

March 22, 2017

United States Preventive Services Task Force

**Comment on draft research plan for prevention of Human Immunodeficiency Virus (HIV) infection:  
Pre-Exposure Prophylaxis**

We researchers at the Fenway Institute, Emory University Rollins School of Public Health, and the O'Neill Institute for National and Global Health Law at Georgetown University Law Center welcome an opportunity to comment on the USPSTF's draft research plan for PrEP for HIV prevention.

*Proposed analytical framework*

In general we think the proposed analytical framework is strong.

*Proposed key questions to be systematically reviewed*

We offer comments specific to each proposed question to be systematically reviewed below:

1. What are the benefits of pre-exposure prophylaxis (PrEP) in persons without pre-existing HIV infection versus placebo or delayed PrEP for the prevention of HIV infection and associated clinical outcomes?

We believe that these are important questions for the USPSTF to evaluate. PrEP is a relatively new prevention intervention and significant research is underway on various agents, delivery mechanisms, and dosing strategies. There have now been 7 RCTs which included placebos studying TDF-based PrEP regimens, with 5 (iPREX; Partners' PrEP; Thai IDU; TDF2 (Botswana); IPERGAY) demonstrating efficacy, and 2 (FEM-PrEP and VOICE) failing to do so, because of suboptimal adherence. There has also been an open label RCT, comparing immediate versus delayed PrEP (PROUD), that also demonstrated the efficacy of oral tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) in preventing HIV acquisition.<sup>1</sup>

While it may be appropriate for the USPSTF to consider a broader range of PrEP agents in the future, we recommend that the USPSTF limit its current review to evaluating clinical effectiveness of oral TDF-FTC, the medication approved by the U.S. Food and Drug Administration in 2012 for use as PrEP for HIV prevention. iPrEx, a placebo-controlled randomized study of 2,499 MSM and transgender women, demonstrated a 44% reduction in HIV incidence among all participants who were assigned to the TDF-FTC arm, and a 99% reduction in HIV infection in study participants whose drug levels suggested daily adherence.<sup>2</sup> 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, randomized the HIV-uninfected partners to receive one of the following regimens: oral TDF once daily, oral TDF-FTC once daily, and a placebo once daily. Compared with the placebo group, those receiving TDF were 62% less likely to contract HIV; those receiving FTC-TDF were 73% less likely.<sup>3</sup> Another oral daily PrEP study involved 1200 heterosexual men and women in Botswana. Half received oral TDF-FTC, half a placebo. Those receiving TDF-FTC were 62.6% less likely to contract HIV than those receiving the placebo.<sup>4</sup> An RCT with people who inject drugs in Thailand found a 48.9% reduction in HIV incidence among the arm assigned TDF compared to the placebo arm.<sup>5</sup>

In the IPERGAY study, 414 MSM and transgender women were randomized to receive pericoital TDF-FTC as PrEP or placebo. Participants randomized to receive TDF-FTC were directed to take 2 pills of TDF-FTC

2 to 24 hours prior to sexual activity, followed by a third pill 24 hours after the first dose, and a fourth pill 24 hours later. Study results demonstrated an 86% reduction in HIV incidence.<sup>6</sup>

In subsequent open-label studies, in which the efficacy of PrEP had been proven and when individuals were educated about the importance of adherence to efficacy, efficacy results were higher. For example, in the PROUD study, MSM on PrEP in English STI clinics had an 86% lower incidence of HIV compared to MSM who were randomly assigned to a waiting list for PrEP.<sup>7</sup> The USPSTF should plan to review other agents or forms of PrEP at a later date as the clinical science develops.

a. How do benefits differ by population subgroups?

Evaluating the differential benefits by subgroups should be an important component of the USPSTF review. Data from other countries (e.g. among heterosexuals and injection drug users) as well as the U.S. will be useful in determining the indications for PrEP among Americans in specific subpopulations. Critical subgroups for review should include men who have sex with men (MSM), transgender people, heterosexual women in communities with high HIV prevalence (i.e. in the U.S. among Black and Latina women), persons in HIV serodiscordant partnerships, persons who inject drugs, and persons who engage in transactional sex. Due to the population sizes of many of these groups in the U.S., it is often challenging to conduct high quality studies on individual subgroups.

