficacy study of this approach, and the mean number of pills taken per month was 15. A subanalysis in a small group provided proof of efficacy in those having infrequent sexual contact and thus using PrEP less frequently [81]. Event-driven PrEP is currently offered in demonstration projects in Amsterdam and Antwerp, and in Canada and France [82-84].

**Risk compensation, behavior and sexually transmitted infection**

Concerns have been raised that PrEP provision will induce risk compensation, that is, PrEP users will engage in more CAS if they perceive that the medication is protective. However, increases in sexual risk have antedated PrEP availability. Increasing condomless sex, STI and HIV spread among MSM began after effective antiretroviral drugs became widely available in 1996 and HIV was no longer considered a deadly disease [85-87]. Sexual risk compensation has not been universal, for example, after circumcision, men in Kenya reduced risky sexual behavior [88].

The potential decreased use of condoms by PrEP users perceiving decreased HIV acquisition risk may be associated with increased risk for acquiring bacterial STI, which could potentiate HIV transmission in non-adherent PrEP users, in addition to causing STI-related morbidities [89]. The possibility exists that increasing rates of bacterial STI observed among MSM [90, 91] may be associated with increased PrEP use [92]. However, the earliest rises in incident bacterial STI preceded the availability of PrEP by several years in those areas where PrEP has become widely available, and rising STI incidence has also been observed in regions where PrEP was not been made widely available. So the observed changes in STI epidemiology in the PrEP era are complex and multifactorial.

Most of the early PrEP clinical trials did not report risk compensation [29, 30, 90], but because participants were usually unaware if they received placebo or active medication, and received enhanced counseling, the generalizability of these findings to real-world settings may be limited.

The PrEP demonstration projects and observational studies that are currently underway [93] will be more informative about risk compensation in real-life settings. Preliminary results from these projects and studies are conflicting [39, 55, 78, 94-96]. The fact that routine and frequent STI screening and behavioral counseling are part of comprehensive care for PrEP users might explain the discrepancy between trends in risk behavior and STI. On one hand,
frequent STI screening might increase early detection and treatment of asymptomatic STI, and prevent onward transmission, in particular when PrEP programs attract a group previously not seen in sexual health clinics. [85]. On the other hand, ascertainment bias may also be playing a role in the increase in STI detection in people who might not regularly present for routine screening. It has been demonstrated that STI increase might lag behind an increase in risk behavior [86]. The maximum follow-up time in the published studies was 1.4 years and this might be too short to observe an effect on STI incidence. Interestingly, estimates from modeling studies suggest that risk compensation is unlikely to decrease the preventive impact of PrEP, and one study even suggested that PrEP might result in a decrease in STI [97, 98].

Although most PrEP studies excluded MSM with hepatitis C virus (HCV) infection, tested only a subset of the participants or did not report on HCV infection, both prevalent HCV infections at PrEP start (5%) and incident HCV infections (range: 0.7-1.3/100 person-years) while using PrEP have been documented [12, 29, 30, 99, 100]. These rates are higher than previously described in HIV-uninfected MSM [101-103], but data on temporal changes in HCV incidence among PrEP users are lacking. MSM who were HCV-positive at PrEP start in the Netherlands were infected with HCV strains already circulating among HIV-infected MSM, suggesting an overlap between sexual networks of HIV-uninfected and HIV-infected MSM [12]. PrEP use is likely to increase this overlap, which might result in expanding epidemics of HCV and other STI that are more frequent among HIV-infected MSM than among HIV-uninfected men [104].

Finally, especially in regions where PrEP was recently implemented, early adopters are the first to use PrEP and future PrEP users might behave differently. Hence, continued follow-up is required to assess the long-term effects of PrEP use on STI incidence and whether risk compensation results in a lower net effect of PrEP on HIV incidence. Importantly, risk compensation in HIV-infected MSM and HIV-uninfected MSM not on PrEP, who now live and have sex in a world with PrEP and non-PrEP using partners, might also contribute to changing patterns of STI and HIV spread, and should be closely monitored. A recent study found indications, based on national cross-sectional behavioral surveys among MSM in the period 2004-2014, that PrEP’s introduction and scale-up may be accelerating pre-existing trends of increasing STI [105]. These data suggest that frequent STI screening, including HCV, should be offered to all PrEP users, and risk reduction measures, including the role of condom use in preventing STI should be discussed.

