Published in final edited form as:

AIDS. 2017 October 23; 31(16): 2179–2191. doi:10.1097/QAD.0000000000001627.

Preexposure prophylaxis for men who have sex with men and transgender persons in early adopting countries: a narrative review

E. Hoornenborg^{1,*}, D.S. Krakower^{*,3,4}, M. Prins^{1,2}, and K.H. Mayer^{3,4}

¹Public Health Service of Amsterdam, Department of Infectious Diseases, Amsterdam, the Netherlands ²Academic Medical Center, Department of Infectious Diseases, Center for Immunity and Infection Amsterdam (CINIMA), University of Amsterdam, the Netherlands ³Beth Israel Deaconess Medical Center, Department of Medicine, Division of Infectious Diseases, Harvard Medical School, Boston, Mass, USA ⁴The Fenway Institute, Fenway Health, Boston, Mass, USA

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

Corresponding author and requests for reprints: Elske Hoornenborg, Public Health Service Amsterdam, department of infectious diseases, Nieuwe Achtergracht 100, 1018WT Amsterdam, The Netherlands, Phone: +31205555193, ehoornenborg@ggd.amsterdam.nl.

*Both authors contributed equally

Conflicts of interest: EH: my institute received financial reimbursement for time spent serving on advisory boards of Gilead Sciences. We received the study drug for the Amsterdam PrEP study from Gilead Sciences. KM received unrestricted research grants from ViiV Healthcare and Gilead Sciences. DK participated in research funded by unrestricted research grants from Gilead Sciences. Maria Prins reports no conflicts of interests.

Author's contributions: Paper outline, determination of structure, critical revision and editing of the manuscript: all authors. Drafting of the manuscript: all authors.

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

PrEP in the United States

In 2012, the United States (U.S.) became the first nation in which PrEP had been granted regulatory approval. PrEP uptake has been gradual in the U.S., but studies have found that rates of new PrEP prescriptions have increased steeply in recent years [8, 9]. About 100,000 started PrEP (table 1). Of the 80,000 individuals who initiated PrEP from 2012 through 2015, about 75% were men and nearly 75% were white, which did not reflect the U.S. epidemic, suggesting that racial and gender disparities in PrEP utilization remain [10, 11]. Addressing these disparities is an urgent priority given disproportionately high rates of new HIV infections in the U.S. among people of color [12, 13]. Although few data are available about PrEP use by transgender persons in the U.S., 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 [14]: after implementing a more inclusive health care environment for transgender people, their PrEP utilization increased substantially [14].

Within the U.S., 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 [15]. 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 U.S..

PrEP 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 [16] or event-driven basis [17]. Subsequently, France began rolling out PrEP in January 2015, after temporary regulatory approval, and reported having around 3400 people using PrEP by mid-2017 [18]. 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 [19, 20]. 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 [21]. 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 [22, 23]. This may be contributing to decreases in HIV infections as observed in London [24].

PrEP in Canada

One of the sites for the Ipergay study was in Quebec [17] 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[25]. A clinic in Montreal has more than 1000 people on daily and event-driven PrEP [26].

PrEP 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 EPIC-NSW program, in New South Wales [27], the PREPX program in Victoria and South Australia [28]; and Q PrEP'd program in Queensland [29]. 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 [30]. 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

1. Identifying appropriate PrEP 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 [31]. 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 [32], 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 U.S., black MSM represent a group at very high risk of acquiring HIV infection [33-35], however, PrEP uptake has been disproportionately low compared to non-black MSM [36-38] 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 health care access, and distrust of culturally-insensitive health care systems [39, 40]. Some data suggest that 85% of the infections among migrant MSM in Europe occur post-

migration [41], but there is limited evidence [42] about PrEP uptake among specific racial and ethnic MSM subgroups in Europe and Australia. Transgender women also bear a disproportionate HIV burden. In the U.S., estimated HIV prevalence among transgender women is 22% [43] and in Europe, limited studies among transgender sex workers also suggest increased HIV risk [44, 45]. However, the number of transgender persons in the major PrEP studies (0 to 29) [2, 17, 46] has been too small to draw definitive conclusions about PrEP efficacy for transgender people [47, 48]. 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 [16], and the Ipergay [17] and US PrEP Demo Project [46] 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 [49] and subsequent eligibility for PrEP [50]. Some providers have applied this score in their clinical practice [51], 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 [52, 53].

2. Clinical Monitoring

After many thousands of person-years of experience with PrEP, side effects are common (39% in the iPREX 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 [54]. Clinical trials and a systematic review found that most adverse events did not significantly differ among individuals using TDF-based PrEP versus placebo [2, 55-58]. Since TDF can cause small, albeit reversible, reductions in estimated glomerular filtration rate (eGFR) [2, 55, 56], 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 [59, 60]; routine bone mineral densitometry 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 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 [32], 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 5 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 [61]. 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 non-adherence, 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 [62-64]. 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.

3. Adherence

Adherence is the primary factor moderating the impact of PrEP on HIV acquisition [32]. Hence, maintenance of consistent adherence has an impact on the cost per infection averted [65, 66]. 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 [67]. 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 [68, 69]. However, in the real world retention in PrEP care may be a challenge. One study of PrEP utilization in clinics in 3 mid-sized U.S. 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 [70].