There is published clinical effectiveness research showing the benefits of PrEP for men who have sex with men (MSM) and transgender women in U.S. clinical settings.<sup>8,9</sup> There is also effectiveness research on MSM in clinical settings in England.<sup>10</sup> Published research on PrEP with heterosexual women and men is limited to clinical settings outside of the U.S., mostly in Africa. We recommend that the USPSTF consider study inclusion/exclusion criteria that will enable the USPSTF to broadly assess the effectiveness of PrEP. We recommend that the USPSTF specifically consider the generalizability of results, and rely on epidemiological or other data to make more tailored recommendations for subgroups. We do not believe that it is appropriate to evaluate the effectiveness of PrEP in small subgroups by excluding studies from outside the United States or U.S. studies in other subgroups, as this would likely never lead to the USPSTF to evaluate the effectiveness of PrEP in these critical U.S. subgroups. We also believe that consideration should be given to a recommendation for persons that self-identify to their providers as being at high risk of HIV infection.

Assessment of benefit differences by population subgroups should only be conducted with studies that were designed to test for differences in population subgroups. Inferring population subgroup differences from general efficacy trials that were not designed or powered to assess subgroup differences may misrepresent actual or perceived differences.

b. How do benefits differ by dosing strategy or regimen?

We believe that it is premature to evaluate dosing strategies and regimens at this time. The only FDA-approved regimen is daily oral TDF-FTC. Given that the preponderance of the efficacy trial data are derived from individuals prescribed daily TDF-FTC, we feel that this should be the primary regimen to analyze, but also feel that the USPSTF should evaluate TDF alone as a potential alternative, given that efficacy was demonstrated in 3 trials—one of the arms of Partners PrEP, TDF-2 (heterosexuals in Botswana) and the Thai injection drug user study. Given that efficacy was demonstrated with PrEP on demand, two pills within 24 hours of anticipated anal intercourse and a pill a day for 2 days afterwards

in the IPERGAY study, this regimen should also be reviewed as a potential alternative for high risk MSM, who are likely to adhere to the regimen, as the French and Canadian participants did.

2. What is the diagnostic accuracy of methods used to identify persons who are candidates for PrEP due to increased risk of HIV acquisition?

We think this is an important topic for the USPSTF to explore. It may be that more has been published on HIV risk assessments more broadly than on the algorithm for identifying priority individuals who should consider PrEP for HIV prevention. There have been more than 10,000 persons enrolled in the primary efficacy trials, so review of their behavioral risks could help inform guidelines. Further, data from cohorts which prospectively assessed risks according to current criteria and assessed subsequent HIV infections should be considered.

3. What are rates of adherence to PrEP in U.S. primary care–applicable settings?

A study of tenofovir hair concentrations among men and transgender women enrolled in two open-label PrEP studies found that tenofovir hair concentrations were detectable in 75% of person-visits in iPrEx OLE and in 98% of person-visits in PrEP Demo.<sup>11</sup> Among participants in the iPrEx OLE study with TDF concentrations of 700 fmol per punch or greater, there were no HIV infections at visits.<sup>12</sup> In the PrEP Demo project, 80.0% to 85.6% of participants who underwent measurement of TDF levels had protective levels (consistent with at least 4 doses per week) at follow-up visits.<sup>13</sup> Adherence in the open-label PROUD study was high, with tenofovir detected in the plasma of all 52 sampled participants who reported that they were taking PrEP.<sup>14</sup> A study of PrEP adherence in a clinical setting found that, among a random sample of patients on PrEP who attended a follow-up appointment, TDF levels consistent with at least 4 doses a week were found in 90% of these patients.<sup>15</sup>

Adherence rates should only be systematically reviewed from studies powered and designed to test the effectiveness of PrEP, not studies designed to demonstrate the initial efficacy of PrEP. Efficacy studies may demonstrate substantially lower adherence because researchers and participants do not know if the drug will produce the intended outcome even with perfect adherence. Once a drug has been proven efficacious, however, adherence can be more accurately evaluated through effectiveness studies. Placebo-controlled trials have been found to have lower rates of adherence than primary care-based service delivery.<sup>16</sup>

When assessing PrEP adherence, the USPSTF should consider the effectiveness of adherence support interventions for people living with HIV, including treatment adherence counseling and support interventions provided through the Ryan White HIV/AIDS Program and other public health programs targeting high risk populations. These interventions may inform strategies to increase PrEP adherence. Lessons should also be drawn from the open-label PrEP studies and the PrEP demonstration projects described above.

