Global implementation of PrEP as part of combination HIV prevention – Unsolved challenges

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No one left behind: how are we doing in the roll-out of PrEP as part of combination HIV prevention?

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The 2015 World Health Organization (WHO) Guidelines on when to start antiretroviral (ARV) therapy and on pre-exposure prophylaxis (PrEP) for HIV [1] made two landmark recommendations: 1) the offer of ARV treatment to anybody diagnosed with HIV infection, regardless of CD4 levels (i.e. “test and offer”); and 2) the offer of oral HIV PrEP with a tenofovir-containing scheme to any person at substantial risk. As of mid-2016, many of the concerns about potential roll-out that emerged from clinical trials are quickly fading: real-life effectiveness has been demonstrated in 2015/2016 and qualified the role of some of the important undesired occurrences that had been anticipated such as low adherence and “risk compensation” leading to viral resistance and new infections [2]. Studies such as PROUD [3] have shown that at least men who have sex with men (MSM) who use PrEP are at significant risk (due to frequent condomless anal intercourse with casual partners of unknown serostatus), are highly adherent, and can benefit from PrEP effectiveness. PrEP uptake with high adherence in certain communities (e.g. the gay community in San Francisco) [4] is contributing to significant reductions in HIV infections in that city. In addition, studies assessing intermittent PrEP (e.g. the on-demand PrEP scheme used in Ipergay [5], and alternative schemes for MSM included in a Thai study) have also contributed exciting results [6].

On 8 June 2016, the UN General Assembly signed the political declaration on HIV and AIDS: on the fast-track to accelerate the fight against HIV and to end the AIDS epidemic by 2030 [7]. To fulfil the aspirations of the political declaration, UNAIDS has established a 2016–2021 strategy [8] with targets set in HIV prevention and care at the local and regional levels: an ambitious target of ensuring access to PrEP for three million people at substantial risk by 2020. This is based on reaching an overall estimate of 10% of populations at increased risk, namely key populations including MSM, transgender people, and sex workers as well as young women of reproductive age living in the most highly affected communities and people in serodiscordant partnerships where the viral load of the positive partner is not known to be reliably suppressed.

Despite recent progress and these aspirational goals, actual roll-out at a global scale is just beginning, and considerable challenges remain unmet. The planning and organization of demonstration studies beyond MSM in the United States and the UK has been slow, and implementation-relevant information for both the general population and specific key populations (e.g. female sex workers in generalized epidemic contexts, and MSM and transwomen in Asia and Latin America) is still lacking. While concerns about adherence and effectiveness (particularly among MSM) have abated, some other issues have emerged, including 1) the preferred ARV agent, although tenofovir–emtricitabine is the only licensed agent at present; 2) potential of less frequent dosing, cost and sustainability (as much in lower-middle income as in higher-income countries); and 3) a long list of implementation questions that vary by setting and target population. The latter may make monitoring of impact and outcome more complex.

NEMUS, in collaboration with UNAIDS, has followed its first supplement on PrEP beyond clinical trials [9] with this new collection of papers focused on PrEP roll-out, identifying barriers and solutions, again with a focus on regions and populations not considered before. In this editorial, we highlight the main messages of the papers included in this new series. Together with other tools that will be published soon, such as the upcoming WHO implementation guidelines, this publication will help to document progress and guide implementers through a rapidly changing field.

Contributions included in this special issue

A paper by Cáceres et al. [9] discusses PrEP scale-up to date, including the observed levels of access and policy development, and elaborates on key emerging policy and research issues to consider for further roll-out, with a special focus on lower-middle income countries. While feasibility, acceptability and potential impact have been demonstrated, creative solutions will be needed to overcome challenges, which include operational and health systems barriers, drug cost and regulatory policies, health providers’ openness to prescribing PrEP to populations at substantial risk, demand creation and legal and human rights issues.

The contribution by McGillen et al. [10] examines what role PrEP should play in an optimal patterning of combination
prevention in the complex and dynamic landscape of sub-Saharan Africa. The authors use a previously described mathematical model and focus on PrEP to explore how best to distribute PrEP within broader prevention resources. They propose that if current year-on-year financial contributions to prevention funding were to be maintained, an incidence benchmark, as per the new WHO guidelines, would serve as a reasonable way to determine where and to whom PrEP should be offered.

Also focusing on sub-Saharan Africa, Cowan et al. [11] state that at least 3 million individuals in Africa are likely to be eligible for PrEP according to WHO’s criteria and that several African countries have already approved guidelines for PrEP for individuals at substantial risk of HIV as part of combination HIV prevention, but key questions remain about how to identify and deliver PrEP to those at greatest need. Over-arching issues in each of the target populations remain, such as creating demand for PrEP, addressing supply-side issues and providing appropriate and tailored adherence support. Some key action areas identified included the normalization of HIV prevention to help demand creation; community level interventions involving opinion leaders as well as empowerment interventions for those at highest risk; access to quality services for all, including for stigmatized populations; and provision of adherence support that recognizes social and structural factors. They predict that combining interventions that build self-efficacy, empowerment and social cohesion is most likely to be effective in PrEP provision.

A paper by Zablotska-Manos et al. [12] discusses the progress towards PrEP implementation in the Asia/Pacific region. In this region, key PrEP implementation barriers include poor knowledge about and limited access to PrEP, weak or non-existent HIV prevention programmes for MSM and other key populations, high cost of PrEP, stigma and discrimination against key populations, and restrictive laws. While trials and implementation research is taking place only in Thailand and Australia, novel approaches to PrEP implementation have emerged (such as researcher-, facility- and community-led models of care, with PrEP services for fee and for free), and there is growing community interest in PrEP in the region. They conclude that countries in the Asia/Pacific region will benefit from adding PrEP to their prevention packages, but this will need investment.

Ravasi et al. [13] discuss the barriers encountered and potential solutions needed for a fair consideration of PrEP as part of combination HIV prevention strategies in Latin America. No Latin American country has yet implemented a PrEP programme, and so first steps including education of policy makers, programmatic guidance and costing models are still needed. Providers are not prescribing PrEP due to a lack of national policies and guidelines and lack of training. Encouragingly, key populations (MSM, transgender women (TW) and sex workers) have participated in demonstration projects and show high awareness and willingness to use PrEP, especially if accessible in the public sector for free or at affordable price. As in many regions, concerns about safety, adherence, effectiveness and risk compensation need to be addressed through targeted social communication strategies. The authors conclude that an alliance between policy makers, civil society and representatives from key populations, healthcare providers and researchers will kick-start implementation of PrEP demonstration projects and other steps needed for the successful roll-out of PrEP in Latin America.

The final regional paper by McCormack et al. [14] focuses on Europe, where PrEP is only available in France to date. In a region with considerable differences in health systems and government commitment to HIV prevention and care, the number of HIV infections is increasing, even in countries with free access to screening and treatment, among MSM and other key populations. As in many parts of the world, prevention funding is a fraction of care funding. Standards of care are generally good in Western Europe, but less satisfactory in Eastern Europe and central Asia, given limited national health budgets and diminishing foreign aid. Even in Western Europe’s high-income countries, the cost of Truvada® is a major barrier to PrEP implementation, together with inadequate health systems and a weakening civil society.

This special issue includes three papers focused on specific populations. One contribution by Sevelius et al. [15] focuses on TW, one of the key populations most affected by HIV, and discusses unique considerations for maximizing the impact of PrEP in this vulnerable population. They report that, to date, PrEP demonstration projects and clinical trials have largely excluded TW, or failed to include them in a meaningful way, limiting the ability of such studies to draw conclusions about TW’s unique needs and devise strategies to meet them. The need for gender affirming services to facilitate the provision of PrEP to TW is critical. There is a need to engage trans communities, utilize trans-inclusive research and marketing strategies, and identify and/or train health care providers to provide gender affirming health care to trans women; in turn, health systems must consider and address TW’s unique barriers and facilitators to uptake and adherence.

Hosek et al. [16] focus on the potential role of PrEP among young people and discuss data from the United States and South Africa on the use of oral PrEP for HIV prevention in adolescent minors, along with some of the implementation challenges and potential strategies to address those challenges. Adolescents and young adults less than 25 years of age in many geographical settings meet the definition of a key population in the HIV epidemic, with very high HIV incidence rates and limited access to prevention services. Completed and ongoing studies in the United States and South Africa among youth under age 18 should provide the safety data needed by the end of 2016 to contribute to licensure of Truvada® as daily PrEP in adolescents. A number of general and unique challenges have arisen in this age group. Prime among these is adherence to daily medication, which is particularly challenging among younger populations, but other individual level barriers (e.g. limited familiarity with ARV-based prevention, stigma, product storage and social support) and structural challenges (e.g. healthcare financing for PrEP, clinician acceptability and comfort with PrEP delivery, and limited youth-friendly health services available) are also described.

In turn, Coleman and McLean [17] provide a discussion on the value of PrEP in HIV epidemics among people who use drugs (PWUD). While PWUD are at significant risk for HIV in many parts of the world and should be offered PrEP
according to current recommendations, the actual feasibility of this strategy may require an enabling legal and policy environment for delivery of health services to those in need. The need to address structural barriers to services and human rights violations, and to improve access to comprehensive harm reduction programmes are of prime importance and may have higher value than a single focus on HIV prevention, is argued by the authors. If those conditions are not met, shifts in funding priorities, for example, to include PrEP, could threaten programme comprehensiveness, hence facing opposition by PWUD. Nevertheless, nuanced needs of subpopulations of PWUD and their partners must be explored. As for all key populations, the involvement of PWUD in shaping comprehensive services is vital and too often ignored.

Finally, Cairns and Race [18] present a community viewpoint, which reminds the readers that PrEP has been and continues to be an intervention causing controversy and debate between providers, advocates and potential users. Such controversies, they sustain, extend beyond access and can be related to contemporary tensions: medical risk versus benefit; trust versus distrust of healthcare interventions; and individual responsibility versus community cohesion. In that sense, PrEP might lead people to perceive a risk of losing control over any of those tensions. They close by suggesting that the development of greater community “ownership” of PrEP and concomitant improvements in the sense of individual over sexual risk might reduce the insecurities derived from those tensions and facilitate a more neutral uptake of this strategy.

Given the need presented in this series and the promise and potential of the clinical trials and recommendations from WHO, it is hoped that we will see an impressive expansion of combination prevention including PrEP in the next 2 – 5 years. With just 14 short years before the UNAIDS target to end AIDS by 2030, unless we urgently, actively and extensively deploy all of the effective interventions at our disposal, this goal will slip away from our grasp. No one should be left behind [19].

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CFC wrote the first draft of this editorial and produced the final version based on comments from co-editors. LGB and PGF provided detailed comments to the version shared by CFC. All authors have read and approved the final version.

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Commentary

Implementation of pre-exposure prophylaxis for human immunodeficiency virus infection: progress and emerging issues in research and policy

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Abstract

Background: In this article, we present recent evidence from studies focused on the implementation, effectiveness and cost-effectiveness of pre-exposure prophylaxis (PrEP) for HIV infection; discuss PrEP scale-up to date, including the observed levels of access and policy development; and elaborate on key emerging policy and research issues to consider for further scale-up, with a special focus on lower-middle income countries.

Discussion: The 2015 WHO Early Release Guidelines for HIV Treatment and Prevention reflect both scientific evidence and new policy perspectives. Those guidelines present a timely challenge to health systems for the scaling up of not only treatment for every person living with HIV infection but also the offer of PrEP to those at substantial risk. Delivery and uptake of both universal antiretroviral therapy (ART) and PrEP will require nation-wide commitment and could reinvigorate health systems to develop more comprehensive “combination prevention” programmes and support wider testing linked to both treatments and other prevention options for populations at highest risk who are currently not accessing services. Various gaps in current health systems will need to be addressed to achieve strategic scale-up of PrEP, including developing prioritization strategies, strengthening drug regulations, determining cost and funding sources, training health providers, supporting user adherence and creating demand.

Conclusions: The initial steps in the scale-up of PrEP globally suggest feasibility, acceptability and likely impact. However, to prevent setbacks in less well-resourced settings, countries will need to anticipate and address challenges such as operational and health systems barriers, drug cost and regulatory policies, health providers’ openness to prescribing PrEP to populations at substantial risk, demand and legal and human rights issues. Emerging problems will require creative solutions and will continue to illustrate the complexity of PrEP implementation.

Keywords: HIV; pre-exposure prophylaxis; implementation science; combination prevention; health systems; acceptability; program cost; scale-up.

Introduction

The timely publication, in September 2015, of the World Health Organization (WHO) Early Release Guidelines on Use of Antiretrovirals for HIV Treatment and Prevention [1] not only confirmed the recommendation of oral HIV pre-exposure prophylaxis (PrEP) as an additional prevention strategy for members of key populations but also extended it to any person at substantial risk. This has reinvigorated discussions on combination prevention, by adding a new, effective prevention choice, and requires efforts to facilitate scale-up where it might be most beneficial.

Globally in mid-2016, PrEP scale-up is just starting. Many countries are beginning to consider if and how PrEP could be employed in their HIV responses to increase impact. To date, roughly 50,000 people are on PrEP in the United States, the country with the greatest experience in PrEP delivery. The U.S. Centers for Disease Control suggest 1.2 million persons at substantial HIV risk, particularly men who have sex with men (MSM), should be on PrEP in the United States [2].

Recently, a number of countries in Africa, Asia, Europe and Latin America have started measures to enable PrEP implementation, such as the approval of tenofovir–emtricitabine for prevention; the inclusion of PrEP in the national prevention policies and guidelines; and the conduct of implementation research or other efforts to define roll-out conditions (see below). Nevertheless, most countries have not taken any steps yet, due to concerns about local relevance, costs and sustainable funding [3], potential competition with treatment expenditures and other health systems issues (e.g. prioritizing potential beneficiary populations, implementation concerns about safety, drug resistance, adherence and “risk compensation”). Stigma and discrimination against some key
populations often result in poor access to health services in general and inadequate prioritization of their needs, contributing to low PrEP awareness among some key population groups. Conversely, some communities of MSM, much more aware of PrEP, are establishing informal channels to obtain PrEP medications in locations where they are officially unavailable and lobbying for PrEP availability.

Building from our 2015 commentary [4], in this article we will present evidence of the implementation process of PrEP programmes in 2015–2016, with data on potential impact and cost-effectiveness when available; discuss correlates of the observed levels of access and policy development; and analyze key emerging policy and research issues to consider for further scale-up, with a special focus on lower-middle income countries (LMIC).

Discussion

Can PrEP curb HIV incidence?

A crucial factor in the relevance of PrEP scale-up in a combination prevention framework is its estimated impact on HIV incidence and cost-effectiveness. A few recent modelling studies, and reviews of such studies, indicate that consideration of the local epidemic context, including the current coverage of other interventions, is key to achieving efficiency:

A systematic review focused on seven modelling studies published in 2015 that evaluated the cost-effectiveness of introducing PrEP. Three of these were in LMIC and investigated the introduction of PrEP among African heterosexual serodiscordant couples. The incremental cost-effectiveness ratio varied between $5000 and $10,000 per disability-adjusted life year (DALY) averted, when PrEP was used for a limited time period before and after the HIV-positive partner had initiated antiretroviral therapy (ART) [5]. In South Africa, such an intervention was found to be cost-effective under a threshold of three times the national GDP/capita. In Nigeria, it was found to be cost-effective under this threshold only if PrEP was integrated in addition to condom promotion and treatment as prevention. In Uganda, PrEP in addition to ART was not found to be cost-effective under this threshold. In all studies, PrEP cost-effectiveness was improved when “infections averted” was used as the outcome (as opposed to DALYs averted), or when taking a longer-term perspective. This is due to PrEP being a prevention intervention, and as such, its impact on HIV-associated DALYs is not apparent on a 10-year or even 20-year time frame.

Another modelling study [6] investigating the introduction of PrEP among women in Western Kenya found that it could have a substantial impact on incidence (22–28% reduction over four years) if implemented alone and that in combination with increased voluntary medical male circumcision and the implementation of 2013 WHO ART guidelines it could reduce incidence by 46–67%, but cost-effectiveness was not evaluated. Cremin and Hallett [7] used Nyanza, Kenya, as a case study to investigate PrEP intervention efficiencies associated with longer residual protection and changes in cost, adherence and prioritization as a function of coverage and time. They found that the ability to adequately prioritize PrEP to groups with high HIV incidence was the strongest determinant of intervention efficiency and highlighted the extent to which dynamic interactions could affect PrEP intervention impact, warning policy makers of the importance of considering the potential effects of programme scale and duration on efficiency.

Mukandavire et al. [8] investigated the impact of PrEP among female sex workers (FSW) in comparison with that of increasing condom use and found that the latter was likely to be larger given its greater efficacy and its effect on both acquisition and transmission, resulting in the protection of both FSW and their clients. When including non-commercial partners of FSW, the relative impact of PrEP over condoms improved but only substantially when the contribution of these partners to HIV transmission was assumed to be high. The authors conclude that PrEP could be a valuable prevention tool among FSW once condom interventions have been maximized and to protect FSW who are unable to increase their condom use. In a study where PrEP introduction among transgender women (TW) sex workers in Peru was considered along with other four strategies, all possible combinations were modelled for joint effectiveness and cost-effectiveness. At current retail Truvada® prices, it was found that the inclusion of PrEP was effective but required lower costs to become cost-effective [9].

The focus of some modelling studies on populations at high risk of infection over limited periods of time and in combination with other interventions, compared to that of earlier modelling studies that explored large PrEP scale-up, suggests the recognition of the need for a strategic implementation of PrEP to increase its cost-effectiveness. In addition, as pointed by Cambiano et al. [5], cost-effectiveness does not necessarily translate into affordability, and therefore, budget impact analyses that carefully consider implementation and funding strategies are the necessary next step to plan for PrEP scale-up.

As of mid-2016, empirical evidence of effectiveness is not yet available from LMIC. In the United States, referrals for and initiation of PrEP increased in clinical practice since 2012, with very low rates of HIV acquisition among adherent PrEP users. However in one study, high rates of sexually transmitted infections (STIs) continue to be reported, as were seen in the delayed arm in PROUD, and reported decreases in condom use were seen in a small subset of PrEP users [2]. Similarly, a three-city demonstration project in the United States found that annualized HIV incidence was very low despite high incidence of other STIs [10], and the pivotal PROUD study among MSM in sexual health clinics in the UK found an effectiveness greater than efficacy in iPrEX, in part due to reaching high-risk individuals who were motivated to take PrEP and whose adherence was high. HIV incidence was very low but bacterial STI incidence has been high, indicating that high-risk MSM are using PrEP and that STI screening is an important part of PrEP delivery [11].

Global PrEP scale-up, as of early 2016

Internationally, HIV prevention implementers and funders are beginning to recognize the potential of PrEP and support implementation efforts (including formative research, demonstration and pilot projects) in lower-middle income countries. By the end of 2016, WHO will be releasing full PrEP
implementation guidelines to support countries to provide PrEP safely and effectively to a range of populations and in various settings. UNAIDS is recognizing PrEP for populations at substantial risk as an important intervention and has included PrEP in the UN global Fast Track prevention targets [12]. The Global Fund to fight AIDS, tuberculosis and malaria is willing to fund PrEP components of combination prevention in eligible countries according to their overall plans and regulations for types of countries [13]. The U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) new policy is supporting the provision of PrEP to young women and sex workers in Africa through the DREAMS initiative, as well as to people in serodiscordant couples (as a bridge to antiretroviral therapy in positive partners) and to people at substantial risk in key populations of MSM, female sex workers and injection drug users [14]. UNITAID is considering funding PrEP implementation science projects in LMIC regions [15].

As indicated, the number of countries where any PrEP-related policy has already been put in place is limited (see Table 1). Only three countries – the United States and France and, recently, South Africa, have formally incorporated PrEP in their regular HIV prevention programming. In June 2016, South Africa started to provide PrEP for sex workers as a national programme, and other countries in the region are planning for PrEP and developing national policies and guidelines for implementation. We observe two other kinds of activities: regulatory changes (approval of the use of tenofovir–emtricitabine for PrEP) and an increasing number of ongoing or planned projects and programmes to deliver PrEP.

### Awareness/acceptability of PrEP among stakeholders

As the number of recent studies on PrEP has grown over the past 18 months, here we are focusing on publications from LMIC, as those face greater challenges for implementation.

#### Healthcare providers

Data from LMIC are limited. In a qualitative study in Peru (2014–2015), providers maintain limited awareness about PrEP and express skepticism about its use in prevention, linked to drug complexity, cost and presumed risk compensation [16].

#### General public

A study to explore the public opinion, community interest and perceptions about the use and access to PrEP in Nigeria concluded that increasing PrEP uptake by HIV serodiscordant couples requires motivating the HIV-negative male partners and establishing effective stigma reduction strategies [17].

#### Potential and current users

PrEP use has been associated with feelings of empowerment, agency and safety during sex, and partners’ honesty in sharing

| Country        | TDF-containing drug approved for PrEP | Demonstration projects | National guidelines for PrEP | Source of funding |
|----------------|---------------------------------------|------------------------|-----------------------------|-------------------|
| Australia      | Effective                              | Ongoing                | Effective                   | Domestic          |
| Brazil         | Pending                                | Ongoing (1); Pending approval (2) | Planned (3)               | (1) US NIH; (2) UNITAID; (3) Domestic |
| Canada         | Effective                              |                         |                             |                   |
| India          | Generic can be sold for prevention     | Planned/ongoing        |                             | BMGF              |
| France         | Effective                              |                         | Effective (daily and on-demand use) | Domestic          |
| Kenya          | Effective                              | Planned/ongoing        | Effective                   | BMGF and others   |
| Malaysia       | Generic can be sold for prevention     |                         | Effective for out-of-pocket use | Out of pocket     |
| Mexico         | –                                     | Pending approval       |                             | UNITAID           |
| Mozambique     | –                                     | Planned/ongoing        |                             | BMGF and others   |
| Peru           | Effective                              | Ongoing (1); Pending approval (2) | Planned (3)               | (1) amfAR; (2) UNITAID |
| Philippines    | –                                     | Planned/ongoing        |                             | Several sources   |
| South Africa   | Effective                              | Planned/ongoing        | Effective                   | Several (domestic and foreign) |
| Thailand       | Generic can be sold for prevention     | Ongoing/planned/pending approval | Effective for out-of-pocket use | Several (domestic and foreign) |
| United States  | Effective                              | Completed/ongoing      | Effective                   | Domestic          |
| United Kingdom | –                                     | Completed/ongoing      | Pending                     | Domestic          |
| Zimbabwe       | –                                     | Ongoing/pending approval |                            | Several sources   |

BMGF, Bill and Melinda Gates Foundation; PrEP, pre-exposure prophylaxis.
their HIV status [18]. Data from LMIC are limited. In Peru in 2014, among MSM communities and stakeholders alike, prior to the licensing of Truvada® for PrEP, condoms were still described as the mainstay of prevention, yet condom use among MSM has always been insufficient. The men interviewed for the study showed some knowledge of PrEP, coexisting with skepticism about potential utilization [11].

One study among MSM and female sex workers participating in a PrEP trial in Kenya in 2009–2010 reported that PrEP acceptability was high. Adherence was 83% (interquartile range [IQR] 63–92) for daily PrEP, 55% (IQR 28–78) for fixed intermittent dosing and 28% (IQR 14–50) for post-coital dosing. Social impacts (stigma, rumours and relationship difficulties due to being perceived as HIV-positive) were prevalent. Qualitative data on adherence barriers and better measurements of sexual activity are necessary to determine whether adherence to post-coital PrEP is comparable to more standard regimens [19,20]. HPTN 067/ADAPT’s three randomized trials, assessing the feasibility and acceptability of different PrEP regimens with three different populations, in Bangkok, Harlem (New York) and Cape Town found, across all sites, that adherence was higher for the daily rather than the non-daily doses. For example, in Bangkok, 85% of daily doses, 79% of twice-weekly doses and 65% of event-driven doses were taken as prescribed. In Harlem, the respective figures were 65, 46 and 41%. Several advantages of daily regimens were identified – likely to offer more protection, more forgiving of missed doses and helping people develop habits of daily pill-taking [21].

A high uptake of PrEP, and retention in PrEP for the duration of risk, was found among serodiscordant couples in the Partners Demonstration Project, an open-label implementation study evaluating integrated delivery of PrEP and ART in Kenya and Uganda [22]. A sub-study used qualitative methods to gather insights into couples’ early experiences with PrEP use. Couples reported that PrEP offered them an additional strategy to reduce HIV risk, meet their fertility desires and cope with HIV serodiscordance; remaining HIV negative at follow-up visits, as well as their providers’ advice and service friendliness, reinforced couples’ decisions and motivated continued adherence to PrEP [23].

Health systems: challenges and strategies
Health systems are at the core of PrEP implementation. Remaining and emerging challenges should be addressed with policy dialogue and implementation research.

Who pays for PrEP?
As potential PrEP users often report inconsistent condom use, in the long term paying for PrEP during people’s higher-risk life periods is more affordable than paying for lifelong ART [24]. Nevertheless, after the publication of the WHO recommendations, sustainable funding has become a key issue to consider in both high-income countries and LMIC before deciding to establish PrEP programmes. In the UK, which was home to the successful PROUD study [11], the National Health Service has not as yet been able to fund PrEP [25], given that local authorities are the responsible commissioner for HIV prevention services, leading to community mobilization to demand access [3].

In high-income countries and in upper-middle income signatories of free-trade agreements, tenofovir-emtricitabine (TDF-FTC) is only available as very costly Truvada® (although the expiration of its patent protection in 2017 may change this). Conversely, generic TDF-FTC is already being produced and is available for less than USD10 per month, for the benefit of LMIC with a high burden of HIV infection [26]. Some United Nations partners have established regional procurement mechanisms to increase drug access, too.

