

PrEP: Roadmap to the Real World

Establishing the Real-World Effectiveness of PrEP Through Demonstration Projects

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Introduction

Thirty years into the HIV epidemic in the United States, we are at an important crossroads. Exciting new data have emerged in the last year from several clinical trials demonstrating that pre-exposure prophylaxis (PrEP)—whereby HIV-negative individuals take antiretroviral (ARV) drugs to protect themselves from infection—can significantly reduce the chance of HIV acquisition when offered as part of a comprehensive prevention package (including condoms, risk-reduction counseling, and screening and management of other sexually transmitted infections).

However, worrisome statistics from the U.S. Centers for Disease Control and Prevention (CDC) were also recently reported, showing sharp increases in new HIV infections in African American gay men and other men who have sex with men (G/MSM).¹ These data highlight the urgency of knowing whether and how the efficacy of PrEP in the trials reported so far translates into effectiveness—that is, the ability to reduce new HIV infections in the real world.

Proving real-world effectiveness will require leadership, resources, and the engagement of multiple stakeholders: three key ingredients that have yet to be fully realized. As such, we— the AIDS Foundation of Chicago, AVAC, the Black AIDS Institute, National Minority AIDS Council, Project Inform, and San Francisco AIDS Foundation—are calling on the Department of Health and Human Services (DHHS) to lead an expedited process to clearly outline and commit to a comprehensive plan for implementing PrEP demonstration projects focused on G/MSM. The data suggest that PrEP can be an important HIV prevention strategy for G/MSM and transgender women, who continue to bear the brunt of the HIV epidemic in the United States. We look forward to the further analysis of existing PrEP efficacy data in other populations and to the results ongoing trials, yet we feel it is critical to move *now* to address how to successfully deliver PrEP to G/MSM and transgender women while we await those additional analyses and results.

We urge the DHHS to develop a plan addressing:

- the number and geographic location of projects that will be needed to assess the relevance, feasibility, and potential efficacy of PrEP for different communities of G/MSM and transgender women;
- the questions to be addressed through these projects; and
- the human and financial resources (both governmental and non-governmental) necessary to implement the projects.

At least two demonstration projects targeting G/MSM have been proposed and are under discussion among researchers, program implementers, and funders, but these two projects will not be sufficient to determine how to implement PrEP in diverse communities of G/MSM. Moreover, robust funding of a suite of projects, a critical next step, remains uncertain. It is time for the DHHS and its partner agencies to put into effect a thorough, integrated, and strategic plan for demonstration projects that are fully funded, complementary rather than duplicative, and able to answer critical questions related to the feasibility, desirability, and potential impact of PrEP programs in G/MSM communities across the country.

This document offers a roadmap to stakeholders for critical questions that we feel must be addressed by demonstration projects and the overarching structure and focus of these projects. The report is intended to start a dialogue that must involve all stakeholders—government agencies, pharmaceutical manufacturers, researchers, and especially the community of people living with and affected by HIV.

PrEP's Promise: What the Data Show

Fortunately, most individuals do not become infected with HIV, even in the groups and regions in the United States with the highest HIV prevalence and incidence. Moreover, some existing behavioral interventions are relatively effective at reducing risk behaviors in those who have found it challenging to consistently use condoms. However, the recent CDC data highlight that these existing interventions are not reaching those most in need and creating sustained behavior change.

The iPrEx PrEP study found that daily oral tenofovir (TDF) plus emtricitabine (FTC), combined with standard prevention practices, reduced the risk of infection by 42% overall in G/MSM and the small number of transgender women also enrolled in the trial in several countries. The trial ran to its expected completion date and data were reported in November 2010.ⁱⁱ

Additional data from more recent clinical trials with heterosexual men and women are also quite encouraging. In the Partners PrEP study—reported in July 2011 at the IAS Conference in Rome—the HIV-negative partner in serodiscordant heterosexual couples in Kenya and Uganda received either oral TDF alone, oral TDF/FTC, or a placebo pill, along with the standard prevention package.ⁱⁱⁱ Researchers with the Partners PrEP study reported that, due to significant evidence of benefit, the study's Data Safety Monitoring Board (DSMB) recommended that the placebo arm of the study be discontinued and that placebo participants be offered the chance to enroll in one of the active arms of the study. Both TDF and TDF/FTC (along with standard prevention practices) were able to decrease risk of infection in the HIV-negative partners: TDF reduced risk of infection by approximately 62% overall and TDF/FTC reduced risk of infection by approximately 73% overall.