4. What is the association between adherence to PrEP and effectiveness for preventing HIV acquisition?

This is an important question with major clinical implications. An analysis of 7 PrEP clinical trials found a strong correlation between adherence and effectiveness of PrEP for preventing HIV acquisition.<sup>17</sup> PrEP adherence is a key element in the HIV pre-exposure prophylaxis continuum.<sup>18</sup> Different levels of adherence to PrEP may be needed in different populations in order for PrEP to prevent HIV infection.<sup>19</sup>

Sufficient intracellular drug concentrations that protect against HIV infection for MSM may be achieved by approximately 1 week of daily dosing.<sup>20</sup>

5. What are the harms of PrEP in persons without pre-existing HIV infection versus placebo or delayed PrEP for the prevention of HIV infection?

This is an important question for the USPSTF to explore in its systematic review. Although the PrEP efficacy and demonstration studies to date found a mild, transient start-up syndrome, increased numbers of creatinine elevations, and decreases in bone mineral density, the adverse events were mild, not associated with clinical harm, and reversible with drug discontinuation.

*Proposed contextual questions*

1. What factors are associated with increased or decreased adherence to PrEP?

When assessing PrEP adherence, the USPSTF should consider the effectiveness of adherence support interventions for people living with HIV, including treatment adherence counseling and support interventions provided through the Ryan White HIV/AIDS Program and other public health programs targeting high risk populations. These interventions may inform strategies to increase PrEP adherence. Research presented at the 2016 Conference on Retroviruses and Opportunistic Infections found that PrEP was accepted by 79% of Black MSM study participants in the HPTN073 trial. At 26 weeks 68% remained on PrEP. Self-reported adherence above 50% was 85% at 4 weeks and 78% at 36 weeks.<sup>21</sup>

2. What is the risk of antiretroviral drug-resistant HIV infection in persons treated with PrEP, and what is the effect of PrEP-related, antiretroviral drug-resistant HIV infection on antiretroviral treatment outcomes?

We agree that these are both important contextual questions for the USPSTF to explore. The incidence of transmission of resistant virus was about 0.1% when all the participants in the PrEP efficacy RCTs were reviewed. However, 3 unique cases of transmitted infection in medication adherence patients have been reported, 2 with multi-drug resistant virus and one with a drug sensitive virus, suggesting that resistance transmission can occur, but is infrequent to date.

*Proposed research approach*

<b>Comparisons</b>	Placebo or delayed PrEP; well-designed open label demonstration project data	One PrEP regimen vs. another
<b>Outcomes</b>	Risk of HIV acquisition, quality of life, risk of other sexually transmitted diseases, renal dysfunction, adverse bone effects, pregnancy-related outcomes, and adherence	All other outcomes not listed, including condom use
<b>Setting</b>	Primary care-relevant settings, including sexually transmitted disease clinics, Ryan White clinics, and public health departments	
<b>Study Design</b>	Randomized, controlled	

	trials for effectiveness and harms Controlled observational studies for harms,* if randomized, controlled trials are lacking Diagnostic accuracy studies for risk assessment	
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We encourage the USPSTF to consider including effectiveness research and implementation research on PrEP in clinical settings that reflect studies that did not use a randomized, controlled trial model. Implementation of PrEP in U.S. clinical settings does not always lend itself to such a rigorous research model. Restricting the location of the randomized controlled trials that have evaluated the effectiveness and safety of oral PrEP could limit the Task Force’s ability to stratify results by adherence and for subpopulations by age, sex, mode of HIV acquisition, as well as by dosing strategy or regimen. A recent meta-analysis of PrEP clinical trials indicates that only two randomized controlled trials of PrEP effectiveness were conducted exclusively in locations within the United States. These two studies account for only 2.6% of the total number of participants studied across the 11 clinical trials.<sup>22</sup> Therefore, we recommend inclusion of effectiveness studies conducted outside of the United States. We encourage the Task Force to also review well-done observational studies.

