



CDC TRIALS:

Pre-Exposure Prophylaxis for HIV Prevention

PrEP: A New Approach to HIV Prevention

New tools to prevent HIV are urgently needed to stem the estimated 2.6 million new HIV infections that occur worldwide each year. Recent research has shown that a new approach called pre-exposure prophylaxis, or PrEP, can reduce the risk of contracting HIV in gay and bisexual men at high risk of infection, when combined with existing prevention measures. Ongoing studies are evaluating this approach in other populations at risk for HIV, including heterosexuals and injection drug users.

In this new approach to HIV prevention, people who are uninfected take an HIV treatment pill daily to reduce their risk of becoming infected. By inhibiting HIV from replicating as it enters the body, PrEP can prevent the virus from establishing permanent infection. The concept of providing a preventative treatment before exposure to an infectious agent is not new. For example, when individuals travel to an area where malaria is common, they are advised to take malaria treatment medication before and during travel to prevent illness.

As part of its commitment to developing new HIV prevention strategies, the Centers for Disease Control and Prevention has sponsored several clinical trials to evaluate the safety and efficacy of PrEP for HIV prevention.

PrEP Medications

Current PrEP trials, including those sponsored by CDC, are testing the antiretroviral drug tenofovir disoproxil fumarate (or tenofovir, brand name Viread®) used alone or in combination with emtricitabine (together, known as the brand name Truvada®) taken as a preventative drug.

Tenofovir was approved by the U.S. Food and Drug Administration in 2001 as a treatment for HIV infection, and the tenofovir plus emtricitabine combination pill was approved for use as an HIV treatment in 2004. Data from Gilead Sciences, Inc., the manufacturer of the drugs, indicate that more than one million HIV-infected people around the world have now used these drugs. As treatments for HIV-infected individuals, tenofovir and tenofovir plus emtricitabine have been shown to be both safe and effective. They have relatively low levels of side effects and slow development of associated drug resistance, compared with other available HIV treatments.

Characteristics of Current PrEP Candidates

- Established safety as HIV treatments
- Potent antiretrovirals
- Long duration of action
- Once-daily dosing
- Low levels of resistance

PrEP Proven Safe and Effective in Gay and Bisexual Men

In a major advance in HIV prevention research, investigators recently reported that PrEP is safe and effective in preventing HIV infection — when combined with other comprehensive prevention approaches — among men who have sex with men who are at high risk of HIV infection.



iPrEx Study

In November 2010, the National Institutes of Health (NIH) announced results from a multinational, randomized, double-blind, placebo-controlled, phase III clinical trial of tenofovir plus emtricitabine to prevent HIV infection.

The iPrEX trial showed that a once-daily pill containing tenofovir plus emtricitabine was safe and provided an average of 44 percent additional protection against HIV infection to men who have sex with men and transgendered women who have sex with men, who also received a comprehensive package of prevention services. These services included use of condoms, monthly HIV testing, counseling to reduce risk behavior and encourage adherence to the daily pill regimen, and management of other sexually transmitted infections.

The level of protection shown varied widely depending on how consistently participants used PrEP. Among those whose data (based on self-reports, bottles dispensed, and pill counts) indicate use on 90 percent or more days, HIV risk was reduced by roughly 73 percent, while among those whose adherence by the same measure was less than 90 percent, HIV risk was reduced by only about 21 percent.

CDC U.S. Tenofovir Extended Safety Trial

In July 2010, CDC reported results of a Phase II extended safety trial examining the clinical and behavioral safety of once-daily oral PrEP with tenofovir and adherence to the drug among gay and bisexual men in the United States.

The study was conducted at three sites in collaboration with the San Francisco Department of Public Health, the AIDS Research Consortium of Atlanta, and Fenway Community Health in Boston. The study enrolled 400 HIV-negative MSM who reported having had anal intercourse with a man in the prior 12 months. Participants were randomly assigned to one of four study arms. Two arms received either tenofovir or placebo immediately upon enrollment, while the other two arms received either tenofovir or placebo after nine months of enrollment. This design allowed researchers to compare risk behaviors among those taking a daily pill and those not taking pills.

Preliminary analyses suggest no serious safety concerns. While analysis of behavioral safety data are not yet complete, preliminary analyses suggest there was no increased risk in men taking a study pill compared to those not taking a study pill during their first nine months of study participation. Additional analyses of clinical, behavioral, and adherence data are underway.

CDC-Sponsored PrEP Trials—Botswana and Thailand

CDC is sponsoring additional clinical trials that are designed to answer important questions about the safety and efficacy of a tenofovir or tenofovir plus emtricitabine pill taken as a daily oral HIV preventative among populations at high risk for infection — heterosexuals in Botswana and injection drug users in Thailand. Both trials are assessing the effects of taking a daily pill on HIV risk behaviors, adherence to and acceptability of the regimen, and in cases where participants become HIV-infected, the resistance characteristics of the acquired virus. Importantly, the trial in Thailand will also examine the efficacy of PrEP in preventing HIV infection among injection drug users.