**Pre-exposure prophylaxis as part of comprehensive prevention measures**

Provision of PrEP offers an opportunity to integrate STI care and address sexual and psychosocial healthcare relevant for prevention of HIV and other STI. Innovative ways to
integrate STI and PrEP-related care could offer promising approaches to addressing STI among persons who use PrEP. The Dean Street Express Clinic in London, United Kingdom [99], offers a service that helps clients obtain PrEP, either by purchasing the medications at retail prices at the clinic or by ordering these medications online at lower cost, and provides free HIV and STI testing and clinical monitoring for individuals who use PrEP. These services are provided in an efficient, client-centered manner and include self-administered STI tests and rapid reporting of test results using mobile technology, with the goal of minimizing barriers to entry and retention in STI and PrEP care [106]. In Oakland, California, a program that was specifically designed to provide PrEP and affirming sexual health services for young MSM, which included flexible clinic hours and other client-centered features to create a “clinic without walls,” was associated with high utilization of STI services and PrEP; 91% of 262 HIV-uninfected youth in the program who were offered PrEP elected to initiate it [107]. In addition to innovative ways to integrate STI and PrEP care, provision of PrEP in STI clinics with more traditional infrastructure could represent an additional strategy to optimize STI testing and treatment for persons using PrEP. This approach resulted in successful provision of PrEP and STI-related care to MSM at an STI clinic in San Francisco as part of a demonstration project [55]. However, some STI clinics may lack the infrastructure or budget for providing the longitudinal care that accompanies PrEP provision, so the scale-up may require restructuring of and extra budget for some of these clinics in order to implement PrEP successfully.

Similar to STI, behavioral health conditions (e.g. depression, anxiety, and substance use disorders) are prevalent among persons who may benefit from PrEP and among those who have initiated PrEP [80, 108, 109], so provision of PrEP also offers an opportunity to address these conditions. In a study of the safety and acceptability of PrEP among black MSM in three US cities (HIV Prevention Trials Network Study 073), representing a population with high rates of new HIV infections, 30% of participants reported behavioral health co-morbidities at enrollment [110]. Behavioral health conditions have also been associated with unplanned discontinuations of PrEP [111]. Ensuring access to effective behavioral healthcare could support persistence with PrEP and thus increase its effectiveness. Additionally, MSM who are candidates for PrEP may often use recreational drugs, and ideally comprehensive PrEP programs will address this issue, since “chemsex” can lead to high-risk sexual behavior, many adverse health consequences and nonadherence [29, 30, 80, 112, 113].

Cost-effectiveness of pre-exposure prophylaxis

In resource-rich settings, PrEP is currently a costly intervention, as annual medication costs exceed $10,000 per person [94]. Given budgetary constraints, public health programs and healthcare insurers will need to consider whether investing in PrEP represents good value, despite its cost. Studies that have modeled the cost-effectiveness of implementing PrEP in
resource-rich settings have produced variable conclusions, depending on the populations included in these models and the assumptions underlying model development. For example, modeling studies focused on MSM in the Netherlands, Australia, and the United States have found that PrEP is likely to be cost-effective if it is used by subpopulations of MSM who are at highest risk for acquiring HIV\(^7\)\(^5\),\(^1\)\(^1\)\(^4\),\(^1\)\(^1\)\(^5\). In contrast, a study that modeled the cost-effectiveness of PrEP use in the United Kingdom suggested that the use of PrEP for MSM during periods of CAS is not cost-effective at current antiretroviral prices, but it would become cost-effective if drug prices would be reduced\(^\cite{116}\). Use of event-driven PrEP by individuals with occasional HIV exposures could decrease the medication costs associated with implementing PrEP, as was modeled in the Netherlands\(^\cite{75}\). However, an economic evaluation of the use of event-driven PrEP in France, based on data from the Ipergay study, found that event-driven PrEP might not be cost-effective despite its high efficacy without substantial reductions in the price of TDF/FTC\(^\cite{117}\). Importantly, results from these cost-effectiveness analyses need to be interpreted in light of methodological differences and limitations, including limited data on the effectiveness of PrEP, long-term medication adherence, and risk compensation when used outside of controlled studies, so further economic assessments of PrEP will be informative. The recent approval of generic TDF/FTC for use as PrEP in the U.S. could alter cost considerations significantly, but the price of the medication has not yet been announced.