Selecting the right drug
Clinical trials such as Partners’ PrEP showed comparable efficacy between the TDF-FTC and tenofovir-only arms [27]; likewise, the Bangkok PrEP study also found efficacy for a TDF-based PrEP regime for people who inject drugs [28]. Given the partial availability of TDF-FTC in the world at present, the WHO recommendations defined oral PrEP as the use of tenofovir-containing pills. Although high efficacy for TDF alone was found for the prevention of heterosexual HIV transmission, its comparative effectiveness in preventing HIV transmission in anal sex between men is not proven. In addition, given the treatment equivalence of lamuvidine (3TC) and FTC, and higher availability of such drug in some countries, WHO guidance is forthcoming on 3TC as an alternative to FTC in combination with TDF for PrEP.

Ensuring safety
Based on the evidence available, the WHO Early Release Recommendations [1] for HIV Treatment and Prevention in both higher- and LMIC have indicated that before starting PrEP, subjects’ baseline renal function should be assessed, together with HIV status [1]. Safety monitoring data from PrEP programmes in LMIC are still not available. To assess the relative importance of the adverse effects of TDF-FTC used for PrEP, a recent study compared the number needed to harm (NNH) for TDF-FTC in MSM, transwomen and seronegative partners in heterosexual serodiscordant couples, with adverse effects of aspirin used for the prevention of cardiovascular disease among middle-aged men and women [29]. It was found that, if the populations and the frequency of use are comparable, the NNH for TDF-FTC compared favourably with the NNH for aspirin concerning adverse effects.

Defining delivery models with appropriate monitoring and optimal adherence
The administration of PrEP implies coordination of various components: initial eligibility assessment (including HIV testing), regular follow-up testing, safety and adherence monitoring, and drug supply. HIV testing is fundamental to confirm eligibility and rule out subsequent infection. As HIV testing and counselling in LMIC is often facility-based, to increase testing of people at substantial HIV risk who do not visit clinical services, other approaches such as workplace, outreach, mobile and potentially HIV self-testing should be considered [30,31]. Links with community-based organizations and key population networks to support linkage following testing are essential to ensure people living with HIV link to ART services and that those HIV-negative link to prevention services where PrEP and other options are available.
People taking PrEP require regular follow-up, at least quarterly for HIV and STI testing and periodic kidney function assessment. There are many different possible approaches for PrEP delivery and possibilities for integrating into other clinical services – for example, STI, reproductive health services or other services for key populations. Task-sharing should be considered for PrEP delivery with nurse and clinical officer-led services. A PrEP demonstration project conducted in three different settings in San Francisco recently reported that the integration of PrEP into busy clinical settings is feasible [32].

Integration of PrEP with relevant services will increase sustainability and foster comprehensive care. Recent programmatic data from the United States indicate that as PrEP programmes must deal with substantial rates of other STI, they provide an opportunity to integrate periodic STI screening and management [33].

The various barriers to reaching and delivering services for adolescent girls and young women in settings of high incidence in southern and Eastern Africa [34–37] should be identified and tackled [38]. Demonstration projects to explore PrEP implementation in those populations are a priority. Medication adherence in younger women has also been recognized as a significant challenge [39,40]. Risk assessment tools have been designed for men who have sex with men (MSM) and people who inject drugs (PWID) but have not been critically evaluated yet in terms of their usefulness in PrEP implementation. Regardless of population and point of entry, evidence-based strategies to support adherence should be considered, without losing a user-centred approach, where risk reduction is the goal – rather than PrEP adherence per se [41]. Within the Partners PrEP study among HIV-negative members of serodiscordant couples in Kenya and Uganda, objective measures of PrEP adherence were collected using unannounced home-based pill counts and electronic pill bottle monitoring; participants received individual and couples-based adherence counselling at PrEP initiation and throughout the study; participants were followed monthly and counselling was intensified if unannounced pill count adherence fell to <80%. Median adherence was 99.1% (IQR 96.9–100%) by unannounced pill counts and 97.2% (90.6–100%) by electronic monitoring over 807 person-years [42].

Improving provider training

Given the need to prioritize individuals at high risk of infection to improve PrEP cost-effectiveness, training of health providers to better identify potential PrEP beneficiaries will be important. Sexual history training among a sample of U.S. physicians resulted in increased frequency of documented sexual history discussions and greater comfort with sexual health discussions [43]. Risk assessment tools relying on self-reported risk behaviours to estimate HIV risk have been successfully implemented among MSM [44] and PWID [45]. Applying algorithms to routinely collect behavioural or STI history data from patients’ electronic health records provides additional support in this task [46].

Involving communities and dealing with structural barriers

Meaningful, effective community involvement is the other key factor in PrEP scale-up [47]. The prevailing legal and human rights barriers to access care affecting MSM, TW and sex workers may pose significant challenges to providing PrEP to these key populations, in many settings, particularly in LMIC in Africa and the Caribbean where homosexuality and sex work remain criminalized [48,49]. PrEP scale-up for key populations provides an opportunity to improve services and increase service utilization among key populations as well as possibility of “programmatic risk” [50].

Using implementation research

Focused implementation research can be used to resolve some of the challenges described above, such as dynamic stakeholders’ attitudes and information needs; PrEP awareness and demand creation; best options for the target drug (i.e. source, purchase mechanism and funding); refinement of target population(s); programme organization, modes of delivery and integration with other services; health provider training; and strategies to manage STIs and tackle structural barriers to programmatic success [51].

Conclusions

The 2015 WHO recommendation to support the offer of PrEP to people at substantial HIV risk was based on compelling effectiveness evidence to prevent HIV acquisition in various populations. To date, PrEP implementation outside the United States seems to be moving to a new phase, given increasing numbers of demonstration and pilot programmes underway or being considered. The challenge is to learn from those and support wider use for populations that continue to experience high incidence and for whom additional prevention choices are needed. Community advocates and networks in many countries are leading the demand for greater access. Many challenges remain for implementation in LMIC, but the evidence of effectiveness of PrEP, the acceptability and uptake by people who could benefit most and the cost-effectiveness of PrEP if offered to people at highest risk are compelling reasons to push for greater availability and implementation. It is hoped that future long-acting formulations such as injectable [52] will be effective, and the experience gained from implementing daily PrEP will be crucial to facilitate their introduction.

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Competing interests

The authors declare that they have no conflict of interest.

Authors’ contributions

CFC wrote the first draft and managed the subsequent versions. AB and RB proposed text and references for specific sections and general suggestions for the full text. JDK and CB provided suggestions for specific topics. All authors have read and approved the final version.

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PrEP as a feature in the optimal landscape of combination HIV prevention in sub-Saharan Africa

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Abstract

Introduction: The new WHO guidelines recommend offering pre-exposure prophylaxis (PrEP) to people who are at substantial risk of HIV infection. However, where PrEP should be prioritised, and for which population groups, remains an open question. The HIV landscape in sub-Saharan Africa features limited prevention resources, multiple options for achieving cost saving, and epidemic heterogeneity. This paper examines what role PrEP should play in optimal prevention in this complex and dynamic landscape.

Methods: We use a model that was previously developed to capture subnational HIV transmission in sub-Saharan Africa. With this model, we can consider how prevention funds could be distributed across and within countries throughout sub-Saharan Africa to enable optimal HIV prevention (that is, avert the greatest number of infections for the lowest cost). Here, we focus on PrEP to elucidate where, and to whom, it would optimally be offered in portfolios of interventions (alongside voluntary medical male circumcision, treatment as prevention, and behaviour change communication). Over a range of continental expenditure levels, we use our model to explore prevention patterns that incorporate PrEP, exclude PrEP, or implement PrEP according to a fixed incidence threshold.

Results: At low-to-moderate levels of total prevention expenditure, we find that the optimal intervention portfolios would include PrEP in only a few regions and primarily for female sex workers (FSW). Prioritisation of PrEP would expand with increasing total expenditure, such that the optimal prevention portfolios would offer PrEP in more subnational regions and increasingly for men who have sex with men (MSM) and the lower incidence general population. The marginal benefit of including PrEP among the available interventions increases with overall expenditure by up to 14% (relative to excluding PrEP). The minimum baseline incidence for the optimal offer of PrEP declines for all population groups as expenditure increases. We find that using a fixed incidence benchmark to guide PrEP decisions would incur considerable losses in impact (up to 7%) compared with an approach that uses PrEP more flexibly in light of prevailing budget conditions.

Conclusions: Our findings suggest that, for an optimal distribution of prevention resources, choices of whether to implement PrEP in subnational regions should depend on the scope for impact of other possible interventions, local incidence in population groups, and total resources available. If prevention funding were to become restricted in the future, it may be suboptimal to use PrEP according to a fixed incidence benchmark, and other prevention modalities may be more cost-effective. In contrast, expansions in funding could permit PrEP to be used to its full potential in epidemiologically driven prevention portfolios and thereby enable a more cost-effective HIV response across Africa.

Keywords: PrEP; combination prevention; optimisation; sub-Saharan Africa.

Introduction

The long-term provision of HIV treatment presents a financial burden that is likely to approach the sum total of the national debt of some affected countries [1]. Scaling up combination HIV prevention is widely recognised as vital for ensuring progress against the epidemic and alleviating this economic burden on low- and middle-income countries. Clinical trials have shown oral pre-exposure prophylaxis (PrEP) to be an effective method for preventing HIV transmission [2–7], with protection and adherence strongly correlated [8]. Ahead of results from these trials, the early PrEP literature laid the groundwork for considering the future role of PrEP and how its introduction was expected to change the prevention landscape [9,10]. More recently, practical issues of implementation in resource-limited countries have been discussed [11–13], and the importance of determining how best to position PrEP within combination prevention efforts has been emphasised [13–15].

The WHO guidelines now recommend offering PrEP to people who are at substantial risk of HIV infection [16]. What this looks like at scale, in terms of where and how PrEP should be implemented, comprises an open question of immediate importance for shaping our progress toward ambitious global goals [17]. This is particularly true for sub-Saharan Africa, where the burden of disease is highest in the world [18,19] and resources available for the HIV response...
are likely to remain limited [20,21]. There is thus considerable scope for mathematical modelling to confront the complexity of the HIV epidemic in sub-Saharan Africa and inform our approach to PrEP implementation there.

A recent modelling study [22] evaluated the potential of a five-year PrEP intervention targeting the general adult population in sub-Saharan Africa. PrEP was found to be cost-effective in countries with high HIV burdens and low rates of male circumcision, though this was against a backdrop of homogeneously sexual behaviour and fixed national coverage levels for other interventions. Anderson et al. [23] included PrEP in the first rigorous comparison of the cost-effectiveness of intervention portfolios across heterogeneous subnational regions, with the scope of Kenya. We recently reported how funds for combination prevention could be rebalanced within and across multiple countries for a more effective continent-wide response against HIV [24]. PrEP emerged as an important prevention modality in this analysis, with a role in the optimal prevention strategy that is complex and merits closer examination.

Here, we use the optimal prevention strategy from our previous work [24] as a springboard to carry out an analysis of where, and to whom, PrEP would ideally be offered in the resource-limited, heterogeneous setting of sub-Saharan Africa. Our study serves as a demonstration of the principle that widening the context in which an intervention is evaluated can increase both the effectiveness of that intervention and the cumulative impact of combination prevention.

### Methods

#### Model structure and prevention optimisation approach

Full details of the model structure used here, its parameters, and their calibration to data can be found in the recent paper by McGillen et al. [24]. For brevity, we restrict our description to a summary of key features. At the centre of this framework is a dynamic compartmental model that describes sexual HIV transmission, deaths, and prevention. The model is used to describe each top-level administrative subnational region in 18 countries (Benin, Botswana, Burkina Faso, Cameroon, Congo, Democratic Republic of the Congo, Ethiopia, Kenya, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Swaziland, Tanzania, Zambia, and Zimbabwe), in total capturing 80% of the burden by people living with HIV in sub-Saharan Africa.

In each subnational region, the population is grouped by risk level. Key high-risk populations are female sex workers (FSW) and men who have sex with men (MSM). The general population includes low-risk women and men, who tend to form stable long-term partnerships; moderate-risk women and men, who form casual partnerships; and high-risk male clients of sex workers. Heterosexual HIV transmission links men and women, homosexual HIV transmission links MSM, and risk structure further differentiates how the population groups interact and how HIV is transmitted among and between them. Parameters representing sexual behaviours and sexual mixing patterns comprise the proximate determinants of risk and can vary between these groups. After HIV infection, the model tracks disease progression by CD4 status [25].

In [24], parameters governing biological aspects of HIV (such as disease progression rates) were held constant across subnational regions. For each subnational region, parameters governing sexual behaviours, local epidemiological characteristics, population demographics, and historical treatment and prevention initiatives were incorporated into a standard likelihood expression, which was maximised using a direct-search simplex algorithm. This produced epidemic dynamics consistent with local data on prevalence levels [26–28], prevalence trends [29], historical circumcision levels [26], demographic characteristics of the general population [30,31] and high-risk population groups [32–50], and historical scale-up of antiretroviral therapy (ART) coverage [51]. The calibration process was repeated for all subnational regions (detailed fully in [24]).

Although detailed data on sexual behaviours among MSM are available for some of Kenya’s major urban centres [52,53] and coastal districts [54,55], these do not necessarily generalise to other locations in sub-Saharan Africa, and data are otherwise extremely scarce. This limits the sophistication of our representation of MSM. However, viral genotyping data indicate that transmission between MSM is not isolated from transmission in the general population [56], and studies from across Africa suggest that 41% to 86% of MSM have also had sex with women in their lifetime [50]. We thus assumed that all MSM can form partnerships with both sexes, and allowed the ratio of male to female partnerships to vary among subnational regions between a value of 1 (no preference for male partnerships) and 20 (strong preference for male partnerships).

Prevention interventions can be targeted to different population groups to change their proximate determinants of risk and thereby affect the cumulative incidence across population groups. Prevention interventions considered in [24] are oral PrEP, behaviour change communication, voluntary medical male circumcision, and outreach testing with the offer of ART to all HIV-positive people, which we call “early” ART as it typically reaches people who are early in disease progression and would otherwise be unlikely to present for care. In the model, PrEP and voluntary medical male circumcision reduce the per-partnership probability of HIV acquisition, and behaviour change communication reduces the mean rate of changing partners. Early ART amplifies the number of HIV-positive people on ART, reducing onward transmission. PrEP and behaviour change communication can be offered to HIV-negative people, voluntary medical male circumcision to uncircumcised HIV-negative men, and early ART to all HIV-positive people who have not already presented for care.

We assigned unit costs to these prevention modalities in accordance with the UNAIDS Fast Track framework [17] and made a set of assumptions around achievable maximum coverage levels in the population groups (Table 1). Current coverage levels vary by subnational region for behaviour change communication and voluntary medical male circumcision, depending on historical initiatives, while early ART and PrEP are assumed to start from the beginning of the 15-year intervention period (2016 to 2030). In the absence of prevention scale-up, we assume that the effects of past behaviour change and circumcision campaigns would persist, but early ART and PrEP would not be introduced. In assuming a maximum possible scaled-up PrEP coverage of 50% for the key
Table 1. Prevention interventions

| Intervention | Target population | Effectiveness | Unit cost | Achievable coverage (%) |
|--------------|------------------|--------------|-----------|-------------------------|
| VMMC         | Eligible men     | 60% reduction in RoA | $68 per procedure | 80          |
| BCC          | Heterosexual men | 20% reduction in RoA | $63 pppy  | 100         |
|              | Low-risk women   | 20% reduction in RoA | $63 pppy  | 100         |
|              | FSW              | 50% reduction in RoA | $28 pppy  | 100         |
|              | MSM              | 50% reduction in RoA | $28 pppy  | 100         |
| Early ART    | Heterosexual men | 70% reduction in RoT | $457 pppy | 33          |
|              | Low-risk women   | 70% reduction in RoT | $457 pppy | 33          |
|              | FSW              | 70% reduction in RoT | $457 pppy | 66          |
|              | MSM              | 70% reduction in RoT | $457 pppy | 66          |
| PrEP         | Heterosexual men | 75% reduction in RoA | $95 pppy  | 25          |
|              | Low-risk women   | 75% reduction in RoA | $95 pppy  | 25          |
|              | FSW              | 75% reduction in RoA | $95 pppy  | 50          |
|              | MSM              | 75% reduction in RoA | $95 pppy  | 50          |

A unit cost is assigned to each intervention following the UNAIDS Fast Track framework [17]. For continuity with previous studies [23,24], we assume homogeneity of individual-level efficacies of early ART and PrEP with respect to risk. As this is not a forecast analysis, we do not include discounting of costs or effects, nor do we make assumptions about whether intervention costs would decrease [61] or increase [62] with scale. VMMC, voluntary medical male circumcision; BCC, behaviour change communication; Early ART, antiretroviral therapy as prevention comprising outreach testing and offering of ART to all HIV-positive people; PrEP, pre-exposure prophylaxis; FSW, female sex workers; MSM, men who have sex with men; RoA, risk of HIV acquisition; RoT, risk of onward HIV transmission; pppy, per person per year.

Exploration of PrEP in the optimal resource distribution

Throughout this study, we focus on the role played by PrEP in the optimal allocation of prevention resources that was set out in our previous work [24]. As an example, we can consider a representative net expenditure level of $20 billion for the continent over the next 15 years (from 2016 to 2030) and examine what role PrEP plays in scale-up of the optimal prevention at this total expenditure. The $20 billion figure is obtained by assuming that current levels of HIV funding [51] will be maintained annually in the near future [21], the prevention share in HIV spending will approach 25% [57], and 90% of this prevention share will be directed to scaling up current methods (rather than to research and development of new methods). As this avoids assumptions about future domestic growth in the modelled countries and also likely declines in HIV funding by international donors, we can consider $20 billion to represent a moderate spending level for the intervention period.

Retaining the costing and coverage assumptions from the optimisation [24] (Table 1), we can see where and in which population groups PrEP is used when the $20 billion expenditure is allocated optimally in our model (Figure 1). At this expenditure, PrEP is funded for the highest risk population groups, with FSW receiving PrEP in 63% of the modelled regions, concentrated in southern and eastern Africa where incidence and prevalence are high in this population group. MSM are also at high risk, but in the absence of detailed data, our model represents them as a more insular population and as contributing less to onward transmission than FSW. Consequently, they receive PrEP in fewer regions (29%) at this expenditure level. Additionally, the available funds allow scope for provision of PrEP to the lower incidence general population in 12% of the modelled regions.
Having illustrated the utility of our modelling framework for examining where and to whom PrEP is favoured at a given level of total prevention expenditure, we will vary this expenditure hereafter. We start from a low expenditure level at which very little prevention scale-up is possible ($1 million over the 15-year period) and increase this to a level at which all interventions can be funded in all regions ($1 trillion over the 15-year period). Over this range, we carry out a series of further analyses as follows.

Over the full range of prevention expenditures—that is, from $1 million to $1 trillion over the 15-year intervention period—we calculate the baseline HIV incidence among each population group receiving PrEP in our model. For example, at a given expenditure level, if PrEP is targeted to FSW in a subnational region, we determine what the incidence among that group would have been in 2015 in the absence of PrEP. We repeat this calculation for all groups and expenditure levels. For each expenditure level, we then determine the minimum baseline incidence over the relevant subnational regions for each group. This gives us a measure of the minimum-incidence threshold at which PrEP is implemented in the optimal allocation, as a function of overall prevention expenditure.

To examine the marginal impact of PrEP in the optimal prevention landscape, we remove PrEP from our collection of prevention interventions and repeat our optimisation analysis for the full range of total expenditure levels. This allows the three remaining prevention mechanisms (behaviour change communication, early ART, and voluntary medical male circumcision) to rebalance across locations and population groups and find a new optimal pattern in the absence of PrEP.

Finally, we consider how the prevention landscape would look if decisions regarding PrEP implementation were not optimised freely, but instead were governed by an incidence benchmark of 3 per 100 person-years, as recommended by the new WHO guidelines [16]. To do this, we determine which regions contain population groups with incidence levels of at least 3 per 100 person-years in 2016, and “force” PrEP to be funded for those population groups in those regions. Any population groups with incidence levels lower than this do not receive PrEP, even if sufficient funds are available. If funding is insufficient to provide PrEP according to the benchmark in a given region, we allow the remaining interventions to optimise in that region instead, as if PrEP were not an available option in the array of interventions. This assumes that funding is freely transferrable between prevention modalities, rather than going unused where PrEP is not affordable.

Results

The choice of where and for whom PrEP is funded in the optimal prevention landscape depends partly on the incidence levels of the population groups. However, the full picture of the role played by PrEP is more intricate and rich than a straightforward dependence on incidence. We find that the prioritisation of PrEP also changes with the total amount of funding available for prevention and is responsive to the surrounding context of other favourable intervention modalities as determined by the local epidemiology.

Other interventions are more favourable than PrEP when resources are very limited (Figure 2). However, PrEP plays an increasingly significant role in the optimal landscape of combination prevention as the total expenditure increases from $6 billion onwards, under these assumptions for unit costs. As a function of expenditure, the interventions prioritised earliest are voluntary medical male circumcision and behaviour change communication for the high-risk groups, and early ART for the general population. These are followed at higher expenditures by early ART for the high-risk groups, PrEP for the high-risk groups, PrEP for the general population, and finally behaviour change communication for the general population. PrEP is prioritised earlier (with respect to expenditure) for FSW than for MSM. This is because the former group contributes more to onward transmission than the latter group in our modelling framework and thus tends to be a more cost-effective group in which to intervene.

The baseline incidence in populations receiving PrEP is not static but decreases for all target groups as the total prevention expenditure increases (Figure 3). Until the total prevention expenditure reaches $6 billion, PrEP is prioritised to MSM only in regions where this group has a very high baseline incidence (11.3 per 100 person-years or higher) and to FSW in regions where their baseline incidence is at least...
incidence of 3 per 100 person-years. The x-axis is on a log scale over the 15-year intervention period. The horizontal line marks an population (plain curve), as a function of net prevention expenditure who have sex with men (triangles), and the lower-risk general years occurring in 2015 in the absence of PrEP, in the subnational Minimum baseline incidence, or minimum incidence per 100 person-years or higher [16] for PrEP implementation, and the PrEP-Modalities. If we enforce a provisional benchmark incidence of 3 per 100 person-years or higher [16] for PrEP implementation, and allow the other interventions to optimise around this, the impact pattern changes (Figure 4). At lower expenditures (between $100 million and $6 billion), a loss of impact occurs relative to both the fully optimal strategy and the strategy that would be optimal in the absence of PrEP. These two strategies are similar in this expenditure range—other interventions are more cost-effective and hence PrEP would be offered in very few places even if available—and the PrEP-benchmark scenario is worse than both. At these low expenditure levels, forcing the funding of PrEP in population groups with incidence levels that exceed the benchmark is costly and leaves little capacity for providing the other interventions that would be more favourable. Higher expenditures provide sufficient prevention capacity for the impact of the benchmark-based strategy to exceed that of the no-PrEP strategy. However, the fully optimal strategy would give PrEP to some regions in which the target population groups have incidence levels below the benchmark of 3 per 100 person-years. Without capitalising on this opportunity for extra impact, the benchmark-based strategy reduces incidence by up to 7% more than the no-PrEP strategy, in contrast to the 14% marginal gain that can be achieved by allowing PrEP to optimise freely among the other interventions.

Figure 2. Prioritisation of PrEP among other intervention modalities. Percent of subnational (top-level administrative) regions in which PrEP (black), early ART (blue), behaviour change communication (green), and voluntary medical male circumcision (orange) are implemented among the general population (plain curves), female sex workers (circles) or men who have sex with men (triangles), over a range of net prevention expenditures for the 15-year intervention period. Female sex workers and men who have sex with men are high-risk groups, while the general population comprises low-risk women and heterosexual men. Voluntary medical male circumcision can be implemented only among uncircumcised men in regions where circumcision coverage is not already high prior to the intervention period (40% of all regions). The x-axis is on a log scale (m = million, b = billion, t = trillion).

4.7 per 100 person-years. However, very few regions receive PrEP at such expenditure levels (as can be seen in Figure 2). For expenditures above $6 billion, the minimum baseline incidence levels among the high-risk populations receiving PrEP decline to zero, and these groups receive PrEP in an increasing number of regions. The general population—which comprises low-risk women and heterosexual men and has a lower average incidence than the highest risk population groups—also becomes favourable for PrEP at higher expenditures. At an expenditure of $4 billion, the optimal prevention strategy includes PrEP for the general population in regions where the baseline incidence is 4.1 per 100 person-years or higher. As with the key populations, this minimum baseline incidence declines to zero as expenditure increases. All target groups fall below the provisional WHO incidence benchmark of 3 per 100 person-years [16] at expenditures above $40 billion.

If we remove PrEP from the array of available prevention modalities and optimise the implementation of the remaining modalities, we see an overall loss of impact at moderate-to-high expenditure levels (Figure 4), despite a rebalancing of the other interventions in the absence of PrEP. At expenditures below $6 billion, PrEP is used in too few places to have a significant marginal impact, but the marginal loss of impact due to removing PrEP increases with net prevention expenditure, because PrEP is most valuable at higher expenditures where it can be used in more places and population groups. At maximum—that is, for a $1 trillion expenditure—PrEP increases the impact of optimal combination prevention by 14%, and an 80% reduction on 2010 incidence is achieved by 2030, as compared to a 66% reduction without PrEP. We note diminishing returns as this maximum expenditure is approached. This is because of saturation of the populations in which it is possible to intervene, given our assumptions of imperfect effectiveness and coverage levels for the interventions (see Table 1).

