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POLICY FOCUS

**PRE-EXPOSURE  
PROPHYLAXIS FOR  
HIV PREVENTION:  
MOVING TOWARD  
IMPLEMENTATION**

*SECOND EDITION, JULY 2012*

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## POLICY FOCUS

# Pre-exposure prophylaxis for HIV prevention: Moving toward implementation

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### *EXECUTIVE SUMMARY*

Initial results from clinical prevention trials of pre-exposure chemoprophylaxis (PrEP) indicate that PrEP could be a key part of the “game changer” needed to more effectively fight HIV. PrEP entails that at risk HIV-uninfected people take antiretroviral medications to prevent HIV transmission through unprotected sex or sharing needles. Oral PrEP uses antiretroviral medications that are currently available for treatment. A related experimental technology involves topical microbicides, a term that can refer to any anti-infective agent, but in the current usage refers to topical gels that contain anti-retroviral medications that are applied vaginally or rectally to prevent HIV transmission. Future approaches to the use of antiretrovirals for prevention include the use of intravaginal rings or injectable medication.

Some oral PrEP and topical microbicide trials have shown promise, while others have not. The use of pre-exposure prophylaxis (PrEP) for HIV prevention has shown efficacy with men who have sex with men (MSM) and heterosexuals. Biomedical prevention interventions such as PrEP have great potential, especially if coupled with expanded testing, diagnosis, and linkage to earlier initiation of treatment and care (TLC+). Modeling demonstrates the most effective deployment of PrEP to slow the spread of HIV will be in combination with scaled-up treatment.

PrEP must be accompanied by sustained care and behavioral interventions to ensure adherence, minimize risk compensation (people increasing risk because of anticipated protection), and monitor side effects and drug toxicities. Because many people who are at greatest risk to acquire HIV do not access regular clinical care, alternative implementation arrangements will be necessary. National monitoring systems are critical to preventing the spread of drug-resistant HIV.

Some have raised concerns about PrEP related to potential side effects, risk compensation (the idea that people will stop using condoms if PrEP becomes available), drug resistance, and cost. However, reviews of five major clinical trials involving about 6,000 participants by the Forum for Collaborative HIV Research shows no greater risk of side effects, no risk compensation, and no clinically significant development of drug resistance in participants.



**PrEP could be a key part of the “game changer” needed to more effectively fight HIV.**

Guidance from the U.S. Public Health Service, U.S. Food and Drug Administration, and World Health Organization are expected in 2012. Demonstration projects are underway or set to launch soon in San Francisco, Miami, in sub-Saharan Africa, and elsewhere. While the cost of PrEP in the U.S. would be substantial, private insurers and state Medicaid departments are open to coverage, and low-cost generic medications could enable access in low-income countries. The passage of the Affordable Care Act and the recent ruling that it is constitutional by the U.S. Supreme Court could result in wider access to PrEP, if the FDA approves the use of tenofovir-emtricitabine for prophylaxis. The prioritization of highly vulnerable populations could increase the cost-effectiveness of PrEP. Providing PrEP to at risk persons for finite periods of time is also much less expensive than treating someone for HIV over the course of a lifetime.

The most effective prevention interventions will be those that combine behavioral interventions, structural interventions, and emerging biomedical technologies. Recent modeling of PrEP implementation coupled with scaled up antiretroviral treatment—focusing on the general adult population in Botswana<sup>1</sup>, and serodiscordant couples in South Africa<sup>11</sup>—predicts that PrEP could significantly reduce HIV incidence and prevalence.

This review of PrEP implementation issues summarizes the state of PrEP and microbicides research as of June 2012, looks at willingness to use PrEP among various populations, addresses concerns about PrEP that could present obstacles to implementation, offers strategies for effective implementation, and examines policy issues related to cost and how to make PrEP accessible to those most vulnerable to HIV who could benefit most from PrEP. It examines regulatory developments and planning underway both within the U.S. and globally.

This analysis concludes with recommendations for implementation of PrEP. Among the recommendations are the following:

### **CLINICAL TRIALS AND DEMONSTRATION PROJECTS**

- Oral PrEP and topical microbicides research should continue with priority populations, and examine new compounds, intermittent PrEP, injectables, intravaginal rings, implants and other delivery modalities that could increase adherence.
- Funders should support demonstration projects to understand real-world implementation issues and develop best practices. Demonstration projects should make PrEP available to populations most vulnerable to HIV who could benefit most from it. These include gay and bisexual men (particularly those from racial and ethnic minorities); transgender women; high-risk heterosexual women and men, including serodiscordant couples; and sex workers.

## **IMPLEMENTATION IN CLINICAL SETTINGS**

- PrEP should be combined with comprehensive, sustained medical care and behavioral interventions to ensure adherence, minimize risk compensation and monitor side effects.
- PrEP should be combined with scaled-up testing and early treatment of HIV-infected people to reduce incidence in high-prevalence countries and in concentrated epidemics, for example among MSM.
- Provision of PrEP to MSM and transgender women should occur in a broader context of ensuring clinically competent health care to gay, lesbian, bisexual and transgender people.
- Community-based organizations, health departments and others should preemptively take steps to destigmatize PrEP use among key priority populations.

## **COMBINING BIOMEDICAL INTERVENTIONS WITH STRUCTURAL INTERVENTIONS**

- Public health entities should educate most vulnerable populations about the difference between PrEP and post-exposure prophylaxis (PEP), and use the emergence of PrEP as an HIV prevention approach to educate people about PEP. Some people seeking PEP and/or HIV testing after a possible risk exposure should be prioritized to be educated about PrEP coupled with sustained behavioral interventions.
- Funders should support community education and engagement campaigns to increase community literacy about PrEP and other biomedical interventions, and to enhance community involvement in scale-up and roll-out of PrEP and other interventions.

## **REGULATORY STEPS**

- The U.S. Food and Drug Administration (FDA) should accept the May 10, 2012 recommendation of its Antiretroviral Drugs Advisory Committee that emtricitabine/tenofovir disoproxil fumarate (FTC-TDF) be indicated for use as an HIV prevention tool as pre-exposure prophylaxis for men who have sex with men (MSM), uninfected partners in serodiscordant couples, and for other adults at risk for HIV through sexual activity.<sup>1</sup>
- The World Health Organization (WHO) should issue guidance on PrEP that takes into account the promising results of the iPrEx study, Partners PrEP, and the Botswana CDC study.
- Following the release of the Bangkok injection drug user (IDU) trial results, if appropriate the U.S. Centers for Disease Control and Prevention, the U.S. Public Health Service, and the WHO should issue guidance for PrEP with IDUs.

**PAYING FOR PREP, AND ENSURING ITS ACCESSIBILITY TO LOW-INCOME AND MOST AT-RISK POPULATIONS**

- Pharmaceutical companies should be encouraged to offer PrEP at a discount and to create a Patient Assistance Program for the medications. Government incentives could encourage such moves.
- States should provide access to PrEP as a critical prevention service and prescription medication under the Essential Health Benefits provision of the Affordable Care Act. For highly vulnerable populations such as MSM and people in serodiscordant relationships, PrEP can potentially be a cost-saving measure that will improve public health and save money in the medium and long term.
- Subsequent to FDA approval of PrEP, State Medicaid programs should also cover PrEP as a potentially cost-saving measure that will improve public health and ultimately save money in health care costs.
- Global funders of HIV prevention and care should make resources available for PrEP and treatment as prevention. The WHO, PEPFAR, UNAIDS, and the Global Fund to Fight AIDS, Tuberculosis and Malaria should provide the latest research to country planners to help policy makers review the dynamics of their local epidemics in order to strike the right balance between funding for PrEP, other prevention services, and treatment.

**THE POTENTIAL OF PREP**

As we enter the fourth decade of the HIV epidemic, an estimated 50,000 people are newly infected each year in the U.S. and about 2.5 million globally. Men who have sex with men (MSM) constituted 64% of new infections in 2009, even though they comprise only 2% of the adult population.<sup>1,5</sup> Black and Latino MSM are disproportionately vulnerable to HIV. New infections among black MSM in the U.S. age 13–29 increased 48% from 2006 to 2009. Of the 2.5 million people who were newly infected in 2009,<sup>2</sup> the majority of HIV transmissions were among heterosexuals in low- and middle-income countries, but there are concentrated epidemics of HIV among MSM and other most at risk populations.<sup>3</sup>

While there has been some reduction in new infections in sub-Saharan Africa<sup>4</sup>, nearly 2 million are newly infected each year in this region, and millions don't have access to anti-retroviral treatments.<sup>5</sup> Clearly, the status quo is not sufficient to keep the epidemic in check, let alone end it.<sup>6</sup> Initial results from clinical prevention trials of pre-exposure chemoprophylaxis (PrEP), in oral pill form (oral PrEP), indicate that PrEP could be part of the “game changer” needed to more effectively fight HIV. PrEP involves taking antiretroviral medications to prevent HIV transmission through unprotected sex or sharing needles. A related experimental technology involves microbicides, a term that can refer to any anti-infective agent, but in the current usage refers to topical gels that contain anti-retroviral medications that are applied vaginally or rectally to prevent HIV transmission.<sup>7</sup> One major microbicide trial showed promise (CAPRISA 004), while another (VOICE) did not. Early studies of other forms of chemoprophylaxis (vaginal rings, injectable medication) are underway, but in the short term, only oral medication is currently available and will be the focus of this monograph.

As President Obama's 2010 National HIV/AIDS Strategy states, biomedical prevention interventions such as PrEP have great potential, especially if coupled with expanded testing, diagnosis, and linkage to treatment and care (TLC+) to find the estimated 20% of people living with HIV who are undiagnosed, and to increase the percentage of people diagnosed with HIV who receive ongoing care, and initiate antiretroviral treatment.<sup>8</sup> Recent studies have demonstrated a dramatic decrease in HIV transmission when infected individuals initiate suppressive antiretroviral therapy at higher CD4 counts.<sup>9</sup> But in this primarily heterosexual sample, about one quarter of the new infections occurred with non-primary partners, underscoring the need for different groups of at risk individuals to have access to primary chemoprophylactic approaches.

It is essential that PrEP be combined with behavioral interventions to maintain both PrEP adherence and continued fidelity to safer sex practices. A concurrent focus on TLC+ as well as behavioral interventions to support treatment adherence and safer sex practices would decrease community viral load and complement the effectiveness of PrEP. Implementing both PrEP and TLC+ together can be done efficiently through public health programs that maximize the effectiveness of both.

The most effective prevention interventions will be those that combine behavioral interventions, structural interventions, and emerging biomedical technologies.<sup>10</sup> Recent modeling of PrEP implementation coupled with scaled up treatment—focusing on the general adult population in Botswana, and serodiscordant couples in South Africa—predicted that PrEP could significantly reduce HIV incidence and prevalence.<sup>11</sup>

This review of PrEP implementation issues summarizes the state of PrEP and microbicides research as of June 2012, looks at willingness to use PrEP among various populations, addresses concerns about PrEP that could present obstacles to implementation, offers strategies for effective implementation, and examines policy issues related to cost and how to make PrEP accessible to those most vulnerable to HIV who could benefit most from PrEP. It examines regulatory developments and planning underway both within the U.S. and globally. This analysis concludes with recommendations for implementation of PrEP, related to demonstration projects, clinical trials research, implementation in clinical settings, combining biomedical interventions with structural interventions, regulatory steps, and how to pay for PrEP and ensure access to it for most vulnerable populations.

## **CLINICAL PREVENTION TRIALS**

### **PREP AND MICROBICIDE TRIALS THAT HAVE SHOWN EFFICACY WITH MSM AND HETEROSEXUAL MEN AND WOMEN**

The first microbicides trial to show efficacy was CAPRISA 004, which studied the use of a tenofovir gel applied to the vagina pericoitally in high-risk South African women. Women using the microbicide gel were 39% less likely to get HIV than those using a placebo after 30 months. The protective effect was over 54% among highly adherent women (80% or more adherence to pericoital gel use).<sup>12</sup> All women in the trial were provided with HIV prevention education and tested for HIV and other STIs frequently.

The first oral PrEP trial to demonstrate efficacy among was iPrEx, which enrolled 2499 MSM in Peru, Ecuador, Brazil, the US, South Africa and Thailand. The participants who took coformulated oral emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) had a 44% lower rate of HIV infection than those assigned the placebo. All were provided comprehensive HIV prevention services, including risk reduction counseling and HIV/STI testing. In a nested case-control study, among subjects with a detectable study-drug level (i.e. the most treatment adherent), there was a 92% lower rate of HIV infection than among those without a detectable level of FTC-TDF tested in the visit before seroconversion.<sup>13</sup>



**In the Partners PrEP study, those receiving TDF were 62% less likely to contract HIV; those receiving FTC-TDF were 73% less likely.**

Results of two PrEP studies involving heterosexual men and women were released in July 2011 at the International AIDS Society meetings in Rome; both showed chemoprophylaxis efficacy.<sup>14</sup> The first was the Partners PrEP study. Involving 4758 serodiscordant couples in Kenya and Uganda in which the HIV-infected partner is not yet medically eligible for ART, the study randomized the HIV-uninfected partners to receive one of the following regimens: oral TDF once daily, oral FTC-TDF once daily, and a placebo once daily. As in other trials, all were given comprehensive prevention and testing services. Compared with the placebo group, those receiving TDF were 62% less likely to contract HIV; those receiving FTC-TDF were 73% less likely.<sup>15</sup>

The second oral daily PrEP study involved 1200 heterosexual men and women in Botswana. Half were randomized to use oral FTC-TDF, half a placebo; all received comprehensive HIV prevention counseling and testing. Those who were assigned to take FTC-TDF were up to 75% less likely to contract HIV than those receiving the placebo.<sup>16</sup> As of June 2012, results of these two studies have not yet been published.