A second PrEP study reported positive results in July 2011. TDF2, conducted among young heterosexual men and women in Botswana, compared TDF/FTC with a placebo tablet; both study arms also received the standard prevention package. In that study, PrEP reduced the risk of infection by approximately 63% overall.^{iv}

On the other hand, a third study with heterosexual women in several African countries, called FEM-PrEP, was not able to show an effect PrEP versus a placebo, and is being stopped early due to “futility.”^v Analyses of the data are ongoing to help understand this anomalous outcome.

Another study among heterosexual women, called VOICE, is ongoing and is studying oral TDF, oral TDF/FTC, and topical tenofovir gel. There is also an ongoing study of oral TDF among intravenous drug users in Bangkok, Thailand. Both of these studies are expected to conclude in 2012.

Thus far, all of the reported studies have found TDF and TDF/FTC to be well tolerated and relatively safe under the study conditions and for the time period in which the drugs were administered. The studies have also shown that, in the context of a clinical trial, PrEP use has not had a significant adverse effect on safe sex practices and may have helped to improve them. Drug resistance has been an issue only for those few trial participants who initiated PrEP use while already infected with HIV.

Unanswered Questions

We believe that the results of iPrEx, along with the recent CDC incidence data, call for moving ahead immediately with demonstration projects to study the implementation of PrEP primarily for G/MSM and transgender women in the United States. As promising as PrEP may be, significant questions remain unanswered, chief among them being whether the efficacy that was demonstrated within the confines of a clinical trial—where people were not certain whether they were taking drug or placebo, were told that the safety and efficacy of PrEP was unknown, and in which they received extensive monitoring and support—can be translated into effectiveness in practice. Such clinical translation efforts are not unique to PrEP and can be expected with the introduction of any new biomedical advance for any disease. But, in particular, this translation effort is needed now in order to achieve the public health benefit for which PrEP is so promisingly suited—progress in reducing HIV infections as directed by the National HIV/AIDS Strategy.^{vi}

There are other promising prevention options still under investigation, including the potential benefits of scaling up testing and early care and treatment (TLC+) for people found to be HIV-positive, the possibility of both vaginal and rectal microbicides, and development of an AIDS vaccine. It will take significant time and resources to validate and scale up these interventions, even in the United States. Moreover, none of these approaches – nor PrEP – will be sufficient on their own to completely halt new infections; those at risk for HIV need a range of options. It is the comprehensive nature of these multiple options that urges us forward to improve our understanding of the roles this new intervention may play.

We must, therefore, understand as quickly as possible who will benefit most from PrEP, and how best to provide it in an effective, safe, sustainable, and cost-effective manner.

To facilitate and maximize our ability to answer these questions through demonstration projects, it is also important to support the FDA review and potential approval of a prevention indication for TDF/FTC, so that marketing of these drugs for this new prevention use is conducted and monitored in a responsible fashion that complements and serves to support further implementation studies.

Designing the Demonstration Projects

Over and above the key research questions that must be addressed by the demonstration projects, which are detailed below, there is a set of overarching issues that we hope researchers, funders, and other stakeholders take into account:

PrEP Project Participants

As the recent CDC statistics make clear, there are no communities in the United States more urgently in need of effective new prevention options than African American and Latino G/MSM. Moreover, other studies have documented the exceptionally high rates of new HIV infections in transgender females.^{vii} There are also geographic areas that have been particularly hard hit by the epidemic. As such, every effort should be made to ensure that demonstration projects are prioritized in these communities and populations and that the projects are able to document the effects of race, ethnicity, primary language, and health literacy on effectiveness.