If we enforce a provisional benchmark incidence of 3 per 100 person-years or higher [16] for PrEP implementation, and allow the other interventions to optimise around this, the impact pattern changes (Figure 4). At lower expenditures (between $100 million and $6 billion), a loss of impact occurs relative to both the fully optimal strategy and the strategy that would be optimal in the absence of PrEP. These two strategies are similar in this expenditure range—other interventions are more cost-effective and hence PrEP would be offered in very few places even if available—and the PrEP-benchmark scenario is worse than both. At these low expenditure levels, forcing the funding of PrEP in population groups with incidence levels that exceed the benchmark is costly and leaves little capacity for providing the other interventions that would be more favourable. Higher expenditures provide sufficient prevention capacity for the impact of the benchmark-based strategy to exceed that of the no-PrEP strategy. However, the fully optimal strategy would give PrEP to some regions in which the target population groups have incidence levels below the benchmark of 3 per 100 person-years. Without capitalising on this opportunity for extra impact, the benchmark-based strategy reduces incidence by up to 7% more than the no-PrEP strategy, in contrast to the 14% marginal gain that can be achieved by allowing PrEP to optimise freely among the other interventions.

Figure 3. PrEP implementation by incidence. Minimum baseline incidence, or minimum incidence per 100 person-years occurring in 2015 in the absence of PrEP, in the subnational regions where PrEP is funded for female sex workers (circles), men who have sex with men (triangles), and the lower-risk general population (plain curve), as a function of net prevention expenditure over the 15-year intervention period. The horizontal line marks an incidence of 3 per 100 person-years. The x-axis is on a log scale (m = million, b = billion, t = trillion).
Discussion

Here we have considered the role of PrEP in an optimal response to the heterogeneous epidemiology of HIV, viewing it as one of several intervention modalities and taking the strategic scope of sub-Saharan Africa. We have found that an optimal prevention pattern would prioritise PrEP for high-risk key populations, particularly FSW, across sub-Saharan Africa at moderately high levels of total prevention expenditure. The lower-risk general population would also receive PrEP in some regions at higher expenditures. The choice to implement PrEP in a population group depends not only on the incidence and overall expenditure but also on the potential for impact of other possible interventions. This in turn depends upon the patterns of transmission in the population and scope for expansion of different strategies. Our analysis has shown that an optimum strategy for combination prevention without PrEP would be less effective over a range of expenditure levels than one with PrEP. Moreover, the marginal impact of PrEP would be greater at higher expenditures, achieving a reduction on 2010 incidence levels of up to 14% more than what is possible without PrEP.

The WHO guidelines provisionally define eligibility for PrEP as those with an HIV incidence meeting or exceeding the benchmark of 3 per 100 person-years in the absence of PrEP [16]. Our model finds that, under optimal allocation of total prevention funds, the minimum baseline HIV incidence among populations receiving PrEP drops as the overall expenditure increases, with all population groups receiving PrEP at incidence levels below 3 per 100 person-years at higher total expenditures. A strategy in which prevention is optimised around this PrEP benchmark incurs losses in impact for low-to-moderate expenditure levels, suggesting that if resources are thus limited, it may be preferable to forgo the offer of PrEP in favour of other interventions that are less expensive for their impact. At higher expenditure levels, the benchmark-based strategy becomes more impactful than not offering PrEP. However, it also becomes less impactful than offering PrEP in an optimal way, with losses growing considerably as the opportunity is missed to fund PrEP for population groups with incidence thresholds below the benchmark. The marginal loss reaches 7% at the highest expenditure considered here, fully half the loss that would be incurred by not implementing PrEP at all.

Conclusions

PrEP pilot studies and demonstration projects are planned and ongoing in several countries across sub-Saharan Africa. Although many past modelling studies have estimated the impact and cost-effectiveness of PrEP as an individual intervention (reviewed in [58]), few have done so in the wider context of combination prevention and none has confronted epidemic heterogeneity both within and across multiple countries. Our study has demonstrated how PrEP can be used strategically to maximise impact with full consideration of the epidemic and financial context of sub-Saharan Africa. It is a proof-of-principle that the offer of PrEP at scale should be guided not only by incidence in the affected populations but also by total funding capacity and the context of other interventions appropriate for the local epidemics. In advocating for nuanced evaluations of PrEP and other modalities for combination prevention in resource-limited settings, this work takes an important conceptual step toward more flexible, epidemic-responsive, and effective HIV prevention decisions.

Because of data limitations, we have assumed that unit costs and effect sizes are scale invariant and the same in all countries, and that countries would not incur additional costs by sustaining a given programme in some regions and not others. Moreover, we have assumed that target populations are all equally accessible, when in reality isolated areas may be more expensive to reach than well-connected ones [59]. These factors may exaggerate the extent to which a flexible approach to programming leads to benefits. Using a finer geographical resolution than top-level subnational regions may offer further insight into the relative priority of different populations for receiving PrEP in the combination prevention landscape. For example, a microscale case study has suggested that PrEP should be prioritised first for male sex workers, then for MSM and FSW, in Nairobi (Cremin et al. Unpublished data). Stratification of the population by age may also be important, particularly for young women, who have been proposed as a priority group for PrEP implementation [60]. Differences in adherence between women aged 15 to 25 and those over 25 could, for example, raise the relative cost of reaching the younger group. If we have overestimated PrEP adherence here, then the marginal effect
of PrEP has likewise been overestimated. Differences in the modelled use of PrEP among MSM and FSW are linked to our assumptions about the positions of these key populations in the sexual network and the potential for the epidemic to spread from each. As these factors are not well known in many settings, such differences should be interpreted with caution.

A number of extensions could be considered for this analysis. Further insights may be gained through exploring the sensitivity of our findings to key parameters, such as costs and levels of coverage achievable. In particular, if PrEP were to be less expensive relative to the other intervention choices, we would expect it to be implemented at lower incidence thresholds, such that it would be included in the optimal prevention bundles for more regions and population groups at lower levels of overall prevention expenditure. Conversely, if PrEP were to be more expensive at scale than what we have considered here, its role in the optimal prevention strategy could be reduced for the amount of prevention funding that is likely to be available in the future. Nevertheless, if deployed selectively with consideration of the full epidemic context, PrEP can play an important role in the optimal prevention landscape, with its full benefits to be realised if the coming years see a redoubling of financial contributions to the collective fight against HIV.

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**Competing interests**

The authors declare no competing interests.

**Authors’ contributions**

JBM and TBH conceived the study. JBM, S-JA and TBH developed the methods. JBM did the analyses and wrote the paper. All authors reviewed and approved the final version.

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PrEP implementation research in Africa: what is new?

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Abstract

Introduction: Of the two million new HIV infections in adults in 2014, 70% occurred in sub-Saharan Africa. Several African countries have already approved guidelines for pre-exposure prophylaxis (PrEP) for individuals at substantial risk of HIV as part of combination HIV prevention but key questions remain about how to identify and deliver PrEP to those at greatest need. Throughout the continent, individuals in sero-discordant relationships, and members of key populations (sex workers, men who have sex with men (MSM), transgender women and injection drug users) are likely to benefit from the availability of PrEP. In addition, adolescent girls and young women (AGYW) are at substantial risk in some parts of the continent. It has been estimated that at least three million individuals in Africa are likely to be eligible for PrEP according to WHO’s criteria. Tens of demonstration projects are planned or underway across the continent among a range of countries, populations and delivery settings.

Discussion: In each of the target populations, there are overarching issues related to (i) creating demand for PrEP, (ii) addressing supply-side issues and (iii) providing appropriate and tailored adherence support. Critical for creating demand for PrEP is the normalization of HIV prevention. Community-level interventions which engage opinion leaders as well as empowerment interventions for those at highest risk will be key. Critical to supply of PrEP is that services are accessible for all, including for stigmatized populations. Establishing accessible integrated services provides the opportunity to address other public health priorities including the unmet need for HIV testing, contraception and sexually transmitted infections treatment. National policies need to include minimum standards for training and quality assurance for PrEP implementation and to address supply chain issues. Adherence support needs to recognize that social and structural factors are likely to have an important influence. Combining interventions that build self-efficacy, empowerment and social cohesion, with evidence-based individualized adherence support for PrEP, are most likely to be effective.

Conclusions: Efficacy of tenofovir-based PrEP is proven but many issues related to implementation remain unclear. Here, we have summarized some of the important implementation questions that need to be assessed as PrEP is rolled out across Africa.

Keywords: empowerment; key populations; HIV/AIDS; pre-exposure prophylaxis; prevention; Africa; adherence; implementation.

Introduction

Of the two million new HIV infections in adults in 2014, 70% occurred in sub-Saharan Africa (SSA). With the scale-up of antiretroviral treatment (ART), the number of new infections has stabilized [1]; however, to reach UNAIDS 90:90:90 target, it will be necessary to both scale up treatment and further intensify prevention efforts [2]. Mathematical models suggest that 25% of future HIV investments should go to effective combination HIV prevention [3]. In 2015, WHO recommended the use of tenofovir-based pre-exposure prophylaxis (PrEP) in individuals at substantial risk of HIV as part of combination prevention [4]. This recommendation was based on a systematic review of 18 studies across a range of populations and settings [5]. The review found that PrEP was effective in reducing HIV risk across gender, PrEP regimen, dosing and mode of acquisition, and that increased adherence was associated with a demonstrable increase in PrEP effectiveness. There was no evidence that PrEP use was associated with risk compensation, increased pregnancy-related outcomes or of hormonal contraception effectiveness [5]. Among trials with adherence ≥80%, PrEP reduced risk of infection by 70% (RR = 0.30, 95% CI: 0.21–0.45, p = 0.001) [5]. Several African countries have already licensed tenofovir plus emtricitabine for PrEP [6], while others have started the guideline development process, but key questions remain about how to identify and deliver PrEP to those at greatest need.

Maximizing the impact and cost-effectiveness of PrEP

Modelling studies suggest that the impact and cost-effectiveness of PrEP will be greatest when used by populations at highest risk of infection, that is, those that have a HIV incidence of about three per 100 person-years or higher [7]. Preliminary work by UNAIDS which aims to chart sub-national HIV incidence across southern and eastern Africa in men and women suggests that incidence is ≥3% in at least one age/sex group in Kenya, Lesotho, Mozambique, South Africa, Swaziland and Uganda [8]. Throughout the continent, individuals in sero-discordant relationships and members...
of key populations (sex workers, men who have sex with men (MSM), transgender women and injection drug users) are likely to benefit from the availability of PrEP. UNAIDS 2016–20 has set a global target of putting 3 million people on PrEP annually, focused particularly on key populations and people at high risk in high prevalence settings [9].

While the case for making PrEP available across the continent is clear, it is important to recognize that not all those at substantial risk of HIV acquisition will opt to start it. To make an informed choice, people (and their healthcare providers) need to be able to accurately perceive their risk of HIV as well as their ability to mitigate it, have access to accurate information about the effectiveness, benefits and possible harms, and have the support and resources to be able to tailor its use to their requirements and to adhere to it. The availability of information about PrEP across Africa has not been formally mapped but is likely suboptimal, both among general and key populations and among healthcare providers. How best to generate demand for PrEP to those at highest risk of infection, without further stigmatizing them (or PrEP use) is not well understood.

**PrEP demonstration projects in SSA**

Since completion of the efficacy trials, tens of PrEP demonstration projects are underway or planned across Africa (see Table 1), with projects enrolling female sex workers (FSW), MSM, adolescent girls and young women (AGYW), as well as the general population across a range of countries. In addition, studies are addressing the use of PrEP as bridge in sero-discordant couples before the infected partner becomes virologically suppressed on treatment and/or has acute HIV infection [10].

**PrEP provision in FSW**

FSW are less engaged in HIV prevention and care services than women in the general population [11–13]. Sex work is criminalized in much of Africa leading to anxiety about confidentiality and contact with authorities [14]. FSW frequently face discrimination from health providers when they do access services [15]. Multipronged structural and community-led interventions are required to increase access and subsequent retention in services [16–20]. PrEP implementation projects targeting FSW have been conducted or are underway in Benin, Kenya [21], Senegal, South Africa and Zimbabwe [22] (Table 1). Of note, South Africa has recently become the first country in Africa to announce that it will make antiretroviral therapy (ART)-based prevention available for sex workers [23]. In Benin, a comprehensive prevention package is being implemented among FSW, with PrEP and ART being offered to 250 HIV-negative and 100 HIV-positive FSW, respectively. Women are seen quarterly (as is the case in most demonstration projects) and adherence is monitored using self-report and pill count, as well as tenofovir blood levels for those on PrEP, and HIV viral load (VL) monitoring for those on ART. Given concerns that PrEP use may lead to reductions in condom use, and increased risk of sexually transmitted infections and pregnancy, the project will determine whether the use of PrEP results in decreased use of condoms by measuring Y chromosome DNA and prostate-specific antigen in vaginal fluid [24,25].

In Zimbabwe, PrEP is being administered as part of the SAPPH-IRe trial, a clustered randomized trial of a community empowerment combination with onsite access to ART and PrEP, and supported by the ‘Adherence Sisters Programme’; which includes an adherence buddy programme and reminder SMS combined with active follow-up of defaulters [26]. The primary analysis will compare the proportion of all sex workers with a VL over 1000 copies/ml living in intervention and comparison communities [27]. The population-level impact and cost-effectiveness will be modelled.

**PrEP provision among MSM**

Where there are data, HIV-1 incidence among MSM in Africa is high and higher than among FSW in some settings [28–30]. The pervasive homophobia that extends across Africa [31] coupled with the widespread criminalization of sex between men has resulted in MSM being very poorly engaged with prevention and care across the continent [32]. In some African countries, there are clinics that provide tailored services for MSM and where they exist, these are likely to be the optimal delivery channel. In other countries, where there is no specific service provision, more creative solutions will be required to engage MSM with services. There is limited evidence that PrEP may be acceptable to MSM in Africa. Qualitative assessments during a phase I PrEP trial of four-month duration among MSM and FSW in Nairobi and Coastal Kenya in 2009–2010 found that while side effects were experienced early in the study these diminished over time, and that characteristics of pills could improve comfort and use. Social impacts such as stigma, rumours and relationship difficulties due to being perceived as HIV positive were prevalent; interventions to address HIV and ART stigma will be important in this context [33]. Three demonstration projects are in progress among MSM in Kenya and South Africa (see Table 1) while one more is planned and another has been completed.

**PrEP provision among adolescents and young people**

There are 10 demonstration projects either planned, completed or underway among AGYW (see Table 1) in Kenya, South Africa, Uganda and Zimbabwe. Young women (15–24) in east and southern Africa are an important population for PrEP implementation. They represent three of the four million young people living with HIV in SSA [34]. Participants in recent HIV prevention trials, who were recruited specifically because they felt themselves at high risk of infection, had annual HIV incidence of 5–9% [35,36]. Evidence from treatment scale up suggests that adolescents find it more difficult to adhere to treatment than adults [37] and may require increased adherence support, tailored to their age group and lifestyle. One completed trial of PrEP in young women from Cape Town demonstrated that this population was able to adhere to daily dosing when supported to do so [38]. Of note, younger women in this study adhered more reliably to daily rather than intermittent or event-driven dosing. Several projects that are enrolling AGYW are either underway or are in the final stages of planning, with sites in South Africa, Kenya, Zimbabwe and Tanzania (see Table 1).
Table 1. Summary of ongoing and planned PrEP demonstration projects in Africa (as of July 2016)

| Project name                                                                                   | Type of project                                      | Sites                                      | Target population                                                                 | Proposed enrolment | Dates                                                                 |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------|
| **Ongoing projects**                                                                         |                                                     |                                            |                                                                                  |                    |                                                                     |
| Partners demonstration project                                                                | Demonstration project PrEP as a bridge to ART       | Kenya, Uganda                              | HIV sero-discordant couples                                                      | 1013 HIV sero-discordant couples | Ongoing since August 2013; to complete follow-up: June 2016. Initial results presented at CROI 2015 |
| Choice for Adolescents Methods for Prevention in South Africa (CHAMPS)                        | Demonstration project (Pluspills, combined with 2 other projects) | South Africa                              | Heterosexual male and female adolescents aged 15–19                             | 150                | Ongoing since July 2011; Pluspills is expected to be completed in October 2016; UChoose is expected to be completed in June 2016 | Ongoing since February 2015; expected completion in May 2016 |
| Sibanye Health Project: Comprehensive HIV Prevention Package for MSM in Southern Africa Pilot Study | Demonstration project (pilot and integrated in a preventive package) | South Africa                              | MSM                                                                               | 200 MSM            |                                                                     |
| Sisters Antiretroviral Therapy Programme for Prevention of HIV – An Integrated Response (SAPPH-IRe) | Open label (combined with TasP)                      | Zimbabwe                                   | FSW                                                                              | 1200 FSW eligible for PrEP (500 women enrolled as June 2016) | Ongoing since July 2014; expected completion in mid-2016 |
| Gender-Specific Combination HIV Prevention for Youth in High Burden Settings (MP3-Youth)       | Demonstration project (within a combination prevention package) | Kenya                                      | Adolescent men and women aged 15–24                                             | Only women on PrEP (enrolling 1215 total) | Ongoing since November 2014; expected completion in November 2016 |
| Benin Demonstration Project with CHU de Québec (Canada)                                      | Demonstration project (combined with TasP)           | Benin                                      | FSW                                                                              | 250 in PrEP; 100 in TasP | Ongoing since October 2014; expected completion in January 2017     |
| Senegal Demonstration Project with Reseau Africain De Recherche Sur Le Sida, University of Washington and Westat | Demonstration project                               | Senegal                                    | FSW                                                                              | 275                | Ongoing since mid-2015; expected completion in late-2016            |
| TAPS Demonstration Project (Wits RHI)                                                         | Demonstration project (combined with TasP)           | South Africa                              | FSW (≥ 18 years)                                                                 | 400 in PrEP; 300 in TasP | Ongoing since April 2015. Expected completion April 2017            |
| LVCT Health and SWOP Kenya (IPCP-Kenya)                                                       | Demonstration project (within a combination prevention package) | Kenya                                      | FSW (≥ 18 years), MSM (≥ 18 years), young women at high HIV risk (15–29 years)     | 2100 participants   | Ongoing; started December 2015. Expected completion December 2016   |
| POWER                                                                                       | Demonstration project (within a package including microbicides) | South Africa, Kenya                        | Adolescent girls and young women aged 16–24; women aged 25–29                    | 1500               | Ongoing, started July 2015, PrEP delivery cohort to begin late 2016. Expected completion June 2020 Ongoing; started December 2015. Expected completion early-2016 |
| Anova Health Institute’s Health4Men initiative                                                | Demonstration project                               | South Africa, Lesotho, Tanzania, Swaziland, Thailand, Uganda                        | MSM                                                              | 300                |                                                                     |
| Project name                              | Type of project                                      | Sites                          | Target population                                                                 | Proposed enrolment               | Dates |
|------------------------------------------|------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------|----------------------------------|-------|
| CAPRISA 082                               | Demonstration project (observational cohort study)   | South Africa                  | Adolescent girls and young women aged 18–24; women aged 25–30                     | Total enrolment of 2500, PrEP uptake expected to be 750 | Ongoing, started March 2016. Expected completion April 2021 |
| Nigerian National Agency for the Control of AIDS | Demonstration project (combined with TasP)          | Nigeria                       | Heterosexual HIV sero-discordant couples                                          | Enrolling 600 individuals on PrEP | Ongoing; started late 2015. Expected completion in late 2017 |
| Planned projects                          |                                                      |                               |                                                                                   |                                  |       |
| EMPOWER Consortium Demonstration Project   | Demonstration project (within a combination package including violence prevention) | South Africa, Tanzania         | Adolescent girls and young women aged 16–24                                       | To be determined                 | Planned; expected start mid-2016 |
| Seasonal use of PrEP in Mozambique        | Demonstration project on periodical use of PrEP (feasibility phase) | Mozambique                    | Women and men                                                                     | To be determined                 | Feasibility study planning underway |
| DREAMS                                    | Implementation initiative                            | Kenya, South Africa, Uganda, Zimbabwe | Young women aged 18–24                                                           | 15,119; 3000; 1000; 1451         | Demonstration projects starting mid-2016. Planned |
| Right to care (under DREAMS)              | Demonstration project                                | South Africa                  | Adolescent girls and young women                                                  | To be determined                 | Planned |
| Tambua Mapema-PLUS                        | Pilot study                                          | Kenya                         | Sero-discordant couples including patients with acute HIV infection, identified at care seeking | 75                               | Planned, expected start Q4 2016 |
| Médecins Sans Frontières (MSF) International – South Africa PrEP Project | Demonstration project                               | South Africa                  | Adolescent girls (<24 years old) and MSM                                          | To be determined                 | Planned |
| HealthRight PrEP Project – Kenya          | Demonstration project (observational cohort study)   | Kenya                         | Male sex workers (MSW)                                                           | To be determined                 | Planned; start date pending ethics submission, expected start in July 2016. Expected completion in August 2018 |
| HPTN 082                                  | Demonstration project                                | South Africa, Zimbabwe        | Young women aged 16–25 years                                                      | 600                              |       |
| UNICEF PrEP Demonstration Program         | Demonstration project                                | South Africa, Brazil, Thailand | Adolescents                                                                       | Total target 15,071 (South Africa 10,000; Brazil 2671; Thailand, 2400) | Planned; expected start end-2016. Expected completion 2021 |
| Champs PlusPills (DTHF, University of Washington) | Demonstration project                                | South Africa                  | Adolescent girls and young women aged 16–25                                       | To be determined                 | Planned |
| Church of Scotland PrEP Project           | Demonstration project                                | South Africa                  | Adolescent girls who are pregnant                                                  | To be determined                 | Planned |

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### Table 1 (Continued)

| Project name | Type of project | Sites | Target population | Proposed enrolment | Dates |
|--------------|----------------|-------|-------------------|--------------------|-------|
| P3: Private Sector Provision of PrEP | Demonstration project | South Africa and Zimbabwe | Young women aged 20–34 | Planned enrollment is 10,000 in each country | Planned; expected start end-2016 |
| IMPAACT 2009 | Observational study | Malawi, South Africa, Uganda, Zimbabwe | Adolescent girls and young women aged 16–24 who are pregnant | To be determined | Planned; expected start early-2017. Expected completion in 2019/2020 |
| MTN 034/IPM 045 | Phase IIa open label (randomizing participants to either dapivirine ring or oral PrEP) | South Africa, Uganda, Zimbabwe | Adolescent girls and young women aged 16–17 | 300 | Planned; expected start early-2017 |

### Completed projects

| Project name | Type of project | Sites | Target population | Proposed enrolment | Dates |
|--------------|----------------|-------|-------------------|--------------------|-------|
| iPrEx OLE | Open-label extension | South Africa, (Brazil, Peru, Ecuador, Thailand, USA) | MSM and transgender women | 1250 (across all sites) | Completed. Open-label extension of the iPrEx trial | |
| Partners PrEP OLE | Open-label extension | Kenya, Uganda | HIV sero-discordant couples | 1262 (assigned to TDF or FTC/TDF) | Completed. Open-label extension of the partners PrEP trial; started in July 2011 and was completed in December 2012. | |
| CDC 494 (TDF2 follow-up) | Open-label extension | Botswana | Heterosexual men and women aged 18–39 | 1219 total (611 assigned to take daily TDF/FTC pill; 608 assigned to placebo) | Completed. Open-label extension of the trial among heterosexual men and women | |

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As with any medication prescribed or offered to those under age 18, there will be questions related to who provides consent. The only licensed drug currently available for PrEP use is Truvada, and PrEP is currently only a licensed indication for those aged 18 and over. There may be reluctance among providers to include PrEP for off-label usage. Drug safety is also an issue; there are concerns about bone safety with long-term use in younger populations. CHAMPS Pills Plus is an ongoing open-label study examining the safety, feasibility and acceptability of daily oral Truvada as PrEP in HIV-negative adolescents.

Although there is recognition that more intensive adherence support for young people will likely be required, this needs to be scalable. Approaches under investigation include individual adherence counselling, “adherence support clubs”, which either meet in person or virtually through “whatsapp” or both, use of treatment buddies, SMS and counselling on tenofovir drug levels (HPTN 082, Pluspills). The EMPOWER project in South Africa and Tanzania is also supporting young women to negotiate PrEP use within their intimate partnerships and within the broader social context. The DREAMS initiative is offering PrEP to young women as part of a comprehensive prevention package in Kenya, South Africa, Swaziland, Uganda and Zimbabwe with the intention of supporting prevention uptake and adherence using structural and behavioural interventions.

### PrEP provision in sero-discordant couples

There are three PrEP demonstration projects either completed or underway among sero-discordant couples (see Table 1) in Kenya and South Africa. Estimates of new HIV infections occurring within stable, heterosexual partnerships in Africa range from 30 to 60% [39-44]. WHO has provided guidance on use of PrEP for sero-discordant couples since 2013 [45,46], but the extent to which this has been incorporated into national guidelines across Africa is not clear. Identifying sero-discordant couples is critical as it allows for a range of treatment and prevention interventions, including those to allow safe conception [47] and to prevent transmission in pregnancy, tailored to the couple’s particular situation. While combining ART and PrEP for couples creates a package of mutual support and presents HIV care facilities as favourable service delivery venues, the efficiency and acceptability of delivery through HIV care facilities for HIV sero-discordant couples has not been evaluated. The Partners demonstration project has enrolled 1013 HIV sero-discordant couples in Kenya and Uganda since 2013, with near elimination of HIV infection (effectiveness of 96%) [10]. Plans are underway to recruit 1200 couples in a PrEP demonstration project in Nigeria (see Table 1).