## **RECTAL MICROBICIDES**

Rectal microbicides, currently in development, involve an agent that can be included in topical gels, lubricants, douches or enemas and applied to the rectum to prevent HIV transmission.<sup>17</sup> A tenofovir rectal gel was found effective in preventing simian immunodeficiency virus (SIV) transmission among macaques.<sup>18</sup> A number of safety and acceptability studies have been conducted with humans since 2004. For example, one study found UC781 (a gel that includes a thiocarboxanilide non-nucleoside reverse transcriptase inhibitor)<sup>19</sup> to be safe and well tolerated when used rectally in humans.<sup>20</sup> Another study looked at how much microbicide gel would be acceptable, and found that MSM generally tolerated up to 35 ml while having receptive anal intercourse.<sup>21</sup>

Study results released in February 2011 moved research closer to proof of concept for rectal microbicides in both men and women. In the study, 18 HIV-negative men and women were given a vaginal formulation of tenofovir gel to use rectally once a day for one week; another 18 men and women were given a placebo vaginal formulation gel to use rectally. Rectal tissue samples were gathered and send to a laboratory,

where they were exposed to HIV. The study found that HIV was “significantly blocked” in tissue samples from study participants who had used tenofovir gel compared with participants who had used a placebo gel.<sup>22</sup> According to a presentation by Peter Anton at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, “[r]ectal dosing was associated with 100 times more active TFV-DP [tenofovir] in the target mucosa than oral dose.”<sup>23</sup> In other words, rectal tenofovir gel appeared to provide higher concentrations of tenofovir to rectal tissue than oral FTC-TDF taken once.

Similar findings resulted when vaginal gel was compared with taking a daily tenofovir disoproxil fumarate (TDF) tablet. Craig Hendrix presented data at the 2011 CROI conference from MTN 001, a study that compared 1% tenofovir gel to oral tenofovir. Similar to Anton’s report of higher rectal tissue concentrations with gel versus oral PrEP administration, Hendrix reported that those who used the topical vaginal gel had greater than one hundred-fold higher concentrations of tenofovir in vaginal tissue compared with those using oral PrEP.<sup>24</sup>

While these findings are promising, it is important that their significance not be overstated. The sample size for RMP-01 was small (n=36), and it was not designed to demonstrate efficacy. Despite the promising pharmacological and virological data seen when vaginal tenofovir gel was applied rectally, the product was not optimally tolerated, probably because of a high concentration of glycerin, which can stimulate an urge to defecate, not an ideal feature for a rectal microbicide. A subsequent study, MTN 007, which tested a reduced glycerin formulation of the tenofovir vaginal gel in the rectum for safety and acceptability, was conducted among 63 men and women in Boston, Pittsburgh and Alabama.<sup>25</sup> The MTN 007 study found the rectal tenofovir gel to be safe and acceptable, in results released at the Conference on Retroviruses and Opportunistic Infections (CROI) in March 2012.<sup>25.5</sup> Plans are underway for MTN 017, which will enroll at-risk MSM and transgender women in the U.S., Thailand, Peru and South Africa in an expanded safety trial that will evaluate the acceptability and tolerability of oral FTC-TDF pills versus the reduced glycerin tenofovir gel administered rectally. MTN 017 will be launched before the end of 2012. While rectal microbicides may deliver more tenofovir to rectal tissue than oral tenofovir, the amount delivered by oral PrEP may be sufficient to prevent HIV transmission. Unlike gels, which are still experimental, oral medication can be readily prescribed today if indicated.

In the future, other modes of rectal delivery of antiretrovirals may be explored. For example, Craig Hendrix presented exploratory research on the safety and acceptability of rectal douches and enemas as delivery systems for PrEP at the 2011 CROI conference.<sup>26</sup>

## **PREP TRIALS THAT HAVE NOT SHOWN EFFICACY TO DATE**

FEM PrEP, a study of 1,951 heterosexual women in South Africa, Kenya and Tanzania, was discontinued in April 2011 after it became apparent that women assigned to the daily oral FTC-TDF arm did not develop lower rates of HIV infection than those assigned to take a daily placebo. FEM PrEP failed to prevent HIV among women in Africa because more than half the women failed to take their medication (TDF-FTC), according to an analysis released at CROI 2012. Lut Van Damme of FHI 360 said that women in the study

“seriously overestimated adherence.” Participants told researchers they took their assigned medicines 95% of the time, but tests for TDF-FTC in the blood of participants in the TDF-FTC arm showed that only about 40% of the women had taken the once-daily medication within the past 48 hours.<sup>27</sup>

The VOICE trial conducted by the NIH-funded Microbicide Trials Network (MTN) was designed to compare two different oral PrEP regimens (TDF alone or FTC-TDF) versus placebo, or tenofovir gel vs. placebo gel. In September 2011, this study of 5,029 women in Uganda, Zimbabwe and South Africa stopped evaluation of the oral tenofovir pills (TDF) arm after its independent Data and Safety Monitoring Board (DSMB) determined that it was not possible to show whether oral TDF was more effective than a placebo in preventing HIV among the women assigned to that study group.<sup>28</sup>

Two months later, the DSMB suspended the tenofovir and a placebo gel arms after it found that the tenofovir gel could not be shown to prevent HIV transmission among the study’s participants. The HIV incidence<sup>29</sup> between the tenofovir gel and placebo gel arms was nearly identical, 6.0% and 6.1%, respectively.<sup>30</sup> One other active comparison in the VOICE study—of oral FTC-TDF versus a placebo—continues.<sup>31</sup> As with FEM PrEP, the reasons for these outcomes are currently unknown, but it is anticipated that some answers may be presented either at the upcoming retrovirus conference in Seattle in March or at the International AIDS Society conference in Washington, DC in July.

## **DIFFERENCES IN RESULTS FOR WOMEN VERSUS MEN**

The questions raised by the failure to show efficacy in the oral and vaginal tenofovir arms of the VOICE study involve pharmacology and physiology: the jury is still out on whether oral PrEP or vaginal tenofovir gel can consistently deliver high enough concentrations of ARV to vaginal tissue to prevent HIV transmission for women, since one gel study and two oral PrEP studies demonstrated protection for them, while one gel and two oral studies did not. For men, three oral PrEP studies demonstrated protection, one for MSM and two that primarily enrolled heterosexual men.

## **ONGOING PREP AND MICROBICIDE TRIALS**

HPTN 069 will be the first PrEP study to examine the safety and tolerability of drugs other than tenofovir and FTC-TDF. HPTN 069 will compare maraviroc, maraviroc plus emtricitabine, maraviroc plus tenofovir, and tenofovir plus emtricitabine as oral PrEP for men who have sex with men and women in the U.S. This protocol is being finalized and should begin during the first half of 2012.<sup>32</sup>

The VOICE study continues to test oral FTC-TDF against a placebo in African women. Safety and efficacy results may be released in late 2012.<sup>33</sup>

In Bangkok, oral TDF PrEP is being compared to placebo among 2,413 injection drug users (IDUs) enrolled in this study from 2005–2010. Safety and efficacy results are expected in 2012.<sup>34</sup> Other research indicates that PrEP has the potential to effectively prevent intravenous HIV infection. Denton et al. argue that “PrEP could be particularly effective at slowing the spread of HIV-1 if a single antiretroviral combination were

found to be broadly protective across multiple routes of transmission.” They tested FTC-TDF in humanized Bone marrow/Liver/Thymus mice (humanized BLT mice) and found it highly effective in preventing rectal and intravenous HIV-1 transmission.<sup>35</sup>

An open-label extension phase of the iPrEx study is ongoing in the US, three Latin American countries, South Africa and Thailand with HIV-negative MSM from the iPrEx study and another cohort of young HIV-negative MSM. Participants are offered open label daily oral TDF-FTC; there is no placebo arm, but participants can elect to be followed and provided other HIV prevention services even if they don’t want to take medication. Results are expected in 2013. Several PrEP demonstration projects are being planned, with implementation studies shortly getting underway in San Francisco and Miami.

A second open-label extension study will be launched in Botswana in 2012 with daily oral TDF-FTC. Results are expected in 2013.<sup>36</sup>

A study of rectal microbicide safety and acceptability among young gay and bisexual men (Project Gel) is currently underway at the University of Pittsburgh, at Fenway Health in Boston, and at the University of Puerto Rico in San Juan.<sup>37</sup>

As mentioned above, MTN 007 tested a reformulated tenofovir rectal gel that contains lower amounts of glycerin.<sup>38</sup> The study found the gel to be safe and acceptable, in results released at CROI in March 2012.<sup>38,5</sup> The first multicountry rectal microbicide study of MSM and transgender women, MTN 017, will be launched in the US, Peru, South Africa, and Thailand before the end of the year.<sup>39</sup>

There are a number of ongoing vaginal microbicide trials evaluating other compounds.<sup>40</sup> These include a number of safety and acceptability studies of gels, as well as of a vaginal ring containing other antiretroviral drugs, dapivirine and maraviroc, either alone or in combination. The vaginal ring trial (MTN-013/IPM 026) is the first clinical trial of a combination intravaginal microbicide. It has enrolled 48 women in Pittsburgh, Boston, and Birmingham, Alabama.<sup>41</sup> If this study demonstrates safety and favorable pharmacological properties, an efficacy trial of the vaginal ring will get underway in Africa in the second or third quarter of 2012. The four-week dapivirine vaginal ring study will enroll 3,476 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe (MTN 020).<sup>41,1</sup>

It may be that a combination of oral PrEP and microbicides could be most effective for certain populations—perhaps a daily or less frequently administered pill and gel applied before sex.

In the past year, the first studies of injectable microbicides have gotten underway, using a novel



**The questions raised by the failure to show efficacy in the oral and vaginal tenofovir arms of the VOICE study involve pharmacology and physiology.**

suspension of the non-nucleoside reverse transcriptase agent, Rilpivirine.<sup>41,2</sup> Expanded studies are planned over the next year prior to future efficacy trials. Pre-clinical work is underway evaluating the potential for long acting integrase inhibitors to prevent HIV transmission (see below).

## **INTERMITTENT PREP**

### **Two intermittent PrEP trials are scheduled to get underway soon.**

Intermittent PrEP, or iPrEP, has shown efficacy in preventing simian retroviral infection following rectal exposure in macaques.<sup>42</sup> iPrEP has potential benefits over daily PrEP, including lower cost, decreased pill burden, and possibly, fewer side effects and reduced toxicity.<sup>43</sup>

Van Griensven et al. found that nearly two thirds of a sample of HIV-negative MSM surveyed in Bangkok reported that their last sexual encounter was planned.<sup>44</sup> This, coupled with frequency data (85.8% said they had sex two days a week or less), led the authors to conclude that “about two-thirds of MSM had a window of opportunity to take a pre-exposure dose of chemoprophylaxis prior to sexual activity.”<sup>45</sup> The authors argue that, given these findings, “iPrEP may be a more appropriate regimen than daily PrEP.”<sup>46</sup>

Two intermittent PrEP trials are scheduled to get underway soon, one with MSM in France and Quebec<sup>47</sup>, and one focusing on MSM in Bangkok and New York, and with heterosexual women in Cape Town, South Africa (Project Adapt, HPTN 067).<sup>48</sup> The Ipergay study is enrolling an oral pericoital FTC-TDF PrEP trial with MSM and transgender women and men who have had at least two different sexual partners in the past six months. This study was launched in January 2012 in Paris and Lyon, France and Montreal, Quebec by the French National Agency for Research on AIDS and Viral Hepatitis.<sup>48.1</sup>

Older gay men who use sexual networking sites, plan their sexual encounters, and have anal sex fewer than three times a week may be well suited for intermittent PrEP, according to a study published in *JAIDS* in June 2012. Nearly one-third of a sample of 1013 gay and bisexual men reported that they had less frequent sex and planned their sexual encounters, making them good candidates for intermittent PrEP. Older and better educated MSM were most likely to have sex less frequently and to plan it.<sup>48.2</sup>

While intermittent PrEP may be desirable due to cost and adherence concerns related to daily PrEP, a recent study found that adherence to daily dosing regimes of PrEP was higher than adherence to intermittent PrEP. The study of 67 African MSM and five female sex workers compared daily dosing to intermittent dosing on Monday, Friday and within two hours of sexual intercourse. The study found that 83% of participants were adherent to the daily regimen, versus 55% adherence to the fixed intermittent dosing regimen (Monday and Friday each week) and only 26% adherence to post-coital dosing.<sup>48.5</sup>

## **ACCEPTABILITY OF DIFFERENT MODALITIES: PILL VERSUS GEL**

The optimal PrEP regimen may vary across populations and regions. MTN-001, a study of adherence and pharmacokinetics of oral and vaginal preparations of tenofovir, found that U.S. women preferred oral tablets over vaginal gel (72 vs. 14%), while African women were split, with close to half preferring each

method (40% preferred oral tablets while 42% preferred vaginal gel). African women were more likely to indicate that the gel improved sexual pleasure.<sup>49</sup>

A study of a 1% tenofovir vaginal gel in Pune, India found that women who used the gel pericoitally were 2.5 times less likely to report non-acceptability of the gel compared with daily users. Women liked the gel's easy use and its protective effect against HIV; they disliked its messiness. The researchers called for "extensive and systematic education of men" about the gel, because in India "the majority of decision-making is done by men."<sup>49,5</sup>

## **INJECTABLES AND IMPLANTS**

While most antiretroviral medications are taken orally, Enfuvirtide is an HIV-fusion inhibitor that cannot be administered orally. Instead, it is formulated as a powder that is reconstituted and injected subcutaneously.<sup>50</sup> Future research in PrEP may examine not only intermittent oral PrEP, but also injectable ARVs and implants. Contraceptives can now be used this way, through an injection once every three months that costs \$35–\$75 in the U.S.<sup>51</sup> Birth control can also be provided by a matchstick-sized implant into the arm that costs \$400–\$800 and lasts three years.<sup>52</sup> While such technologies do not yet exist for HIV chemoprophylaxis, they are conceivable.