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 two days following) was highly effective in one the Ipergay study for MSM[17], and was preferred by 27% of participants when offered the choice between daily and event-driven use [71]. This approach might improve cost-effectiveness as compared to daily PrEP, as fewer pills would generally be needed [66]. 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[72]. Event-driven PrEP is currently offered in demonstration projects in Amsterdam and Antwerp, and in Canada and France [73-75].

4. Risk compensation, Behavior and STI

Concerns have been raised that PrEP provision will induce risk compensation, i.e. 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 [76-78]. Sexual risk compensation has not been universal, e.g. after circumcision, men in Kenya reduced risky sexual behavior [79].

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 [80]. The possibility exists that increasing rates of bacterial STI observed among MSM [81, 82] may be associated with increased PrEP use [83]. 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 had 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 [16, 17, 84], 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 [85] will be more informative about risk compensation in real-life settings. Preliminary results from these projects and studies are conflicting [28, 46, 69, 86-88]. 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 [77]. 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 [89, 90].

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 [16, 17, 91-93]. These rates are higher than previously described in HIV-uninfected MSM [94-96], 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 [93]. 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 [97].

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 [98]. 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.

5. PrEP as part of comprehensive prevention measures

Provision of PrEP offers an opportunity to integrate STI care and address sexual and psychosocial health care 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, U.K. [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 [99]. 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 [100]. 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 [46]. 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 [71, 101, 102], 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 U.S. 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 [103]. Behavioral health conditions have also been associated with unplanned discontinuations of PrEP [104]. Ensuring access to effective behavioral health care 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 non-adherence [16, 17, 71] [105, 106].

6. Cost-effectiveness of PrEP

In resource-rich settings, PrEP is currently a costly intervention, as annual medication costs exceed \$10,000 per person [107]. Given budgetary constraints, public health programs and health care 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 U.S. 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 [66, 108, 109]. In contrast, a study that modeled the cost-effectiveness of PrEP use in the U.K. 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 [110]. 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 [66]. 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 [111]. 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.

7. Health Care Providers and PrEP

Effective scale-up of PrEP in resource-rich settings will require the engagement of large numbers of health care providers. In the U.S., for example, there are an estimated 1.2 million individuals who are likely to benefit from using PrEP [4], which means that there will need to be 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 [112, 113], about practical barriers to prescribing PrEP, and concerns about people's financial barriers to accessing PrEP [112, 113]. A recent survey of primary care providers affiliated with a large academic medical center in the Southeastern U.S. 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 patients with indications for PrEP [114]. They indicated that they would be more likely to prescribe PrEP with additional training, reference materials, and access to consultations with infectious diseases specialists by phone or pager.

PrEP 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 non-clinician health system navigators, who could assist clinicians in helping patients to access financial assistance programs or delivering behavioral counseling [115]. 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 U.S.[116, 117]. To avoid over-burden of health care providers, innovative models for delivering PrEP care are needed, e.g. community-based services [118]. A recent study demonstrated the feasibility of a pharmacist-led, community-based PrEP clinic [119]. 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 health care providers in a recent pilot study [120].

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 [91], primary care clinicians [121], and STI clinicians [46]) 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 [122, 123]. 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 health care 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 [124]. 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 [51] and clear communication of acceptance towards LGBT individuals.

Conclusions

PrEP 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 U.S.. 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, e.g. transgender persons in Europe and the U.S. and Black MSM in the U.S., and these populations face numerous social, structural, and economic barriers to accessing PrEP and being retained in PrEP care [125], 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 as well as 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.

Acknowledgments

the authors wish to acknowledge the following persons for providing information regarding PrEP in their countries: Silke David, Sarika Desai, Andrew Grulich, Michelle Hanlon, Adam Jones, Sheena McCormack, Rak Nandwani, Sofia Ribeiro, John Saunders, Anouk Urbanus, Bea Vuylsteke, Edwina Wright, and Iryna Zablotsky-Manos.