### PrEP provision following acute HIV-1 infection diagnosis

While PrEP may be initiated by the HIV-negative partner in an established HIV sero-discordant partnership, identification of discordancy for the vast majority of cases assumes detection of prevalent HIV. The HIV-negative partner is at greatest risk of HIV-1 acquisition when the infected partner has acute or early HIV infection [48,49]. Increasingly, there is interest in using risk and symptom score screening algorithms combined with point-of-care qualitative RNA tests [50].

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**Table 1 (Continued)**

| Project name | Type of project | Dates | Proposed enrolment | Target population | Sites | Project name |
|--------------|----------------|-------|--------------------|-------------------|-------|--------------|
| HPTN 067 (ADAPT) | Phase II open-label (comparing timings for drug taking) | Started in August 2011 and was completed in December 2014; final analyses are underway. Results from analyses of potential sexual exposure, women in Cape Town show daily dosing fosters better adherence, better coverage of potential sexual exposure, and more sustained use of PrEP by South African women. Most study participants had higher coverage of sex events and better adherence when they were assigned to the daily dosing arm | 622 | Women (South Africa); MSM and transgender women (Thailand & USA) | South Africa (Thailand, USA) | Adapted from AVAC’s “Ongoing and Planned PrEP Demonstration and Implementation Studies” table, www.avac.org/prepdemo and www.prepwatch.org.

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Cowan FM et al. Journal of the International AIDS Society 2016, 19(Suppl 6):21101

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to identify patients with acute HIV infection (AHI) at care seeking [51]. The opportunity to identify sero-discordancy based on AHI patients presents a new dimension for PrEP initiation, as HIV-1 has been acquired from outside the partnership, and the HIV-negative partner is at greatest risk of HIV acquisition. A study among 1500 patients seeking care for symptoms and screened for prevalent HIV and AHI will start in Coastal Kenya in the second half of 2016, and PrEP uptake among sero-discordant couples identified in the context of care seeking will be assessed.

Discussion

In each of the populations discussed above, there are overarching issues related to (i) creating demand for PrEP for both potential users and for providers, (ii) addressing supply-side issues and (iii) providing appropriate and tailored adherence support [52]. It is widely agreed that PrEP will need to be delivered as part of a comprehensive package of HIV prevention services. The numerous demonstration projects now underway will evaluate different strategies for reaching the target populations and different approaches to implementation across populations and settings. Results of these projects then need to inform locally developed and context-specific policy recommendations which in turn facilitate delivery and uptake of PrEP.

Demand creation

A critical first step in creating demand for PrEP is the normalization of HIV prevention, without this the stigma which undermines many HIV prevention interventions will persist. MSM, FSW and young women are important advocates for PrEP; empowering them with correct knowledge is likely to strengthen community trust, mitigate against rumours, increase acceptance, uptake and adherence. While empowerment of key populations is critical, community-level interventions that engage sex partners, opinion leaders and the general population about their role in HIV prevention are warranted. Of note, there is concern among the sex work community that sex workers will be targeted as “high risk” or “promiscuous”, this could greatly undermine uptake.

Of note, there is concern among the sex work community internationally that promoting PrEP may undermine condom and community empowerment programmes where they exist [53,54], and that rolling out PrEP to some could distract from ensuring provision of services for all. In addition, FSW worry that it could “re-medicalize” prevention, undermining community initiatives. In some settings, there is potential for PrEP administration to be coercive (particularly if long-acting preparations become available) and stigmatizing. Implementation of PrEP in sex workers needs to be in full collaboration with sex workers themselves and be sensitive to the local concerns and realities that women face. Consideration of the rights of sex workers (and all those eligible for PrEP) is critical when formulating national implementation plans [16].

Risk perception among young women is often poor even among those at high risk of infection and was one of the greatest barriers to uptake in some, but not all, of the earlier PrEP trials [55]. Creating demand for PrEP among young women will necessitate addressing barriers to prevention uptake that young people face more generally, in addition to providing information about the effectiveness and availability of PrEP specifically. Raising community awareness using messages that resonate with young women to improve knowledge and establish norms around PrEP use and maximize its acceptability will be critical. Use of social media, video and community outreach both to create demand and inform risk assessment is planned or underway in many of the demonstration projects listed in Table 1.

Supply side

Critical to supply of PrEP is that services are accessible for all, including stigmatized populations. For sero-discordant couples, it may be possible to make PrEP available through existing treatment facilities, but this will not be appropriate for the majority of potential users. For key populations, PrEP needs to be made available through specific programmes tailored to their requirements as well as through primary care. Establishing accessible integrated services for young women and their partners will be critical to scaling-up PrEP to this group and provides the opportunity to address other public health priorities for young people, including the unmet need for contraception.

Testing for HIV is the gateway to both treatment and biomedical prevention interventions, including for PrEP. Although rates of testing are increasing, there are still many people in Africa who are unaware of their status [56]. Scaling-up testing through a range of community-based approaches including self-testing, house-to-house and work-based approaches, with support for linkage to services is required. Training of health providers both to provide PrEP and transform judgmental and stigmatizing behaviours is important. In many parts of the world, misconceptions among health providers about the effectiveness and side effects of PrEP, as well as the likelihood it will induce drug resistance have slowed uptake [57]. National policies need to include minimum standards for training and quality assurance for PrEP implementation, as well as addressing supply chain issues which secure drug availability [58].

Making antiretroviral-based PrEP available through prevention services will require a shift in how they are organized. Antiretroviral drugs are currently procured, distributed and monitored through treatment programmes. Services providing PrEP using outreach may require adaptation of pharmacy or healthcare regulations. First-generation products will likely require a prescription from a healthcare provider, regular re-supply and monitoring and surveillance to detect ART resistance. As increasing evidence of safety emerges, barriers to access will likely reduce (as happened with hormonal contraception) [59]. There are several new products in the pipeline [60] and services need to be positioned so that they can introduce these as and when they are approved.

Cost is a significant consideration particularly where there is a culture of underinvestment in prevention [3]. For key populations and AGYW, risk is heterogeneous both between and within countries and finding ways to identify and support those at highest risk will be critical. The use of risk score tools may be appropriate but needs to be carefully
evaluated [61,62]. Studies addressing the issues of willingness to pay are planned in some settings globally although the consequences of paying for PrEP when treatment is freely available need to be considered.

**Adherence support**

PrEP adherence has generally been better in recent trials and open-labelled studies, when the efficacy of PrEP was already known likely changing the motivation for participation [63]. Adherence to PrEP does not need be lifelong and it is only required to cover periods of high risk [63,64]. For MSM, 100% adherence is likely not required for prevention of transmission, whereas pharmacokinetic studies among women suggest that adherence will need to be more consistent [65–67]. Some studies are exploring the use of tenofovir levels to support adherence. While the scalability of drug levels to monitor PrEP adherence is unlikely to be feasible using existing technology, point-of-care urine assays for tenofovir are in development. The cost of these assays will likely range from $10 to $20 per test, which may be potentially affordable for PrEP implementation programmes in some settings [68–70].

Adherence interventions need to be responsive to the social and structural factors that are likely to have an important influence. Combining interventions that build self-efficacy, empowerment and social cohesion, with evidence-based individualized adherence support for both PrEP and ART, are likely to be effective and mutually reinforcing [71–74]. Interventions that work across the cascade are likely to be more scalable and cost-effective than those that work on only one aspect [75].

FSWs are highly mobile. Supporting continuation of access to PrEP (or ART) despite this mobility is likely to be critical. Drawing on differentiated care models from the treatment world where those stable on treatment can collect drugs less frequently should be considered (possibly in combination with confirmation of adherence through drug levels) [76]. Alternatively, medication refill groups that facilitate less frequent collection of drug by alternating collection among group members may be an option [77].

**Research monitoring and evaluation**

Implementation research is underway to determine how to take PrEP delivery to scale across Africa in a way that is sustainable, durable, non-stigmatizing, cost-effective and has...
the greatest impact. Data are required on the relative merits and disadvantages, including costs, of different demand creation, delivery and adherence support models, as well as real-world patterns of PrEP usage (see Table 2). Leakage of drug from treatment programmes, particularly in the event that PrEP is socially marketed in some settings will be important. Determining the population-level impact will also be important – several modelling projects are already under way to do this and will be strengthened by increasing the availability of programme data. Ongoing research to increase the choice of agents for PrEP needs to remain a priority [60].

Conclusions
Efficacy of tenofovir-based PrEP is proven, but many issues related to implementation are still unclear. Here, we have summarized some of the important implementation questions that need to be assessed as PrEP is rolled out across Africa.

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All authors are or have been investigators on trials that have received a donation of Truvada from Gilead Sciences.

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Commentary

PrEP implementation in the Asia-Pacific region: opportunities, implementation and barriers

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Abstract

Introduction: HIV epidemics in the Asia-Pacific region are concentrated among men who have sex with men (MSM) and other key populations. Pre-exposure prophylaxis (PrEP) is an effective HIV prevention intervention and could be a potential game changer in the region. We discuss the progress towards PrEP implementation in the Asia-Pacific region, including opportunities and barriers. Discussion: Awareness about PrEP in the Asia-Pacific is still low and so are its levels of use. A high proportion of MSM who are aware of PrEP are willing to use it. Key PrEP implementation barriers include poor knowledge about PrEP, limited access to PrEP, weak or non-existent HIV prevention programmes for MSM and other key populations, high cost of PrEP, stigma and discrimination against key populations and restrictive laws in some countries. Only several clinical trials, demonstration projects and a few large-scale implementation studies have been implemented so far in Thailand and Australia. However, novel approaches to PrEP implementation have emerged: researcher-, facility- and community-led models of care, with PrEP services for fee and for free. The WHO consolidated guidelines on HIV testing, treatment and prevention call for an expanded access to PrEP worldwide and have provided guidance on PrEP implementation in the region. Some countries like Australia have released national PrEP guidelines. There are growing community leadership and consultation processes to initiate PrEP implementation in Asia and the Pacific. Conclusions: Countries of the Asia-Pacific region will benefit from adding PrEP to their HIV prevention packages, but for many this is a critical step that requires resourcing. Having an impact on the HIV epidemic requires investment. The next years should see the region transitioning from limited PrEP implementation projects to growing access to PrEP and expansion of HIV prevention programmes.

Keywords: pre-exposure prophylaxis; the Asia-Pacific region; implementation; demonstration studies; PrEP policy; PrEP awareness; PrEP use; MSM.

Introduction

In 2014, the Asia-Pacific region was home to more than half of the world’s population and 15.2% of the estimated 36.9 million people living with HIV globally [1]. Most of the region’s HIV-positive people (~90%) live in five countries – China, India, Indonesia, Thailand and Vietnam [2]. Epidemics in the region can be characterized as concentrated and growing in key populations, mainly among men who have sex with men (MSM), particularly young MSM, or shifting towards MSM as the main mode of transmission. Below, we focus on 12 countries with the largest number of people living with HIV (see Table 1) [3].

From 2000 to 2014, the estimated number of new infections in the Asia-Pacific declined by 31%, although it stalled during the last eight years, and the estimated number of AIDS-related deaths increased by 11% [1]. Globally, HIV incidence decreased by 35% after 2000 and AIDS-related deaths dropped by 42% after 2004 [4]. New HIV infections declined in some countries in the region (India, Myanmar, Thailand, Cambodia and Vietnam) but increased in others (Pakistan, Philippines and Indonesia).

HIV prevalence is 5 to 15 times higher among MSM compared to the general population in South and South-East Asia [5]. Infections among female sex workers (FSW) have slowed but remain important contributors to HIV transmission in the region [6]. Limited data are available about the HIV epidemics in transgender people (TG), estimated to number 9 to 9.5 million in the region [7], and small-scale research is mostly limited to TG women who have sex with men. In several cities HIV prevalence in this group was substantially higher than in the general population of reproductive age and even higher than in MSM [8].

While disproportionately affected by HIV, the key risk populations are mostly underserved by HIV prevention programmes. Throughout Asia, less than 60% of MSM and FSW know where to get tested for HIV or have received condoms through distribution programmes [9] (level of condom use >80% is considered to have an impact on an
In Asia, there are currently three demonstration projects underway and a large-scale implementation trial, EPIC-NSW (Expanded PrEP Implementation in Communities in New South Wales) [30]. Based in the state with the largest overall population and MSM community [31], EPIC-NSW is a partnership of the key NSW government, community, medical and research organizations. The project aims to rapidly scale up PrEP implementation to about 3700 high-risk participants [32]. Its scope and size were estimated based on the high-risk PrEP-eligibility risk criteria of the NSW PrEP guidelines, data from previous Australian studies about HIV transmission factors in the Australian context and on estimation of the expected impact this project may have on the HIV epidemic in NSW [33].

Thailand, the first country in the region to host the PrEP trial sites, has several PrEP implementation projects underway (see Table 1). The PrEP-30 project [38], led by the Thai Red Cross AIDS Research Centre (TRCARC), is using a fee-based PrEP service delivery model. The PrEP implementation project for MSM and TG evaluates a community-led PrEP service delivery model (services provided by non-medical staff of the four community-based organizations) and a facility-based model (services provided by two hospitals). The Princess PrEP project (also based on the community-led PrEP service delivery model) is the result of the TRCARC’s Princess Soamsawali Prevention of Mother-to-Child Transmission Fund, which recently transformed into the Princess Soamsawali Fund for HIV Prevention. It aims to provide PrEP to 3000 MSM and TG women over three years, starting in 2016. TRCARC has also started exploring innovative technology-based interventions [39], especially for targeting young and closeted individuals and for those who are typically hard to reach. Adam’s Love has been the leading online outreach platform for PrEP awareness and counselling among Thai MSM and TG to facilitate recruitment and enrolment into the PrEP-30 and Princess PrEP Projects [39]. Its online-to-offline recruitment model has demonstrated the feasibility of reaching the previously un-reached MSM and TG through the use of technology-based interventions, linking them to offline PrEP services, helping them with adherence and following them up through the use of its innovative electronic health record system.

PrEP pilot projects are being planned in other Asian settings including Manila, the Philippines, and Ho Chi Minh City, Vietnam.

PrEP implementation issues

Almost four years after PrEP approval by the US Food and Drug Administration [40], PrEP implementation in the United States remains a work in progress: the number of people receiving PrEP started to increase rapidly in about 2014 [41]. Elsewhere, PrEP implementation has been limited due to a number of issues.

Although awareness about PrEP has been increasing [23], its levels and pace of growth are still insufficient to produce a reasonable service demand. Scale-up of education about PrEP is necessary in the communities around the region.

Access to PrEP is part of a much broader issue in the Asia-Pacific. Many countries are struggling to provide access to antiretroviral therapy (ART) to all eligible people with HIV. In 2014, 36% of all adults living with HIV in the Asia-Pacific were

Discussion

Levels of PrEP awareness and acceptability

Recently, several surveys on PrEP awareness and use have been reported from the Asia-Pacific, including from China [19], India [20–22], Thailand [23] and Australia [24–27] (see Table 1). Overall, there has been no systematic data collection about PrEP in the region. Where available, results from published studies are not consistent and are incomparable, as different measures were used. Overall awareness about PrEP among Asian MSM is very low outside of Australia and Thailand, but among those aware about PrEP, willingness to use it is relatively high. Almost no PrEP-related data exist about other population groups. The Asia and Pacific Coalition on Male Sexual Health (APCOM) is planning surveys of PrEP acceptability among MSM and their health providers in countries with high HIV prevalence to inform future PrEP implementation [28].

PrEP trials and demonstration studies

Some sites in Asia have participated in randomized trials of PrEP, which helped to generate local evidence and advocacy for further PrEP research and implementation. Among MSM, Chiang Mai in Thailand was a site of the original iPrEx study [13] and the Silom Community Clinic in Bangkok participates in the ongoing HPTN 067/ADAPT study examining alternative PrEP dosing in MSM and TG women [29]. The only study to evaluate PrEP efficacy in PWID globally was conducted in Bangkok [16]. There have been no randomized clinical trials of PrEP focused on heterosexuals or TG women in the region.

PrEP research in the region is moving to PrEP demonstration studies (see Table 1). They are a critical step to implementation, because they generate experiences and highlight local barriers to PrEP uptake and challenges for future PrEP implementation (e.g., adherence to PrEP) in the region.
Table 1. HIV epidemics in 12 countries of Asia-Pacific region (end of 2014)

| #  | Country | Estimated number of new infections in 2014 | HIV prevalence in 2014, adults 15 to 49 | Key characteristics of the epidemic | Levels of PrEP awareness, acceptability and use | PrEP demonstration and implementation projects |
|----|---------|-----------------------------------------|---------------------------------------|------------------------------------|---------------------------------------------|--------------------------------------------------|
| 1  | Australia | 1300 (630 to 1700) | 0.2% | Sexual transmission, mainly among MSM (70% of new cases in 2014). | • In 2013, 77% of HIV non-positive MSM had heard of PrEP; 29% knew someone taking PrEP; 17% discussed PrEP with a doctor [25] | 1. Demonstration project PRELDUE [34] (2014 to present): 300 participants taking daily oral TDF/FTC in Sydney, Australia. **Aim**: Establish and evaluate PrEP service delivery model in NSW, Australia; evaluate PrEP acceptability, adherence, behaviour, STI incidence among MSM. **Sponsor**: The Kirby Institute, UNSW Australia. |
|    |         |                                        |                                       |                                    |                                             | 2. Implementation study EPIC-NSW [30] (2016 to 2018): 3700 participants taking daily oral TDF/FTC in NSW, Australia. **Aim**: Evaluate effect on HIV incidence from providing PrEP to high-risk population group/s. **Sponsor**: The Kirby Institute, UNSW Australia. |
|    |         |                                        |                                       |                                    |                                             | 3. Demonstration project VicPrEP [35] (2014 to 2019): 115 MSM and women at high risk of HIV infection taking daily oral TDF/FTC in Melbourne, Australia. **Aim**: Determine the effectiveness of PrEP in the local setting and the factors contributing to its success. **Sponsor**: Alfred Health, in conjunction with the Victorian AIDS Council. |
|    |         |                                        |                                       |                                    |                                             | 4. Demonstration project QPrEP [36] (2016 to present): 50 MSM taking daily oral TDF/FTC in Cairns, Australia. **Aim**: Evaluate PrEP delivery in Queensland health services. **Sponsor**: Queensland Health. |
| 2  | Cambodia | 860 (440 to 2200) | 0.6% | Sexual transmission; an urban epidemic among three key populations and their partners. | N/A | – |
| 3  | China   | 60,000 (15,000 to 130,000) | 0.1% | Sexual transmission, mainly among MSM; nationally declining epidemic, with regional variations. | • In 2009 to 2010, 11.2% of MSM in Beijing had heard of PrEP; 67.8% were willing to accept it if it was effective [19]. | – |
| 4  | Indiaa | 86,000 (56,000 to 129,000) | 0.3% | HIV epidemic heterogeneous in its distribution, concentrated among high-risk groups. Nationally declining epidemic, with regional variations. | • In 2010 to 2011, > 75% of MSM reported they would be willing to take PrEP, mainly in an injectable form [20]. | 1. Prospective intervention PrEP-India (April 2016–June 2018, not active yet): 2000 SW taking PrEP plus peer educator home visits every other day, as part of regular DMSC (Kolkata) and Ashodaya (Mysore/Mandya) outreach prevention activities. **Aim**: Demonstrate safety and effective delivery of daily oral PrEP as part of an HIV combination preventive intervention for sex workers in Kolkata and Mysore-Mandya, India. **Sponsor**: University of Manitoba. |
|    |         |                                        |                                       |                                    |                                             | 2. Demonstration project QPrEP [36] (2016 to present): 50 MSM taking daily oral TDF/FTC in Cairns, Australia. **Aim**: Evaluate PrEP delivery in Queensland health services. **Sponsor**: Queensland Health. |
| #  | Country          | Estimated number of new infections in 2014*  | HIV prevalence in 2014, adults 15 to 49a | Key characteristics of the epidemic                                                                 | Levels of PrEP awareness, acceptability and use | PrEP demonstration and implementation projects |
|----|------------------|---------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 5  | Indonesia        | 69,000 (63,000 to 76,000)                   | 0.5% Shift from injecting drug use to sexual transmission. Key population groups involved in the epidemic: transgender SW, male and female SW, PWID and MSM. | N/A                                                                                                    | –                                             |
| 6  | Malaysia         | 6200 (5700 to 6800)                         | 0.4% In earlier phases epidemic was driven by PWID, then shifted to sexual transmission, with heterosexual/homosexual ratio = 2:1. | N/A                                                                                                    | –                                             |
| 7  | Myanmar          | 8700 (7800 to 9500)                         | 0.7% Epidemic mainly evolving in PWID, but increasing in this group and in MSM.                        | N/A                                                                                                    | –                                             |
| 8  | Nepal            | 1500 (1300 to 1600)                         | 0.2% Most HIV infections happen in low-risk males and females, PWID, MSM and TG. Infections have declined in PWID but have increased in MSM. | N/A                                                                                                    | –                                             |
| 9  | Papua New Guinea | 2000 (1500 to 2500)                         | 0.7% Epidemic recently downgraded from generalized to concentrated; men and women who sell sex and MSM are key population groups engaged in the epidemic. | N/A                                                                                                    | –                                             |
| 10 | Philippines      | 6400 (1500 to 12,000)                       | 0.1% Homosexual contact is the main mode of HIV transmission, and people who inject drugs in certain geographical areas. | N/A                                                                                                    | –                                             |
| 11 | Thailand         | 7900 (3700 to 13,000)                       | 1.1% Key affected populations: FSW, MSW, MSM and TG with very high incidence among young MSM. Number of new HIV infections continues to decline but at a slower pace since 2010. | - 1. PrEP implementation project in MSM and TG (2015 to 2018): 600 MSM and TG, including 300 in community-based settings (four CBOs: SWING Foundation in Bangkok and Pattaya, Rainbow Sky Association of Thailand in Bangkok and Sisters Foundation in Pattaya) and 300 in the facility-based setting (two hospitals in the Test and Treat project in Bangkok and Pathumthani), taking daily oral TDF/FTC. **Aim:** Assess PrEP uptake and factors influencing decision-making among MSM and TG. **Sponsor:** Department of Disease Control, Thai MOPH, and Thailand MOPH-US CDC Collaboration, Thai Red Cross AIDS Research Centre. 2. Observational study Princess PrEP project (2016 to 2018): 3000 MSM and TG taking daily oral TDF/FTC. **Aim:** Expand oral PrEP access among MSM and TG through seven CBOs in Bangkok, Pattaya, Chiang Mai and Hat Yai; study the characteristics of these MSM and TG. **Sponsor:** Thai Red Cross AIDS Research Centre, USAID ROMA, FHI360. | –                                             |
### Table 1 (Continued)

| #  | Country | Estimated number of new infections in 2014a | HIV prevalence in 2014, adults 15 to 49° | Key characteristics of the epidemic | Levels of PrEP awareness, acceptability and use | PrEP demonstration and implementation projects |
|----|---------|-------------------------------------------|----------------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|
| 12 | Vietnam | 15,000 (13,000 to 16,000)                  | 0.5%                                   | Number of new infections rapidly declined between 2007 and 2009 and stabilized after that. Transmission stabilized and declined in all groups except MSM. Infections are increasing in remote and mountainous areas. | N/A                                           | 3. Observational study PrEP-30 project [38] (2014 to present) [38]: Unlimited number of MSM, TG, women taking daily oral TDF/FTC. **Aim:** Assess feasibility of a self-paid oral PrEP programme (clients pay 30 THB per day or 1 USD per day to cover the cost of generic TDF/FTC, laboratory screening, monitoring and counselling) at the Thai Red Cross Anonymous Clinic. **Sponsor:** Thai Red Cross AIDS Research Centre. 4. Open label intervention COPE4YMSM (2015 to 2020): 1240 young MSM, including 620 who chose PrEP and 620 who did not choose PrEP. Combination intervention: daily oral TDF/FTC with or without regular HIV testing, risk reduction counselling, condom and condom-compatible lubricant distribution. **Aim:** Assess the effectiveness of a combination HIV prevention intervention with and without daily oral Truvada® (PrEP). **Sponsor:** Johns Hopkins Bloomberg School of Public Health. 5. Implementation study PrEP @ PIMAN (2015 to 2017): 200 MSM and TG women in Chiang Mai. **Aim:** Assess acceptability of daily oral PrEP among MSM and TGW, factors that influence the decision to take daily oral PrEP and assess adherence to PrEP among PrEP users. **Sponsor:** Research Institute for Health Sciences, Chiang Mai University, Chiang Mai. |

FSW, female sex worker; MSM, men who have sex with men; MSW, male sex worker; PrEP, pre-exposure prophylaxis; PWID, person who injects drugs; STI, sexually transmitted infection; SW, sex workers; TGW, transgender women; CBO, community-based organization.

aData about new HIV infections and HIV prevalence provided by WHO. bData not available. cIndia HIV Estimate 2015, NACO 2015.
receiving treatment, compared to 40% globally [42]. Some countries have made significant progress: for example, 83% of eligible HIV-positive people in Thailand and 82% in Cambodia were on ART in 2012. However, some countries with large numbers of eligible people (under the 2010 WHO HIV treatment guidelines) were lagging behind with respect to ART coverage (examples include India (57%), Indonesia (18%) and Myanmar (45%)).

HIV testing is the entry point for HIV prevention and treatment, but the regional median coverage of MSM with testing remains low (less than 50% of MSM in the majority of countries with available data in 2013 [43]). The lack of community-based testing and policies to allow lay and peer provider testing are barriers to reaching MSM though community outreach approaches in many countries. HIV self-testing has the potential to reach people who do not have contact with health services. It is available informally via the Internet and pharmacies but is not as yet included in national testing policies, and most countries do not have quality assurance systems in place to ensure the control of and access to high-quality testing services [44].