The International Partnership for Microbicides has partnered with Tibotec Pharmaceuticals to develop a long-acting injectable form of TMC278, also known as rilpivirine, for PrEP. TMC278 is a non-nucleoside reverse transcriptase inhibitor, and its oral formulation has been approved for the treatment of HIV disease.<sup>53</sup>

A study published in 2009 showed proof-of-concept for injectable, long-acting TMC278 for HIV treatment in experiments with mice and dogs.<sup>54</sup> Other animal studies of injectable antiretroviral chemoprophylaxis are currently under way.

Another study, TMC278-TiDP15-C158, examined the safety, tolerability and pharmacokinetics in humans of a single dose or three successive doses of intramuscularly injected long-acting formulation of TMC278. Completed in 2011, it identified no safety concerns.<sup>55</sup> Another trial, SSAT 040,<sup>56</sup> examined different doses of TMC278LA injected intramuscularly.<sup>57</sup> The study, conducted by the St. Stephens AIDS Trust in London, reported results at CROI 2012. It showed that an injectable, once-a-month formulation of rilpivirine could maintain sufficient drug levels to protect against HIV infection; the drug has also produced very few side effects apart from tenderness and swelling at the injection site. The study was with 27 HIV-negative women age 18-50, more than half Black African or Caribbean, and six men. Among the women, drug levels were measured over three months in blood, vaginal fluid and vaginal tissue; among the men, drug levels were measured in blood, rectal fluids and rectal tissue.<sup>57,1</sup>

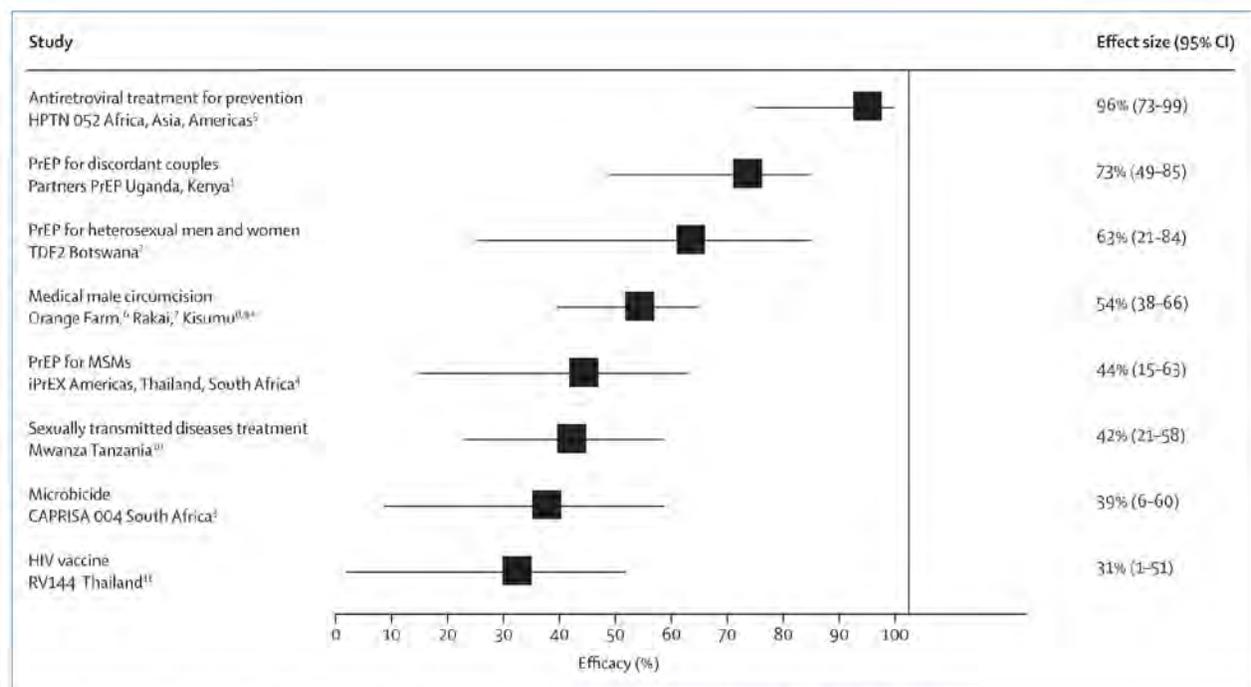
A recent study of nearly 1800 members of potential user groups for PrEP (female sex workers, MSM, injection drug users, serodiscordant couples and young women) from Peru, Ukraine, India and four African countries found that an injectable, long acting form of PrEP was the most preferred mode of

administration. A bimonthly injection in the buttocks was the most preferred mode of administration, followed by a monthly injection in the arm. A pill taken daily or before and after sex were the least preferred modes of administration of PrEP.<sup>57,2</sup>

Other experimental treatment delivery technologies are in development, including a transdermal patch that delivers up to 96 percent of a dose of HIV medication over seven days. The new delivery method was presented by Anthony Ham and colleagues from ImQuest Biosciences at the 2011 American Association of Pharmaceutical Scientists annual meeting.<sup>58</sup>

Also of note, HIV researcher David Ho was recently awarded \$500,000 a year over five years to develop a monoclonal antibody that can be delivered monthly. Dr. Ho’s approach involves “antibody-like molecules that could be administered monthly for the treatment of HIV,” as opposed to the current daily regimen.<sup>59</sup> A monoclonal antibody could supply or generate immune response to prevent HIV transmission. Such a monthly therapy would likely improve treatment adherence, and could also have implications for PrEP and PrEP adherence.

Deborah Anderson of Boston University is leading a study to develop new techniques for the delivery of monoclonal antibodies vaginally.<sup>59,5</sup>



**Figure: HIV prevention technologies shown to be effective in reducing HIV incidence in randomised controlled trials<sup>1-12</sup>**  
PrEP=Pre-exposure prophylaxis. \*Meta-analysis of circumcision trials.

Reprinted with permission from Abdoool Karim and Abdoool Karim, Antiretroviral prophylaxis: A defining moment in HIV control. *The Lancet*. 2011.

## **THE CONNECTION OF PREP TO POST-EXPOSURE PROPHYLAXIS (PEP)**

Post-exposure prophylaxis (PEP) involves taking antiretroviral treatment to prevent HIV infection shortly after one is exposed to HIV. PEP is used to address workplace exposures, such as a healthcare worker accidentally stuck with a needle that has been used by an HIV-infected patient, as well as exposure through sexual activity or sharing a needle. nPEP, non-occupational post-exposure prophylaxis, refers specifically to exposure through sexual activity or sharing needles and excludes workplace exposures. Rape survivors are sometimes offered PEP if the HIV status of the rapist is known to be HIV-infected, or the status is not known. PEP must be started as soon as possible after an exposure—within 72 hours of exposure—and continued for 28 days, based on animal studies.<sup>60</sup>

Mimiaga et al., studied a racially diverse survey of gay and bisexual men in the Boston area and found that a just over one in four MSM connected to an LGBT health center had heard about nPEP (28%). Most heard about nPEP through involvement in HIV prevention research or community outreach/education (27%), from medical providers (27%), from the media (22%), and from friends (20%). However, only 3.1% of the MSM surveyed reported having used nPEP in the past after a high-risk HIV exposure.<sup>61</sup> A smaller percentage (19%) had heard about PrEP than nPEP, and only 1 individual (less than half of 1%) had used PrEP, using his HIV-positive brother's medications. The surveys were conducted at Fenway Health in Boston in 2007, when PrEP was still very much a nascent, experimental prevention technology, prior to the iPrEX results. Mimiaga et al. expressed concern that knowledge about nPEP was so uncommon, more than a decade after it had been first recommended for people who had been exposed to HIV.<sup>62</sup>

Knowledge of post-exposure prophylaxis among gay and bisexual men is limited. A survey of over 4500 MSM on a popular social networking site after the iPrEX study results were released in December 2010 found that only 36.2% had heard of post-exposure prophylaxis.<sup>62,5</sup> Anecdotally, it appears that there is limited knowledge among both gay men and providers about nPEP, even in large metropolitan areas such as the New York City area.<sup>63</sup> There is also a lot of confusion between PEP and PrEP. Therefore, it is essential that providers, health departments and community-based organizations educate disproportionately vulnerable communities, including gay men and African Americans, about PEP and PrEP so that they understand what is currently available, where they can access what is available, and what the difference is between the two prevention approaches.

## **MOVING TOWARD IMPLEMENTATION**

### **FROM CLINICAL TRIAL EFFICACY TO REAL WORLD EFFECTIVENESS**

Imrie et al. distinguish between efficacy in clinical trials and public health effectiveness, i.e. “impact on health, under real-world conditions, for entire populations.”<sup>64</sup> While PrEP trials have demonstrated efficacy with MSM and heterosexual men and women, the recent early terminations of the FEM PrEP trial and the oral TDF and TDF gel arms of the VOICE study raise questions about the effectiveness of tenofovir-based chemoprophylaxis for women.

“[E]fficacious interventions need to be embraced, incorporated into our repertoire, and scaled up quickly.” Imrie et al., *The Lancet*, 2007

Referring to male circumcision as a prevention strategy, Imrie et al. argue that “efficacious interventions need to be embraced, incorporated into our repertoire, and scaled up quickly.”<sup>65</sup> However, some researchers and advocates have recommended a go-slow approach. Leibowitz et al raise concerns about cost, the ethics of paying for PrEP when there are waiting lists for ARVs for treatment, presumed lower real-world adherence rates, and the potential for risk compensation—i.e. concerns that sexual risk behavior will increase with PrEP use.<sup>66</sup> Other concerns about PrEP include low uptake at the population level, negating a community benefit, and the selection for drug resistance mutants in individuals who are not optimally adherent and continue to engage in unprotected sex. Each concern is addressed below. One AIDS service organization has also raised concerns and lobbied the FDA to block approval of PrEP.<sup>67</sup> However, more than a dozen leading AIDS and health care organizations across the U.S., and more than 100 leaders in the HIV-positive, gay and bisexual male community, have encouraged the FDA to consider PrEP on its scientific merits.<sup>68</sup>

### **WIDESPREAD WILLINGNESS TO USE PREP**

With thoughtful leadership, community involvement, and effective public education campaigns, scaling up PrEP use among gay and bisexual men is feasible. Research indicates that when at risk people learn about PrEP, they are willing to use it. Liu et al. found that 67% of a sample of 1,819 HIV-negative gay and bisexual men in California indicated they would use PrEP if it were proven to be safe and effective.<sup>69</sup> (Several studies have now demonstrated safety for both oral and topical PrEP, for both heterosexuals and MSM.)<sup>70</sup> The Fenway Institute surveyed MSM at manhunt.com, a social networking site. It surveyed MSM prior to the 2010 release of the iPrEx results and after. It found a significant increase in awareness among MSM of PrEP, and that most respondents indicated they would use PrEP if it becomes available.<sup>71</sup> Mimiaga et al. found that 74% of a sample of high-risk Boston area MSM were willing to use PrEP in the future after learning about its potential for HIV prevention.<sup>72</sup> A study in Toronto, Canada also found widespread willingness to try PrEP among MSM, especially among high-risk MSM.<sup>73</sup> A global survey of 5,066 MSM conducted by the MSM Global Forum in 2010 found limited awareness of PrEP but a strong desire to learn more about biomedical prevention.<sup>73.5</sup>

Given the disproportionate burden of HIV on black and Latino MSM in the U.S., it is essential that there be support for PrEP among black and Latino gay men if it is to be effective. The manhunt.com sample was representative of manhunt’s users but more white and less black than MSM in general: 3% were black, 84% white, 6% Hispanic, 3% Asian Pacific Islander, 1% Native American, and 4% multiracial.<sup>74</sup>

The Mimiaga et al. study of MSM in Boston provides a more racially diverse sample: 46% white, 44% black, 1% American Indian, 9% “other”. Some 10% were Hispanic/Latino (a separate question from race). Of this sample “74% reported a willingness to use PrEP in the future after being educated about its potential for HIV prevention.” Nonwhites were more likely than whites to intend to use PrEP: 77.7% vs 69.9%.<sup>75</sup> This study indicates that there is support for PrEP among gay men/MSM of various racial backgrounds, including black and Latino MSM.

In a more recent study, Krakower et al. found that awareness of PrEP among MSM using a popular internet social networking site increased from 13% to 19% after the iPrEx study results were published in December 2010. When PrEP was explained, 76% and 79%, respectively (pre- and post-iPrEx results being released), said they were interested in using PrEP.<sup>75.1</sup>

Other recent studies have shown substantial willingness to use PrEP among gay and bisexual men in Australia (28%), the United Kingdom (50%), and China (68%).<sup>75.2</sup>

A recent study of nearly 1800 members of potential user groups for PrEP (female sex workers, MSM, injection drug users, serodiscordant couples, and young women) from Peru, Ukraine, India and four African countries found that participants were generally willing to use PrEP. Sixty-one percent said they would “yes, definitely” use it, while 30% said they would “yes, probably” use PrEP; roughly the same percentages said they would use it “as soon as it becomes available.” Support for personally using PrEP was widespread even after participants were reminded of potential side effects, cost, the need to continue using condoms, and the need to be regularly tested for HIV. Women and younger participants were most likely to indicate a willingness to use PrEP. Most participants also said PrEP would give them hope.<sup>75.3</sup>

The large scale enrollment of African heterosexuals, including HIV serodiscordant couples, in PrEP trials also bodes well for scale-up of PrEP in heterosexual populations in high prevalence countries, and possibly in high prevalence heterosexual communities in the U.S. It should also be noted that approval and support of medications by regulatory bodies such as the U.S. Food and Drug Administration and the World Health Organization (WHO) often lead to higher levels of awareness and willingness to use the product among affected populations. In this sense, data on willingness to use PrEP should be viewed as preliminary, and could increase significantly after action by the FDA and/or the WHO, as is expected in the first half of 2012.