Project Venues

Ideally, demonstration projects should evaluate offering PrEP in the types of venues where people most likely to benefit from this intervention are also most likely to obtain sexual health services after a demonstration project concludes. This will be especially critical in regions where an infrastructure for sexual health services is weak or nonexistent, and should take into account the social, language, and practical needs of potential PrEP users. These include publicly funded neighborhood health and sexually transmitted infection (STI) clinics, mobile HIV and/or STI testing services or local community-based organizations (each with links to medical providers), and clinics within hospitals and academic settings. The selection of research sites should emphasize health care service providers that can sustainably continue offering (either solely or through strong partnerships) the full roster of HIV prevention services, including HIV and STI testing and treatment, condom and lube provision, and HIV counseling and behavioral interventions.

Coordination of Data Selection and Collection

It is critical that a single entity is identified that can assure sufficient coordination of PrEP demonstration projects to guarantee that certain core data are collected across all of the projects and that can be compared over time. Also, the leaders of the various demonstration projects should come together regularly to share their experiences and their data.

Community Engagement

International research principles and ethics demand that people who are to be the participants in research should ideally be involved in every step of the research process in some manner. This ensures that the research is ethical and that informed consent is meaningful to a range of participant concerns. It has also been demonstrated in a number of cases to improve the acceptability and conduct of such research. Given the marginalization of many at-risk individuals, the lack of culturally competent health services, and the stigma attached to seeking out HIV testing and care, it will be critical that members of those communities targeted for a PrEP intervention are consulted at every step of the process as laid out in the Good Participatory Practice Guidelines published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and AVAC.^{viii}

Resource Allocation

PrEP is emerging at a time of great economic hardship in the United States. HIV prevention budgets have been slashed at both state and federal levels, and there are currently more than 9,000 HIV-positive people on waiting lists for ARV medications covered by ADAP. As such, conversations must commence *now*, while the demonstration projects are in their formative stages, about how PrEP will fit into the overall package of prevention methods that we strive to make available to at-risk individuals and to HIV-positive individuals. Though the future of the Affordable Care Act is also uncertain, policy analysis should begin now to determine how the implementation of health care reform might alter the HIV prevention landscape, specifically in regards to PrEP.

What's more, we fully support the goal of the National HIV/AIDS Strategy to bring equitable care and treatment to all people living with HIV as well as prevention services to those who are at risk of becoming HIV infected. Some have begun to express concern that resources allocated for PrEP will potentially diminish those available to ensure access to treatment for all who chose it. We believe, however, that with sufficient advocacy on the part of the community and the support of all stakeholders, we can accomplish both treatment and prevention in the United States at levels sufficient to eventually end the epidemic.

Key Questions

As the issues above are addressed, preferably through a consultative process that involves all relevant stakeholders, we need to turn ourselves to the specific questions that must be addressed by the demonstration projects. Although the list is long and possibly complex, it is not unusual in bringing new biomedical advances forward to consider such issues and answer them in clinical settings. These questions include:

1. What are the best criteria for defining the populations most appropriate for a PrEP intervention, and what outreach and recruitment strategies are most effective in reaching them?

Given the devastating impact HIV/AIDS has had on G/MSM and transgender communities, the first demonstration projects in the United States should focus on G/MSM and transgender women who have sex with men. There remains variation in HIV incidence and prevalence by race, ethnicity, gender identity, and geography. Therefore, it may be necessary to define and assess risk differently within different demonstration projects. For instance, a history of unprotected receptive anal intercourse might be sufficient to designate some individuals as appropriate for PrEP outreach efforts, while in others this history might need to be accompanied by a documented lack of success with other behavioral interventions.