References

1. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. *AIDS*. 2013; 27(3):447–458. [PubMed: 23296196]
2. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010; 363(27):2587–2599. [PubMed: 21091279]
3. UNAIDS. [accessed 03-08-2017] New HIV infections. 2017. <http://www.unaids.org>
4. Smith DK, Van Handel M, Wolitski RJ, Stryker JE, Hall HI, Prejean J, et al. Vital Signs: Estimated Percentages and Numbers of Adults with Indications for Preexposure Prophylaxis to Prevent HIV Acquisition--United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2015; 64(46):1291–1295. [PubMed: 26606148]
5. Mera RM, S, Palmer B, Mayer G, Magnuson D, Rawlings K. Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). Presented at the International Aids Conference, Durban. 2016 Abstract TUAX0105LB.
6. AVAC. [accessed 03-08-2017] <http://www.avac.org/resource/regulatory-status-tdfttc-prep>
7. World Health Organization. [accessed 03-08-2017] 2017. <http://www.euro.who.int/en/health-topics/communicable-diseases/hiv-aids/policy/policy-guidance-for-key-populations-most-at-risk2/men-who-have-sex-with-men-msm>
8. Wu H, Mendoza MC, Huang YA, Hayes T, Smith DK, Hoover KW. Uptake of HIV Preexposure Prophylaxis Among Commercially Insured Persons--United States, 2010-2014. *Clin Infect Dis*. 2016
9. Mera, R., McCallister, S., Palmer, B., Mayer, G., Magnuson, D., Rawlings, K. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States (2013-2015). Abstract TUAX0105LB
10. Bush, S., Magnuson, D., Rawlings, K., Hawkins, T., McCallister, S., Mera Giler, R. ASM Microbe Conference 2016. Boston: Jun 16-20. 2016 Racial Characteristics of FTC/TDF for Pre-exposure Prophylaxis (PrEP) Users in the US.
11. Bezemer D, van SA, Lukashov VV, van der Hoek L, Back N, Schuurman R, et al. Transmission networks of HIV-1 among men having sex with men in the Netherlands. *AIDS*. 2010; 24(2):271–282. [PubMed: 20010072]
12. Nwangwu-Ike N, Hernandez AL, An Q, Huang T, Hall HI. The Epidemiology of Human Immunodeficiency Virus Infection and Care among Adult and Adolescent Females in the United States, 2008-2012. *Womens Health Issues*. 2015; 25(6):711–719. [PubMed: 26316020]
13. Wejnert C, Hess KL, Rose CE, Balaji A, Smith JC, Paz-Bailey G. Age-Specific Race and Ethnicity Disparities in HIV Infection and Awareness Among Men Who Have Sex With Men--20 US Cities, 2008-2014. *J Infect Dis*. 2016; 213(5):776–783. [PubMed: 26486637]
14. Radix, A., Carneiro, P., Stephanos, S., Mosher, S., Meacher, P., Belkind, U., et al. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Transgender patients at risk: ensuring access to PrEP in a NYC community health centre. Abstract WEACO202

15. Oldenburg CE, Perez-Brumer AG, Hatzenbuehler ML, Krakower D, Novak DS, Mimiaga MJ, et al. State-level structural sexual stigma and HIV prevention in a national online sample of HIV-uninfected MSM in the United States. *AIDS*. 2015; 29(7):837–845. [PubMed: 25730508]
16. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016; 387(10013):53–60. [PubMed: 26364263]
17. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med*. 2015; 373(23):2237–2246. [PubMed: 26624850]
18. Molina JM. One-year experience with pre-exposure prophylaxis (PrEP) in France with TDF/FTC. Presented at IAS2017, abstract WEPEC0939.
19. European Medicines Agency. [accessed 03-08-2017] First medicine for HIV pre-exposure prophylaxis recommended for approval in the EU. 2017. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002578.jsp&=WC0b01ac058004d5c1
20. HIV Scotland. [accessed 03-08-2017] 2017. <http://www.hivscotland.com/our-work/prep-in-scotland/>
21. NHS England. [accessed 03-08-2017] 2017. <https://www.england.nhs.uk/2016/12/hiv-prevention-programme/>
22. AIDES Flash PrEP survey. 2016. <http://www.aides.org/FlashPrEPinEurope>
23. ECDC; accessed 03-08-2017. 2017. <http://ecdc.europa.eu/en/publications/Publications/pre-exposure-prophylaxis-hiv-prevention-europe.pdf>
24. Delpech, V. Presented at the HepHIV conference. Malta: Jan. 2017 Test and link to care: How do we measure our success?.
25. Rajchgot J, Siemieniuk RA, Sivachandran N, Murphy P, Sharp A, Cicci A, et al. Feasibility of HIV Pre-Exposure Prophylaxis as Part of Routine Care in Toronto, Canada. *J Acquir Immune Defic Syndr*. 2016; 72(3):e80–81. [PubMed: 27035886]
26. Zoë Greenwald, MvB, Gabriel, Girard, Alexandre, Goyette, Louise, Charest, Stéphane, Lavoie, Danièle, Longpré, Réjean, Thomas. Who opts for Daily versus On-Demand Pre-Exposure Prophylaxis? presented at Adherence. Jun.2017
27. EPIC-NSW. [accessed 03-08-2017] 2017. <https://epic-nswstudy.org.au/>
28. Lal LA, J, Murphy D, Fairly CK, Stooze M, Roth N, Moore R, Tee BK, Puratmaja N, Anderson P, Leslie D, Grant R, de Wit J, Wright E. Medication Adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users: interim results from the Victorian Preexposure Prophylaxis Demonstration Project. *AIDS*. 2017 accepted.
29. Q PrEP'd. [accessed at 03-08-2017] 2017. <http://www.comeprepd.info/qprepd-project/>
30. Edwina ea, Wright. Health systems and study design features permitting rapid enrolment of individuals at high-risk of HIV acquisition into a pre-exposure prophylaxis study in Melbourne, Victoria, Australia. Presented at IAS2017, abstract WEAC0104.
31. Golub, SP., S, Hilley, A., Pachankis, J., Radix, A. BRIEF BEHAVIORAL INTERVENTION INCREASES PREP DRUG LEVELS IN A REAL-WORLD SETTING; Presented at the Conference on Retroviruses and Opportunistic Infections (CROI); 2017. Abstract number 965
32. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'reilly KR, Koechlin FM, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS*. 2016; 30(12):1973–1983. [PubMed: 27149090]
33. Hall HI, Song R, Tang T, An Q, Prejean J, Dietz P, et al. HIV Trends in the United States: Diagnoses and Estimated Incidence. *JMIR Public Health Surveill*. 2017; 3(1):e8. [PubMed: 28159730]
34. Millett GA, Peterson JL, Flores SA, Hart TA, Jeffries WLt, Wilson PA, et al. Comparisons of disparities and risks of HIV infection in black and other men who have sex with men in Canada, UK, and USA: a meta-analysis. *Lancet*. 2012; 380(9839):341–348. [PubMed: 22819656]