**When at risk people learn about PrEP, they are willing to use it.**

## **ADDRESSING CONCERNS ABOUT IMPLEMENTING PREP**

### **CONCERN THAT REAL WORLD ADHERENCE RATES WILL BE LOWER THAN IN CLINICAL TRIALS**

Leibowitz et al. argue that the iPrEx study’s participants were more likely to commit to taking a pill a day than were individuals who refused to participate, and that, despite this selection bias, only 49% of iPrEx study participants took their medication on 90% or more of days. They claim that, in the real world, PrEP adherence is likely to be even lower, especially if participants must pay—even just for part—of the cost of their medication.<sup>76</sup> Other researchers argue that this concern of suboptimal adherence is why medications must be accompanied by behavioral interventions focused on potential PrEP users, as well as their health

care providers.<sup>77</sup> Additionally, it can be argued that in the earlier studies, participants had a substantial chance of getting a placebo, so they might have been less motivated to adhere than patients who request PrEP from their care providers.

Several groups are working on developing culturally tailored interventions to enhance PrEP adherence, using social media, and the engagement of significant others, including partners and health professionals. Optimizing adherence is necessary for oral or topical chemoprophylaxis to be effective. In the CAPRISA 004 vaginal microbicide study adherence correlated with effectiveness: those with greater than 80% adherence based on returned gel applicators experienced 54% effectiveness, compared with 28% effectiveness for those with 50% adherence or less.<sup>78</sup> Adherence also correlated with effectiveness in the iPrEx study of oral FTC-TDF in MSM.<sup>79</sup>

## **MEDICAL RISKS**

Possible side effects of PrEP include renal impairment, loss of bone density, gastrointestinal discomfort, and flare-ups of chronic hepatitis B after discontinuation of use.<sup>80</sup> High tenofovir disoproxil fumarate (TDF) levels in people living with HIV have been shown to correlate with kidney tubular dysfunction (KTD).<sup>80.1</sup> Ezinga et al. found that, among 161 people taking TDF for at least one year, 63% had at least one marker of KTD; 10.6% “met the definition of KTD.” The investigators proposed that the association between long-term TDF use and KTD “could suggest cumulative toxicity.”<sup>80.2</sup>

Babies born to pregnant women who take tenofovir are not smaller or shorter, according to a National Institutes of Health-funded study made public May 1, 2012. At one year of age, however, “children born to tenofovir-treated mothers were slightly shorter and has slightly smaller head circumference—about 1 centimeter each, on average—than were infants whose mothers did not take tenofovir.” The study’s authors said the findings were “reassuring,” and that the study did not identify any serious safety concerns during pregnancy for tenofovir.”<sup>80.3</sup>

Research is limited on the long-term effects of tenofovir use, particularly in HIV-uninfected populations. However, it is not a given that people will use PrEP for a long period of time. Many may just use it temporarily, for limited periods during times of greatest risk. If intermittent PrEP is found to be effective, toxicities will be likely to be minimized.

The Forum for Collaborative HIV Research reviewed five clinical trials involving more than 6,000 individuals—iPrEx, Partners PrEP, the CDC safety trial of 400 MSM in San Francisco, Atlanta and Boston, the CDC Botswana trial of young heterosexuals, and Fem-PrEP. The Forum found that “[c]linical adverse effects, including serious adverse effects, other than such gastrointestinal events such as nausea, weight loss, and diarrhea in the early stages of therapy, do not appear to be different between placebo and drug study groups and are similar to labeled events for TDF and TDF-FTC use in HIV-infected patients.”<sup>81</sup>

While the Forum for Collaborative HIV Research’s finding is promising for PrEP implementation, providers prescribing PrEP should clearly state all risks of side effects and ensure that those considering PrEP

fully understand and consent to taking it. It is important that people using ARVs for PrEP be fully informed of potential risks, and that side effects be monitored closely. While ARVs can have side effects, HIV is also a serious illness. People at high risk for HIV who are considering using PrEP should weigh the potential costs and benefits with their providers and make an informed decision whether to use ARVs for PrEP.

## RISK COMPENSATION

Leibowitz et al. and the AIDS Healthcare Foundation argue that PrEP could lead to increased rates of unprotected anal intercourse among gay and bisexual men, undermining HIV prevention. Leibowitz et al. point to a study of high-risk MSM in New York City in which 35% reported that if they used PrEP, they would likely decrease their personal condom use.<sup>82</sup> Clearly, increases in unprotected sex among MSM could mitigate prevention benefits from PrEP. However, PrEP trials indicate that if comprehensive risk counseling accompanies the provision of ARVs, PrEP need not lead to increased unprotected sex. Among iPrEx study participants, “high risk behavior decreased substantially after enrollment and remained lower than at baseline during the trial.” This was true of both groups, that taking FTC-TDF and that taking a placebo. Grant et al. believe that this is due to the comprehensive HIV prevention services provided. They also hypothesize that “taking a pill a day may have served as a daily reminder of imminent risk and may have promoted planning for sex, which has been associated with lower HIV risk.”<sup>83</sup> Grant et al. cite Van Griensven et al., who found that almost two thirds (65.3%) of a sample of 823 HIV-negative MSM in Bangkok planned the first sexual encounter on the most recent day they had sex. This meant they could have taken PrEP as a preventive strategy.<sup>84</sup> The Partners PrEP study in east Africa also saw a decrease in unprotected sex among study participants. The percentage reporting unprotected sex dropped from 27% to about 10% after 30 months enrolled in the study.<sup>85</sup>

The Forum for Collaborative HIV Research, examining five major clinical trials of PrEP, looked for evidence of “disinhibition and reduction in use of condoms as an adjunct safety measure.” It found “no evidence of change in socio-behavioral risk (e.g., frequency of condom use, unprotected receptive anal intercourse in MSM, or number of sexual partners. Indeed, there was a trend toward decreased sexual risk behavior but this finding is based on self-reporting in a clinical trial setting.”<sup>86</sup>

The lesson from all these studies is clear: coupled with the right behavioral counseling, PrEP need not lead to risk compensation. It can be argued that in the real world counseling may not be as effective as in clinical trials, so ongoing behavioral surveillance will be needed as PrEP is rolled out in different settings. Clinicians will need additional training to optimize the use of PrEP as part of a comprehensive prevention package.



**PrEP trials indicate that if comprehensive risk counseling accompanies the provision of ARVs, PrEP need not lead to increased unprotected sex.**

**DRUG RESISTANCE**

Another concern related to implementation of PrEP is the risk of the development and spread of drug-resistant HIV. This could occur if someone becomes infected with HIV, not promptly diagnosed, and HIV is allowed to replicate in a person taking ARVs insufficient to cause complete viral suppression.<sup>87</sup> It could also occur if someone starts PrEP a few weeks after being infected, before traditional antibody tests are able to detect HIV infection (the so-called window period).<sup>88</sup>

National monitoring and evaluation systems are critical to catch such a development in its early stages and adjust PrEP implementation protocols to decrease the risk of PrEP users' contracting HIV.<sup>89</sup> Van de Vijver and Boucher reviewed research on FTC and TDF and found that “the risk of emergence of drug-resistant

HIV [in the context of PrEP with FTC/TDF] is small.” Studies show that “infections that occurred despite the use of PrEP had reduced peak viremia, which could reduce HIV transmissibility.”<sup>90</sup> These include an individual who was taking FTC as intermittent PrEP who was infected with HIV. This individual did not develop resistant HIV, had a slowing of seroconversion and low viremia. The study's authors—Prada, Davis, Jean-Pierre et al.—argue that the low viremia “likely reduced the probably of subsequent forward transmissions during the acute phase.”<sup>91</sup> Van de Vijver and Boucher conclude that “the clear preventive benefits [of PrEP] that were identified in the analysis outweigh the risks

“[T]he clear preventive benefits [of PrEP...]outweigh the risks associated with drug resistance.” Van de Vijver and Boucher, *Current Opinion in Infectious Diseases*, 2010.

associated with drug resistance.”<sup>92</sup> Another study modeled “the likelihood that a UK man who has sex with men (MSM) would be exposed to PrEP-resistant HIV in a homosexual encounter with an HIV-infectious partner.” The study found “low levels of resistance to proposed PrEP drugs, and predicted that “circulating PrEP drug resistance will have a negligible impact on PrEP efficacy at the population level.”<sup>93</sup>

The Forum for Collaborative HIV Research, in its analysis of HIV drug resistance in five major PrEP trials, found “no clinically significant development of drug resistance in participants on drug with newly emergent HIV infection, although there were a few cases among participants with acute HIV infection at study entry (identified retrospectively).” It concluded that “care should be taken to ensure individuals are not infected at the time of the initiation of biomedical prevention.”<sup>94</sup>

Supervie et al. modeled the implementation of PrEP with gay and bisexual men and other MSM in San Francisco. They predicted that if risk behavior increases, that PrEP could significantly increase transmitted resistance. However, if risk behavior remains stable, PrEP is “likely to decrease transmitted resistance.”<sup>95</sup>

Concerns about drug resistance mandate close monitoring of the population-level impact of PrEP, including risk compensation, but need not preclude deploying PrEP as a complement to existing prevention strategies. Parikh and Mellors point out that “HIV-1 drug resistance resulting from antiretroviral therapy far exceeds that from pre-exposure prophylaxis.” They note that there were only

three cases of resistance from PrEP from three large HIV prevention trials. All three had cases of unrecognized acute HIV infection before taking tenofovir-containing PrEP.

No cases of resistance have yet been identified in trial participants who become infected after starting ARV-containing gel or tablets. By contrast, first-line antiretroviral therapy (ART) fails to suppress viremia in 22% of persons on therapy and up to 95% of those who fail ART have drug-resistant HIV-1. Given that more than 6.6 million persons worldwide have started ART, failure of ART to suppress viremia, rather than failure of PrEP to prevention HIV infection, is driving the spread of drug resistance in the developing world.<sup>95.5</sup>

The greatest risk for PrEP implementation resulting in increased levels of circulating drug-resistant HIV would be if PrEP users were intermittently adherent, and did not get regularly tested to know that they had become infected, and continued to engage in unprotected sex with uninfected partners. This “worst case scenario” can be ameliorated by provider education of potential PrEP users regarding the importance of adherence and frequent monitoring for seroconversion, as well as behavioral risk interventions.

## RESOURCE LIMITATIONS AND ETHICAL DILEMMAS

Leibowitz et al. raise questions about the cost of PrEP and how it would be covered. They question the ethics of offering PrEP to individuals when thousands of people living with HIV are on state AIDS Drug Assistance Program waiting lists, unable to access ARVs.<sup>96</sup> The situation is even worse in Africa, where millions who need ARVs cannot access them.

Others argue that there is an ethical imperative to make new prevention technologies available, particularly to those most vulnerable to HIV. Myers and Mayer argue: “If a clear population benefit for PrEP can be determined—either intermittently or daily— withholding it would be unethical. Thus, it will be the responsibility of normative bodies including the CDC and WHO [World Health Organization] to work with funders to ensure access to it.”<sup>97</sup>

**“If a clear population benefit for PrEP can be determined— either intermittently or daily— withholding it would be unethical.” Myers and Mayer, *AIDS Patient Care and STDs*, 2011.**

There is a history of policy makers’ and others’ pitting HIV prevention against treatment, and vice versa.<sup>98</sup> However, as the results of the HIV Prevention Trials Network study 052 (HPTN 052) demonstrated in May 2011, the conceptual boundary between treatment and prevention is breaking down: HPTN 052 found that men and women who take antiretrovirals (ARVs) significantly decrease their risk of passing HIV to uninfected partners.<sup>99</sup> In fact, the most effective deployment of PrEP may be in combination with scaled up provision of ARVs to those already infected with HIV to drive down community viral load.<sup>100</sup>

**IMPLEMENTATION IN CLINICAL SETTINGS**<sup>101</sup>

Despite the concerns raised above, the general consensus among both researchers and advocates is to prepare for scale-up of PrEP, at least for the most-at-risk populations such as MSM. As Connie Celum, Principal Investigator of the Partners PrEP study said at the 2011 CROI conference, quoting 18th Century English writer Samuel Johnson, “Nothing will ever be attempted if all possible objections must first be overcome.”<sup>102</sup> The Center for Disease Control and Prevention’s interim guidance on PrEP for MSM, published in January 2011, states that, until safety and efficacy are shown among heterosexuals and IDUs, “PrEP should be considered only for MSM.”<sup>103</sup>

In August 2011 seven leading AIDS service and advocacy groups called on the U.S. Department of Health and Human Services to increase funding and coordination to prepare to implement PrEP among MSM. Specifically, this group called for HHS to fund and coordinate demonstration projects “to evaluate PrEP in the real world and determine the best ways to use it.”<sup>104</sup> Two PrEP demonstration projects with MSM, funded through the National Institutes of Health, were launched in fall 2011, one in Miami and one in San Francisco. The California HIV Research Program has funded several joint TLC+/PrEP demonstration projects in Californian cities focusing on MSM. HPTN 073 is being developed to focus on a culturally tailored program combining PrEP with clinical and social service coordination for Black MSM in several U.S. cities.

In October 2011 thirteen leading AIDS service and advocacy groups, including Fenway Health, sent a letter calling on the FDA and Gilead to consider approving PrEP for MSM separately from considering approving it for heterosexual couples.<sup>105</sup> In December 2011, Gilead Sciences submitted a supplemental New Drug Application to the U.S. Food and Drug Administration for approval of once-daily Truvada for pre-exposure prophylaxis to reduce the risk of HIV infection among uninfected adults. Gilead’s application was for use of PrEP among “uninfected adults,” i.e. heterosexual men and women as well as MSM. The FDA reviewed Gilead’s submission in May 2012 and will decide whether to indicate FTC-TDF for PrEP by September 2012.