In some countries, such as Myanmar [45], Cambodia [46] and the Philippines [47], old punitive laws are still in action. As a result, stigma and discrimination against marginalized groups remain common barriers to PrEP implementation. Of note, most countries acknowledge the existent issues and some have achieved progress in eliminating stigma and discrimination. For example, the Vietnam Health Insurance Law is intended to cover 100% of the costs of HIV-related services for poor people and 95% for the near-poor [48].

The cost of antiretrovirals (ARVs) has been a major problem. In many Asian countries, ARVs are not available outside of government-accredited treatment hubs (e.g. Philippines) [42] due to high medication cost. In some countries (e.g. Thailand, Vietnam, Singapore, Malaysia), ARV medications are available in the private sector. Issues that impact access to PrEP are related to drug licensing (e.g. generic TDF/FTC is not yet approved by regulatory authorities in Australia) and pricing. Although generic TDF/FTC is produced in the region, it is not registered for preventive use there. Furthermore, restrictions on access to ARVs due to the complexity of intellectual property laws may affect the rapid implementation of PrEP in many countries in the region [49]. Meanwhile, projects like PrEP-30 in Thailand have introduced a fee-based PrEP service delivery model with a user fee of 30 Thai baht (approximately US$1) per day to cover facility and physician fees, laboratory testing and generic TDF/FTC costs [38]. In Australia, TDF/FTC (marketed as Truvada® by Gilead Sciences, Inc.) was approved for preventive use in May 2016. However, to make it affordable to all Australians, the medications should also be approved under the national Pharmaceutical Benefits Scheme. Several innovative approaches have emerged to start PrEP implementation, including investment by state governments in large-scale PrEP implementation studies in NSW [50] and Victoria [51], clinicians prescribing PrEP outside demonstration projects and community initiatives providing education about access to PrEP [52].

Even if PrEP was made available, there is little practical guidance for countries with concentrated epidemics on how to target PrEP to high-risk groups. WHO guidelines recommend targeting PrEP to population groups with HIV sero-incidence above 3 per 100 person-years [53]. HIV infection in the Asia-Pacific region is concentrated among MSM and other key populations, but there is a general lack of data about HIV sero-incidence in these groups. In Australia, eligibility criteria for PrEP target high-risk MSM based on local HIV sero-incidence data derived from research cohorts [33].

There is another reason for a lack of PrEP uptake – simply, provision of ARVs for HIV-negative people as primary HIV prophylaxis is a new service just about everywhere around the world. Different service delivery models have recently emerged across the Asia-Pacific region: large-scale implementation trials led by researchers [15,50], as well as facility-based and community-based initiatives (e.g. in Thailand). In Thailand and Australia, some projects are investigating the use of PrEP navigators and nurses in providing PrEP services.

The WHO consolidated guidelines on HIV testing, treatment and prevention call for an expanded access to PrEP [54]. No nations in the Asian region provide free PrEP to those at risk of HIV, although there are scale-up implementation projects in Thailand and Australia that provide free PrEP to a limited number of participants. Some PrEP access projects, like the PrEP-30 project in Bangkok, charge nominal fees for PrEP and associated services [38]. However, even in high-income countries, such PrEP access programmes are only a temporary solution. Thus, solutions are important for Truvada costing and widespread access to generic TDF/FTC.

Policy on PrEP

In 2012, the WHO published a framework for PrEP implementation and research [55] and consolidated guidance on HIV prevention, diagnosis, treatment and care for key populations internationally [54]. Some countries have chosen to develop their own prescriber guidelines. Australia released NSW state and then national guidance for PrEP prescribers in 2014 to 2015 [33,56]. Australian guidance differs from current clinical guidelines in the United States [56,57], South Africa [58] and the European Union [59] in its approach to determining eligibility for PrEP. In the current environment with limited access to TDF/FTC, the guidelines target daily PrEP to those at high and ongoing risk of HIV infection, which in the Australian context is mainly MSM [56]. These recommendations may expand to those at only moderate risk of HIV as access to PrEP improves.

Other countries in the region have also been working on PrEP policy development. Thailand included a PrEP recommendation for high-risk populations in the Thailand National Guidelines on HIV/AIDS Treatment and Prevention in 2014 [60]. The new Malaysian National Strategic Plan for Ending AIDS 2016-2030 also recommends studying uptake of self-paid PrEP [61].

Community involvement and leadership

The Asia-Pacific hosts some prominent examples of community participation, leadership and partnership in promoting PrEP implementation. APCOM is a regional and global advocate of delivering PrEP to MSM. In 2015, APCOM hosted the first community-led regional dialogue in Bangkok – a community and stakeholder consultation, to inform the
development of PrEP demonstration projects among MSM in countries with high HIV prevalence where PrEP rollout is in planning [62]. Examples of community leadership as to PrEP have emerged mainly in two countries. In Australia, traditionally active partners in HIV response [63], the AIDS Councils of NSW and Victoria, are also key partners in rolling out PrEP demonstration projects. The state Ending HIV campaigns promoted by these AIDS Councils are now supporting the implementation of PrEP [64]. In 2015, new examples of community advocacy for PrEP have also emerged, mostly driven by limited access to and high cost of PrEP, such as community information resources on how to access PrEP outside demonstration projects in Australia (the PrEP Access Options paper [15]). In Thailand, the SWING Foundation, Rainbow Sky Association of Thailand and Sisters Foundation have worked closely with TRC/AR under USAID/PEPFAR on generating PrEP awareness and demand and providing PrEP services.

However, even more community involvement is needed to advocate for the need for PrEP in other countries and in other key population groups yet overlooked for PrEP implementation (particularly TG people, FSW, MSW and their clients).

Conclusions

Issues specific to HIV epidemics in Asia-Pacific, particularly the concentration of HIV among MSM and other key population groups, make PrEP a suitable HIV prevention intervention for the region. Very few countries in the Asia-Pacific region have implemented PrEP, and those that have are in the inception stages of PrEP implementation. Overall there is a general lack of available data about progress towards PrEP implementation in countries other than Thailand and Australia. There have been clinical trials and demonstration projects of PrEP in Thailand and Australia, and several more are in planning across the region. However, in countries other than Australia and Thailand, there is little information about government policy and strategy, as well as demand from communities about PrEP implementation. Awareness about PrEP in the region is growing. Among MSM who have heard about PrEP, in some settings there are high levels of acceptability and willingness to use PrEP but low levels of uptake, while less is known about other population groups. In most countries in the region, there is no systematic collection of information about PrEP awareness, acceptability and use in key population groups to understand PrEP needs and inform introduction of PrEP in national HIV strategies. Few data are available about PrEP use among MSM, and hardly any data are available in other key population groups, which have been generally overlooked in PrEP access programmes. Issues of stigma and discrimination are common in many counties. Some still have restrictive laws that have implications for access by the key risk populations to HIV prevention in general and to PrEP. Moreover, access to ART for eligible people living with HIV has been improving but not to the level expected yet, so introduction of PrEP is challenging in many countries of the region and costly for all. Countries of the Asia-Pacific will benefit from adding PrEP to their HIV prevention packages, but for many this is a critical step that requires resources and access to TDF/FTC. Having an impact on the HIV epidemic requires investment in PrEP. The interest and leadership in the region associated with bringing this intervention to communities is encouraging and exciting. There are already prominent examples of action, at least in Thailand and Australia. The next years should see the region transitioning from limited PrEP implementation projects to increasing access to PrEP and expansion of HIV prevention programmes.

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Towards a fair consideration of PrEP as part of combination HIV prevention in Latin America

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Abstract

Introduction: Despite progress in scaling up antiretroviral treatment, HIV prevention strategies have not been successful in significantly curbing HIV incidence in Latin America. HIV prevention interventions need to be expanded to target the most affected key populations with a combination approach, including new high impact technologies. Oral pre-exposure prophylaxis (PrEP) is recommended as additional prevention choice for individuals at higher risk of infection and could become a cost-effective prevention tool. We discuss the barriers and solutions for a fair consideration of PrEP as part of combination HIV prevention strategies in Latin America.

Discussion: Although demonstration projects are ongoing or being planned in a number of countries, to date no Latin American country has implemented a public PrEP programme. The knowledge of policymakers about PrEP implementation needs to be strengthened, and programmatic guidance and cost estimate tools need to be developed to support adequate planning. Despite high levels of awareness among health providers, especially if engaged in HIV or key population care, willingness to prescribe PrEP is still low due to the lack of national policies and guidelines. Key populations, especially men who have sex with men, transgender women and sex workers, have been engaged in demonstration projects, and qualitative research shows high awareness and willingness to use PrEP, especially if accessible in the public sector for free or at affordable price. Concerns of safety, adherence, effectiveness and risk compensation need to be addressed through targeted social communication strategies to improve PrEP knowledge and stimulate demand. Alliance among policymakers, civil society and representatives from key populations, healthcare providers and researchers will be critical for the design and successful implementation of PrEP demonstration projects of locally adapted delivery models. The use of mechanisms of joint negotiation and procurement of antiretrovirals could reduce costs and significantly increase the cost-effectiveness of PrEP.

Conclusions: PrEP is an additional prevention tool and should be implemented in combination and synergy with other prevention interventions. PrEP programmes should target high-risk individuals from key populations for higher cost-effectiveness. Demonstration projects may generate strategic information for and lead to the implementation of full-scale PrEP programmes.

Keywords: pre-exposure prophylaxis; HIV; prevention; antiretrovirals; Latin America.

Introduction

By the end of 2014, Latin America had achieved substantial results in expanding antiretroviral treatment (ART) coverage to 47% of estimated people living with HIV [1]. However, progress in halting and beginning to reverse the HIV epidemic by 2015 [2] has been less successful, and despite some progress (13% reduction between 2000 and 2014 in the estimated number of new HIV cases per year), the region fell short against expected targets [1,3]. Considering current trends in HIV incidence, Latin American countries will need to accelerate the scale-up of ART to fully benefit from the preventive effect of treatment, as well as expand HIV combination prevention interventions, targeting key populations and including new effective technologies [4].

Among newly available tools, daily oral pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine (TDF/FTC) has been proven safe and effective to prevent HIV among men who have sex with men (MSM), transgender women (TGW), heterosexuals at high risk, uninfected partners in serodiscordant couples and injection drug users [5–11]. In 2014, the World Health Organization (WHO) released a recommendation on the use of oral PrEP as additional HIV prevention choice for MSM within a comprehensive HIV prevention approach, reviewed in 2015 to expand PrEP indication to all people at substantial risk of HIV infection [12,13].

To date, PrEP demonstration projects have been expanded worldwide; however the United States remains the only country in the Americas to have started large-scale implementation of PrEP regulated by normative bodies and based on clinical guidelines [14–16].

Considering that the HIV epidemic in Latin American countries is mainly concentrated in key populations, frequently...
hidden epidemics involving hard-to-reach individuals with inequitable access to services and victims of stigma, discrimination and criminalization in some cases. HIV prevention interventions should be focused, acceptable and tailored to the needs of these most affected groups [17,18]. As part of HIV combination prevention packages, PrEP could become a cost-effective tool, especially when used by individuals at higher risk of infection and in addition to traditional prevention interventions. Nevertheless, implementing PrEP in resource-limited settings entails several challenges related to demand, service delivery, regulatory aspects and affordability of medications [19].

The purpose of this paper is to discuss the barriers and solutions for a fair consideration of PrEP as part of combination HIV prevention policies and programmes in Latin America.

Discussion

Current status of PrEP in Latin America

Since the implementation of the first proof-of-concept multicountry trial in MSM, which included sites in Peru, Brazil and Ecuador, an open-label follow-up continued enrolling MSM and TGW to evaluate PrEP uptake, adherence, safety and effectiveness [20,21]. Despite the contribution of Latin American countries to these trials, policy development and programming have shown little progress, and no country has yet launched public PrEP services.

Brazil is currently carrying out multiple demonstration projects. The PrEP Brasil Project (clinical trial NCT01989611), coordinated by the Oswaldo Cruz Foundation, initially implemented in Rio de Janeiro and São Paulo in partnership with non-governmental organizations (NGOs), is expanding to additional sites in Porto Alegre and Manaus (Grinsztejn, private communication). The objective of this project is to assess the uptake, safety and feasibility of free access to PrEP for high-risk MSM and TGW, aiming at generating information for the subsequent PrEP implementation in the public sector. In addition, a demonstration project in MSM, sex workers and drug users is being planned to start in 2016 in multiple sites (São Paulo, Porto Alegre, Ribeirão Preto and Fortaleza) [22].

In Peru, oral PrEP is prescribed on demand to a few MSM who can purchase antiretroviral (ARV) medications (Guanira, personal communication), and a larger demonstration project among MSM and TGW is being planned at three sites (i.e. Lima-Callao, Northern Coast and Amazon) in late 2016 (Caceres, personal communication). Other PrEP projects are being implemented in Mexico City at Clínica Condessa, where PrEP is offered to a limited number of male sex workers and other MSM (Baruch, private communication), and Guatemala City by the NGO Amigos Contra el SIDA (Ghidinelli, private communication).

The cautious attitude of Latin American countries vis-à-vis the implementation of PrEP was also reflected in the 2015 Rio de Janeiro Call to Action, a consensus statement endorsed by representatives from governments, academia, health services and civil society from 26 Latin American and Caribbean countries. This statement includes regional goals and targets for HIV prevention, one of which refers to the implementation of PrEP projects in 10 countries by 2020 [23].

The introduction of PrEP requires engaging policymakers. Qualitative research conducted in Peru in 2010 to 2011 showed that less than 50% of policymakers interviewed were aware of PrEP [24]. Although recognizing its value as a prevention tool for people at higher risk, policymakers highlighted concerns about risk compensation, adherence, effectiveness and side effects.

Awareness and willingness to provide PrEP services among healthcare providers is critical. In a survey conducted in Peru in 2012, 57.5% of providers were aware of PrEP, although awareness was higher in ART prescribers (81.3%), in those that were providing care to more than 50 MSM (80.4%), or to at least 50 HIV-positive persons (77.1%). On the other hand, only 44.6% reported willingness to prescribe PrEP, and the likelihood increased if national policies and guidelines were issued (70.3%), if more evidence on effectiveness (68.5%) and more friendly regimens were available (62.2%) [25]. Health providers from Peru and Brazil involved in the early stages of PrEP trials reported concerns about adherence and risk compensations, as well as doubts about the support from national health authorities [26]. Another barrier on the health provider side may be the discriminatory attitude towards members of key populations, in particular MSM and TGW, which may prevent individuals from accessing services or openly discussing their needs and therefore receiving adequate care [27].

Finally, awareness, acceptability and willingness to use PrEP among target populations is key to shape the demand for PrEP. Research conducted in 2015 among 68 MSM in urban sites in Mexico showed that 100% of participants were aware of PrEP and 70% were willing to use it if available for free or offered at an affordable price (Baruch et al. Unpublished data). In Brazil, although approximately 60% of 734 MSM from Rio de Janeiro interviewed in 2014 to 2015 were aware of PrEP, 95% stated they would be very interested in using it if it were available in the public sector [28]. In Peru, a survey conducted in 2011 among MSM, TGW and female sex worker (FSW) showed very limited awareness about PrEP, with the exception of few individuals who had taken part in the initial iPrEx study [29], but subsequent surveys showed that 91% MSM and FSW were willing to use PrEP and adopt it as soon as it became available [30] and that MSM and TGW had high acceptance of either oral (96.2%) or rectal (91.7%) PrEP administration [31].

Across studies, common concerns about PrEP from key populations were related to safety, dosing, route of administration, adherence and effectiveness, as well as costs and acceptable service delivery [32]. Peruvian MSM and TGW showed concerns about risk compensation, although Brazilian MSM and Peruvian FSW understood that PrEP does not substitute condoms nor prevent other sexually transmitted infections (STIs) [26,29–31].

Additional challenges for the implementation of PrEP programmes in Latin America are related to the cost of medicines and regulatory aspects. Many Latin American countries have been utilizing mechanisms of joint price negotiation and procurement of ARVs for ART programmes with significant price reduction; for example, the generic fixed-dose combination of TDF/FTC is currently available through the Strategic Fund (SF) of the Pan-American Health Organization (PAHO) at a
price of US$5.37 per pack (30 tabs) [33]. However, not all countries in the region are signatories of the SF or are using it to purchase ARVs, and prices continue to be higher in countries like Mexico and Chile [34]. FDA approval of the TDF/FTC combination for preventive use was granted in 2012 [35]. Since then Gilead Science has applied for approval in countries worldwide, including Brazil. Nevertheless, approval by the Brazilian Drug Regulatory Authority is still on hold and to date in Latin America only Peru has registered TDF/FTC for prevention use [36,37].

The potential role of PrEP for HIV prevention in Latin America
Gaps still exist in the extent and consistency of condom use in key populations in Latin America: 65% of FSW report using a condom with the last client (median based on data from 21 countries, 2011 to 2014); 47% of MSM report using a condom in the last episode of anal sex (median based on data from 30 countries, 2011 to 2014) [38].

Considering that MSM frequently engage in unprotected anal intercourse [39–42], MSM who engage in risky sexual behaviour, but also male sex workers and TGW, could be candidates for the initial phase of implementation of PrEP programmes. The observation that higher willingness to use PrEP among MSM was significantly associated with exclusive or more frequent receptive anal sexual behaviour [31], and history of unprotected anal intercourse with more than two men [28] and perceived risk of HIV infection [32] also supports this approach. In addition, MSM, TGW and FSW recognized the potential value of PrEP as protection in case of condom rupture or non-availability, or in case of unprotected casual sex [29].

Mathematical models provide further evidence in support of PrEP programmes targeting key populations. A study conducted in Peru to assess the population-level impact, cost and cost-effectiveness of PrEP in MSM and TGW in Lima showed that with a relatively low PrEP coverage (5%), over 8% of new infections could be averted if individuals at higher risk were prioritized (TGW and sex workers) and guaranteeing adherence levels observed in clinical trials. However, when the averted downstream costs of ARVs are included in the model, most PrEP scenarios become cost-effective [43]. If we compare the price of TDF/FTC used in mathematical modelling (US$420 to 600 per year for Truvada [41]) with the regional reference price of the generic TDF/FTC combination (approximately US$65 per year through PAHO SF [33]; plus 15% for shipment and insurance), the potential cost-effectiveness of PrEP in high-risk individuals could be enormously improved with the use of generics.

Implementing PrEP may require in most countries an initial phase of formative assessment to define target populations and criteria to identify PrEP candidates at higher risk, assess acceptability and likely uptake of PrEP, as well as a demonstration project to test feasibility and effectiveness of locally adapted models of delivery. For the design of PrEP delivery models, the alliance and collaboration among policymakers, civil society and representatives from key populations, health service providers and research groups will be critical.

The experience gained from demonstration projects will provide strategic information for the full-scale implementation of PrEP. Modelling tools for the projection of population-level estimates of PrEP needs, as well as other programmatic costing tools, will contribute to more accurate budgeting and planning.

In addition, strengthening the PrEP literacy of potential users through targeted social communication strategies will be critical to disseminate information about the purpose and rationale for the use of ARV medicines to prevent HIV (not STIs), eligibility criteria, dosing and monitoring requirements, and the combination with other preventive tools for greater preventive benefit. Such strategies will stimulate demand for PrEP among most appropriate candidates (i.e. uninfected individuals from key populations at higher risk for HIV acquisition), minimize expectations and demand from people not at higher risk, and ensure the successful introduction of cost-effective PrEP programmes.

Furthermore, national protocols on the use of PrEP need to be developed for healthcare providers, together with comprehensive training packages that include aspects of HIV risk-assessment for PrEP eligibility, as well as prescription, delivery and monitoring guidelines. Provision of person-centred care for key populations, taking into account their needs and vulnerabilities, addressing aspects of sexual orientation and gender identity, sexual behaviour and sexual health in a stigma- and discrimination-free environment, should also be included in training packages to promote access to care in key populations and improve the assessment of individuals that will most likely benefit from PrEP and the overall cost-effectiveness of PrEP programmes [44].

The implementation of PrEP programmes should be integrated within existing HIV prevention services for key populations to minimize the need for additional resources while ensuring access to the comprehensive package of services that safe and effective PrEP implementation requires: periodic HIV screening, renal function monitoring, adherence counselling, promotion of STI/HIV prevention and provision of condoms and lubricants, and effective and timely linkage to care in case HIV infection occurs [6,45].

Finally, the feasibility and sustainability of PrEP programmes also requires minimizing the financial burden of the procurement of ARVs (TDF/FTC), especially as national programmes face the challenge of decreased donor funding and increased domestic expenditure for ARV medicines while adopting the new WHO “treat all” recommendation. The anticipated financial burden of PrEP programmes may be another factor for the cautious approach to PrEP by policymakers. In contrast, joint negotiations and pooled procurement mechanisms, such
as the PAHO SF, may offer an opportunity for more efficient use of resources and significant savings by acquiring WHO prequalified generic ARVs for both ART and PrEP at competitive prices.

**PrEP implementation research needs**

Through the implementation of demonstration projects, as well as monitoring and evaluation of the several local initiatives of PrEP delivery currently underway, it will be possible to generate more evidence on the most effective service-delivery models in the context of different types of health services (e.g. primary level, specialized facilities, STI clinics, etc.), community-based services or a combination of both, as well as models based on public-private partnership. Implementation research should also assess the effectiveness of PrEP prescription and monitoring by medical providers (e.g. specialist physician vs. generalists), compared to models based on task-shifting to other health cadres or lay providers, especially in case of community NGO-based models.

In addition, demonstration projects will offer an opportunity to address additional research topics, such as integration of STI screening and management, alternative testing options (e.g. mobile testing; self-testing) and non-daily regimes (e.g. “on demand” PrEP), as well as knowledge gaps (e.g. long-term effectiveness and safety, topical and injected administration, use of other ARVs for prevention, etc.). Participating in global and regional research networks will assure that research methodologies are harmonized for comparison among countries and compilation of data for regional and global analysis.

**Conclusions**

Considering the epidemiological context of the HIV epidemic in Latin America and the available evidence from cost-effectiveness studies, we anticipate that PrEP implementation may achieve higher impact on HIV prevention when targeting individuals at significantly higher risk of HIV exposure within most affected key populations identified in each country. If Latin American countries intend to pursue the goal of ending AIDS as a public health problem by 2030, HIV combination prevention strategies need to be expanded and focused on the most affected populations, tailored to their needs and updated to include all available innovative tools of proven efficacy. PrEP is certainly one additional option and should be implemented in combination and synergy with condom/lubricant programmes and traditional behaviour change strategies, while addressing the unfinished business of scaling up HIV testing and access to ART. Finally, addressing criminalization, stigma and discrimination against key populations is an overarching imperative to create an enabling environment to ensure equitable access to the whole range of HIV prevention, care and treatment services.

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**Competing interests**

The content is solely the responsibility of the authors. The authors declare no conflict of interest.

**Authors’ contributions**

The authors jointly conceived the structure and content of the article. GR developed the main text with review and contributions from all co-authors. All authors have read and approved the final version.

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PrEP in Europe – expectations, opportunities and barriers
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Abstract
Introduction: In contrast to the global trend showing a decline in new HIV infections, the number reported in the World Health Organization (WHO) region of Europe is increasing. Health systems are disparate, but even countries with free access to screening and treatment observe continuing high rates of new infections in key populations, notably men who have sex with men (MSM). Pre-exposure prophylaxis (PrEP) is only available in France. This commentary describes the European epidemics and healthcare settings where PrEP could be delivered, how need might be estimated for MSM and the residual barriers to access.
Discussion: Health systems and government commitment to HIV prevention and care, both financial and political, differ considerably between the countries that make up Europe. A common feature is that funds for prevention are a small fraction of funds for care. Although care is generally good, access is limited in the middle-income countries of Eastern Europe and central Asia, and only 19% of people living with HIV received antiretroviral therapy in 2014. It is challenging to motivate governments or civil society to implement PrEP in the context of this unmet treatment need, which is driven by limited national health budgets and diminishing assistance from foreign aid. The high-income countries of Western Europe have hesitated to embrace PrEP for different reasons, initially due to key gaps in the evidence. Now that PrEP has been shown to be highly effective in European MSM in two randomized controlled trials, it is clear that the major barrier is the cost of the drug which is still on patent, although inadequate health systems and diminishing investment in civil society are also key challenges to overcome.
Conclusions: The momentum to implement PrEP in European countries is increasing and provides a welcome opportunity to expand and improve clinical services and civil society support focused on HIV and related infections including other sexually transmitted and blood-borne infections.

Keywords: health systems; Europe; MSM; PWID; migrants.

Introduction
In contrast to sub-Saharan Africa, estimates of HIV incidence have not decreased in the World Health Organization (WHO) region of Europe. Indeed they increased, and in 2014 the highest number and rate of HIV infections were reported [1]. The majority (77%) were reported from the East (15 countries). Even though numbers appear “stable” in Western Europe (23 countries), this disguises high and rising incidence in subpopulations of men who have sex with men (MSM) [2] confirmed in two recent studies [3,4]. The epidemic in Eastern Europe differs substantially from the West; only 2% of new cases are in MSM, and access to treatment remains a major obstacle to infection control [2]. People who inject drugs (PWID) accounted for 3 and 28% of new diagnoses in Western and Eastern Europe respectively, in 2014. Although outbreaks have been observed in the West and Centre (15 countries), for example in Greece and Romania, they have been rapidly controlled by harm reduction interventions including needle exchange and opiate substitution therapy [5]. This commentary describes the European epidemics and healthcare settings where PrEP could be delivered, how need might be estimated for MSM and the residual barriers to access.