35. Wejnert C, Hess KL, Rose CE, Balaji A, Smith JC, Paz-Bailey G, et al. Age-Specific Race and Ethnicity Disparities in HIV Infection and Awareness Among Men Who Have Sex With Men--20 US Cities, 2008-2014. *J Infect Dis.* 2016; 213(5):776–783. [PubMed: 26486637]
36. Cahill S, Taylor SW, Elsesser SA, Mena L, Hickson D, Mayer KH. Stigma, medical mistrust, and perceived racism may affect PrEP awareness and uptake in black compared to white gay and bisexual men in Jackson, Mississippi and Boston, Massachusetts. *AIDS Care.* 2017:1–8.
37. Eaton LA, Matthews DD, Driffin DD, Bukowski L, Wilson PA, Stall RD, et al. A Multi-US City Assessment of Awareness and Uptake of Pre-exposure Prophylaxis (PrEP) for HIV Prevention Among Black Men and Transgender Women Who Have Sex with Men. *Prev Sci.* 2017
38. Kuhns LM, Hotton AL, Schneider J, Garofalo R, Fujimoto K. Use of Pre-exposure Prophylaxis (PrEP) in Young Men Who Have Sex with Men is Associated with Race, Sexual Risk Behavior and Peer Network Size. *AIDS Behav.* 2017
39. Millett GA, Flores SA, Peterson JL, Bakeman R. Explaining disparities in HIV infection among black and white men who have sex with men: a meta-analysis of HIV risk behaviors. *AIDS.* 2007; 21(15):2083–2091. [PubMed: 17885299]
40. Sullivan PS, Rosenberg ES, Sanchez TH, Kelley CF, Luisi N, Cooper HL, et al. Explaining racial disparities in HIV incidence in black and white men who have sex with men in Atlanta, GA: a prospective observational cohort study. *Ann Epidemiol.* 2015; 25(6):445–454. [PubMed: 25911980]
41. Alvarez-del Arco IF, D., Monge, S., et al. Presented at the European AIDS Clinical Society meeting. Barcelona: 2015. HIV acquisition among migrants living in Europe Results from aMASE.
42. Fakoya I, Alvarez-del Arco D, Woode-Owusu M, Monge S, Rivero-Montesdeoca Y, Delpech V, et al. A systematic review of post-migration acquisition of HIV among migrants from countries with generalised HIV epidemics living in Europe: implications for effectively managing HIV prevention programmes and policy. *BMC Public Health.* 2015; 15:561. [PubMed: 26085030]
43. Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013; 13(3):214–222. [PubMed: 23260128]
44. van Veen MG, Gotz HM, van Leeuwen PA, Prins M, van de Laar MJ. HIV and sexual risk behavior among commercial sex workers in the Netherlands. *Arch Sex Behav.* 2010; 39(3):714–723. [PubMed: 18815876]
45. Poteat T, Scheim A, Xavier J, Reisner S, Baral S. Global Epidemiology of HIV Infection and Related Syndemics Affecting Transgender People. *J Acquir Immune Defic Syndr.* 2016; 72(3):S210–219. [PubMed: 27429185]
46. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. *JAMA Intern Med.* 2016; 176(1):75–84. [PubMed: 26571482]
47. Sevelius JM, Keatley J, Calma N, Arnold E. 'I am not a man': Trans-specific barriers and facilitators to PrEP acceptability among transgender women. *Glob Public Health.* 2016; 11(7-8): 1060–1075. [PubMed: 26963756]
48. Grant RM, Sevelius JM, Guanira JV, Aguilar JV, Chariyalertsak S, Deutsch MB. Transgender Women in Clinical Trials of Pre-Exposure Prophylaxis. *J Acquir Immune Defic Syndr.* 2016; 72(3):S226–229. [PubMed: 27429187]
49. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States. *J Acquir Immune Defic Syndr.* 2012; 60(4):421–427. [PubMed: 22487585]
50. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. available at <https://www.cdc.gov/hiv/risk/prep/index.html>
51. Calabrese SK, Magnus M, Mayer KH, Krakower DS, Eldahan AI, Gaston Hawkins LA, et al. Putting PrEP into Practice: Lessons Learned from Early-Adopting U.S. Providers' Firsthand Experiences Providing HIV Pre-Exposure Prophylaxis and Associated Care. *PLoS One.* 2016; 11(6):e0157324. [PubMed: 27304883]