**A COMBINATION PREVENTION APPROACH**

Successful implementation of PrEP at the population level requires a conceptualization that is broader than simply providing medications.<sup>106</sup> Provision of ARVs must be accompanied by comprehensive preventive care and sustained behavioral interventions to ensure a high rate of adherence as well as to minimize risk compensation. These should include testing and assessment protocols, behavioral interventions, long-term interactions between PrEP users and health care providers, and monitoring the population-level impacts of PrEP use.<sup>107</sup>

The CDC’s interim guidance on PrEP use among MSM states that “PrEP has the potential to contribute to effective and safe HIV prevention for MSM if 1) it is targeted to MSM at high risk for HIV acquisition; 2) it is delivered as part of a comprehensive set of prevention services...and 3) it is accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals.”<sup>108</sup>

Underhill et al. argue that strategies for PrEP implementation should focus on clinical settings. While initial safety data indicate minimal side effects, sustained clinical monitoring is necessary to monitor and treat any side effects associated with use of PrEP.<sup>109</sup> Close monitoring of individuals using PrEP will also help to identify early and address any drug-resistant variants of HIV that emerge.<sup>110</sup>

For these reasons, clinical settings are the “most feasible” implementation site for PrEP, according to Underhill et al.<sup>111</sup> Clinical settings include community health centers, private practice, AIDS service organizations that provide prevention and care services (including to serodiscordant couples), STI clinics, and emergency rooms.<sup>112</sup> PrEP could also be offered in substance abuse treatment sites to reach highly vulnerable populations such as injection drug users.<sup>113</sup>

Because many of those at greatest risk for HIV do not access regular clinical care, alternative implementation arrangements should be explored. This could include working with community-based AIDS service providers to offer long-term behavioral counseling that can increase adherence and reduce the incidence of risk compensation. Collaborations could be developed between clinical and nonclinical providers, such as exist in the delivery of methadone to injection drug users in treatment, or the delivery of long-term risk reduction counseling by non-clinicians following diagnosis and treatment for a sexually transmitted infection (STI).<sup>114</sup> Training of health providers and non-clinicians in PrEP delivery is also a key component of PrEP scale-up.<sup>115</sup>

Providers should counsel high-risk individuals that PrEP will not prevent their contracting syphilis or other STIs; it may be partially effective in preventing HIV, but the only fool proof way to ensure against STIs, including HIV, is to use condoms when having anal or vaginal sex. Many STIs can be transmitted through oral sex as well. These include herpes, gonorrhea, and human papilloma virus.<sup>116</sup>

## **RESOURCE AND ACCESS ISSUES**

Resource issues will vary between high- and middle-income countries and lower-income countries, and between countries with concentrated versus generalized epidemics. In the former, implementation challenges include securing insurance coverage for PrEP, developing guidelines to regulate access to PrEP, prioritizing services to most vulnerable populations, and ensuring that services are available for underserved populations (often the same as the most vulnerable populations). In the latter, challenges may include limited resources for purchasing PrEP medications and supportive services, infrastructural limitations, the lack of resources to provide ARVs for people already infected with HIV, and tensions between the goals of providing treatment and providing PrEP.<sup>117</sup> Existing barriers to accessing prevention and treatment services for most at risk populations (MARPs), such as MSM or injection drug users (IDUs), must also be taken into account when developing strategies to prioritize MARPs. A 2008 Amfar report found that only 10% of MSM worldwide have access to HIV prevention and care services.<sup>118</sup>

While cost estimates of PrEP vary depending upon the extent to which PrEP is targeted to the most high-risk individuals (such as MSM with multiple partners engaging in unprotected anal sex), the cost will inevitably be substantial. But, the cost of chronic HIV treatment with three drugs for life could be

even more expensive, so the key for public health will be to determine which individuals are most likely to benefit from PrEP.

### **A COMPREHENSIVE APPROACH TO PROVIDING PREP**

The experience of providing ARVs in low-income countries with generalized epidemics has highlighted challenges that would likely accompany PrEP scale-up. These include staff development and training; the creation of

**Provision of ARVs must be accompanied by comprehensive preventive care and sustained behavioral interventions to ensure a high rate of adherence as well as to minimize risk compensation.**

infrastructure, especially in rural areas; financing the medications; serving areas of high demand; overcoming barriers to accessing care, including stigma; creating monitoring and evaluation systems; maintaining adherence; and monitoring and managing side effects and the emergence of drug-resistant HIV.<sup>119</sup> Current PrEP trials are informing guidelines for eligibility to use PrEP, as well as optimal dosing and route of administration (oral or topical).<sup>120</sup>

Underhill et al. recommend four complementary components in PrEP implementation: the provision of the drugs themselves, safety monitoring, behavioral intervention, and the integration of PrEP into a broader comprehensive care program.<sup>121</sup> Given the experience with

ARV treatment for people living with HIV, effective implementation of PrEP will likely succeed best if accompanied by input from a wide range of stakeholders, including health care providers, government officials, civil society organizations, advocates representing vulnerable and most at-risk populations, as well as scientific experts in PrEP.<sup>122</sup>

### **IDENTIFYING THOSE WHO MIGHT BENEFIT MOST FROM PREP**

The deployment of PrEP among the highest risk members of MARPs—such as high-risk MSM—could also improve its cost effectiveness. Assessment protocols will have to be developed to identify those whose characteristics (demographic, behavioral) make them eligible to take PrEP such that PrEP gets the most bang for the buck.<sup>123</sup> Myers and Mayer argue that PrEP should be prioritized for two high-risk groups in the U.S.: MSM engaging in unprotected anal sex, and female and male sex workers. The authors note that sex workers are often pressured into having sex without a condom.<sup>124</sup> Clients sometimes pay more to have unprotected sex.

Supervie, Garcia-Lerma, Heneine and Blower modeled implementing PrEP with gay and bisexual men and other MSM in San Francisco. They found that:

...PrEP may be able to reduce infectivity in humans (by reducing viral load) and could therefore indirectly reduce HIV transmission...PrEP could significantly reduce transmission in the MSM community in San Francisco even if efficacy is only moderate [this article appeared before the iPrEx results were announced], provided coverage is high and risk compensation does not occur.<sup>125</sup>

Based on national data on condom use and number of partners in the last year, Dawn Smith, M.D., of the Centers for Disease Control and Prevention, estimates that 275,000 MSM in the U.S. could benefit from PrEP.<sup>126</sup> Coupling PrEP to high-risk negative MSM with expanded ARV access and treatment adherence to MSM living with HIV could be particularly effective in reducing new infections among MSM. Such an approach could also be effective with serodiscordant heterosexual couples.

The provision of PrEP to MSM should occur in a broader context of ensuring clinically competent health care to gay, lesbian, bisexual and transgender people.<sup>127</sup> Trainings to increase such clinical competence are key to reducing HIV and other health disparities affecting MSM and transgender women.<sup>128</sup>

The World Health Organization argues that PrEP may be prioritized for MARPs including MSM, IDUs and sex workers, as well as for “all those at risk of sexual transmission in areas with endemic or hyperendemic HIV transmission such as southern Africa.”<sup>129</sup> The WHO also states that PrEP could meet the urgent need for female initiated and controlled HIV prevention method given gender power imbalances and cultural barriers to condom use.<sup>130</sup>

Mujugira et al., describing the enrollment process of the Partners PrEP study of serodiscordant heterosexual couples in East Africa, write that if the study eventually showed efficacy—which it did in results released in summer 2011, with those receiving oral TDF 62% less likely to contract HIV, and those receiving FTC-TDF 73% less likely<sup>131</sup>—then PrEP should be offered to high-risk individuals with normal renal function, including serodiscordant couples.<sup>132</sup>

Hallett et al. modeled early initiation of antiretroviral therapy (ART) for HIV infected partners in serodiscordant couples, and compared it to the provision of PrEP to the HIV uninfected partner. They found that PrEP used prior to ART can prevent HIV infections in the serodiscordant couple. They also found that, “although the initial costs are high, they are substantially offset by reduced future ART costs among HIV-1 uninfected partners who remain uninfected. In some circumstances (e.g. with effectiveness of 80% and used in couples that remain at high-risk), PrEP could be cost-saving overall.”<sup>133</sup>

Ware et al., in a qualitative analysis of Partners PrEP participants, found that PrEP could stabilize serodiscordant couples and their relationships, thereby helping keep marriages intact at the same time as preventing the infection of the HIV-negative spouse:

Serodiscordance de-stabilizes couples, as the HIV-negative partner reacts with anger, fear and sadness to the implication of infidelity represented by HIV infection. A “discordance dilemma”



**The provision of PrEP to MSM should occur in a broader context of ensuring clinically competent health care to gay, lesbian, bisexual, and transgender people.**

ensues, as the desire to avoid acquiring HIV and the advantages of preserving the relationship become competing priorities. PrEP is seen as a solution—a means of safeguarding health without ending the relationship. PrEP users benefit from the support of partners, who reinforce adherence. Where discord in the relationship persists, adherence suffers.<sup>133,5</sup>



**PrEP is not meant to supplant existing prevention approaches, but instead to complement them.**

**SAFETY SCREENING**

Frequent HIV testing is an essential element of safe PrEP use that can reduce the risk of acquiring drug-resistant HIV. Although it is likely that side effects will be rare, PrEP providers will need to provide clinical and laboratory monitoring of potential side effects, including aggravation of renal impairments and loss of bone density. Screening for STIs should also be offered regularly. The cost of these screenings must be factored in to the cost of PrEP.<sup>134</sup> Before initiating PrEP, providers need to know a patient’s Hepatitis B status, and should vaccinate all susceptible patients. PrEP may not be appropriate for some people with chronic active hepatitis B. Since tenofovir and emtricitabine are used to treat hepatitis B, stopping treatment can sometimes cause flares and liver damage.<sup>135</sup>

**THE SECOND PRONG: COMBINING PREP WITH BEHAVIORAL INTERVENTIONS**

PrEP represents a new tool in the fight against HIV/AIDS. It is not meant to supplant existing prevention approaches, but instead to complement them. Interventions that can be coupled with PrEP to minimize risk compensation and strengthen adherence must be developed and tested.<sup>136</sup> The Centers for Disease Control and Prevention recommend that the most effective mix of interventions—including a combination of biomedical and behavioral interventions—be used, based on the latest prevention research science.<sup>137</sup> Behavioral interventions should include promotion and distribution of condoms and water-based lubricants, and education that use of condoms is essential to minimizing HIV risk.

Underhill et al. stress the importance of PrEP initiation among at-risk individuals. Priority populations could include sex workers, high-risk MSM (i.e. those who report unprotected anal sex in the past year), HIV-negative people in serodiscordant relationships, and high-risk IDUs. Education campaigns can educate community members about PrEP, describing both its potential benefit as well as its limitations, such as partial efficacy. They can also stress the importance of PrEP adherence and continuing to practice safer sex and, in the case of IDUs, continuing to use clean needles.

Effective communication regarding the relative risk of PrEP and its partial efficacy is critical to allowing potential users to make informed decisions after systematic deliberation. This requires that providers provide information about PrEP in settings that allow sufficient time to process the complex information, and in ways that make the information relevant to the individual and induce motivation. A clear and empathetic communication style is most effective.<sup>138</sup>

It is also important that individuals considering PrEP fully consider the risks of side effects caused by taking anti-retrovirals, particularly over an extended period of time. Because of what we know and don't know about PrEP, doctors should explain clearly the risk of side effects, the risk of the development of drug-resistant HIV and ways to minimize this risk (including regular testing), and the fact that, even if PrEP is effective, it will not protect one against syphilis or other STDs. Regular testing for a range of STDs should accompany regular HIV testing to protect the sexual health of those on PrEP.<sup>139</sup>

The effectiveness of both provider interactions as well as social marketing campaigns promoting PrEP uptake, adherence, and continued risk reduction practices can be measured by examining PrEP uptake among target populations, as well as rates of PrEP adherence and risk compensation.<sup>140</sup>

### **THE THIRD PRONG: COMBINING PREP AND BEHAVIORAL INTERVENTIONS WITH STRUCTURAL INTERVENTIONS**

In addition to combining biomedical interventions like PrEP and microbicides with behavioral interventions, these interventions would be most effective if coupled with structural level interventions that address factors that increase vulnerability to HIV. This could include social exclusion and isolation caused by anti-gay prejudice, whether in the form of family rejection or harassment in schools or other institutions. Anti-gay harassment and violence in schools and other social institutions correlates with higher rates of unprotected sex among young MSM.<sup>141</sup> Anti-gay stigma should be treated as a public health threat. Structural interventions, including social marketing campaigns, can challenge such prejudice and encourage social acceptance of gay and bisexual men and transgender women by peers, parents, and other members of society.<sup>142</sup> Research shows that young gay men who are accepted by their families are less likely to engage in unprotected sex.<sup>143</sup> Shifting these structural forces would likely make PrEP and behavioral interventions more effective.

### **UNDERSTANDING OPTIMAL DOSAGE**

While many studies of oral PrEP have involved a daily dose, studies of topical gel usually involve coitally dependent dosage. Van Griensven et al. suggest that two thirds of a sample of young Bangkok MSM could use intermittent PrEP instead of daily PrEP based on frequency of sexual activity and the planned nature of this activity.<sup>144</sup> Intermittent use could significantly increase cost-effectiveness and facilitate scale-up due to lower per-person cost. However, there are concerns that intermittent PrEP may pose adherence challenges that daily PrEP does not. One way to reinforce adherence to intermittent PrEP is through electronic media, such as text messaging.