European epidemic
In 2004, representatives of 53 countries that constitute Europe as defined by the WHO, including the 31 countries that make up the single market of the European Economic Area, met in Dublin and issued a declaration of partnership to fight HIV/AIDS in Europe and central Asia. Part of the declaration was an agreement to monitor progress on the 33 actions to be taken, in alternate years from 2006. These progress reports, together with routine national surveillance data, enable the WHO and the European Centre for Disease Prevention and Control (ECDC) to generate a picture of the regional epidemics, the national responses which depend to a substantial degree on the national economy and the residual challenges.
In 2014, there were 142,197 new diagnoses made in 50 of the 53 countries, the highest annual number since reporting started in the 1980s [2]. Of these diagnoses, 56,945 were officially reported by 49 countries to ECDC and a further 85,252 were reported by the Russian Federal Scientific and Methodological Centre for Prevention and Control of AIDS. The variation in epidemic patterns is considerable across the region with the most striking differences among the 23 countries that make up Western Europe and the 15 countries that make up...
Eastern Europe. The epidemic change in the West is most apparent among MSM. There has been a sustained increase in estimated incidence of HIV and other sexually transmitted infections (STIs) in this population since 2005, even in countries with good access to treatment and care [6,7]. During the same period, new diagnoses due to the second most common route, heterosexual transmission, declined. However, this was not due to a decline in heterosexual HIV acquired within Western Europe but rather the 52% decline in cases that had acquired their HIV outside the region. Nearly half of those living with HIV present with a CD4 count <350 at diagnosis, and this underscores the need to expand and promote HIV testing services to improve uptake of regular testing in key populations and strengthen linkage to care [2]. In contrast to the countries of Western Europe, the change in the epidemic between 2005 and 2014 is most apparent in females in Eastern Europe, where the two largest countries are Russia and Ukraine. Rates in women have increased by 74% compared with a 49% increase in cases of men. Although women are more susceptible to HIV for biological and sociological reasons (no independent income and domestic violence), this does not entirely explain the gender difference, especially as a substantial proportion of new diagnoses in heterosexual men may be misclassified as MSM and PWID. The higher rates reported in women in this region may represent the “second wave” of infections from a predominantly male population of injecting drug users.

It is important to recognize that the surveillance data do not provide an accurate estimate of the incidence of HIV in subpopulations. In the UK, where the mathematical models of the epidemic are a good fit to the surveillance data, the national estimate of incidence in MSM attending sexual health clinics was 1.6 per 100 person years (PY) in 2014 [8], whereas the observed incidence in the PROUD study participants drawn from the same population was much higher at 9 per 100 PY [3]. Each country has hot spots (geographically) and sexual networks that facilitate HIV transmission. In the IPERGAY trial, for example, HIV incidence in the placebo arm among MSM reporting condomless sex with two or more partners in the previous six months was 9.17 per 100 PY in Paris compared with 2.45 in other large cities (Molina JMM, personal communication). Also, 45% of all newly discovered infections in France in 2014 were diagnosed in the Ile-de-France region, which accounts for only 18% of the overall French population of 66M [9]. These data imply that, even though risk behaviours may be similar, the risk of acquiring HIV infection varies geographically, with MSM living in Paris and the larger Ile-de-France region having a nearly threefold increase in HIV risk acquisition.

The information is most limited for sex workers, trans women, trans men and migrants. Where data do exist, it is clear that the prevalence of HIV is higher than the general population [9–11]. Migrant women account for one in four new diagnoses in France each year but it is not entirely clear where they acquired their HIV and, when in France, whether this was from sex work, or from their partners who may be having sex with men without considering themselves to be gay, or from partners who migrated from countries with high prevalence. Nonetheless, within these populations, the offer of PrEP is likely to appeal most to individuals who recognize their risk, as was the case in PROUD and IPERGAY.

Service organization

Public health services are highly variable across the region, ranging from open access to free services for HIV and STI testing and treatment through to access only with significant copayments or in the worst-case scenario extremely limited access to non-confidential and pejorative services. Healthcare is funded by the public sector through tax and social insurance contributions in most countries, with a small contribution from private insurance schemes (<5%). In a few countries, including Germany and the Netherlands, healthcare is delivered by the public sector but funded mainly through insurance schemes and/or formal and informal copayments [12]. Regardless of the model, expenditure on health in the European countries that belong to the Organization for Economic Co-operation and Development (OECD), particularly those in Southern Europe, is lagging behind other OECD countries and has been static or shrinking over the last five years, due to the economic crisis [13].

Community-based organizations do offer HIV/STI screening in some settings, frequently tailored to key populations. These services collaborate for post-exposure prophylaxis as antiretroviral prescribing is only available from specialist services.

Discussion

Estimating need

The two countries in which the PrEP trials were conducted, France and England, have attempted to estimate the need for PrEP among key populations. In the 2014 French report, there were 6600 new diagnoses of HIV: 42% in MSM (an increase of 5% compared to 2013), 23% among women and 16% among men born in foreign countries. Twenty-one per cent of those from sub-Saharan Africa were thought to have acquired HIV in France. This may be an underestimate, as the ANRS PARCOURS study found that 35% had acquired HIV after migration to France (30% of women and 44% of men) [14]. Hardship was common among migrants from sub-Saharan Africa, with more than 40% living for at least one year without a residence permit and more than 20% with no stable housing. Women who reported hardship were also more likely to report casual and transactional partners. This observation may help services to identify heterosexuals who would benefit from PrEP.

Data from the UK are similar with 6151 new diagnoses in 2014. Although the majority (3360) was in MSM, 1460 heterosexual HIV infections were estimated as acquired in the UK by migrants living in the UK or by those born in the UK. Unfortunately, it is not yet clear how to identify the heterosexuals at risk who would benefit from PrEP. Late presentation among heterosexuals remains unacceptably high and efforts to increase testing in this population are a priority.

Having gathered robust evidence for clinical effectiveness in two randomized controlled trials in MSM, it is possible to identify the characteristics of MSM who would benefit from PrEP. Policy makers have used this information to estimate the likely size of each national PrEP programme to determine the budget impact. In France (66 million inhabitants in 2013),
the MSM population is estimated to be around 330,000 persons [15]. In a large anonymous cross-sectional survey conducted in 2011 in France, 20.8% of HIV-negative MSM reported no discernible risk reduction behaviour and can be considered at high risk of HIV acquisition [16]. A seroprevalence survey in Paris found 17.7% of MSM to have HIV, so this suggests that about 50,000 MSM in France may need PrEP [17]. According to the most recent national UK survey of attitudes to sex and lifestyles conducted between 2010 and 2012, 2.6% (95% CI 2.1–3%) of men aged 16 to 74 have had a same sex experience in the preceding five years. Although the majority self-identified as gay, 28% considered themselves to be straight and 19% bisexual [18]. Applying 2.6% to the 2011 UK census estimate of 20 million men aged 15 to 64 suggests that there are 500,000 MSM in this age group. The sexual health clinic network sees 100,000 HIV-negative MSM at least once each year. Behavioural data from clinic surveys (unpublished data, Public Health England) suggest that half or more have had anal sex without a condom in the preceding six months. This generates a similar maximum number to France (50,000) although not all of these individuals may want or need PrEP, as a substantial proportion will be in a monogamous relationship with a concordant negative partner or a positive partner on treatment with undetectable viral load. In the United States PrEP has been available since 2012. Only 49,000 to 80,000 individuals have started PrEP in the United States among an overall population of 323 million with an estimated need among MSM of 492,000 (Grant R, personal communication). Further, a substantial proportion of the early adopters was women. Based on the US experience, a target of 50,000 MSM seems highly aspirational for France and the UK. If 50,000 MSM took PrEP for one year, the budget impact for drug alone would be €150M in the region to support an IPERGAY regimen and almost double to support a daily regimen.

For non-MSM populations, it is less clear who will come forward to access PrEP, what their likely incidence would be without PrEP and how effective PrEP will be. In England, estimated HIV incidence in Black African heterosexuals that access the sexual health clinics is higher than overall heterosexuals (0.17% per year compared to 0.03% in 2012) but still low. About 1000 heterosexual women accessed PEP in 2012, and the numbers were similar in 2013.

Movement in the right direction

The French authorities approved Truvada® (TDF/FTC) under a recommendation for temporary use, effective from 4 January 2016. Truvada is fully covered by the healthcare system but visits and tests will be covered at the usual rate, which is 60% of costs reimbursed. This process is independent of the European Medicines Agency (EMA), was initiated under pressure from civil society and was supported by the Minister of Health for France, who agreed to fully reimburse the costs for drug. Widespread concern about the possibility that PrEP would lead to a decrease in condom use and precipitate an increase in other STIs inspired the PROUD trial design to compare immediate access to PrEP to a delayed access after 12 months.

There were differences in behaviour with a significantly higher proportion of PrEP users reporting 10 or more partners with whom they had had receptive anal sex without a condom in the preceding 90 days (21% immediate PrEP compared to 12% deferred) [3]. However, there were no differences in the proportion who acquired other STIs. In reality, the rates of other STIs have been increasing for the last decade, driven largely by infections in HIV-positive MSM but accompanied by a steady increase in syphilis, gonorrhoea and chlamydia in HIV-negative MSM [6,19]. The introduction of PrEP offers an opportunity to control STIs through regular asymptomatic screening, prompt treatment, and active notification and treatment of partners. Importantly, PROUD demonstrated that the efficacy of PrEP was not undermined by the presence of these other STIs.

The success of the two randomized trials and subsequent implementation of demonstration projects in Amsterdam and in Antwerp have strengthened the partnership between civil society and the medical community in Europe, broadly through the activities of the European AIDS Treatment Group and the EuroPrEP collaboration. The partnership between EATG members and the EuroPrEP clinicians started at the country level around the trials, for example the role of AIDES in the French IPERGAY trial, and the Community Engagement Group that supported PROUD. To date, the European partnership has been concentrated in the countries of Western Europe, but it will be important to expand and support countries in Eastern Europe and central Asia as they embark on demonstration projects or national programmes. A common problem for all countries is the cost of the drug which makes large-scale national PrEP programmes look unaffordable. This is the underlying reason that the PrEP policy has stalled in England and Wales, where the National Health Service is only willing to contribute £2M to the early implementation activities. The EuroPrEP collaboration wrote to Gilead Sciences, the sole source of Truvada® for European governments, on 1 December 2015 with two requests: first that Gilead submit to the EMA as regulatory approval is considered essential for national policy in some countries, and second that they consider reducing the price of drug. Gilead has now submitted to the EMA. While we are not aware of any reductions in the cost of the drug, the company is clearly willing to negotiate at the country level as demonstrated by Portugal and Georgia, where hepatitis C treatment is being fully implemented.

Residual barriers and solutions

A key challenge for Europe is to meet the needs of other high-risk groups, particularly migrants, for whom the links with community-based organizations and the healthcare system are much lower than for MSM.

While those that purchase health care are concerned that uptake will be higher than planned, advocates and clinicians recognize the reality that many of those in need will not take up the offer of PrEP, especially young MSM aged 15 to 24 – a group in whom the number of new diagnoses has more than doubled since 2003. Their health-seeking behaviours differ considerably from older MSM, and health promotion efforts, as well as services, need to adapt and innovate to meet their needs. An important modification to services will be to build
on the partnerships developed during the trials and shift tasks away from clinicians and hospitals towards community-based organizations which are more acceptable venues for individuals who do not consider themselves to be “patients.”

The two major components driving cost-effectiveness are the price of drug and HIV incidence [20]. PrEP is cost saving at the incidence rates reported in the two trials, but barely cost-effective as a daily regimen when the national incidence rates are applied over an 80-year time horizon [21]. The event-driven, on-demand regimen used in IPERGAY and recommended for MSM by the European AIDS Clinical Society [22], utilized about half the amount of drug required to support a daily regimen, equating to a 50% reduction in price. The US Centre for Disease Control and Prevention [23] and WHO [24] do not yet recommend this regimen, but guidelines are likely to be revised as evidence gathers from the European studies. Importantly, TDF/ FTC could be available from generic manufacturers in 2017 and European countries should encourage manufacturers to prepare for large-scale demand for this drug, which is also popular as a treatment option.

Assuming the issue of drug costs can be resolved, there are additional requirements to implement a combination prevention strategy incorporating PrEP. This includes raising awareness of PrEP with information campaigns aimed at the “late majority and the laggards,” and building capacity to deliver prevention and care in a more integrated service than currently exists in most countries. This will require political will from government, purchasers and providers of services but could be done by strengthening partnerships and empowering a broader range of providers to undertake screening with minimal additional funding. Governments may need to see a demonstration of these partnerships to be convinced that it is easy to accommodate PrEP within existing reconfigured services. Over the last few years, there has been diminishing investment in civil society and this trend needs to be reversed if we are to effectively raise awareness of PrEP and promote a holistic approach to prevention, which starts with a HIV test. Scaling up and normalizing HIV testing will be critical for countries where HIV has spilled into the general population.

An important starting point for Europe is to strengthen the role and scope of the European Centre for Disease Control and Prevention. This organisation has the data, albeit limited, and is best placed to advise individual countries on the model of prevention and care to adopt.

Conclusions

There has never been a better time to advocate for strengthening prevention services and increasing access for key populations with increased risk of acquiring HIV and other sexually transmitted and blood-borne infections. These populations are invariably vulnerable, with other health and social care needs. Screening is at the core of this and services need to increase throughput, taking advantage of innovations in self-sampling, self-testing and community-based testing. Governments should be confident of success. With political will, the epidemic trends in Europe could be reversed.

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Competing interests

SMC has received research grants from Gilead, and fees have been paid by Gilead to UCL for her attendance at an Advisory Board and various invited talks. J-MM has received research grants from Gilead and Merck and has participated in advisory boards for Gilead, Merck, Janssen, Bristol Myers Squibb and VIH.

Authors’ contributions

SMC created the first draft, and J-MM and VN commented and expanded. SMC created the final draft and submitted the manuscript. All authors have read and approved the final version.

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Introduction
Transgender ("trans") women are disproportionately impacted by HIV worldwide [1]. A meta-analysis found that transgender women are 49 times more likely to be living with HIV than the average population, with an estimated global pooled prevalence of 19% [2]. This overwhelming disparity calls attention to the urgent need for effective HIV prevention strategies that meet the unique needs of this population. The World Health Organization’s Consolidated Guidelines for Key Populations state “the high vulnerability and specific health needs of trans people necessitate a distinct and independent status in the global HIV response” [1]. This paper reviews relevant literature to describe the current state of the science and the potential role of PrEP among transgender women, including a discussion of unique considerations for maximizing the impact of PrEP for this vulnerable population.

Transgender identities are diverse and nuanced, varying between and within cultures. The terms “transgender” and “trans” are often used as umbrella terms to describe people whose gender identity differs from the sex assigned at birth; however, many people included in discussions of trans people may use other or additional terms to describe themselves [3] and/or may identify outside of the typical male/female binary altogether. While the terms “transgender” and “trans” are more common in Western cultures, they are also gaining more widespread use as the movement for transgender human rights becomes globalized. Some cultures acknowledge genders outside of the binary, sometimes referred to as “third gender” classifications, such as Native American berdaches or “Two Spirit” people, or the Fa’afafine of Samoa. Other terminology used to describe trans people includes the terms mak nyah in Malaysia [4], kathoey in Thailand [5], hijra in India, Bangladesh and Pakistan [6–8], waria in Indonesia [9], rae rae and mahu in French Polynesia [10] and travesti in South America [11].

Furthermore, there is great variation in access to healthcare, human rights and availability of transition-related medical care. Thus no singular, monolithic transgender identity or classification exists. For the purposes of this discussion, the terms “transgender” or “trans” women describe people who share a common experience of being assigned male sex at birth, but who identify as female, transgender or trans female, or another identity along the trans-feminine spectrum, while acknowledging that cultural context introduces variability...
along many dimensions of life experience. At this time, there is limited information about the feasibility, acceptability and effectiveness of PrEP for trans women cross-culturally. Much of the existing information comes from one international clinical trial where enrolment of trans women was limited to a few sites and from regional studies in North and South America and Thailand.

Despite contextual differences, trans-related stigma (“trans-phobia”) is pervasive cross-culturally and can limit opportunities and access to resources in a number of critical life domains (e.g. employment, healthcare), persistently affecting the physical and mental health of trans people, including HIV [12]. Trans women face unique challenges related to sex work and need for gender affirmation that can increase their vulnerability to HIV [13–15]. Worldwide, trans women who engage in sex work experience unique structural, interpersonal and individual vulnerabilities that contribute to a disproportionate risk for HIV compared with non-trans (or “cisgender,” a term often used to describe people who do not identify as transgender) male and female sex workers [16,17]. In addition, there is a clear need for increased HIV testing among trans women [18], with some preliminary evidence for feasibility and acceptability of self-testing [19]. While rates of HIV among trans men are lower than those of trans women, there is evidence of HIV risk behaviours among trans men who have sex with men (MSM) and subsequent speculation that HIV rates may increase among this population in the years to come [20,21].

Recently, PrEP has garnered a great deal of interest and attention as the newest and most promising biomedical HIV prevention intervention developed and tested to date. The first clinical trial of PrEP (iPrEx) included both high-risk MSM and trans women; risk of HIV acquisition was reduced by 44% [22]. However, a sub-analysis of the iPrEx data found no effectiveness (based on intention to treat rather than whether PrEP was actually used) among the sub-group of trans women in the study [23]. As with MSM, all of the trans women who became infected had low or undetectable drug concentrations, suggesting use of fewer than four tablets per week. The detection of PrEP drug concentrations among trans women using feminizing hormones was similar to trans women not using hormones and MSM for the first 12 weeks of the study, then dropped off afterward. This pattern suggests that long-term adherence was the issue rather than a drug-drug interaction. Lower levels of uptake and adherence among trans women compared to MSM likely contributed heavily to the differential rates of efficacy, but there have not yet been pharmaco kinetic studies to rule out a drug-drug interaction of PrEP with hormones [24]. To date, iPrEx is the only clinical trial of PrEP for HIV prevention with confirmed enrolment of trans women [25]. Trans women are eligible for enrolment in the majority of PrEP studies that enrol MSM [26], including Ipergay [27] and HPTN 067 ADAPT (R. Grant, International AIDS Conference 2015, Vancouver). However, very few if any trans women have actually been enrolled in these trials [28].

PrEP demonstration projects to date have reported low or unclear levels of enrolment of trans women [28,29]. The Demo Project, a three-city PrEP demonstration project conducted in the United States, is usually described as a cohort of MSM and trans women [28]. However, the project enrolled only seven trans women across all three sites, out of a total of 557 enrolled participants. Due to low enrolment numbers, it is impossible to make comparisons or draw conclusions about unique correlates of uptake and adherence among trans women. Furthermore, there are currently no guidelines for PrEP demonstration projects that provide specific considerations for provision of PrEP to trans women. The World Health Organization guidance mentions trans women but there is no consideration of specific needs among this population. Guidance on PrEP from the US Centers for Disease Control and Prevention makes no mention of trans women whatsoever [30,31]. In 2016, the California HIV/AIDS Research Program funded the first large-scale PrEP demonstration projects specifically for trans populations, including trans men [32]. As this funding is recent, there are not yet any data available.

PrEP awareness and acceptability among trans women

Low levels of PrEP awareness among trans women have been noted in San Francisco [33], Brazil [15], Chicago and Boston [34]. Some studies, however, have found that while PrEP awareness is low among trans women, interest in PrEP is high once patients are informed [34,35]. A study of 107 trans women and 131 MSM in Chang Mai, Thailand, found similar levels of PrEP acceptability between the two groups. However, significant differences between MSM and trans women were found in sexual behaviours, patterns of medication use and correlates of PrEP acceptability. For example, trans women were more likely to exclusively engage in receptive anal sex, which may impact their HIV risk perception and thus their willingness to take PrEP [36].

PrEP may be an empowering tool for trans women who are engaged in sex work to increase their sense of personal control over HIV prevention. Sex work is more prevalent in the lives of trans women due to social and economic marginalization, and PrEP programmes seeking to serve trans women may benefit from incorporating messaging about HIV prevention during sex work [35]. Trans women may have significant mistrust of the medical community’s awareness of transgender-specific health concerns [37]. These concerns are well founded given that half of a large sample of trans people in the United States reported having to teach their provider about their own care [38]. Concerns about potential negative effects of PrEP on gender-affirming hormone therapy may also represent a barrier to PrEP acceptability [35]. An interim analysis of 608 HIV-positive trans women of colour in care at several clinics in the United States found that the perception of a negative effect of antiretroviral drugs on gender-affirming hormone therapy was associated with an odds ratio of 2.88 for having taken a higher dose of hormones than prescribed in the prior six months [39]. This finding could suggest that there is a concern regarding a negative action of ART medications on hormones, which may for some result in avoidance of or non-adherence to PrEP.
Building trust in PrEP: gender-affirming clinical practices

Gender-affirming healthcare includes using patients' preferred names and pronouns, respecting diversity in patients' gender identities and expressions, and generally creating safe spaces for trans patients to be themselves, in addition to the provision of hormone and other gender-affirming medical care. Providers and clinical staff should be adequately trained to provide a safe, welcoming and culturally appropriate environment for trans people to seek care. This includes the provision of safe restrooms, comfort with and use of appropriate trans-related terminology, and the display of trans-affirming visuals and health-related information in waiting rooms, as appropriate.

Gender-affirming hormone therapy has been found to improve quality of life and social functioning and to reduce levels of anxiety and depression [40–42]. Bundling of a desired service such as gender-affirming medical interventions with HIV prevention efforts likely has synergistic value [43]. Engaging trans women in both behavioural and biomedical HIV prevention activities at the time and location of provision of gender-affirming hormone therapy fits well into the bundling model. Access to gender-affirming hormones also represents a potential intervention within several constructs of the Model of Gender Affirmation, including reducing barriers to healthcare, reduced body shame, increased access to gender affirmation and reduced use of street hormones or silicone [14].

It is essential to train healthcare providers to provide gender-affirming healthcare to trans women, including hormone provision. It cannot be assumed automatically that providers and clinic staff who serve MSM are equipped to recruit, retain and provide care to trans women [37]. Programming and services that are designed for MSM or offered through clinics that primarily serve MSM often do not meet the needs of trans women, as many trans women do not feel comfortable accessing programmes and services designed for men and these services do not address their unique life context [44]. In San Francisco, trans women described the importance of finding trans-competent, gender-affirming providers as a powerful facilitator to increasing the acceptability of PrEP [35].

While it is important to continue to develop trans-specific services, existing programmes should also be expanded to include effective programming for trans women. In low- and middle-income countries that do not have the resources to justify funding and developing separate trans-specific programming, health ministries should possess basic knowledge in effectively serving local communities of trans women at risk for acquiring HIV. For example, offering PrEP and other sexual health services to trans women through services oriented to cisgender women represents another potential approach. Many women-focused sexual health services are seeking to be more trans-inclusive, but there are currently no data or guidance available to support these efforts. Contextually situated psychosocial drivers of HIV risk among many trans women are more similar to those of non-trans women than those of men. These psychosocial drivers include experiences of trauma, domestic and sexual violence, misogyny, survival

sex work, sexual objectification and unequal power in relationships to negotiate safer sex [37,38,45,46].

Where transition-related services such as hormones are not available, clinicians should still provide care that is gender affirming and assist the person in accessing transition-related care services when possible. Assistance in obtaining legal identification, health insurance and identifying trans-specific support services can all be helpful. If the patient is taking hormones obtained in other ways (i.e. on the street or Internet), clinicians can support a person’s transition by checking hormone blood levels and providing education about safe hormone use.

PrEP services are amenable to algorithmic care protocols, making such services implementable in a large variety of clinical settings including sexual health clinics, family practice clinics, reproductive health clinics, community clinics and student clinics, in both small and large practices. However, clinical familiarity with PrEP protocols and sexual health testing and management is currently limited. A greater limitation arises from the lack of familiarity with best practices for gender-affirming medical care, such that finding a healthcare provider who is able to provide both PrEP and gender-affirming care has been difficult for trans people. As such, another approach to improving PrEP uptake and adherence in trans women is by expanding PrEP-related knowledge and skill among existing providers of gender-affirming clinical services.

Segmentation of sexual health services according to the gender binary is another barrier. Sexual health services oriented exclusively for MSM frequently do not provide services required by trans men, including cervical cancer screening, pregnancy tests and skill in prescribing hormonal contraception. Similarly, practices that are oriented mainly to the needs of cisgender women, such as OB/GYN practices, may not be familiar with evaluation and management of trans women or men. Expanding gender-specific services to include trans people is crucial to improving sexual health within these communities.

Further, trans women may experience unique barriers to obtaining healthcare. In addition to increased rates of unemployment, which can result in un- or under-insurance, trans women may avoid enrolling in safety net insurance programmes or visiting clinics due to lack of legal identification documents that reflect their affirmed gender. Mismatches between the sex listed on legal documents and insurance policies may result in a denial of insurance claims. While insurance coverage should not determine access to PrEP, drug costs can be a major barrier to PrEP rollout, especially in low- and middle-income countries [47].

Building evidence for PrEP: trans-inclusive research strategies

Uniform and universal collection of gender identity data is an essential structural-level HIV prevention intervention in trans populations. Failure to identify, describe and quantify trans populations results in an invisibility at the institutional level, with resultant exclusion from policymaking, funds allocation and research activities [44]. Trans women, their advocates and public health researchers have issued a strong call for the
disaggregation of trans women from MSM in HIV prevention programming and research [2,17,48], as the importance of incorporating gender-affirming practices in addressing HIV among trans women is becoming increasingly recognized [14,37].