Given these differences in how risk is defined, and in how much various groups know about and accept PrEP, a variety of outreach and recruitment strategies will likely be desirable. Demonstration projects should attempt to capture these differences in risk definition, population targeting, and level of community knowledge about and acceptance of PrEP in their determination of the success of outreach and recruitment methods.

2. What characteristics at the individual and population level—such as race/ethnicity and culture—define who might need additional support for initiating and maintaining PrEP use? What additional strategies might help to support adherence and risk-reduction for these groups?

Data from iPrEx and other PrEP studies suggest that social and behavioral factors (e.g., alcohol use) might influence the success or failure of PrEP.^{ix} Previous studies of other types of interventions have demonstrated that these factors are also strongly associated with differences in risk perception,^x attitudes toward health care providers^{xi} and antiretroviral therapy, medication adherence (in people living with HIV),^{xii} and retention in HIV care. What's more, structural issues (e.g. poverty) and issues related to individual resilience may influence adherence. It will, therefore, be ideal for researchers to measure these factors within demonstration projects, in order to inform the design and implementation of procedures that will encourage individuals at highest HIV risk to take PrEP and to maximize their adherence and risk reduction, while managing drug side effects.

3. What are the optimal health care settings for PrEP delivery to reach those most at risk of HIV infection, and what are the common and unique operational challenges that vary across practice settings?

A number of factors have resulted in great variation in how HIV testing and prevention services are provided across regions of the United States. Moreover, linkages between HIV prevention providers, STI testing and treatment facilities, and HIV treatment providers add even greater variation and complexity. As such, it would be ideal for demonstration projects to be able to determine how well PrEP provision can be offered effectively and sustainably across different types of service providers, organizations, and provider networks.

Additionally, data should be sought, both within and outside the projects, through surveys and focus groups on the attitudes toward PrEP among the providers most likely to dispense it, their knowledge of PrEP and HIV prevention in general, their comfort in conducting risk-reduction assessments and frequent monitoring, their professional practice concerns, their ability to integrate this care into operations and payment systems and their capacity for providing support for adherence.

4. What is the optimal PrEP package—including, for example, screening, assessment of readiness to begin PrEP, STI testing, acceptable frequency of visits for follow-up testing, adherence support, clinical monitoring, and counseling—and which intervention packages are most likely to lead targeted individuals to increase condom use and other risk-reduction strategies over time?

Though the screening and follow-up procedures in iPrEx, Partners PrEP, and TDF2—along with the package of prevention services and adherence support offered—resulted in a substantial reduction in new HIV infections, it is not yet clear whether these methods are either sustainable or ideal for every health care system or individual participant. Variations in implementation of PrEP and supportive services—especially those which seek to reduce costs without sacrificing safety or efficacy—may be desirable.

Also, in all of the trials conducted thus far, self-reported condom use actually increased in study participants. This is an encouraging finding and lends weight to the argument that PrEP could be a short- or medium-term intervention that allows individuals a “bridge” to new

risk-reduction behaviors and to address structural barriers to sexual health. It will therefore be ideal to determine, to the degree possible, which prevention packages and health care settings are most likely to lead PrEP users to more rapidly adopt other risk-reduction strategies.

5. What is the longer-term safety and tolerability of TDF/FTC when used for PrEP, and what is the likelihood of a person developing drug resistance to either or both drugs should they become infected while taking PrEP?

Though data on long-term use of TDF/FTC are available for people living with HIV, little is known about their long-term safety of using these drugs in HIV-negative individuals, beyond that observed in the iPrEx trial, which has safety data collected over the longest period of time. So far the data are encouraging that the balance of safety and efficacy in HIV-negative individuals can be managed and monitored to produce a desirable benefit in the time period when use of oral PrEP is most needed. However, while there have been no documented cases of drug resistance in people who became infected after starting PrEP, this could occur. Demonstration projects should prioritize safety, tolerability, and the assessment of drug resistance. They should also document the ability, in real-world settings, of providers to handle issues of safety and tolerability when they arise and to link individuals to appropriate care.