### **AVOIDING RISK COMPENSATION AND PROMOTING PREP ADHERENCE**

Behavioral interventions that can prevent an increase in unprotected sex by PrEP users include clinical counseling and behavioral risk assessment on an ongoing basis. Community education campaigns can also influence social norms related to condom use. Strength-based, or resiliency-based, campaigns have demonstrated particular efficacy in changing an individual's behavior.<sup>145</sup> Behavioral interventions that could support adherence include cognitive behavioral skills training, electronic reminders (such as

text messaging), and social support programs.<sup>146</sup> Underhill et al. propose making continued eligibility for PrEP medications dependent on one's adherence to behavioral risk reduction, i.e. condom use with anal or vaginal sex.<sup>147</sup> The same thing could be done with PrEP adherence; eligibility for PrEP medications could be made contingent upon a certain rate of adherence, which could be measured by periodic blood testing. Non-clinical staff from community-based organizations could play a key role in assessing behavioral risks on an ongoing basis and delivering the behavioral interventions to support risk reduction practices, including safer sex.<sup>148</sup> Nurses could also provide the behavioral intervention, as they currently do with diabetics regarding diet and behavior change.

### **PREEMPTIVELY ADDRESSING PREP-RELATED STIGMA**

People living with HIV report continued stigma about their health condition. Some people do not tell close family members of their status. Many keep their medications in other containers, like vitamin bottles, because of HIV-related stigma and a fear of being found out. Particularly if PrEP is targeted at high-risk individuals only and becomes associated with high-risk groups, PrEP use may develop a stigma that could prove counterproductive.<sup>149</sup>

In general, people taking insulin, medication for high cholesterol, or medication for high blood pressure are not stigmatized. Neither should people taking medication to treat or prevent HIV be stigmatized.

It is important that community-based organizations, public health departments, and health care providers promoting PrEP to reduce HIV transmission send supportive, affirming and non-stigmatizing messages about people who take PrEP. This could take the form of social marketing campaigns portraying those taking PrEP as volunteers in an important struggle against HIV. The connection between PrEP use and recommended continued condom use should also be stressed. It is essential that those taking PrEP not become socially stigmatized. This includes gay men taking PrEP: they should not be stigmatized by other gay men, who may be potential sexual partners. Such stigmatization could affect daily adherence, thereby undermining the intervention itself. It could also negatively affect uptake of PrEP, also undermining its real-world effectiveness.<sup>150</sup>

### **INTEGRATION WITH OTHER LONG-TERM HEALTH SERVICES, AND POPULATION-LEVEL MONITORING**

Those at highest risk for HIV may also have other physical and mental health needs; providing stable, long-term care to them will incur additional health care costs.<sup>151</sup> Providing ongoing, comprehensive care will also be necessary to ensure detection and treatment of side effects and any drug-resistant HIV that may develop, as well as to monitor risk compensation and adherence. Changes in PrEP implementation protocols should be made based on population-level impacts. Underhill et al. write that “the specific content of the PrEP package may shift over time due to evolution in behaviors, social and clinical contexts, risk-reduction strategies, and the virus itself.”<sup>152</sup>

## COMBINING SCALED-UP ARV TREATMENT AND PREP

HPTN 052, the study released in May 2011 that showed providing ARVs to HIV-infected partners lowers the risk of infection of HIV-negative partners, has significant implications for HIV prevention, including PrEP and microbicides. As Abdool Karim and Abdool Karim note, “[t]here is now no doubt that antiretroviral drugs prevent HIV infection.”<sup>153</sup> What is less clear is what its implications are for MSM. Only 3% of the serodiscordant couples in HPTN 052 were gay male couples (about 50 out of 1763 couples). It was difficult to recruit serodiscordant gay male couples in which the positive partner was treatment naïve who were in stable same-sex partnerships.

President Obama’s National HIV/AIDS Strategy (NHAS) prioritizes “increase[ing] access to care and optimiz[ing] health outcomes for people living with HIV” in part by “establishing a seamless system to immediately link people to continuous and coordinated quality care when they are diagnosed with HIV.”<sup>154</sup> This approach is also known as test, treat and link to care (TLC+). Assuming that scaled-up treatment of HIV+ MSM would also reduce new infections in this population (as was shown for heterosexuals in HPTN 052), combining PrEP targeted at highly vulnerable populations with scaled up treatment for these populations could prove more effective than PrEP alone.

**“Treatment of HIV-positive people for HIV prevention and PrEP and microbicides for HIV-negative people are two sides of the same coin, and cannot be viewed in isolation of each other.”  
Abdool Karim and Abdool Karim, *The Lancet*, 2011.**

Abdool Karim and Abdool Karim note:

Treatment of HIV-positive people for HIV prevention and PrEP and microbicides for HIV-negative people are two sides of the same coin, and cannot be viewed in isolation from each other. Although research on treatment for prevention, PrEP, and microbicides has mostly occurred in separate silos, their findings converge into a single focus in HIV prevention and necessitate guidance on how to use all three strategies synergistically for maximum benefit depending on the nature of the HIV epidemic.<sup>155</sup>

A high percentage of MSM, especially black MSM, in U.S. cities are HIV infected and don’t know it. The Centers for Disease Control and Prevention (CDC) National HIV Behavioral Surveillance system (NHBS) interviewed and tested 8,153 MSM in 21 metropolitan statistical areas in 2008 and found that HIV prevalence was 19%. It ranged from 16% for white non-Hispanic MSM to 18% for Hispanic MSM and 28% for black non-Hispanic MSM. Nearly half of the HIV infected MSM (44%) were unaware of their infection. Nearly two thirds of MSM 18–29 (63%) who tested positive were unaware of their infection.<sup>156</sup>

Clearly diagnosing high-risk MSM and getting them into treatment must be a priority of any HIV prevention strategy. As called for under the NHAS, the Health Resources Services Administration (HRSA) should partner closely with the CDC to develop strategies for reducing the percentage of MSM who are HIV infected but don’t know it. HRSA and CDC should also work closely in developing implementation

plans for PrEP, given that PrEP will be most effective if a scaled up TLC+ effort is focused on high-risk MSM.

Abdool Karim and Abdool Karim argue that “[h]yper-endemic communities, such as those in South Africa where HIV prevalence in the community is high, may require both interventions [treatment as prevention and PrEP] synergistically: treatment of people infected with HIV to reduce the risk of transmission within the discordant couple, and PrEP to reduce the HIV-negative partner’s risk of HIV acquisition from outside partners.”<sup>157</sup>

In fact, Hallett et al. modeled just such an approach, and found it effective and, except in cases involving low-risk serodiscordant couples, “cost-saving overall.”<sup>158</sup>

Supervie et al. modeled the scale-up of PrEP, coupled with universal access to treatment, in Botswana, a country with a small population heavily affected by HIV with a strong treatment infrastructure.<sup>159</sup> They predict that implementation of FTC-TDF-based PrEP in Botswana would reduce HIV incidence from 4.5% to 1.6% among women and from 2.7% to 1.0% among men. HIV prevalence would fall from 32% to 20% among women and from 23% to 14% among men. “[V]ery similar results” were found for tenofovir-based PrEP.<sup>160</sup> Over a decade, FTC-TDF-based PrEP coupled with expanded treatment access could prevent 39% of new infections among women in Botswana and 40% of new infections in men.<sup>161</sup>

Scaled-up PrEP and treatment could also be targeted at subpopulations experiencing disproportionate, concentrated HIV epidemics, such as men who have sex with men, sex workers, and injection drug users. Even in countries with relatively low HIV prevalence at the population level, such as Senegal and Cambodia, MSM are about 20 times as likely to be HIV-positive as non-MSM. Combining PrEP with expanded treatment makes sense not only with general populations in hyper-endemic nations like Botswana, but also among MSM around the globe.

## ***PAYING FOR PREP, AND ENSURING ITS ACCESSIBILITY TO THE MOST AT-RISK POPULATIONS***

### **COST AND COST EFFECTIVENESS**

The financing of ARV treatments for use in PrEP is one of the most important policy issues in its implementation. Paltiel et al. estimate that in the U.S., PrEP would cost \$753 per person per month, based on the 2009 average wholesale cost of FTC-TDF (300/200 mg/day), adjusted to reflect Medicaid rebates and retail pharmacy dispensing fees. This amounts to \$9,000 a year.<sup>162</sup> A 2011 cost-effectiveness model from the Centers for Disease Control and Prevention estimated that PrEP would cost \$22 a day, or \$8,030 a year.<sup>163</sup> In addition, screening and monitoring costs per person were assumed to be \$1300 per year.<sup>164</sup> Figuring out how to pay for PrEP is especially important for low income people, but given the current market cost this is an important issue even for middle income individuals.

A number of studies have shown that, by preventing infections, PrEP could be cost-effective and would save money that would otherwise be spent on HIV care.<sup>165</sup> Paltiel et al. modeled efficacy with an assumption of 50% PrEP efficacy and found that PrEP was not cost effective; however, with 90% efficacy, PrEP was cost effective in U.S. models.<sup>166</sup>

Juusola et al. found that PrEP targeted to high-risk MSM in the U.S. could be cost effective. When PrEP is targeted to MSM with an average of five partners per year, representing about 20% of all MSM in the U.S., PrEP costs approximately \$50,000 per quality-adjusted life-year gained. This “compares favorably with other interventions that are considered cost effective but could result in annual PrEP expenditures of more than \$4 billion” for medication and monitoring.<sup>166.5</sup> PrEP with generic TDF-FTC would cost less than \$200 U.S. per year in many international settings, though the per capita income in many of these countries is proportionately lower, so the intervention may still be seen as costly. Generic TDF is available for as low as \$66 a year per person in low-income countries, and generic FTC-TDF is available for as low as \$108 a year.<sup>167</sup> Clearly, PrEP could be delivered in ways that are cost-effective.

**The financing of ARV treatments for use in PrEP is one of the most important policy issues in its implementation.**

Connie Celum, citing research by Walensky et al. and Hallett et al. presented at the 2011 Conference on Retroviruses and Opportunistic Infections (CROI), notes that PrEP could be “very cost-effective” if efficacy is high, if it is targeted to those at highest risk, and if drug and delivery costs can be lower than HIV treatment programs. This last point depends on the cost and availability of generic TDF and TDF-FTC, and on the delivery model.<sup>168</sup>

Walensky et al. found that, for PrEP to be effective for HIV prevention in South Africa, it would need to be targeted at women at very high risk, prove at least 70% effective, and the cost would need to drop by 50%.<sup>169</sup> Hallett et al.’s model of PrEP and ART with serodiscordant heterosexual couples in South Africa found that PrEP saves money on ART costs in general, and is “cost-saving overall” among high-risk couples if PrEP is 80% effective in preventing HIV transmission.<sup>170</sup>

Pharmaceutical companies should be encouraged to offer PrEP at a discount to high risk individuals on limited incomes, perhaps similar to the rate they charge Medicaid or AIDS Drug Assistance Programs. Government incentives could encourage such discounting. This would significantly increase the cost-effectiveness of PrEP. Last year Gilead Sciences, the manufacturer of tenofovir and FTC-TDF, indicated a willingness to consider a Patient Assistance Program to offer PrEP to low-income individuals at reduced or no cost.<sup>171</sup> Project Inform’s David Evans, who works closely with pharmaceutical companies to ensure treatment access for low-income people, reported on Poz.com in May 2012 that “Gilead Sciences has promised to offer PrEP for free to lower-income individuals who don’t have health insurance, as well as to provide vouchers to cover HIV testing and condoms.”<sup>171.5</sup> Gilead’s Treatment Access Program also makes low-cost generic versions of its HIV medications available to 2 million people in low-income countries.<sup>172</sup>

**THE U.S. PREVENTIVE SERVICES TASK FORCE AND PRIVATE INSURER COVERAGE**

The Patient Protection and Affordable Care Act (ACA) requires that insurers cover preventive services with an A or B rating from the U.S. Preventive Services Task Force.<sup>173</sup> The U.S. Preventive Services Task Force (USPSTF) is a Congressionally mandated, independent panel of primary care providers that makes recommendations about clinical prevention services. An A or B rating indicates the Task Force recommends a particular service, a C rating signifies no recommendation (neutral), and a D rating signifies a recommendation against a preventive service. An I rating indicates that there is insufficient information to make a recommendation. A key step toward private insurer coverage in the U.S. will be to nominate PrEP as a new preventive service topic for the USPSTF. The Task Force will review peer-reviewed research on the service, as well as other context such as FDA approval of a drug for preventive use or Public Health Service guidelines for such use, and make a recommendation based on the science. It is not supposed to take into account cost.

Some worry that it is premature to approach the USPSTF, and that the reputedly conservative body would not give PrEP an A or B, even just for MSM, based on the current clinical trials research.<sup>174</sup> Hazelton notes that the USPSTF has only approved two forms of chemoprevention services out of 45 total prevention services it recommends: aspirin to prevent heart disease among older people, and tamoxifen to prevent breast cancer among high-risk women. Both aspirin and tamoxifen were approved by the FDA for these preventive purposes, on the basis of a number of clinical studies.<sup>175</sup>

Advocates could also meet with insurers and ask that they voluntarily offer to cover PrEP. Following the CDC's release of interim guidance for providers' prescribing of PrEP to high-risk MSM in January 2011<sup>176</sup>, Kaiser Permanente and Wellpoint indicated they were willing to reimburse PrEP if prescribed by a doctor along the narrow parameters of the CDC guidance.<sup>177</sup> Aetna also indicated it is covering PrEP in some cases.<sup>178</sup>

**THE “ESSENTIAL HEALTH BENEFITS” PROVISION OF HEALTH CARE REFORM**

It is widely understood that poverty and lack of access to health care are risk factors for HIV. An estimated 15.9 million uninsured adults with household income at 133% of the federal poverty level or below will become covered by Medicaid between 2014 and 2019.<sup>179</sup> How this expansion of Medicaid will be accomplished was called into question by the June 28, 2012 U.S. Supreme Court ruling upholding the individual mandate provision of the Affordable Care Act but striking down the federal government's ability to withhold federal Medicaid funding for states that fail to implement the expansion.<sup>179.5</sup> This expansion of Medicaid coverage is a key element of the Affordable Care Act (ACA). Millions more will qualify for subsidized health insurance through state health exchanges. The ACA mandates full coverage of a range of preventive services by private health plans,<sup>180</sup> and coverage of “essential health benefits” by insurance offered in state health insurance exchanges to individuals and small groups, starting in 2014.<sup>181</sup> Medicaid coverage of services, including PrEP, will be determined on a state-by-state basis.