**Healthcare providers and pre-exposure prophylaxis**

Effective scale-up of PrEP in resource-rich settings will require the engagement of large numbers of healthcare providers. In the United States, for example, there are an estimated 1.2 million individuals who are likely to benefit from using PrEP\(^\cite{4}\), which means that there will be need of thousands of PrEP providers to meet demand. However, in studies of frontline clinicians, many providers have indicated barriers to prescribing PrEP, including concerns about the efficacy, safety, and cost of PrEP\(^\cite{118, 119}\), about practical barriers to prescribing PrEP, and concerns about people’s financial barriers to accessing PrEP\(^\cite{118, 119}\). A recent survey of primary care providers affiliated with a large academic medical center in the Southeastern United States found that even though 78% of clinicians provided care to MSM, 83% of these clinicians had not prescribed PrEP, citing lack of knowledge (60%) and comfort (42%) as barriers to providing PrEP; a majority (56%) perceived that they had not encountered any patient with indications for PrEP\(^\cite{120}\). They indicated that they would be more likely to prescribe PrEP with additional training, reference materials, and access to consultations with infectious disease specialists by phone or pager.

Pre-exposure prophylaxis access could thus be expanded by engaging clinicians through effective training interventions. These interventions may be most effective if they summarize efficacy and safety data for PrEP, provide locally-tailored guidance for overcoming financial barriers to accessing PrEP, and connect clinicians with expert colleagues who can
provide real-time clinical guidance. Busy clinicians have also indicated that they would be more motivated to prescribe PrEP if they had access to nonclinician health system navigators, who could assist clinicians in helping patients to access financial assistance programs or delivering behavioral counseling \cite{121}. Additional studies have found that a lack of consensus about which clinicians should be primarily responsible for prescribing PrEP (i.e. specialists or generalists), could also contribute to the slow uptake of PrEP in the United States \cite{122, 123}. To avoid overburden of healthcare providers, innovative models for delivering PrEP care are needed, e.g. community-based services \cite{124}. A recent study demonstrated the feasibility of a pharmacist-led, community-based PrEP clinic \cite{125}. Other examples can be found in chronic disease management applied to other health conditions (e.g. diabetes), such as self-management or community-based programs. A home-based PrEP support system, including self-testing for HIV and STI was found to be acceptable among participants and healthcare providers in a recent pilot study \cite{126}.

Because providers from a variety of training backgrounds could successfully prescribe PrEP with appropriate training, motivation, and support, efforts to disseminate examples of successful PrEP provision by colleagues with diverse professional roles (e.g. infectious diseases specialists \cite{99}, primary care clinicians \cite{127}, and STI clinicians \cite{55}) might encourage a greater number of providers to consider PrEP as part of their clinical purview.

Another barrier to implementing PrEP is that providers may miss opportunities to identify persons at risk for HIV acquisition, because many clinicians (outside of STI specialty clinics) do not routinely conduct comprehensive sexual health assessments. One innovative strategy to help providers in completing these assessments includes the use of patient-reported outcomes to collect information about HIV risk behaviors, such as with computer tablets in clinic waiting rooms, or with brief risk prediction tools during clinical encounters \cite{128, 129}. A qualitative study with black MSM in New York City to assess barriers to utilizing PrEP found that participants felt mistrustful of and disempowered by healthcare providers when discussing sexual health histories and HIV prevention options, and that a recommendation to use PrEP would not be sufficiently compelling for them to initiate PrEP \cite{130}. These results indicate a need to train providers in how to conduct patient-centered, nonjudgmental sexual health histories and discussions about PrEP, which would ideally include elements of rigorously tested, culturally-tailored prevention messages about PrEP for disenfranchised populations \cite{60} and clear communication of acceptance towards LGBT individuals.
CONCLUSIONS