52. European AIDS Clinical Society (EACS). European Guidelines for treatment of HIV-positive adults in Europe; Guidelines 8.0.
53. World Health organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.
54. Glidden DV, Amico KR, Liu AY, Hosek SG, Anderson PL, Buchbinder SP, et al. Symptoms, Side Effects and Adherence in the iPrEx Open-Label Extension. *Clin Infect Dis*. 2016; 62(9):1172–1177. [PubMed: 26797207]
55. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012; 367(5): 399–410. [PubMed: 22784037]
56. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013; 381(9883):2083–2090. [PubMed: 23769234]
57. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2013; 64(1):79–86. [PubMed: 23466649]
58. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012; 367(5):423–434. [PubMed: 22784038]
59. Bolland MJ, Grey A, Reid IR. Skeletal health in adults with HIV infection. *Lancet Diabetes Endocrinol*. 2015; 3(1):63–74. [PubMed: 24731663]
60. Tinago W, Cotter AG, Sabin CA, Macken A, Kavanagh E, Brady JJ, et al. Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and negative patients. *AIDS*. 2017; 31(5):643–652. [PubMed: 28060010]
61. Parikh UM, Mellors JW. Should we fear resistance from tenofovir/emtricitabine preexposure prophylaxis? *Curr Opin HIV AIDS*. 2016; 11(1):49–55. [PubMed: 26633640]
62. Grossman, H. HIV Research for Prevention (HIVR4P). Chicago, USA: 2016. Newly Acquired HIV-1 Infection with Multi-Drug Resistant (MDR) HIV-1 in a Patient on TDF/FTC-based PrEP.
63. Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis. *N Engl J Med*. 2017; 376(5):501–502.
64. Hoorneborg E, De Bree GJ. Acute infection with a wild-type HIV-1 virus in PrEP user with high TDF levels. presented at the Conference on Retroviruses and Opportunistic Infections (CROI). 2017 Abstract number 953.
65. Kasaie P, Pennington J, Shah MS, Berry SA, German D, Flynn CP, et al. The Impact of Pre-Exposure Prophylaxis Among Men Who Have Sex With Men: An Individual-Based Model. *J Acquir Immune Defic Syndr*. 2017
66. Nichols BE, Boucher CA, van der Valk M, Rijnders BJ, van de Vijver DA. Cost-effectiveness analysis of pre-exposure prophylaxis for HIV-1 prevention in the Netherlands: a mathematical modelling study. *Lancet Infect Dis*. 2016; 16(12):1423–1429. [PubMed: 27665989]
67. Hendrix CW, Andrade A, Bumpus NN, Kashuba AD, Marzinke MA, Moore A, et al. Dose Frequency Ranging Pharmacokinetic Study of Tenofovir-Emtricitabine After Directly Observed Dosing in Healthy Volunteers to Establish Adherence Benchmarks (HPTN 066). *AIDS Res Hum Retroviruses*. 2016; 32(1):32–43. [PubMed: 26414912]
68. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. 2012; 4(151):151ra125.
69. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014; 14(9):820–829. [PubMed: 25065857]
70. Chan PA, Mena L, Patel R, Oldenburg CE, Beauchamps L, Perez-Brumer AG, et al. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities. *J Int AIDS Soc*. 2016; 19(1):20903. [PubMed: 27302837]