The U.S. Affordable Care Act mandated that all insurers cover certain “essential health benefits” (EHB). An insurer's essential health benefits package must cover 10 categories of benefits—including

prescription drugs, outpatient health care, hospitalization, lab services, prevention and wellness programs, disease management, and mental health and substance abuse services. The law also says the package should be equal to current typical employer plans, meet the needs of diverse populations, including those with disabilities, and not discriminate. The EHB categories statutorily mandated “must include...prescription drugs...[as well as] preventive and wellness services...”<sup>182</sup> These categories could be interpreted to include PrEP.

In December 2011 the U.S. Department of Health and Human Services announced that “essential health benefits” would vary state to state, and could reflect varying needs and priorities from one state to the next. Instead of defining “a single uniform set” of essential health benefits, the Obama Administration “will allow each state to specify benefits within broad categories,” including preventive care and prescription drugs, the New York Times reported in December 2011.<sup>183</sup> HHS Secretary Kathleen Sebelius said the Administration was doing this to give states “the flexibility to design coverage options to meet their unique needs.”<sup>184</sup> Such a move also undercuts conservative critiques of the Affordable Care Act as an imposition of federal mandates on states that usurps state authority.

Under the approach announced by HHS in December 2011, each state will designate an existing health insurance plan as a benchmark. The benefits offered by the benchmark plan will be deemed essential, and starting in 2014 all insurers operating in the state will have to provide benefits of the same or greater value as those provided by the benchmark plan. This benchmark plan will be one of the following:<sup>185</sup>

- One of the three largest small-group plans in the state
- One of the three largest health plans for state employees
- One of the three largest national health insurance options for federal employees
- The largest health maintenance organization operating in the state’s commercial insurance market<sup>186</sup>

Advocates for accessible PrEP should work closely with state health officials over the near future to ensure that PrEP is given fair consideration as an “essential health benefit,” at least if prescribed for MSM under the current interim CDC guidelines or U.S. Public Health Guidelines expected to be released in 2012 (see below).

Coverage of PrEP by state Medicaid programs is essential to ensuring that those most at risk of HIV, including low-income black and Latino gay and bisexual men and transgender women, are able to access PrEP. New York’s Medicaid program indicated in April 2011 that it was awaiting FDA approval, further CDC guidance, more clinical studies, or guidance from the U.S. Public Health Service before authorizing reimbursement for PrEP.<sup>187</sup> Advocates should also approach Medicaid officials in states with high prevalence of HIV to ensure access to PrEP for those poor enough to qualify for Medicaid.

Some local health departments are already making PrEP available to high-risk MSM as per the 2011 CDC interim guidance. Michigan’s Ingham County Health Department is making PrEP and post-exposure

prophylaxis (PEP) available to low-income county residents by covering the prescriptions through the Ingham Health Plan, “a free health discount plan administered by the county” with a \$5 co-payment.<sup>187.5</sup>

### **U.S. PUBLIC HEALTH SERVICE GUIDELINES**

The U.S. Public Health Service (USPHS) has drafted guidelines for the use of PrEP. These include guidelines for use with high-risk MSM as well as other populations. Since 2009, CDC has consulted researchers, clinicians, community members and others through a set of working groups, some of them population based (e.g. MSM, women, youth). As of October 2011 the draft guidelines were being reviewed by sister agencies to CDC within the U.S. Department of Health and Human Services (HRSA, FDA, NIH). Once they are agreed upon within HHS, the draft guidelines will be posted for public comment. They will also be sent out for peer review.

USPHS has issued a number of guidelines related to HIV. These include guidelines for preventing opportunistic infections among people living with HIV, and for the management of occupational exposure to hepatitis B and C virus and HIV.<sup>188</sup> USPHS guidelines can facilitate insurer coverage of a procedure or treatment; however, they do not mandate it. USPHS guidelines recommending PrEP, whether for all populations or for MARPs like high-risk MSM, will make it more likely that both private and public insurers will cover PrEP, but will not mandate coverage the way a USPSTF recommendation would.

### **COVERAGE AS A “PREVENTIVE HEALTH SERVICE” UNDER THE AFFORDABLE CARE ACT**

The 2010 Affordable Care Act states that health insurers must cover “preventive health services,” and that they cannot charge for them.<sup>189</sup> On January 20, 2012 the Obama Administration interpreted this provision of the ACA to mean that most health insurers must cover contraceptives approved by the FDA for women free of charge.<sup>190</sup> If the FDA approves PrEP, the Obama Administration should affirm that insurers must cover PrEP as a critical “preventive health service.”

### **THE GLOBAL SITUATION: FUNDING AND PLANNING FOR IMPLEMENTATION**

The Bill and Melinda Gates Foundation, one of the major global philanthropic funders of HIV prevention and treatment, has funded much of the PrEP research, such as the Partners PrEP study in East Africa and, along with the U.S. National Institutes of Health, funded the iPrEx study conducted in multiple locations in the Americas, Asia and South Africa. It has also funded global convenings on PrEP research, such as those organized by the International AIDS Society in Seattle in 2005, Toronto in 2006, and Sydney in 2007. A Gates-funded convening in London in 2009 focused on implementation planning, and was organized by the O’Neill Institute for National and Global Health Law at Georgetown University.<sup>191</sup> The Gates Foundation also funded the PrEP Trials Working Group through the Forum for Collaborative HIV Research in Washington, DC to foster information sharing among researchers involved in PrEP clinical trials. This working group met in Cape Town, South Africa and Boston, Massachusetts in 2008 and 2009.<sup>192</sup>

The Gates Foundation’s HIV work is focused primarily on sub-Saharan Africa. It views PrEP as part of a package of treatment and prevention approaches that include secondary prevention, i.e. treatment as prevention. But even with secondary prevention, no amount of treatment will obviate the need for primary prevention. The Gates Foundation believes that a range of current and potential prevention interventions should be deployed for maximum efficacy to complement existing behavioral interventions such as promoting condoms: these include vaccines, circumcision for heterosexual men, microbicide products (gels and rings), and oral PrEP.

The Gates Foundation is planning PrEP demonstration projects in sub-Saharan African that include MSM as well as heterosexual populations at risk. These projects will help inform normative bodies, such as the WHO and CDC, in issuance of guidelines for use. The Gates Foundation believes that in the current environment of fiscal constraints that policy makers will have to make trade-offs, and strike a balance between devoting resources to treatment and devoting resources to prevention. It focuses on giving public health officials evidence and data to inform their decision-making.<sup>193</sup> Other global funders are considering PrEP demonstration projects in Africa, Asia and Latin America.

The Clinton Foundation, another major funder of HIV treatment in Africa, the Caribbean and elsewhere, funds post-exposure prophylaxis (PEP) and chemoprophylaxis to prevent mother to child transmission of HIV.<sup>194</sup> The Clinton Health Access Initiative (CHAI), a project of the William J. Clinton Foundation, works to strengthen health systems in the global south and expand access to care and treatment for HIV/AIDS, malaria and tuberculosis. The Clinton Foundation has helped 4 million people access HIV treatment in the developing world, about half of those living there who are on HIV treatment.<sup>195</sup> Focused on Africa, Asia and Haiti, CHAI works with the drug and diagnostic industries to improve market dynamics for medicines and diagnostics; lower the cost of treatment; accelerate access to life-saving technologies; and help governments quickly build the capacity required for high-quality care and treatment programs that use the latest innovations and approaches.

Currently CHAI is focused on assisting governments in scaling up treatment and prevention programs to reach universal access goals associated with current funding. As the evidence on PrEP becomes clearer and as government take steps, such as approving antiretrovirals for use as PrEP, CHAI is likely to become more involved in efforts to make PrEP and microbicides available. CHAI is also working to lower the cost of tenofovir by 1) lowering manufacturing costs, 2) working on the process chemistry (finding more efficient synthetic pathways), and 3) dose optimization (finding ways to decrease the amount of active pharmaceutical ingredient to increase affordability).<sup>196</sup> CHAI’s management expertise and experience in scaling up HIV treatment access could be very useful to scaling up PrEP in combination with expanded HIV treatment.



**The Affordable Care Act mandates coverage of preventive services by private health plans, and coverage of “essential health benefits” by insurance offered in state health insurance exchanges.**

The Global Fund to Fight AIDS, Tuberculosis and Malaria, in its 2012–2016 global strategy, does not explicitly mention PrEP. It does, however, leave open the possibility of supporting PrEP. The strategy prioritizes “support for the highest-impact interventions and technologies suitable to the country situation.” This includes “actively seek[ing] opportunities to accelerate the update and scale-up of significantly-underutilized (possibly

**The Gates Foundation is planning PrEP demonstration projects in sub-Saharan Africa that include MSM as well as heterosexual populations at risk.**

new) high-impact interventions or technologies.” These could include PrEP.<sup>197</sup> The fund also prioritizes “prevention intervention services delivered for most-at-risk-populations” and the prevention of mother-to-child transmission of HIV through ARV prophylaxis and treatment.<sup>198</sup>

The perspectives of global regulatory and health promotion bodies toward PrEP will also affect its success and uptake. One of the key “strategic directions” articulated by UNAIDS in its 2011–2015 strategy, *Getting to Zero*, is to “revolutionize HIV prevention by “target[ing] epidemic hot spots...to ensure equitable access to high-quality, cost-effective HIV prevention programmes that include rapid adoption of scientific breakthroughs.”<sup>199</sup> UNAIDS also prioritizes “incorporating new technologies and approaches as they are developed” to “revolutioniz[e] prevention.”<sup>200</sup> UNAIDS also describes PrEP and other “novel biomedical interventions” as having “the potential to vastly reshape HIV prevention approaches if informed by further research, local knowledge and human rights.”<sup>201</sup>

Finally, the World Health Organization recommends “[c]ombining behavioural, biomedical and structural HIV preventive interventions...”<sup>202</sup> It promises to “[d]rive the development of new HIV prevention interventions and approaches” by “support[ing] the evaluation of potentially effective new interventions and approaches, including microbicides, pre-exposure prophylaxis and antiretroviral therapy as prevention, and provide guidance to countries on implementation as results become available.”

The Gates Foundation has been funding the WHO to prepare countries for PrEP upon proof of efficacy. Over the past year the WHO has been developing “rapid advice” recommendations about PrEP. These recommendations, which will be made public, are expected in 2012. It is expected that the WHO recommendation will encourage countries to undertake implementation research on PrEP and will encourage UNAIDS, PEPFAR and other programs and funders to scale-up and implement PrEP. WHO is also developing a generic protocol on how to do PrEP research for demonstration projects, and a framework on how to evaluate such demonstration projects. These documents will not be made public.<sup>203</sup>

In addition to the U.S. FDA and the WHO, the European Medicines Agency (EMA) is another regulatory agency whose rulings are influential globally. On March 14, 2012 the EMA released a “reflection paper” on PrEP and microbicides that makes recommendations on how pharmaceutical companies should study PrEP. The EMA states that PrEP is “a potentially valuable tool as part of an integrated approach for reducing the individual’s risk of HIV acquisition and for combatting the HIV epidemic.” The EMA indicated its preparedness to evaluate “future marketing authorization applications in oral and topical PrEP.”<sup>203.1</sup>

While some professional associations, such as the American Psychological Association, have issued resolutions supportive of combining biomedical prevention approaches with behavioral approaches to HIV prevention, others, like the British HIV Association and the British Association for Sexual Health and HIV, have said more study is needed before PrEP should be made available to people at risk for HIV.<sup>203,2</sup>

**A World Health Organization “rapid advice” recommendation about PrEP is expected in 2012.**

The Southern African HIV Clinicians Society’s Consensus Committee issued guidelines for prescribing PrEP to high-risk HIV-negative MSM in June 2012. The guidelines call for prescribing PrEP to high-risk MSM “who are willing and motivated to use PrEP as part of a package of HIV prevention services (including condoms, lubrication, sexually transmitted infection (STI) management and risk reduction counseling.)” The guidelines state that “[r]isk compensation...while on PrEP may become a concern, and clinicians should continue to support MSM clients to continue to use condoms, condom-compatible lubrication and practice safer sex.”<sup>203,3</sup>

It’s important to point out that national regulatory authorities can authorize the use of FTC-TDF for PrEP now, without WHO action. However, it is expected that a WHO recommendation of FTC-TDF for use as PrEP, which is anticipated sometime in 2012, will make it more likely that countries will give it the green light and allow PrEP to be added to the tool kit in the fight against HIV.

Other private foundations promoting HIV prevention and care in the global south are open to incorporating PrEP into their approach. The Pangaea Global AIDS Foundation, which works in Tanzania, Zimbabwe and southern China, is interested in incorporating PrEP into its prevention and treatment “cascade” in those countries. Pangaea prioritizes HIV prevention with women and girls, MSM, and IDUs.<sup>204</sup> Pangaea believes that despite the efficacy of treatment as prevention shown in HTPN 052, the serodiscordant couple study, many questions remain unanswered. For example, is the success of HTPN 052, a clinical trial, generalizable to the general population? Should ARVs be prioritized for the positive partner to reduce his or her viral load, or for the negative partners to stay negative? It is also important to look at the context of the serodiscordant relationship. For example, is the female partner being abused? Is the couple sexually active but not in a relationship? This context will affect whether PrEP is appropriate for that couple. Pangaea also believes HIV testing should be linked PrEP; if someone is tested and the result is negative, that person may be a good candidate for PrEP given their risk behavior. These are all important questions that must be grappled with in the implementation of PrEP.