Ongoing challenges in collecting valid data on trans people and HIV include cultural variation in language used to describe trans people and lack of standardized measurements [49]. The use of the two-step method for the collection of gender identity data has been recommended by a wide range of experts and institutions [50,51]. This method includes querying both gender identity (using a wide range of locally appropriate options) and birth-assigned sex. Trans people are identified as those with a gender identity that differs from their birth-assigned sex. Failure to use the two-step method can result in some trans people responding to a single question on sex/gender as either “male” or “female” rather than “transgender”; a study comparing these two methods found the two-step method doubled the number of trans people identified within a population [52]. The consequences of a failure to accurately record gender identity were described in the aforementioned sub-analysis of trans participants in the iPrEx trial, in which a more in-depth analysis using surrogate markers revealed that 13% of trans participants had not been identified in the original analysis [24,53].

Low enrolment of trans participants in clinical trials of PrEP to date can likely be attributed to the passive inclusion of trans women without implementation of any trans-specific recruitment strategies or proactively training staff to provide care that is sensitive and supportive to trans people. Enrolment of trans women in future trials can be improved by carefully planning study outreach efforts and intentionally designing recruitment and retention strategies to address the unique needs and potential concerns of trans women. Designing gender-affirming strategies, such as specifically addressing and representing trans women in recruitment materials, hiring trans study staff, offering gender-affirming healthcare and ensuring the representation of trans people at all levels of the project, such as on advisory boards, study staff and involving trans people in the design of the study, can all help improve enrolment of trans people in clinical trials and future PrEP demonstration projects [54].

**Building demand for PrEP: community engagement and empowerment**

While some initial research has shown that there is interest in PrEP among trans women when they are aware of it, demand for PrEP among trans women is yet unproven. Building demand for PrEP will be an important first step in implementation, and community engagement in this process will be crucial. Community mobilization strategies are particularly effective in increasing empowerment and decreasing stigma among marginalized populations and in disseminating novel information via trusted social networks [55]. Social marketing strategies should emphasize gender-affirming, sex-positive messaging about the potential benefits of PrEP, such as increased sexual pleasure and intimacy, increased sense of safety during sex, decreased HIV-related anxiety, decreasing stigmatizing attitudes toward HIV-positive partners, increased sense of community and increased self-efficacy for HIV prevention [56]. PrEP can empower the individual to take control of preventing their own acquisition of HIV without relying on prevention strategies often controlled by one’s partner (i.e. condom use), and the disclosure of one’s own decision to take PrEP is also a personal choice. PrEP champions, or individuals who are willing to publicly share about their own positive experiences with PrEP, may be particularly powerful sources of support and builders of trust when they come from within local trans communities.

Involvement of trans women in the design and development of PrEP studies and programmes that aim to include them is crucial to successful enrolment. This helps to ensure that the messaging, environment and questions being asked are relevant to trans women’s unique needs and concerns. Patient decision-making tools and adherence support strategies should be designed specifically for trans women with their input, rather than adapted from strategies that were designed for MSM.

**Biomedical considerations**

No evidence currently exists to suggest that PrEP interacts with commonly used feminizing hormone regimens, and evidence from studies of antiretroviral interactions with hormonal contraceptives has been reassuring [57]. However, there have not yet been any pharmacokinetic studies of these potential drug-drug interactions with trans women. Studies of interactions between combined oral contraceptives and antiretroviral medications have generally not indicated negative interactions between the classes [58]. Important differences exist in the context of transgender care, where a range of oestrogens are used, most commonly bioidentical 17-beta estradiol, in contrast to the synthetic ethinyl estradiol used in oral contraceptives. Furthermore, use of progestogens is inconsistent among trans women. Further study is needed to explore potential interactions between PrEP medications and commonly used gender-affirming hormones. Also requiring exploration are any changes in the anal epithelium in response to hormone therapy, as well as considerations in trans women who have undergone a penile inversion vaginoplasty, in which penile and scrotal skin is inverted to create a vagina and vulva, possibly with the use of urethral mucosa. The risks of HIV transmission via these organs, as well as the risks and rates of ulcerative genital infections and local concentrations of PrEP medication are unknown and require further study [17].

As previously described, compared with MSM, trans women in the iPrEx study had lower concentrations of active metabolites of tenofovir disoproxil fumarate (TDF) and emtricitabine [53]. Concentrations of PrEP medications were especially low among trans women reporting use of feminizing hormones, which may reflect less PrEP use or a drug-drug interaction. While there are no systemic drug-drug interactions between TDF and oral contraception, there are known interactions at the level of drug transporters between these classes of medications that could affect drug concentrations in target tissues [59]. Drug-drug interactions between TDF and either natural oestrogens or anti-androgenic agents used for gender-affirming hormone therapy among trans women have not been studied. Drug-drug interactions between
emtricitabine and any of these medications have also not been studied.

Conclusions
The future of PrEP among trans women relies on reversal of the relative invisibility of trans women in research and clinical services that inform the structure of programming and access to PrEP. Guidelines developed for the implementation of PrEP must consider the unique barriers to and facilitators of uptake among trans women. Risk assessment tools, adherence support and retention strategies are currently being developed without consideration of issues unique to trans women and are not validated for use with trans women [60]. Structural interventions are needed, such as comprehensive provider training programmes for all level staff to better serve the needs of trans women and increase service utilization and improve wellbeing, while effecting lasting institutional change [61]. It is vitally important that PrEP messaging and information be delivered via trans-specific networks with the unique concerns and life contexts of trans women in mind. Community-based strategies, such as community mobilization to increase knowledge and trust of information about PrEP among trans women, should be explored.

Because trans women may prioritize hormone therapy over other healthcare [35,37], bundling of PrEP with gender-affirming hormones may help address this barrier to PrEP uptake and adherence by both serving as a venue for distribution of accurate information regarding drug interactions and co-packaging of hormones and PrEP medication to overcome any barriers relating to increased pill burden. Multimodal interventions are recommended to increase PrEP uptake and provide adherence support, and all interventions must consider culturally unique barriers to healthcare access and adherence to maximize effectiveness with trans women [30,60,62]. PrEP can be a cost-effective addition to comprehensive sexual health programmes when people with the highest risk of acquiring HIV, such as trans women, are given priority of access [47]. PrEP may also provide additional benefits above and beyond HIV prevention, such as community empowerment and engaging previously marginalized communities of trans women into healthcare. The meaningful engagement and inclusion of trans women in the development of PrEP rollout strategies and the disaggregation of trans women from MSM in ongoing PrEP research and programming are essential initiatives to promote this highly promising HIV prevention tool among a key population that to date has been largely overlooked.

Authors’ contributions
JMS, MBD and RG reviewed the literature and wrote the manuscript.

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Competing interests
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Commentary

Preventing HIV among adolescents with oral PrEP: observations and challenges in the United States and South Africa

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Abstract

Introduction: Adolescents and young adults aged <25 are a key population in the HIV epidemic, with very high HIV incidence rates in many geographic settings and a large number who have limited access to prevention services. Thus, any biomedical HIV prevention approach should prepare licensure and implementation strategies for young populations. Oral pre-exposure prophylaxis (PrEP) is the first antiretroviral-based prevention intervention with proven efficacy across many settings and populations, and regulatory and policy approvals at global and national levels are occurring rapidly. We discuss available data from studies in the United States and South Africa on the use of oral PrEP for HIV prevention in adolescent minors, along with some of the implementation challenges.

Discussion: Ongoing studies in the United States and South Africa among youth under the age of 18 should provide the safety data needed by the end of 2016 to contribute to licensure of Truvada as daily PrEP in adolescents. The challenges of completing these studies as well as foreseeable broader challenges highlighted by this work are presented. Adherence to daily PrEP is a greater challenge for younger populations, and poor adherence was associated with decreased efficacy in all PrEP trials. Individual-level barriers include limited familiarity with antiretroviral-based prevention, stigma, product storage, and social support. Structural challenges include healthcare financing for PrEP, clinician acceptability and comfort with PrEP delivery, and the limited youth-friendly health services available. These challenges are discussed in the context of the work done to date in the United States and South Africa, but will likely be magnified in the setting of limited resources in many other countries that are heavily impacted by HIV.

Conclusions: Adolescent populations are particularly vulnerable to HIV, and oral PrEP in these populations is likely to have an impact on population-level HIV incidence. The challenges of disseminating an HIV biomedical prevention tool requiring daily usage in adolescents are formidable, but addressing these issues and starting dialogues will lay the groundwork for the many other HIV prevention tools now being developed and tested.

Keywords: PrEP; adolescents; HIV/AIDS; implementation.

Introduction

Overview of adolescent HIV epidemic

According to the World Health Organization (WHO) [1], AIDS is the leading cause of death among adolescents in sub-Saharan Africa and second leading cause for adolescents worldwide. In 2014, there were an estimated 2 million adolescents aged 10 to 19 living with HIV, and in 2013, adolescents aged 15 to 19 were infected with HIV every 2 minutes [2]. A recent report by the United Nations Children’s Fund [3] concludes that by the year 2050, the number of Africans under the age of 18 may swell to one billion. Thus, the success of ending the AIDS epidemic depends upon reaching adolescents and engaging them in HIV prevention.

Adolescents are at increased risk for HIV due in part to the multiple co-occurring transitions (i.e. biological and psychological) and developmental tasks (e.g. establishing identity) in this period of the lifespan [4–6], in addition to age and power imbalances [7,8], gender inequality, and interpersonal violence in sexual relationships [9–12]. Among youth, there are also subgroups who bear disproportionate burdens of HIV and are the most vulnerable. These young key populations include men who have sex with men (MSM), transgender people, those who inject drugs, male and female sex workers, as well as youth who belong in multiple groups (e.g. transgender youth who inject drugs). Finally, a compelling case has been made for considering adolescent girls in sub-Saharan Africa, a key population that urgently requires attention and intervention; girls aged 15 to 19 in this region are four to five times more likely to be infected than their male counterparts [13] and HIV incidence rates are 5 to 6% among young women <21 years in recent HIV prevention trials [14,15].

Definition of adolescence

Both the WHO [16] and the United Nations identify adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages...
10 to 19. For the purposes of this article, we consider adolescents those under the age of majority (i.e. the age at which a child becomes a legal adult) for the country (South Africa) or state (within the United States) that they live in. Although there are developmental similarities between those under the age of majority and those just over the age of majority, there are distinct implementation challenges for under age youth that we focus on in this article.

Discussion
Studies of PrEP among adolescents in the United States and South Africa
At the time of this writing, there are no data yet available from PrEP studies among adolescents. There are only two oral PrEP studies currently in the field that exclusively focus on adolescents, which we describe below, as well as several other adolescent-inclusive demonstration projects that began in 2016. Successful enrolment of adolescents into biomedical HIV prevention trials or bridging studies is critical for drug licensure and implementation of PrEP among populations most vulnerable to HIV.

ATN 113 (Clinical trial NCT01769456) – United States
The first adolescent PrEP study, funded through the Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions, is ATN 113 (Project PrEPare). ATN 113 is a demonstration project and phase II safety study that aims to obtain additional data on the safety of TDF/FTC (Truvada®) and to evaluate patterns of use, rates of adherence, and patterns of sexual risk behaviour among young MSM aged 15 to 17. Multiple recruitment methods were employed across sites, including street and venue-based outreach, community and school presentations, and online advertising on social media websites and social networking apps. Of the 1873 individuals approached, 59% were ineligible due to lack of recent sexual activity, and 8% were eligible but declined participation. Enrolling an adolescent cohort of MSM into a PrEP trial required more time and alternative strategies than the young adult cohort enrolled in the parallel study of 18 to 22-year olds (ATN 110) [17]. Internet-based recruitment strategies were more likely than in-person strategies to find eligible adolescent participants. For this study, adolescents were permitted to provide self-consent. Because of this approach to consent, only half of the eligible study sites were allowed by their institutional review boards to participate in the study [18].

Seventy-eight young MSM (mean age = 16 years) were enrolled into ATN 113 from six study sites in the United States (Boston, Chicago, Los Angeles, Memphis, New Orleans, and Philadelphia). The participants are racially/ethnically diverse, with 45% identifying as Latino/Hispanic and 35% as Black/African-American. Study participants engaged in an evidence-based behavioural risk reduction intervention prior to PrEP initiation were then seen monthly for the first 12 weeks of the study, then quarterly thereafter until 48 weeks. All participants are provided with sexual health promotion and adherence counselling at every visit. Study participation has been completed for the primary 48 weeks of the study, and data will be available soon [19]. An extension phase for those 56% of participants who met conservative, prespecified, renal, or bone criteria at the completion of study drug use is ongoing for an additional 48 weeks through October 2016.

CHAMPS PillsPlus (Clinical trials NCT02213328) – South Africa
The second study, CHAMPS PillsPlus, is an ongoing open-label study examining the safety, feasibility, and acceptability of daily oral Truvada as PrEP in HIV-negative adolescents. Ninety-eight female and 50 male participants aged 15 to 19 were recruited in two South African peri-urban settings in Johannesburg and Cape Town. Eligible female participants willing to use hormonal contraception and eligible male participants were consented for daily oral PrEP as part of a combination HIV prevention package that included condoms and sexually transmitted infection screening and treatment. Youth under the age of 18 were required to have parental/guardian consent for study participation. With a target enrolment of 150 youth, this study has completed enrolment and has easily enrolled adolescents (even with adult permission required and a six-month enrolment window) with a median age of 18 (IQR 17–19), more than half having a sexually transmitted infection at baseline and reporting condomless sex at some time (Linda-Gail Bekker, personal communication). Adolescents have been ineligible due to undiagnosed HIV positivity, pregnancy, or not yet sexually active by self-report. Initial plasma tenofovir levels indicate reasonable uptake and use of PrEP [20]. Recognizing that many youth struggle to consistently adhere to daily medication, this programme is also providing specific tailored support using SMS, adherence clubs, and real-time feedback on drug levels. Youth are also counselled by trained youth-friendly counsellors on the continuing need for PrEP with an option to opt out if risk profile has changed.

Other adolescent-inclusive studies
In addition to the above, a pilot study in Kenya is currently under way to examine the uptake, acceptability, and feasibility of a combination prevention package of gender-specific interventions for youth aged 15 to 24 in mobile health settings [21]. The prevention package for all youth includes HIV counselling and testing along with linkage to care for HIV treatment. PrEP is a component of the prevention package for young women who are out of school and test HIV-negative. However, preliminary results indicate that only 9% of those enrolled thus far may be eligible for PrEP, highlighting the need to learn how to target PrEP and reach higher risk young women [21].

Several new studies and demonstration projects that are inclusive of adolescents are set to begin this year. There are two new studies funded by the HIV research networks of the National Institutes of Health (NIH). The first is HIV Prevention Trials Network (HPTN) 082, a randomized multisite prospective study to assess PrEP acceptance and adherence among HIV-negative young women in South Africa and Zimbabwe, which has been launched this year (2016) among adolescent and young adult women, aged 16 to 25. In this study, young women who accept open-label daily oral PrEP were
randomized to receive enhanced adherence counselling based on feedback from observed drug levels obtained in the first two months after PrEP initiation or standard adherence support. This study also follows women who initially decline PrEP and conducts qualitative research about factors that influence PrEP initiation and adherence. The second study is International Maternal Paediatric Adolescent AIDS Clinical Trials (IMPAACT) 2009, which is a parallel, observational cohort study designed to determine the feasibility, acceptability, and safety of oral PrEP among HIV-negative adolescents and young women during pregnancy and early breastfeeding. Participants for this study were enrolled in South Africa, Zimbabwe, Malawi, and Uganda.

Three additional adolescent-inclusive projects are slated to begin this year (2016). The first, a collaborative grant from the NIH and the South African Medical Research Council, will involve a prospective cohort evaluation of PrEP initiation and adherence among HIV-negative young women in Cape Town. This study will evaluate PrEP demand in the context of promotion and communication messages derived through formative research with young women in a Cape Town township and with social marketing about PrEP developed in collaboration with a creative marketing agency. This study will enumerate the proportion and characteristics of PrEP uptake among young women who are offered PrEP and will evaluate the effect of a modest incentive that is conditioned on study drug adherence in the first three months of PrEP use on subsequent PrEP adherence. The second study, POWER, which is funded by the US Agency for International Development (USAID), will involve PrEP delivery to young women in family clinics and youth clinics, and mobile testing programmes in Kisumu, Kenya, and Johannesburg and Cape Town, South Africa. End-user perspectives, scalable delivery strategies, PrEP adherence support interventions for young women, and cost-effectiveness will be evaluated in the context of PrEP delivery in a non-research setting. Finally, the third study, EMPOWER, which is funded by the United Kingdom Department for International Development, will involve PrEP delivery to young women in family clinics and youth clinics, and mobile testing programmes in Kisumu, Kenya, and Johannesburg and Cape Town, South Africa. End-user perspectives, scalable delivery strategies, PrEP adherence support interventions for young women, and cost-effectiveness will be evaluated in the context of PrEP delivery in a non-research setting. Finally, the third study, EMPOWER, which is funded by the United Kingdom Department for International Development, will involve PrEP delivery as part of a combination HIV prevention package that includes intervention to prevent gender-based violence and stigma. The study will evaluate the feasibility and acceptability of incorporating screening for gender-based violence into HIV counselling and testing and strategies for linkage to care, as well as offer PrEP to HIV-negative participants. The package of adherence support will include counselling and SMS reminders. Participants will be randomized to either adherence clubs that include a four-session empowerment curriculum focused on improving communication with sexual partners and addressing PrEP stigma or no clubs. PrEP adherence and retention in care at 12 months are the primary outcomes of interest.

Regulatory approvals and clinical guidance for adolescents

As described elsewhere in this special issue, Truvada was approved by the US Food and Drug Administration (FDA) as PrEP in July 2012. The indication is for adults who are at high risk of contracting sexually acquired HIV. In November 2015, South Africa’s Medicines Control Council approved PrEP for use among adults. Although the number of countries with PrEP approval is accruing rapidly (see map courtesy of AVAC), no country has approved a prevention indication for use with adolescents.

Despite regulatory limitations by age, several international groups have distributed recommendations that include considerations for adolescents. The US Centers for Disease Control and Prevention (CDC) released clinical guidelines in May 2014 [22] which state “currently the data on the efficacy and safety of PrEP for adolescents is insufficient. Therefore, the risks and benefits of PrEP for adolescents should be weighed carefully in the context of local laws and regulations about autonomy in health care decision-making by minors” (p. 9). However, some substantially affected metropolitan areas in the United States, such as New York City, have recently adapted slightly more permissive guidance (i.e. recommends PrEP be offered to adolescents at high risk for HIV infection) with appropriate caveats regarding lack of data and need for clinicians to consult institutional policies regarding parental consent [23].

In September 2015, WHO updated their recommendations on the use of PrEP to reflect that people at “substantial” risk of HIV should be offered PrEP with priority for populations with an HIV incidence of about 3 per 100 person-years or higher [24]. The WHO recommendations are not age-specific, but rather exclusively focused on risk level. Building upon these recommendations, WHO intends to release an implementation guide for PrEP this year (2016), which will also include adolescent-specific considerations. In preparation for the updated WHO recommendations and implementation guidelines, UNICEF organized an expert consultation on the implementation of oral PrEP in sexually active older adolescents aged 15 to 19 in July 2015. The report from that meeting outlines many key considerations for PrEP service delivery as well as identifying research gaps and advocacy needs [25]. Furthermore, although considerations for the cost-effectiveness of PrEP among adolescents and estimations of the population in need of PrEP have been presented in Table 1 [26], similar data for the United States have not yet been generated. However, research among young MSM, the population with the greatest HIV burden in the United States, consistently demonstrates incidence rates well above the 3% threshold suggested by WHO [27].

Thus, even in the absence of regulatory approval for the use of PrEP in adolescents, international guidelines have recognized that adolescents are a key population that is
disproportionately impacted by the HIV epidemic worldwide. Global consensus on the need to focus PrEP implementation efforts on youth is very valuable for politicians and providers as they advocate for service delivery to youth. However, the impact of such guidance may be limited because, in the absence of regulatory approval, substantial structural, legal/ethical, and financial barriers continue to exist which effectively reduce access to youth populations most vulnerable to HIV. It is hoped that bridging studies, such as those described previously, will contribute the important safety and usability data needed to inform regulatory labelling of PrEP for younger populations.

Implementation challenges
As the first country to approve PrEP in 2012, the United States has had the most experience to date with the challenges of PrEP implementation. In fact, recently presented data on PrEP prescriptions in the United States demonstrate that initiation of PrEP has been very low among youth – only 7.6% of all prescriptions were for patients under the age of 25 [28]. Thus, we present some of the barriers encountered by youth in the United States, followed by discussion of the potential barriers that may arise in South Africa as they consider national implementation of PrEP.

PrEP implementation for adolescents in the United States

**Clinician knowledge and comfort**
Almost four years post-FDA approval of Truvada for PrEP in the United States, knowledge of PrEP and comfort with prescribing and monitoring the PrEP regimen remain limited among clinicians [29,30]. However, the providers thought to be likely to prescribe PrEP to adults (e.g. infectious disease or primary care physicians) may be very different than those who work directly with adolescents (e.g. paediatricians/adolescent medicine and family planning clinicians). A small, qualitative study of US-based clinicians specializing in adolescent medicine found that the CDC Interim Guidance (2012) on PrEP use was largely compatible with their practice [31]. However, there was still variability in clinician-reported characteristics of an appropriate PrEP patient based on assumptions about adherence, sexual risk, mental health, and substance-use issues. Some clinicians in this study voiced concerns about ethical/legal and cost barriers for youth under the age of 18, which made some report a preference for prescribing to those over 18 [31]. More recently, a survey of family planning clinicians found very low levels of PrEP knowledge. In fact, only 36% of respondents in this study had seen the PrEP clinical guidelines despite the importance of HIV prevention as a core service for family planning clinics [32]. Given that adolescents are probably less likely than adults to request PrEP at their primary care visits, the limited knowledge and remaining inadequacies in PrEP training among adolescent-focused specialties must be addressed comprehensively.

**Off-label use and cost**
Even if a surge in provider knowledge brought the option of PrEP to the forefront of adolescent care, the lack of FDA approval for those below age 18 in the United States creates barriers for youth, particularly because of the significant cost of the medication. For most adults who meet the indication for PrEP, the option of paying out of pocket for Truvada is cost prohibitive. In response to this, Gilead Sciences offers several programmes to assist with medication costs, including a medication assistance programme for uninsured or underinsured as well as a co-pay assistance programme for insured patients with high co-pays. Because Truvada is only approved for use with “adults,” patients under the age of 18 are not eligible for these programmes. Furthermore, although most insurance companies will likely agree to pay for PrEP off-label eventually, it may take more benefit navigation and advocacy than most adolescents are prepared to tackle. Finally, although costs for the medication itself far exceed the costs of medical monitoring for PrEP, office visits, STI testing, and other laboratory work can create financial barriers that are unfamiliar to adolescents. Thus, adolescents at risk for HIV are even more financially vulnerable than adults and less likely to have unfettered access to important prevention tools.

**Ethical and legal issues for adolescents**
In the United States, local state laws vary tremendously in their language, or absence of language, about the rights of
adolescents to access preventative services. Requirements for parental/guardian consent can greatly inhibit access and uptake of PrEP because requesting consent often forces unwanted disclosure of sexual activity and sexual orientation. Preliminary data from qualitative follow-up interviews of ATN 110/113 participants support these disclosure-related barriers [33]. There have been a few other studies documenting the variability in the legal and ethical interpretation of an adolescent’s ability to seek PrEP with or without parental/guardian consent [18,34,35]. Although several of these studies examine the context of consent within the framework of the ATN 113 study, other literature has compared PrEP to family planning and other HIV prevention programmes [35,36]. Clarity in the laws is critically needed, with PrEP-specific language included whenever possible. However, even if adolescents are widely allowed to consent for themselves in the future, the cost issues described previously will still create barriers because parents will be notified of their child’s PrEP use through insurance statements and explanations of benefits. Again, such unwanted disclosure is a substantial barrier that may result in avoidance of PrEP. Ultimately, this has significant policy-level implications for state regulations that need to be urgently addressed in parallel to the challenges already presented. One example of such progressive policies is the recent legislation introduced by the governor of New York which clearly states that adolescents under the age of 18 should be able to access both PrEP and HIV treatment without parent or guardian consent [37].

**Youth-focused service delivery**

CDC Clinical Guidelines [22] recommend quarterly visits for HIV testing and medical monitoring of PrEP. For adults who are used to seeing a physician one to two times per year, this may be seen as a burden and many care systems and insurance companies are trying to find ways to implement PrEP with minimal time and cost burden for patients. Unfortunately, this may not meet the needs for young people. In the qualitative study by Mullins and colleagues [31], adolescent providers expressed concern that the recommended visit frequency for PrEP monitoring was inadequate based on their expertise in caring for young people. The data from the ATN 110 study with 18 to 22-year olds appear to support this concern. Study participants were seen monthly for the first 12 weeks, then quarterly thereafter until 48 weeks. Results show levels of Truvada that can prevent HIV infection (i.e. ≥4 pills/week) were present for most participants during the monthly visits, but then dropped noticeably when the quarterly visit schedule began [17]. Preliminary data from ATN 113 show a similar, but even more striking drop in adherence with quarterly visits [19], and the CHAMPS PlusPills study is following a similar trend (Linda-Gail Bekker, personal communication). Thus, an augmented visit schedule may be preferable for young people, at least during PrEP initiation, with an even greater focus on adherence interventions especially during times of pill fatigue. Text messaging and mobile application interventions to improve PrEP adherence are currently being tested [38], which may be relatively simple ways to enhance adherence using technology that is highly familiar to youth. The use of adherence clubs and other social support groups has shown promise as a cost-effective strategy for HIV treatment adherence among adolescents and may be a strategy for PrEP users as well [39,40]. Although more comprehensive service provisions may increase cost, the resulting HIV prevention possibilities for youth will have broad social and economic benefits [41].