71. Hoorneborg, E., Achterbergh, R., Schim van der Loeff, M., Davidovich, U., Van der Helm, J., Hogewoning, A., Sonder, G., Van Duijnhoven, Y., De Vries, H., Prins, M. Presented at the International Aids Conference. Durban: 2016. Uptake and preference of daily and intermittent pre-exposure prophylaxis (PrEP) in a demonstration project: baseline characteristics and HIV prevention choices made by Dutch MSM. Abstract WEPEC234
72. Antoni ea G. On-demand PrEP with TDF/FTC remains highly effective among MSM with infrequent sexual intercourse: a substudy of the ANRS IPERGAY trial. Presented at IAS. 2017 abstract TUC0102.
73. Molina, JM. Presented at the 21st International AIDS Conference. Durban, South Africa: 2016. PrEP rollout in France. Abstract WEWS080
74. AMPREP study group. Study protocol AMPREP. 2015. Available online at: <http://www.trialregister.nl/trialreg/admin/rctsearch.asp?Term=amprep>
75. De Baetselier I, Reyniers T, Nostlinger C, Wouters K, Fransen K, Crucitti T, et al. Pre-Exposure Prophylaxis (PrEP) as an Additional Tool for HIV Prevention Among Men Who Have Sex With Men in Belgium: The Be-PrEP-ared Study Protocol. JMIR Res Protoc. 2017; 6(1):e11. [PubMed: 28135199]
76. Jansen IA, Geskus RB, Davidovich U, Jurriaans S, Coutinho RA, Prins M, et al. Ongoing HIV-1 transmission among men who have sex with men in Amsterdam: a 25-year prospective cohort study. AIDS. 2011; 25(4):493–501. [PubMed: 21192230]
77. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS. 2004; 18(2):303–309. [PubMed: 15075549]
78. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. JAMA. 2004; 292(2):224–236. [PubMed: 15249572]
79. Wilson NL, Xiong W, Mattson CL. Is Sex Like Driving? HIV Prevention and Risk Compensation. J Dev Econ. 2014; 106:78–91. [PubMed: 26997745]
80. Katz DA, Dombrowski JC, Bell TR, Kerani RP, Golden MR. HIV Incidence Among Men Who Have Sex With Men After Diagnosis With Sexually Transmitted Infections. Sex Transm Dis. 2016; 43(4):249–254. [PubMed: 26967302]
81. Public Health England. Sexually transmitted infections and chlamydia screening in England, 2015. Health Protection Report. 2016; 10(22)
82. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2015. Atlanta: U.S. Department of Health and Human Services; 2016.
83. Alaei K, Paynter CA, Juan SC, Alaei A. Using PrEP, losing condoms? PrEP promotion may undermine safe sex. AIDS. 2016 ePUB ahead of print. doi:10.1097/QAD0000000000001262.
84. Sagaon-Teyssier L, Suzan-Monti M, Demoulin B, Capitain C, Lorente N, Preau M, et al. Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial. AIDS Care. 2016; 28(1):48–55. [PubMed: 26883400]
85. PrEP Watch. [accessed 03-08-2017] 2017. <http://www.prepwatch.org>
86. Marcus JL, Hurley LB, Hare CB, Nguyen DP, Phengrasamy T, Silverberg MJ, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. J Acquir Immune Defic Syndr. 2016; 73(5):540–546. [PubMed: 27851714]
87. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis. 2015; 61(10):1601–1603. [PubMed: 26334052]
88. Montano M, Dombrowski J, Barbee A, Golden M, Khosropour C. Changes in sexual behavior and STI diagnoses among MSM using PrEP in Seattle, WA. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI). 2017 Abstract number 979.
89. Jenness SM, Sharma A, Goodreau SM, Rosenberg ES, Weiss KM, Hoover KW, et al. Individual HIV Risk versus Population Impact of Risk Compensation after HIV Preexposure Prophylaxis Initiation among Men Who Have Sex with Men. PLoS One. 2017; 12(1):e0169484. [PubMed: 28060881]

90. Jenness SM, Weiss KM, Goodreau SM, Gift T, Chesson H, Hoover KW, et al. Incidence of Gonorrhea and Chlamydia Following HIV Preexposure Prophylaxis among Men Who Have Sex with Men: A Modeling Study. *Clin Infect Dis*. 2017
91. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clin Infect Dis*. 2015; 61(10):1601–1603. [PubMed: 26334052]
92. Midgley, L. Presented at the 23th annual conference of BHIVA. Liverpool: 2017. Acute hepatitis C infection in lower risk MSM: an evolving picture. Abstract O24
93. Hoorneborg E, Achterbergh RCA, Schim van der Loeff MF, Davidovich U, Hogewoning A, de Vries HJC, et al. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. *AIDS*. 2017; 31(11):1603–1610. [PubMed: 28657964]
94. Urbanus AT, Van De Laar TJ, Geskus R, Vanhommerig JW, van Rooijen MS, Schinkel J, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995-2010. *AIDS*. 2014; 28(5):781–790. [PubMed: 24832014]
95. Schmidt AJ, Falcato L, Zahno B, Burri A, Regenass S, Mullhaupt B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? *BMC Public Health*. 2014; 14:3. [PubMed: 24393532]
96. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. *Sex Transm Infect*. 2012; 88(7):558–564. [PubMed: 22859499]
97. Malek R, Mitchell H, Furegato M, Simms I, Mohammed H, Nardone A, et al. Contribution of transmission in HIV-positive men who have sex with men to evolving epidemics of sexually transmitted infections in England: an analysis using multiple data sources, 2009-2013. *Euro Surveill*. 2015; 20(15)
98. Chen YH, Snowden JM, McFarland W, Raymond HF. Pre-exposure Prophylaxis (PrEP) Use, Seroadaptation, and Sexual Behavior Among Men Who Have Sex with Men, San Francisco, 2004-2014. *AIDS Behav*. 2016; 20(12):2791–2797. [PubMed: 26983951]
99. Dean Street Clinic. <http://dean.st/prep/>
100. Udoh, I., Myers, J., Frazier, R., Koester, KA., Horwitz, J., Kang Dufour, MS., et al. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Bringing sexy back: PrEP and sexual health services for young urban men who have sex with men. Abstract TUPEE561
101. Defechereux PA, Mehrotra M, Liu AY, McMahan VM, Glidden DV, Mayer KH, et al. Depression and Oral FTC/TDF Pre-exposure Prophylaxis (PrEP) Among Men and Transgender Women Who Have Sex With Men (MSM/TGW). *AIDS and Behavior*. 2016; 20(7):1478–1488. [PubMed: 26078115]
102. Pines HA, Gorbach PM, Weiss RE, Shoptaw S, Landovitz RJ, Javanbakht M, et al. Sexual risk trajectories among MSM in the United States: implications for pre-exposure prophylaxis delivery. *J Acquir Immune Defic Syndr*. 2014; 65(5):579–586. [PubMed: 24378726]
103. Hightow-Weidman, L., Magnus, M., Shoptaw, S., Emel, L., Beauchamp, G., Piwowar-Manning, E., et al. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Significant health comorbidities in Black men who have sex with men presenting for a US PrEP study. Abstract WEPEC240
104. Krakower, D., Maloney, K., Levine, K., Grasso, C., Melbourne, K., Mayer, K. HIV Research for Prevention Conference 2016. Chicago, Illinois: Oct 17-21. 2016 Unplanned Discontinuations of HIV Preexposure Prophylaxis During Clinical Care. Abstract OA16.06
105. Bourne A, Reid D, Hickson F, Torres-Rueda S, Weatherburn P. Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study. *Sex Transm Infect*. 2015; 91(8):564–568. [PubMed: 26163510]
106. Sewell J, Miltz A, Lampe FC, Cambiano V, Speakman A, Phillips AN, et al. Poly drug use, chemsex drug use, and associations with sexual risk behaviour in HIV-negative men who have sex with men attending sexual health clinics. *Int J Drug Policy*. 2017; 43:33–43. [PubMed: 28189979]
107. Panel on Antiretroviral Guidelines for Adults and Adolescents. [Accessed February 13, 2017] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>