**THE HUMAN RIGHTS CONTEXT: ENSURING ACCESS TO GAY AND BISEXUAL MEN AND TRANSGENDER WOMEN**

In low- and middle-income countries throughout the global south, MSM are 19 times as likely as the general population to contract HIV.<sup>205</sup> In countries with generalized epidemics, such as those in southern Africa, MSM are at least as vulnerable as the general population to HIV. Beyrer et al.’s survey of 537 MSM in Malawi, Botswana and Namibia found an HIV prevalence of 17.4%.<sup>206</sup> Two thirds of African countries legally ban homosexual sex or, at least, male-to-male sex. According to the International Lesbian and Gay Association, altogether 86 countries around the world criminalize homosexuality as of 2010.<sup>207</sup> In some countries, traditional or local religious laws are applied.<sup>208</sup> Punishments range from imprisonment (five years in Cameroon, Senegal, and Ghana; life in Uganda) to death (in Mauritania, Sudan, Afghanistan, and parts of Nigeria and Pakistan).<sup>209</sup> Even more anti-gay laws have been introduced in Uganda, Rwanda, Nigeria and elsewhere.<sup>210</sup> In recent years, state-sponsored crackdowns against LGBT people in Kenya, Malawi, Senegal, Uganda, and Zimbabwe have received international press. Such state oppression not only violates basic human rights, but also drives behaviors which are already stigmatized and may transmit disease further underground, fueling the HIV epidemic. Stigma and discrimination generate economic, political, legal, and social factors that increase both risk and barriers to accessing prevention, treatment, care and support for MSM.<sup>211</sup> UNAIDS estimates that only one in ten MSM worldwide has access to HIV prevention and treatment services they need.<sup>212</sup>

This is the challenging political, social and public health context in which HIV prevention advocates seek to prioritize gay and bisexual men for PrEP. A January 2012 analysis by amfAR and the Johns Hopkins Bloomberg School of Public Health found that:

...countries that criminalize same-sex sexual practices spend fewer resources on HIV-related health services for MSM, do less to track and understand the epidemic in their nations, and are more likely to repurpose donor funds intended to fight the epidemic among MSM.<sup>213</sup>

In other words, countries accept funds from PEPFAR or the Global Fund for use in HIV prevention with MSM and instead use them to prevent HIV among heterosexuals or the general population.

Those seeking to make PrEP available to MSM in contexts with serious human rights violations must take these contexts into account and ensure protections for MSM who seek to access PrEP. They should also support the efforts of local MSM and HIV advocates who seek to change the legal and social context to decriminalize and destigmatize homosexuality. Recent press coverage of discussions of PrEP use in Uganda acknowledged that laws criminalizing homosexuality and prostitution must be lifted “to enable targeting of high-risk populations like prostitutes and homosexuals, who are some of the main beneficiaries of the new drug.”<sup>214</sup> Continued persecution of gay and bisexual men, other MSM, and transgender women—especially government-sanctioned persecution—only exacerbates gay men’s vulnerability to HIV and makes prevention efforts less effective.

## ***NEXT STEPS***

Gilead Sciences submitted a supplemental New Drug Application to the U.S. Food and Drug Administration in December 2011 for approval of once-daily FTC-TDF (Truvada) for pre-exposure prophylaxis to reduce the risk of HIV infection among uninfected adults. In a statement, Gilead cited the results of the iPrEx study with MSM in several countries and the Partners PrEP study of serodiscordant heterosexual couples in Kenya and Uganda.<sup>215</sup> In January 2012 about two dozen leading AIDS and health organizations asked the FDA to grant priority review for the Gilead supplemental New Drug Application.<sup>216</sup> In February 2012 the FDA announced that it would grant Gilead's request priority review, considering FTC-TDF for PrEP by June 15, 2012. An FDA determination in support of FTC-TDF for PrEP would allow Gilead to promote FTC-TDF for preventive use.

May 10, 2012 the FDA's Antiretroviral Drugs Advisory Committee hear oral testimony and reacted to written testimony that had been submitted for several weeks prior. The Committee recommended that the FDA indicate emtricitabine/tenofovir disoproxil fumarate (FTC-TDF) for use as an HIV prevention tool as pre-exposure prophylaxis for men who have sex with men (MSM), uninfected partners in serodiscordant couples, and for other adults at risk for HIV through sexual activity.<sup>217</sup> On June 8, 2012, Gilead Sciences Inc. said in an email that the FDA was delaying its decision by up to three months in order to review its Risk Evaluation and Mitigation Strategy (REMS), a plan by Gilead to ensure that people won't misuse FTC-TDF. Gilead submitted a modified risk strategy to the FDA on June 4, 2012, the company reported.<sup>218</sup> When this monograph went to press (early July 2012) an FDA decision was expected by mid-September, 2012. U.S. Public Health Service guidelines are also expected in 2012. The guidelines are expected to address MSM, heterosexuals, and injection drug users (IDUs). Subsequent to the publication of the Public Health Guidelines will be derivative guidelines, such as clinical practice guidelines.

A number of PrEP demonstration projects are being launched in the U.S., including three funded by the California HIV/AIDS Research Program of the University of California. Two research teams will offer FTC-TDF as well as behavioral counseling and other services to MSM and transgender women in Los Angeles, San Diego and Long Beach. A third research team will conduct a demonstration project with young MSM of color in the East Bay (Oakland, Richmond, Berkeley). Altogether \$11.8 million will fund the demonstration projects in California.<sup>219</sup> HPTN 073 is being designed to develop a culturally tailored PrEP program focusing on Black MSM in several cities in the United States. The study will include support for clinical care coordination based on findings from HPTN 061 and other studies suggesting that for many at risk Black MSM, social and structural barriers, including poverty and unemployment, are impediments to engaging prevention programs.

The WHO is expected to issue "rapid advice" about PrEP in 2012. Global funders and policy makers are awaiting this guidance. We hope that a positive WHO recommendation of PrEP for some vulnerable populations will quickly lead to funding of PrEP demonstration projects and the introduction of PrEP into HIV prevention programs in both high-prevalence countries and concentrated epidemics such as those affecting MSM in many countries.

***SUMMARY: RECOMMENDATIONS FOR IMPLEMENTATION OF PREP*****CLINICAL TRIALS AND DEMONSTRATION PROJECTS**

- Clinical trials of PrEP should continue with priority populations, including serodiscordant opposite-sex and same-sex couples, as well as most at risk populations (MARPs) such as MSM, transgender women, injection drug users, and sex workers. Studies of intermittent PrEP, non-tenofovir-based regimens, and non-oral modes of administration are important, so that the most cost-effective, safest, and most acceptable regimens are available to the diverse array of potential consumers.
- The U.S. government, under both Republican and Democratic Presidents, and the Gates Foundation have been visionary leaders of PrEP and microbicides research. We urge them to continue this funding, which will eventually transform the fight against HIV/AIDS.
- Intermittent PrEP trials should be conducted, with a focus on understanding how to ensure high rates of PrEP adherence.
- Research into injectable PrEP, implants, transdermal patches, and long-lasting treatments should be funded as approaches that could significantly increase adherence and efficacy.
- Clinical trials must now consider ethical issues, especially whether any placebo control is supportable in light of current evidence, and if so, in what circumstances.
- HIV funders should support PrEP demonstration projects in the U.S. and globally to understand real-world issues of implementation and best practices, including uptake, adherence, risk compensation, staff training and infrastructure needs. These demonstration projects should include MSM and other vulnerable populations as participants and community partners in planning to ensure success.
- Demonstration projects should determine the best combination of PrEP with other approaches, such as treatment as prevention, to suit a local context and the unique needs and experiences of vulnerable populations. These findings should be widely disseminated. Demonstration projects in the U.S. and globally should also include high-risk heterosexual women and men, sex workers, and other vulnerable populations.
- Drugs like Maraviroc and TMC278 (rilpivirine) have truly different mechanisms of action. Research institutions such as NIH should continue to fund the development of new drugs with new mechanisms of action, independent of how they are formulated. This is because some patients will not tolerate tenofovir-based PrEP, but may tolerate Maraviroc, TMC278 and other new agents. These may also allow for minimization of selection for resistance to drugs that are the first line of treatment for HIV infection.

## IMPLEMENTATION IN CLINICAL SETTINGS

- PrEP should be accompanied by comprehensive, long-term preventive care and sustained behavioral interventions to ensure a high rate of adherence as well as to minimize risk compensation and to minimize risk. Use of innovative technology, such as text messaging and other reminder methods, could increase adherence.
- PrEP may be most effective if coupled with scale-up of treatment to reduce community viral load. This may be especially impactful in regions with highest prevalence, such as southern Africa, and in concentrated epidemics, e.g. urban MSM.
- Population-level impacts of PrEP must be closely monitored to identify and address emergent drug-resistant HIV.
- Regular safety screening should be conducted with those taking PrEP to minimize the risk of side effects.
- Cost-effectiveness can be maximized by targeting PrEP to those most at risk within an at-risk population, such as MSM who have unprotected anal sex with multiple partners or sex workers who have unprotected sex.
- Effective communication about PrEP, including about risk relative to other prevention interventions and partial efficacy, is essential to encourage uptake and adherence and to minimize risk compensation.
- The provision of PrEP to MSM and transgender women should occur in a broader context of ensuring clinically competent health care to gay, lesbian, bisexual and transgender people.<sup>220</sup> Trainings to increase such clinical competence are key to reducing HIV and other health disparities affecting MSM and transgender women.<sup>221</sup>
- Implementation of PrEP should be informed by a wide range of stakeholders, including representatives of the populations being prioritized for PrEP (such as sex workers or IDUs), health care providers, government officials, and researchers.
- Local and state health departments should prepare for the imminent FDA determination on FTC-TDF as PrEP and educate individuals, health care providers, and community-based organizations about PrEP—what it is, how to access it, how to use it, and how to ensure it complements and strengthens existing HIV prevention efforts.
- Community organizations, health departments and providers should preemptively attempt to destigmatize PrEP use among target populations. Social marketing campaigns can be effective in shifting social norms in supportive and affirming ways to enhance uptake and adherence.

**COMBINING BIOMEDICAL INTERVENTIONS WITH STRUCTURAL INTERVENTIONS**

- Structural interventions should be combined with biomedical and behavioral interventions to reduce structural drivers of HIV vulnerability. These could include repeal of laws criminalizing homosexuality (still extant in more than 70 countries, including more than half of PEPFAR countries), passage of nondiscrimination laws covering sexual orientation and gender identity, and public education campaigns challenging anti-gay prejudice and promoting family acceptance of gay sons.
- Public health entities should promote post-exposure prophylaxis (PEP) and PrEP to vulnerable populations, making people aware of what biomedical interventions are currently available, explaining the difference between PEP and PrEP, and explaining how to access them. People seeking PEP and/or HIV testing after a possible risk exposure should be prioritized for PrEP coupled with sustained behavioral interventions.
- Sub-Saharan African countries, some former Soviet countries in Eastern Europe and Central Asia, and others that have solely focused on heterosexual HIV prevention campaigns should also educate MSM about their vulnerability to HIV through unprotected anal intercourse.
- Funders should support community education and engagement campaigns to increase community literacy about PrEP and other biomedical interventions, and to enhance community involvement in scale-up and roll-out of PrEP and other interventions.

**REGULATORY STEPS**

- The U.S. Food and Drug Administration (FDA) should accept the May 10, 2012 recommendation of its Antiretroviral Drugs Advisory Committee and indicate emtricitabine/tenofovir disoproxil fumarate (FTC-TDF) for use as an HIV prevention tool as pre-exposure prophylaxis for men who have sex with men (MSM), uninfected partners in serodiscordant couples, and for other adults at risk for HIV through sexual activity.<sup>222</sup>
- The U.S. Public Health Service should post its draft guidelines for PrEP soon for public review, and move toward publishing the guidelines as expeditiously as possible.
- The WHO should issue guidance on PrEP that takes into account the promising results of the iPrEx study, Partners PrEP, and the Botswana CDC study.
- Following the release of the Bangkok IDU trial results, if appropriate the U.S. CDC/Public Health Service and WHO should issue guidance for PrEP with IDUs. IDUs are a priority population around the world and especially in Eastern Europe and Asia.

## **PAYING FOR PREP, AND ENSURING ITS ACCESSIBILITY TO LOW-INCOME AND MOST AT-RISK POPULATIONS**

- Pharmaceutical companies should be encouraged to offer PrEP at a discount and to create a Patient Assistance Program for the medications. Government incentives could encourage such moves.
- The U.S. Preventive Services Task Force should consider recommending PrEP for high-risk MSM and other vulnerable populations as additional data become available.
- Insurers should be encouraged to voluntarily cover PrEP as a cost-saving, preventive measure.
- States should provide access to PrEP as a critical prevention service and prescription medication under the Essential Health Benefits provision of the Affordable Care Act. For highly vulnerable populations such as MSM and people in serodiscordant relationships, PrEP represents a cost-saving measure that will improve public health and save money in the medium and long term.
- Subsequent to FDA approval of PrEP, State Medicaid programs should also cover PrEP as a cost-saving measure that will improve public health and ultimately save money in health care costs. Local health departments should follow the lead of Ingham County, Michigan and make PrEP available to low-income, high-risk MSM and other priority populations.
- Global funders of HIV prevention and care should make resources available for PrEP and treatment as prevention. The WHO, PEPFAR, UNAIDS, and the Global Fund to Fight AIDS, Tuberculosis and Malaria should provide the latest research to country planners to help policy makers strike the right balance between funding for PrEP, other prevention services, and treatment.

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