6. What are the optimal methods for predicting, measuring, and supporting adherence and engagement with care providers?

Although self-reported adherence was moderately predictive of efficacy in iPrEx, there was a substantial difference between stated and actual adherence as determined by the subgroup in which researchers monitored TDF and FTC blood levels.^{xiii} While it will not likely be cost-effective or practical to conduct blood level monitoring in real-world settings, it will be critical to utilize this method within the demonstration projects to verify which adherence support measures appear to be most successful for a given population and health care setting. Efforts should also be made to test adherence support methods—including e-health strategies and other new technologies—that are designed with both social and behavioral risk factors in mind.

Additionally, it will be helpful to validate less costly and invasive adherence validation procedures, such as testing TDF in hair samples.^{xiv} According to an unpublished analysis by iPrEx researchers, one explanation for non-adherence in some participants may have been lack of sexual activity. In other cases, reasons for non-adherence were unclear. Therefore, demonstration projects should seek to understand the multiple reasons for non-adherence (both intermittent adherence problems and decisions to stop taking PrEP altogether).

7. What is the likelihood of risk compensation (the possible increase in sexual risk behavior due to perceived protection conferred by PrEP) across social and behavioral characteristics, and which practices best counter risk compensation?

There have been no signs from the clinical trials that receiving PrEP led people to increase their HIV risk behaviors (sometimes referred to as “risk compensation”). In fact, participants in each study actually increased their condom use within the study period. In iPrEx, participants also reduced their number of sex partners. Since these findings are in the context of placebo-controlled trials, we don’t yet know how people will use PrEP when they:

a) know they are getting an active drug; and b) know its degree of efficacy as determined by clinical trials. For these reasons, surveys should be conducted to determine sexual behavior and perceptions of risk prior to initiating PrEP and during its use.

8. What is the total cost of delivering PrEP in various settings, and which strategies for PrEP delivery appear to be comparatively effective in terms of success in recruitment, participant adherence, HIV/STD screening, retention in care, and minimization of risk compensation?

Given that efficacy cannot be measured within the demonstration projects (there will be no placebo against which to measure the drug's efficacy), true cost-effectiveness can't be determined. It should be possible, however, to determine which PrEP-delivery strategies offer the best responses for the variables listed above (e.g. initial uptake, adherence, retention in care, risk compensation, etc.) at the lowest cost.

9. Which types of providers or programs are most likely to ensure linkage to HIV care for those found to be HIV-positive during screening and those who seroconvert during PrEP use?

Though the demonstration projects will not all necessarily be designed to look at linkage to care for participants found to be HIV positive, many in the field do envision PrEP falling well within a greater, comprehensive TLC+ effort. For this reason, it will be desirable to determine whether a participant who tests positive during a demonstration project (at screening or during care) is successfully linked to a health care provider for HIV care. It will also be ideal to determine how effectively PrEP provision can be added to TLC+ programs that are underway or planned.

Conclusion

The past year has been a remarkable turning point in HIV prevention and treatment. Until recently, our only tools to guard people against HIV infection have been behavioral interventions, condoms for those who choose to be sexually active, and aggressive HIV testing campaigns. Now, we are on the threshold of a potential revolution. While optimistic, it is certainly no longer impossible to dream that HIV transmission could be all but eliminated in certain communities if we are able to marshal the resources and the knowledge to use every available tool, both old and new, including PrEP, TLC+, and hopefully—one day—vaginal and rectal microbicides and a vaccine.

To get there, however, we must be smart, especially in a time of limited resources. One of the best ways to ensure that we apply PrEP in the safest, most effective, and most cost efficient manner is to study its real-world implementation carefully. That's why the demonstration projects described here are so critical. What a squandered opportunity it would be if we failed to determine how best to use this promising tool and how best to combine it with other available prevention efforts.

Ensuring that these demonstration projects are designed, funded, and implemented as they ought to be will require the support and engagement of every stakeholder. We hope that this report will stand as a call to action and spur productive dialogue to bring us one step closer to a world without HIV.

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