108. Schneider K, Gray RT, Wilson DP. A cost-effectiveness analysis of HIV pre-exposure prophylaxis for men who have sex with men in Australia. *Clin Infect Dis*. 2014 Apr; 58(7):1027–34. doi: 101093/cid/cit946 Epub 2014 Jan 2 2014. [PubMed: 24385445]
109. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med*. 2012; 156(8):541–550. [PubMed: 22508731]
110. Cambiano V, Miners A, Dunn D, McCormack S, Gill N, Nardone A, Desai M, Cairns G, Rodger A, Phillips A. IS PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION COST-EFFECTIVE IN MEN WHO HAVE SEX WITH MEN WHO ENGAGE IN CONDOMLESS SEX IN THE UK? Presented at the BASH spring conference. Jun.2015 Abstract O1.
111. Durand-Zaleski, I., Mutuon, P., Charreau, I., Temblay, C., Rojas, D., Chas, J., et al. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Cost effectiveness of on demand PrEP in men who have sex with men (MSM) in the ANRS IPERGAY study. Abstract THAW304
112. Krakower DS, Beekmann SE, Polgreen PM, Mayer KH. Diffusion of Newer HIV Prevention Innovations: Variable Practices of Frontline Infectious Diseases Physicians. *Clin Infect Dis*. 2016; 62(1):99–105. [PubMed: 26385993]
113. Krakower DS, Oldenburg CE, Mitty JA, Wilson IB, Kurth AE, Maloney KM, et al. Knowledge, Beliefs and Practices Regarding Antiretroviral Medications for HIV Prevention: Results from a Survey of Healthcare Providers in New England. *PLoS One*. 2015; 10(7):e0132398. [PubMed: 26146824]
114. Seidelman, J., Clement, M., Okeke, L., McGee, K., Murthy, B., Johnston, B., et al. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Are primary care providers in the southeastern U.S. ready to prescribe PrEP?. Abstract WEPEC233
115. Nguyen, T., Agins, B., Stevens, L. 21st International AIDS Conference. Durban, South Africa: Jul 18-22. 2016 Implementation of pre-exposure prophylaxis (PrEP) in New York State. Abstract WEPEC249
116. Krakower D, Ware N, Mitty JA, Maloney K, Mayer KH. HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study. *AIDS Behav*. 2014; 18(9):1712–1721. [PubMed: 24965676]
117. Hoffman S, Guidry JA, Collier KL, Mantell JE, Boccher-Lattimore D, Kaighobadi F, et al. A Clinical Home for Preexposure Prophylaxis: Diverse Health Care Providers' Perspectives on the "Purview Paradox". *J Int Assoc Provid AIDS Care*. 2016; 15(1):59–65. [PubMed: 26293904]
118. Smith DK, Maier E, Betts J, Gray S, Kolodziejewski B, Hoover KW. What Community-Based HIV Prevention Organizations Say About Their Role in Biomedical HIV Prevention. *AIDS Educ Prev*. 2016; 28(5):426–439. [PubMed: 27710082]
119. Tung, E., Thomas, A., Eichner, A., Shalit, P. 2017 Conference of Retroviruses and Opportunistic Infections. Seattle, Washington: Feb 13-16. 2017 Feasibility of a Pharmacist-Run HIV PrEP Clinic in a Community Pharmacy Setting.
120. Siegler AL A, Mayer K, Thure K, Fish R, Andrew E, Gelman M, Sullivan P. An exploratory assessment of the feasibility and acceptability of homebased support to streamline HIV pre-exposure prophylaxis (PrEP) delivery. presented at IAS. 2016
121. Krakower DS, Maloney KM, Grasso C, Melbourne K, Mayer KH. Primary care clinicians' experiences prescribing HIV pre-exposure prophylaxis at a specialized community health centre in Boston: lessons from early adopters. *J Int AIDS Soc*. 2016; 19(1):21165. [PubMed: 27733238]
122. Menza TW, Hughes JP, Celum CL, Golden MR. Prediction of HIV acquisition among men who have sex with men. *Sex Transm Dis*. 2009; 36(9):547–555. [PubMed: 19707108]
123. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2012; 60(4):421–427. [PubMed: 22487585]