**Preparing for PrEP implementation among youth in South Africa**

The South African government has prioritized the key populations of sex workers, MSM, and young women and girls for enhanced prevention programmes, including oral PrEP, and national guidelines are currently being written for the safe use of PrEP in each of these populations. In fact, the programme focused on sex workers was officially launched in June 2016. Initial plans in South Africa are to utilize the vertical service platforms that already exist in country for MSM and sex workers; however, the highly stigmatized nature of work with these groups does raise additional feasibility concerns. Notably, the South African Medicine Control Council has licensed the PrEP indication only for adult use at this time, leaving uncertainty regarding how to implement PrEP for adolescent minors. Questions have already been raised about which platforms can be safely and successfully used to provide PrEP to adolescents and how young women will be appropriately identified without stigmatization and labelling. Additional concerns exist about whether these programmes can be integrated into primary healthcare, including sexual and reproductive health services, antenatal care, or other services where youth can be reached. HPTN 067/ADAPT has provided some encouraging data about the willingness and feasibility of young women in South Africa to take daily PrEP. This study, which investigated daily versus intermittent PrEP, confirmed that better adherence and coverage of sexual events occurred with daily PrEP compared to intermittent dosing [42].

New demonstration projects have been encouraged and are being planned (e.g. Project SOAR and the DREAMS Initiative) as a way to better understand the implementation challenges for South Africa and other heavily impacted African countries. In addition, because a PrEP programme for young women will need to be much larger than one for young MSM or sex workers, there has been a great deal of concern raised about cost and sustainability, although strong evidence exists for the cost-effectiveness of PrEP among adults [43,44]. However, the evidence is strong for PrEP efficacy when adherence is high, and given ongoing high HIV incidence among young persons, there is a critical need to identify effective, scalable, and cost-effective PrEP delivery strategies for this key population.

**Conclusions**

In conclusion, more scientific, programmatic, and policy work is needed to ensure that the adolescents that are most vulnerable to HIV infection will have appropriate access to PrEP. There are barriers to both PrEP access and uptake. To address access barriers, we must rectify the limited availability of youth-friendly health services in many settings,
grapple with insurance and consent issues, including the implementation of consent policies and procedures appropriate for mature minors that avoid further marginalizing these at-risk youth from accessing efficacious prevention services as well as advocate for regulatory approvals that will inform these policies and allow PrEP access for adolescents. In parallel, social marketing and social media reach adolescents and help them recognize their HIV risk and be motivated to use new prevention tools like PrEP will help to increase uptake. We also need to find and scale-up effective strategies to help support adolescents in decision-making about PrEP as well as adherence support while on PrEP. Adolescents, in particular, are likely to need enhanced, developmentally appropriate, and culturally tailored support for risk recognition and consistent use of a daily pill. Ongoing research and careful evaluation of a number of interventions to optimize identification of appropriate PrEP users as well as facilitators and enablers of consistent and effective use are urgently needed.

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None.

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Abstract

Introduction: The offer of pre-exposure prophylaxis (PrEP) is recommended as an additional option for HIV prevention for people at substantial risk of HIV infection as part of combination HIV prevention approaches. Implementing this depends on integrating PrEP in public health programmes that address risky practices with evidence-based interventions, and that operate in an enabling legal and policy environment for the delivery of health services to those at higher risk of HIV infection. What does this recommendation mean in terms of the diverse range of HIV prevention needs of key populations, some of whom are so discriminated against that they exist essentially outside formal systems such as national public health services, and for whom a substantial risk of HIV is part of a larger adverse and hostile situation? We discuss this question with reference to people who inject drugs, informed by concerns and comments that emerged from a series of consultations.

Discussion: HIV prevention is part of a spectrum of injecting drug users’ priorities, and their access and uptake of HIV prevention services is contingent on their wider “risk environment.” The need to address structural barriers to services and human rights violations, and to improve access to comprehensive harm reduction programmes are of prime importance and would have higher value than a mono-focus on HIV prevention. Where existing harm reduction activities are inadequate, fragile or dependent on external donors, shifts in funding priorities, including, for example, towards PrEP, could threaten investment in the broader programmes. For these reasons, it cannot be assumed that PrEP promotion will always be supported by people who inject drugs.

The sexual partners of people who inject drugs, non-opioid users who also inject and for whom there is no established substitution treatment, as well as drug users who are unable to negotiate safe sex may value PrEP. As for all key populations, the involvement of people who inject drugs in shaping services for their consumption is vital and too often ignored.

Conclusions: For people who inject drugs and who experience discrimination, violence or harassment, implementation of PrEP should be guided by understanding and engaging with their interconnected range of needs, risk practices, priorities and options. The differentiated needs of sub-populations that inject a range of drugs, and their sexual partners, require further exploration.

Keywords: PrEP; people who inject drugs; HIV prevention.
exacerbated by poverty, inequality, criminalization, violence and discrimination [13].

WHO, UNAIDS and UNODC have defined and endorsed a range of harm reduction interventions to address and prioritize HIV and related health needs of people who inject drugs [14]. Key interventions include needle and syringe programmes (NSP) and opioid substitution therapy (OST) to reduce unsafe injecting and manage drug dependency, as well as the promotion of condom use, facilitated access to testing and treatment for HIV and other sexually transmitted infections, TB, and HCV, and naloxone provision to prevent overdose, supported by appropriate information, education and communication interventions, and “critical enablers,” such as supportive laws, anti-discrimination interventions, interventions to make health services more accessible and acceptable to people who use drugs and anti-violence interventions [14–16]. This set of interventions represents the formal list of evidence-based “harm reduction” interventions around which significant consensus lies as evidenced by their endorsement by international, regional and national organizations and governments [17,18, para.43]. This harm reduction approach responds to a wide range of adverse health needs, is relatively inexpensive to implement [19] and can have a high impact on HIV and HCV transmission [14,16]. Despite this, only half of all countries that report injecting drug use provide OST and even fewer offer NSP [20]. Where these interventions are available, they are often provided at an insufficient scale to have a public health impact.

Lack of scale of these evidence-based interventions results from a number of factors: lack of funding and prioritization, the design and delivery of services that are not targeted to reach key populations and structural barriers that prevent people who use drugs from accessing services [1,21]. These factors shape the wider risk environments of people who inject drugs [22] and constitute a form of structural violence [23], when associated with repeated incarceration; compulsory registration on official lists as drug users; and high rates of violence, police harassment, homelessness and poverty.

People who inject drugs will need to know about, believe in and value PrEP, alongside other interventions such as clean needles and OST. Without consideration of the sometimes violent and hostile environment in which these harm reduction services are delivered, people who inject drugs may not embrace PrEP and instead view it as a reductionist and potentially destabilizing intervention that could divert attention away from existing harm reduction services.

Discussion
Concerns expressed about PrEP by people who use drugs underline the importance of identifying particular policy environments, geographies and sub-populations of people who inject drugs and their sexual partners for whom PrEP may be of value.

PrEP and harm reduction services
The people who inject drugs who were involved in the consultations agreed that, in a context where other key harm reduction services were in place, PrEP would be a desirable option for some people who inject drugs [9]. It was felt, however, that in countries with the highest injection-drug-associated HIV burden, the reality was far from being realized. Respondents expressed opposition to any introduction of PrEP that was not part of an effort to strengthen broader harm reduction and social justice programmes.

I don’t see why it can’t be a part of a truly comprehensive, universally accessible package of services. But that is not the reality. So, given that, it is simply not a priority. [8, p. 10, participant from Eastern Europe and Central Asia region]

Even if we had PrEP, we would still need clean works.

[8, p. 3, participant from Eastern Europe and Central Asia region]

Sustainability and expansion of harm reduction services is a much bigger priority. [8, p. 10, participant from Asia Pacific]

Any new intervention, including PrEP, should strengthen broader health promotion and combination HIV prevention approaches, bolster any existing effective interventions and respond to the diverse needs of the population [15]. A comprehensive combination HIV prevention programme includes condom and lubricant provision, immediate initiation of antiretroviral therapy and the offer of PrEP and also supports related interventions such as harm reduction programmes for people who inject drugs and voluntary medical male circumcision (VMMC) for men in eastern and southern Africa [24].

HIV prevention spending for key populations such as people who inject drugs in low- and middle-income countries is heavily dependent on international financing which is flattening while domestic funding for key populations is low [17,25,26]. A change in donor priorities could destabilize existing harm reduction programmes if they compete for limited funding [27]. This threat is intensified by weak policy and financial support by many governments who have permitted harm reduction programmes that are funded by external sources but who show no or limited commitment to funding harm reduction from national budgets when donors retreat [25,28]. In contexts where harm reduction programmes are politically unpopular, PrEP could present a convenient and “magic bullet” intervention that allows governments to claim that they are addressing HIV prevention, whilst reducing funding and policy support for other evidence-based harm reduction interventions that people who inject drugs need and prioritize [9]. The ethics of providing PrEP when HIV treatment access for people who use drugs is so poor [2,14] was also questioned at the consultations.

PrEP could give them an excuse to close down harm reduction programmes. [8, p. 8, participant from Eastern Europe and Central Asia region]

[PrEP] is entirely inappropriate, given the exceptionally low levels of access [to treatment] for people who inject drugs who live with HIV. [8, p. 4, participant from Europe]

In any situation, PrEP can only be economically and clinically effective when it is funded as part of an accessible and comprehensive HIV prevention and treatment programme [29].

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PrEP, drug use and sexual transmission of HIV

People who inject drugs account for a disproportionate share of HIV burden whether attributable to injection drug use or in combination with sexual transmission [30,31]. There is a complex and fluid interaction between the injection or other use of drugs and increased sexual HIV transmission risk [30]. People who inject drugs report low levels of condom use [31–33]. In Eastern Europe and Central Asia, where half of new infections are among people who inject drugs, 6% of new infections are among sex workers and one-third of new infections are among clients of sex workers and other sexual partners of key populations [1]. Therefore, PrEP has possible value in the social and sexual networks of people who inject drugs where the incidence of HIV is high. These people might include the sexual partners of people who inject drugs, non-opioid drug users who also inject but for whom there is no established substitution treatment and others within the wider drug-using community who are unable to negotiate safe sex, including both women and men who inject drugs and who have sex with men, people who inject drugs and sell sex, transgender people and those who are vulnerable to sexual violence or exploitation. Given what we know of the overlap [30] and double HIV burden of sex work and injection drug use [34], there is a need for synergy and a broad approach to harm reduction programming. This could include the offer of PrEP to address both sexual and injection-related health risks. The one trial of PrEP that was specific to people who inject drugs was not able to differentiate between the prevention of sexual- and injection-related HIV transmission [35].

Consultations with these linked populations could identify additional situations where PrEP might be valuable. Some parallels may be drawn from the views of sex workers who also experience stigma and discrimination that prevents them from engaging with health services [30]. A comprehensive literature search found an “enthusiasm” to use PrEP among sex workers in China, Peru, sub-Saharan Africa and the United States if it were to be distributed through user-friendly services and promoted with non-stigmatizing information and adherence support [36]. This view is tempered with the caution that PrEP introduction should benefit sex workers and their immediate community and not be introduced only for the public health impact in the general population [37]. For some, debate on PrEP promotion provides an opportunity to engage with policy makers on human rights [38].

PrEP gives us an opportunity to advocate for sex workers’ rights. . . . The conversation about biomedical HIV interventions is not going away, and regardless of individual opinion, the folks at the top are still lumping us all into one category . . . If they’re making us a priority “to address” us as a “key population,” we should be at that table. [38, sex worker activist, Chicago]

This reaction found an echo from a North American INPUD consultation participant and emphasizes the notion that PrEP services should be in step with the varying needs and desires of the priority population for whom it is intended.

Now you might say we have other priorities, . . . people should have their options. . . . And like anything else, if you’re not at the table, but you’re just being a [PrEP] naysayer, you’re going to be left out of how these things actually get rolled out. [8, p. 10]

It is important to remember that people who inject drugs have the same sexual rights and sexual health needs as those in the general population [39] and that in contexts where HIV transmission is at least partly driven by unsafe injecting in combination with risky sex, HIV prevention impact achieved for people who inject drugs can influence HIV transmission dynamics in the wider population [40].

Provision and uptake of PrEP

For all criminalized and highly marginalized (key) populations, an enabling environment where their voices can be heard, supported by legislation and zero tolerance for violence, is vital to meet HIV prevention targets and ameliorate many other adverse health events [2,41]. Where these conditions are still lacking, their absence is a huge constraint to achieving better health and quality of life [22,42]. Without them, improved services can remain under-utilized and inefficient since key populations will often remain underground for fear of arrest or violence. A person’s request for PrEP can require the disclosure of sometimes illegal and risky practices, along with repeated contact with sometimes hostile health services. In conditions such as these, people who are at substantial risk of HIV exposure and who could benefit from PrEP are unlikely to seek it for fear of discrimination, breaches of privacy, criminal sanctions or other threats.

If we’re talking about people who are targeted by evidence of prostitution or injection drug use, they are already going to have trouble accessing the level of institutional care they need to be on PrEP, so PrEP is not a solution for the people who need it most. [43, Daniel Wolfe Director, International Harm Reduction Development]

You wouldn’t be able to get it without giving your name, which would be a barrier for sure. As a mother there is fear of getting children removed, fear of losing one’s job. [43, p. 6, participant from Europe]

The history of rights-based health interventions, including for people who inject drugs, has advanced through a series of small victories [40]. The requirement to attend to the context, practices and priorities of key populations applies to all HIV programme implementation, and the emergence of interest in PrEP presents an opportunity to examine these factors more deeply. Current focus and debate on PrEP implementation provides an opportunity for people who inject drugs who are interested to shape the development and design of PrEP services. Health planners and decision-makers will need to engage with people who inject drugs and their sexual partners in order to understand their interest in PrEP, and how any such interest can be integrated with broader prevention services and, for example, the need for drug dependency treatment, overdose treatment, HCV and HIV treatment and the need for protection from human rights violations [2].
Conclusions
PrEP is best understood as an additional potential HIV prevention option for some people who inject drugs and their sexual partners in specific circumstances. The challenge is to ensure that the potential of PrEP is not undermined by narrow and overly biomedical understandings of its value, removed from the real lives of those most at risk of HIV exposure. Harm reduction programmes are intended to address a range of interests and needs, and it is likely that harm reduction programmes could be an effective implementation platform for PrEP for people who inject drugs. (From data and experience of using the medicines in HIV treatment, no interaction is expected between PrEP containing tenofovir/emtricitabine or tenofovir/lamivudine and heroin, methadone or methamphetamine [44]).

PrEP can be an opportunity to harness a specific intervention for longer term public health and human rights outcomes. PrEP will realize its HIV prevention potential if it is introduced in a way that complements and strengthens existing harm reduction and health promotion activities, if it contributes to reducing discrimination and empowers key populations at risk of HIV infection. Creating opportunities to hear from and engage with people who use drugs about their interests, needs, values and preferences regarding HIV prevention, alongside wider health and other needs, is a priority for health programmers and decision-makers. These are some of the factors that will ensure the potential of PrEP for people who inject drugs is realized in a variety of real-world settings.

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**PrEP: controversy, agency and ownership**

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**Abstract**

Pre-exposure prophylaxis (PrEP) has been and continues to be an intervention that causes controversy and debate between stakeholders involved in providing or advocating for it, and within communities in need of it. These controversies extend beyond the intrinsically complex issues of making it available. In this commentary, some of the possible roots of the air of dissent and drama that accompanies PrEP are explored. The similarities between the controversies that dogged the earliest human trials of PrEP and the ones we see today in the era of licensing and implementation are explored. We outline five mediating principles or cultural norms that may influence arguments about PrEP differently. Three areas of specific concern are identified: medical risk versus benefit, distrust and fear of healthcare interventions, and fears for individual responsibility and community cohesion. The fear that PrEP may somehow represent a loss of control over one or more of these domains is suggested as an underlying factor. The development of countervailing measures, to institute greater community “ownership” of PrEP, and concomitant improvements in the sense of individual agency over sexual risk are outlined and recommended.

**Keywords:** HIV; HIV prevention; pre-exposure prophylaxis; sociology of HIV; HIV prevention implementation; key affected populations; men who have sex with men.

**Introduction**

Although the efficacy of pre-exposure prophylaxis (PrEP) has been proven, the roll-out and general scale-up of PrEP face major challenges, including the potential for creating ongoing polarization in the field. The issues around the roll-out of PrEP have changed over time, but the controversy remains.

In this article, we look at the responses to the main controversies in the history of PrEP research and examine what social attitudes and cultural beliefs about health, illness and power may underpin them.

**The constituents of controversy**

Lasting views and attitudes to PrEP emerged during the first clinical trials. They persist, somewhat transformed, among attitudes to the roll-out of PrEP today. Many are rationally based on concerns about PrEP or its impact. The concerns are potentially magnified by the idea that, in the era of the Internet, what previously might have been considered beliefs about health now is considered knowledge, even though that knowledge is partial [1]. Many other health beliefs based on personal, political or religious factors contribute to current perceptions of PrEP. These are often mediated by other cultural norms; factors include a tension between individualism and communitarianism in human responsibility, the role of colonialism in creating distrust towards former “oppressors,” religious perspectives and discourses about programmatic rationality (i.e. equity, cost–benefit ratio and sustainability). We argue that these factors generate three areas of debate discussed subsequently.

**Risk versus benefit**

This involves a straightforward fear that PrEP will do more harm than good. In the early abandoned PrEP trials (e.g. the Cambodia or Cameroon), participants, their partners, relatives and peers developed beliefs that the pills contained HIV or that researchers were either deliberately infecting participants in blood tests or allowing them to be infected. Beliefs like these are different to the belief that PrEP will lead to toxicities. They are based on suspicions of malignant intent by researchers or the healthcare professionals, rather than on intrinsic medical and pharmaceutical risks. They have been both persistent and markedly more common in populations that are disadvantaged or socio-economically distanced from the researchers. Early trials were also associated with controversies linked to the perception that HIV care and treatment would not be available to people who seroconverted during the trial [2].

A further concern raised is that PrEP is doomed to ineffectiveness because of consequent increased condomless sex or “condom migration.” This is deduced from assumptions that even modest reductions of condom use will negate the effectiveness of PrEP. Contrary to this, a recently published mathematical model demonstrated that while PrEP may have an impact on rates of condom use, even zero condom use would not entirely abrogate the effectiveness of PrEP [3].
An associated concern is that more condomless sex due to PrEP will lead to more sexually transmitted infections (STIs). Again, evidence would show that while STIs have undoubtedly been increasing in men who have sex with men in recent years, the increase predates the introduction of PrEP. Another take is that PrEP is a response to historical decreases in condomless sex rather than a contributor to them.

Finally, controversy has occurred around PrEP access and whether drug would be made available post clinical trial [4]. More recently, attention has focused on what happens to PrEP users when after some time individual’s risk changes – will PrEP eligibility and therefore access for that individual change?

Autonomy and responsibility
Other concerns centre on the fear that PrEP could cause social harm and disempower key affected populations in ways that would cause long-term damage to their autonomy. Women’s risk of HIV tends to be viewed as a function of their vulnerability to exploitation, violence and patriarchal moralities. But gay men’s risk tends to be viewed as a function of their responsibility and therefore reducing that risk is their personal duty. In particular, PrEP is said to have the potential to erode gay men’s sexual responsibility by enabling “unprotected” sex with multiple partners or, rather, reducing the anxiety that would formerly have prevented it.

On a more macro level, this social harm could reduce a community’s power to demand structural and other resources that could be used to prevent HIV, rather than regulating outcomes of people’s behaviour with medications.

PrEP, control and agency
The list of the cultural concerns that have informed key strands of community opposition to PrEP in this article are incomplete. The issues we have not discussed include the idea that PrEP will “medicalize” what should properly be regarded as a structural and social issue and the fact that PrEP simply exemplifies global economic and health disparities an intervention that caters to affected communities in rich countries when over half the people with HIV in the world still cannot get treatment.

PrEP has been described by Professor Robert Grant of UCSF as a “demand-driven” intervention [5], meaning that “the indication for PrEP is that someone asks for it.” This implies that people are good at determining their own risk and that overly tight criteria for offering PrEP are unnecessary because people will self-regulate in terms of use and uptake. But it may also be taken to imply that PrEP will only work if it becomes part of a person’s strategy for maintaining their health and quality of life. PrEP must not just be a medical prescription, but a tool to enable agency.

In the analysis of what went wrong in the early PrEP trials in Cameroon and Cambodia, USAID and the Global Campaign for Microbicides explain that while the trial participants were consulted about the trials, they were not involved in the planning. Involvement, the sense of actually being a stakeholder (whether in the design of clinical trials or in the construction of health strategies with one’s healthcare provider), is a strong predictor of adherence, as qualitative studies of PrEP trials have proved [6].

Clinical researchers have increasingly sought to involve the communities in which PrEP is being studied in the actual design and running of trials. It is possible that one of the reasons the iPrEx trial was the first PrEP trial to report a successful result was due to a lengthy and intensive process of community consultation that occurred before and throughout the trial. This community consultation was not just an exercise in social research but also a way of actively preparing the varied MSM communities involved to develop a sense of being stakeholders [7].

Given the highly controversial nature of PrEP, and the involvement of ACT-UP Paris in activism against the Cambodian and Cameroon PrEP trials, the coordinators of the Ipergay trial actively sought to involve the relevant communities in trial design and delivery, including the counselling and peer-support aspects of the research.

In the PROUD trial, there was also an active community engagement group and a community representative (the lead author of this piece) served as the trial’s co-chair. Increased community involvement has paid off, even in trials among the more difficult and disenfranchised populations. Although the intervention was found to be ineffective, the FACTS001 trial of a tenofovir gel microbicide was not marked by the same distrust as was seen in VOICE and Fem-PrEP; participants’ actual adherence matched their reported adherence, and the intervention did not work because it did not fit with existing social practices [8].

Conclusions
PrEP is on the verge of wide adoption in several countries around the world, and the US experience suggests it should be considered as a public health measure. In Europe, North America, Africa and certain other countries such as Australia and Thailand, PrEP is being implemented in a piecemeal manner amidst the ongoing debate this intervention has generated. Its adoption has been facilitated by activist groups in the United States (see www.facebook.com/groups/PrEPFacts), the UK (see www.prepster.info and www.iwantprepnow.co.uk), France (see www.facebook.com/groups/Prepdial) and a number of others using various platforms including social media. In countries where PrEP is not yet available, affected communities are self-organizing to buy generic PrEP online, and there has been an upsurge of interest and awareness of this intervention.

There continue to be setbacks and delays. In March 2016, the English National Health Service (NHS) rejected an application for a graduated roll-out of PrEP claiming that more research was needed to answer “unanswered questions.” In addition, and perhaps more critical to delay, the NHS insisted that as a prevention measure, PrEP had to be paid for by local boroughs, since prevention responsibility is held at borough-level, not nationally [9].

There are still groups that are hard to reach and do not yet feel that PrEP is a prevention intervention they have ownership over, including young women in Africa and young black gay men in the United States. PrEP is still a long way from
becoming possible or even relevant in areas where the struggle for adequate treatment for people with HIV is still very much a reality. Some of the arguments about PrEP stem from deeply held beliefs that may not be easy to change. But HIV activism has always consisted of coalitions between unlikely partners such as radical gay men and church leaders, and there is no reason this cannot also be true of PrEP. There are other obstacles, including tight health budgets, stigma against sexual minorities and the inertia associated with entrenched practices of health service provision.

If PrEP is a demand-driven intervention, that demand is starting to make itself heard in various ways around the world despite opposition.

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Gus Cairns is a journalist specializing in HIV, sexuality, healthcare, development and related matters and declares to have no competing interest of any kind.

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Gus Cairns and Kane Race have produced this article in close collaboration and both have contributed equally to the final version of the text. Pedro Goicochea contributed in the synthesis of the main ideas to produce a more succinct version of the article.

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## AUTHOR INDEX

**A**  
Alary, M 19  
Anand, T 30  
Anderson, S-J 11  

**B**  
Baggaley, R 4,30  
Baruch, R 39  
Behanzin, L 19  
Bekker, L-G 1,19,56  
Beyrer, C 4  
Borquez, A 4  

**C**  
Cáceres, CF 1,4,39  
Cairns, GP 68  
Celum, C 56  
Coleman, RL 63  
Cowan, FM 19  

**D**  
Delany-Morettwe, S 19,56  
Deutsch, MB 49  

**G**  
Ghidinelli, M 39  
Godfrey-Faussett, P 1  
Goicochea, P 68  
Grant, R 49  
Grinsztejn, B 39  
Grilich, AE 30  
Guanira, JV 39  
Guedou, FA 19  

**H**  
Hallett, TB 11  
Hosek, S 56  

**J**  
Janyam, S 30  

**K**  
Kapogiannis, B 56  
Klausner, JD 4  

**L**  
Lo, Y-R 30  
Luque, R 39  

**M**  
McCormack, SM 44  
McGillen, JB 11  
McLean, S 63  
Molina, J-M 44  
Mugo, NR 19  
Mugurungi, O 19  

**N**  
Noseda, V 44  

**P**  
Phanuphak, N 30  
Poonkasetwattana, M 30  

**R**  
Race, K 68  
Ravasi, G 39  

**S**  
Sanders, EJ 19  
Sevelius, JM 49  

**V**  
van Griensven, F 30  

**W**  
Wilson, CM 56  

**Z**  
Zablotska, I 30
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