Pre-exposure prophylaxis uptake is continuing to grow (summarized in table 1), but challenges remain, including concerns about risk compensation and increases in STI, costs, suboptimal awareness of PrEP in communities who might benefit from its use, and limited engagement in PrEP care by providers. Demonstration projects have introduced the concept of PrEP among those who might benefit from PrEP, and also enabled public health professionals and clinicians around the world to become familiar with PrEP implementation, and to move from being earlier adopters to being key opinion leaders and role models in implementing PrEP, which has enhanced the diffusion of this novel strategy in the United States. However, in Europe and Australia implementation of PrEP is patchy and not yet occurring on a wide scale, suggesting a need for more coordinated efforts at scale-up.

As daily oral TDF/FTC, “PrEP 1.0,” becomes a more established modality for HIV prevention, studies are underway to develop novel modalities for chemoprophylaxis (e.g. long-acting injectables) that could potentially mitigate any adherence challenges that taking daily or event-driven pills may present for some individuals. However, none of the new modalities will be ready for regulatory approval for several years, and there are no guarantees that they will be more effective than TDF/FTC in clinical use. Thus, given that almost 2 million new HIV infections are still occurring each year [3], wider implementation of TDF/FTC for PrEP is warranted. As the rates of new infections continue at alarming rates among specific key populations, for example transgender persons in Europe and the United States and black MSM in the United States, and these populations face numerous social, structural, and economic barriers to accessing PrEP and being retained in PrEP care [131], any efforts at implementing PrEP must be culturally-tailored to engage and support these individuals and must address persistent inequities (Table 2).

A causal relationship between PrEP and increasing rates of STI, which were already present before PrEP implementation, has not been clearly established, but data suggest risk compensation is taking place. More data from demonstration projects and observational studies in implementation settings, collected over a longer period of follow-up are needed to clarify the impact of PrEP on STI and HIV trends in real-life settings. More information on uptake, adherence and effectiveness of event-driven PrEP can guide PrEP implementation programming. Also, as behavioral measurements differ across studies, the use of uniform questions about risk compensation worldwide would help to interpret and compare future outcomes of studies.

In summary, PrEP could have a dramatic impact on the HIV epidemic and HIV-related disparities in resource-rich settings if it is deployed in an effective, equitable, and sustainable
manner. This will require coordinated efforts and firm commitment from public health authorities, funding agencies, researchers, clinicians, and patient advocates operating under diverse local constraints. Concerns about the cost-effectiveness of PrEP, if it is not deployed in a judicious manner, cannot be dismissed in an era of widespread budgetary constraints, even among resource-rich nations. Thus strategies are needed to increase optimal PrEP use among those persons at greatest risk for HIV acquisition and also to determine when it might be appropriate to transition from PrEP to less costly safer sex approaches. In addition, the potential future impact of PrEP on STI epidemics cannot be dismissed. If, however, PrEP can be implemented in a manner that is fiscally sound and integrated with comprehensive preventive care, using the opportunity to address concomitant STI and behavioral health concerns, then investments in PrEP could offer substantial financial and public health value.

Table 2. Key Elements of Successful PrEP Implementation Programs

- Knowledge of local epidemiology, patterns of HIV transmission
- Determination of which facilities are best equipped for PrEP delivery
- Reimbursement of costs of monitoring, testing and medication
- Differentiated service delivery
- Community engagement/Buy-in from key opinion leaders
- Providers trained in the client-centered delivery
- Institutional leadership
- Staff trained to assist patients in navigating local health insurance system
- Access to related health services, e.g. management of STI, harm reduction programs for people who use drugs and behavioral health interventions
- Community education
- Education of potential referral sources

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CONFLICTS OF INTEREST

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