124. Hucks-Ortiz JPL, C., Wheeler, DP., Fields, SD. Presented at the international Aids Conference. Durban: 2016. HPTN 073: successful engagement of Black MSM into a culturally relevant clinical trial for pre-exposure prophylaxis (PrEP). Abstract WEAC0103
125. Rolle, CPM., Siegler, AS., Sanchez, T., Luisi, N., Cutro, S., Del Rio, C., et al. 2017 Conference of Retroviruses and Opportunistic Infections. Seattle, Washington: Feb 13-16. 2017 Challenges Of Translating PrEP Interest Into Uptake Among Young Black Msm In Atlanta.
126. US public health service. Pre-exposure prophylaxis for the prevention of HIV infection in the United States - 2014.
127. ASHM. [accessed 03-08-2017] 2017. <http://www.ashm.org.au/HIV/PrEP/>
128. BREACH. [accessed 03-08-2017] 2017. http://www.breach-hiv.be/media/docs/6a_DeWit_finalpresented.pdf
129. Hoorneborg BR, E., et al. [accessed 03-08-2017] Nederlandse PrEP-richtlijn. 2017. <http://richtlijn hiv.nvhb.nl/index.php/Inhoud>
130. Amsterdam PrEP Project. Study Protocol AMPREP. available online at <http://www.ggd.amsterdam.nl/infectieziekten/soa-hiv-sense/rep/amprep/>, and registered at <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5411>
131. Norsk Forening for Infeksjonsmedisin. <http://legeforeningen.no/Fagmed/Norsk-forening-for-infeksjonsmedisin/Nyheter/Faglige-retningslinjer-for-oppfolging-og-behandling-av-hiv-2017/>
132. PrEP Short Life Working Group. [accessed 03-08-2017] 2017. <http://www.hivscotland.com/our-work/rep-in-scotland/>
133. Hiv Scotland. [accessed 03-08-2017] 2017. <http://www.hivscotland.com/our-work/rep-in-scotland/>
134. Impact trial. [accessed 03-08-2017] 2017. <https://www.gov.uk/government/news/nhs-england-and-phe-extend-hiv-prevention-programme>

Table 1
Countries in North America, Australia or Europe where PrEP implementation or demonstration projects are active

Country	Guidance	Summary of indications for PrEP	Implementation underway vs. demonstration projects only	Estimated numbers of eligible persons	Estimated number on PrEP ¹
North America					
United States	US Public Health Services (2014) ^[12,6]	MSM, heterosexuals and PWID with additional risk factors for HIV infection	Implemented	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]	Around 100,000 ^[5]
Canada ²	Under development	Not available	Patchy implementation, not in all provinces	Not available	Not available
Australia					
Australia ³	Yes ^[127]	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	Large-scale demonstration projects only	Around 30,000 (MSM only, no data on other groups)	around 12,000 people ^[30]
Europe					
Belgium ⁴	Breach 2017 ^[128]	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	Implemented	500-1500 (expected to start PrEP)	Not applicable
France	ANRS (2015)	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.	Implemented	Not available	Around 3,400 on PrEP ^[18]
The Netherlands ⁵	NVHB (2016) ^[129]	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	Demonstration project only ^[93, 130]	Around 5,200-13,100 (rough estimate)	Not applicable
Norway ⁶	Norsk Forening for Infeksjonsmedisin ^[131]	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.	Implemented	Not available	Largest center has 200 persons on PrEP

Country	Guidance	Summary of indications for PrEP	Implementation underway vs. demonstration projects only	Estimated numbers of eligible persons	Estimated number on PrEP ¹
Individuals with HIV-infected partners who are not using antiretroviral treatment or who do not have an undetectable viral load					
Portugal ⁷	Under development	Not available	Implementation underway, a national program has been announced on May 29, 2017	Not available	Not available
United Kingdom					
England ⁸	BHIVA statement (2012, updated in 2016)-Guidelines to be released Q4/2017	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	PrEP Impact trial for 10,000 participants to start September 2017 [134]	Around 20,000-100,000 MSM attending genitourinary clinics. Other populations uncertain.	Not applicable
Scotland ⁹	PrEP Short Life Working Group [132]	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	Implemented summer 2017	1700 (range 1,500 to 1,900) [133]	Not available
Wales ¹⁰	Guidelines by Public Health Wales (not yet available online)	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 17 th , 2017; no limit on the number of participants	Around 560 (range 480-620)	Not available

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.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Abbreviations: PrEP: pre-exposure prophylaxis; US: United States; MSM: men who have sex with men; PWID: persons who inject drugs; PEP: post-exposure prophylaxis; STI: sexually transmitted infections; ANRS: National Agency of Research on AIDS and viral hepatitis; NVHB: Nederlandse Vereniging van Hiv Behandelaren (Dutch association of HIV treating physicians); BHIVA: British HIV Association.

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