Should you have any questions about our comments, please contact Sean Cahill at the Fenway Institute at [scahill@fenwayhealth.org](mailto:scahill@fenwayhealth.org) or 617-927-6016.

Thank you for considering our comments.

Sincerely,

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<sup>1</sup> Silapaswan A, Krakower D, Mayer KH. (2016). Pre-exposure prophylaxis: A narrative review of provider behavior and interventions to increase PrEP implementation in primary care. *J Gen Intern Med* 32(2):192-198.

<sup>2</sup> Grant R, Lama J, Anderson P. et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*. 2010; 363:27; 2587-2599.

<sup>3</sup> Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J et al. (2012). Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 367(5): 399-410.

<sup>4</sup> Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM et al. (2012). Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* (367):423-434. .

<sup>5</sup> Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. (2013). Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 381(9883); 2083-2090.

<sup>6</sup> Molina, JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015;373(23):2237-46.

<sup>7</sup> McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. (2016). Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomized trial. *Lancet* 387(10013):53-60.

<sup>8</sup> Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. (2016). Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med* 176(1); 75-84.

<sup>9</sup> Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. (2015). No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. *Clin Infect Dis* 61(10):1601-1603.

<sup>10</sup> McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R et al. (2016). Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomized trial. *The Lancet* 387(10013):53-60.

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- <sup>11</sup> Koss CA, Bachetti P, Hillier SL, Livant E, Horng H, Mgodhi N, et al. (2017). Differences in cumulative exposure and adherence to tenofovir in the VOICE, iPrEx OLE, and PrEP Demo studies as determined via hair concentrations. *AIDS Research and Human Retroviruses*. DOI: 10.1089/aid.2016.0202
- <sup>12</sup> Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M et al. (2014). Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet* 14:820-29.
- <sup>13</sup> Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. (2016). Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med* 176(1): 75-84.
- <sup>14</sup> McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R et al. (2016). Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomized trial. *The Lancet* 387(10013):53-60.
- <sup>15</sup> Montgomery MC, Olderburgh CE, Nunn AS, Mena L, Anderson P, Liegler T et al. (2016). Adherence to pre-exposure prophylaxis for HIV prevention in a clinical setting. *PLoS One* 11(6): e0157742.
- <sup>16</sup> Spinner CD, Boesecke C, Zink A, Jessen H, Stellbrink HJ, Rockstroh JK, et al. (2016). HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection*. 44(2):151-8.
- <sup>17</sup> AVAC (2013). *AVAC Report: Research and Reality*. 12. [http://www.avac.org/sites/default/files/resource-files/AVAC%20Report%202013\\_0.pdf](http://www.avac.org/sites/default/files/resource-files/AVAC%20Report%202013_0.pdf)
- <sup>18</sup> Nunn AS, Brinkley-Rubenstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R, Chan PA (2017). Defining the HIV pre-exposure prophylaxis care continuum. *AIDS*. 31(5):731-734.
- <sup>19</sup> Haberer JE, Bangsberg DR, Baeten JM, Curran K, Koechlin F, Amico KR, et al. (2015). Defining success with HIV pre-exposure prophylaxis: A prevention-effective adherence paradigm. *AIDS* 29(11): 1277-1285.
- <sup>20</sup> Seifert SM, Glidden DV, Meditz AL, Castillo-Mancilla JR, Gardner EM, Predhomme JA et al. (2015). Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. *Clin Infect Dis* 60(5): 804-810.
- <sup>21</sup> Wheeler D, Fields S, Nelson L, Wilton L, Watkins P, Hightow-Weidman L, et al. (2016). HPTN 073: PrEP uptake and use by Black men who have sex with men in 3 U.S. cities. Poster. <http://www.croiconference.org/sites/default/files/posters-2016/883LB.pdf>
- <sup>22</sup> Fonner VA, Dalgligh SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM, et al. (2016). Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 30(12):1973-83.