CDC Study	Botswana	Thailand
Objective	Evaluate clinical and behavioral safety of and adherence to PrEP regimen among heterosexuals	Evaluate PrEP safety and efficacy among intravenous drug users (IDUs)
Drug	Tenofovir plus emtricitabine	Tenofovir
Participants	1,200 HIV-negative heterosexual men and women in urban areas	2,400 HIV-negative IDUs at 17 drug treatment clinics in Bangkok
Results Anticipated	Mid-2011	Early 2012



Trial Design and Procedures

Both of CDC's current PrEP studies are randomized, double-blind, placebo-controlled trials. All participants receive risk-reduction counseling and other prevention services. Half of the participants are randomly assigned to receive one antiretroviral pill daily (either tenofovir or tenofovir plus emtricitabine, depending on the trial), and the other half are randomly assigned to take one placebo pill daily (a similar tablet without active medication). Neither researchers nor participants know an individual's group assignment. In all, the studies involve approximately 3,600 volunteers.

To make sure that participants fully understand all aspects of their participation, all volunteers are required to pass a comprehension test prior to providing written informed consent. Study participants are also free to withdraw from the trials at any time and for any reason.

To assist participants in eliminating or reducing HIV risk behaviors, extensive counseling is provided at each study visit, and more often if needed. This interactive counseling has proven effective in reducing the risk of HIV and other STDs in multiple populations, including past participants in similar HIV prevention trials. Participants are also offered free condoms and STD testing and treatment to reduce their risk for HIV infection. The health of participants is closely monitored throughout each trial, and participants are linked to any necessary medical care.

To ensure that the studies remain on a solid scientific and ethical foundation, all study procedures and plans have been reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs), as well as IRBs established by each host country and research site prior to trial launch. Additionally, data on safety, enrollment, and efficacy are reviewed regularly by an independent data safety and monitoring board (DSMB) for each trial. The boards review emerging data to ensure that continuing the trial is safe and to determine the point at which the results are conclusive. If scientific questions arise during the course of the research, the boards meet more frequently. CDC has worked closely with community partners at each research site to ensure active community participation throughout the course of the trial.

If the efficacy trial in Thailand proves that tenofovir is effective as PrEP for injection drug users, participants in that trial and their community will be the first to benefit. All trial participants will receive tenofovir for at least one year after efficacy is proven while CDC works with the Thai Food and Drug Administration for approval of use by the Thai health care system. CDC is also prepared to provide technical assistance and support to its international partners in designing PrEP implementation plans in those countries where CDC-sponsored trials are being conducted.

Other Ongoing PrEP Trials

CDC Participation in Partners PrEP Study

The University of Washington is working with collaborators in Kenya and Uganda to conduct the Partners PrEP Study, which is examining the safety and efficacy of two different PrEP regimens — once-daily tenofovir and once-daily tenofovir plus emtricitabine — among heterosexual couples. CDC co-manages two trial sites in Uganda, in conjunction with The AIDS Support Organization (TASO), the largest indigenous non-governmental organization providing HIV care in Uganda.

This randomized, double-blind, placebo-controlled study operates at nine trial sites in Kenya and Uganda and will include 3,900 serodiscordant couples (couples in which one person is HIV-infected and the other is not). Stable serodiscordant couples are the largest risk group for HIV infection in Africa, and this trial will provide important data on whether PrEP could be used to prevent new HIV infections among this population. HIV-uninfected partners are assigned to one of three groups: tenofovir, tenofovir plus emtricitabine, or placebo. All participants receive ongoing risk reduction counseling and HIV testing, and their safety is monitored by the study's DSMB and local IRBs. HIV-infected members of the discordant couples receive ongoing HIV care.



The trial is the first to test the safety and efficacy of both tenofovir and tenofovir plus emtricitabine in the same population and will allow investigators to simultaneously evaluate the two drugs as candidates for use as PrEP.

Other PrEP Studies

Several other PrEP trials are being conducted by other sponsors. For detailed information on the full range of PrEP trials underway, visit www.avac.org.

PrEP Implementation Planning in the U.S.

The positive results from the iPrEx study have immediate implications for HIV prevention among gay and bisexual men the U.S., since tenofovir plus emtricitabine pills are already FDA-approved and available with a prescription for the treatment of HIV infection. As the agency responsible for protecting public health, CDC is pursuing two primary goals in the wake of the iPrEx trial findings: developing guidance on the safe and effective use of PrEP among MSM, and determining how to most effectively use PrEP in combination with other prevention strategies to reduce new infections among MSM in the U.S.

When the iPrEx results were announced, CDC immediately provided initial cautions for anyone considering using PrEP, followed by more detailed interim clinical guidance for physicians electing to provide PrEP for HIV prevention among high-risk gay and bisexual men. For details, see CDC resources (available at <http://www.cdc.gov/hiv/prep>).

- “Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States”
- “Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men”

The next step is developing formal U.S. Public Health Service guidelines for PrEP, which CDC will lead in collaboration with other federal health agencies. The guidelines will be based on a full review of trial data and other research, and will incorporate input from providers, HIV prevention partners, and affected communities. The guidelines will help ensure both physicians and MSM considering PrEP have accurate information to guide decisions.

In addition to developing public health guidelines, CDC will be implementing a range of activities to promote the effective and strategic use of PrEP in the U.S., such as adapting national HIV surveillance systems to help evaluate the use and impact of PrEP, developing updated risk reduction messages for MSM that address PrEP and other proven HIV prevention strategies, and examining the costs, impact, and cost-effectiveness of PrEP compared to and in combination with other interventions.

CDC has also identified other activities that could help address remaining research questions and is currently exploring all avenues to identify resources to support them. Key among these is the need for demonstration projects in clinics serving MSM to assess feasibility, acceptability, and the impact of PrEP in real-world settings.

As results from PrEP efficacy trials among injection drug users and heterosexuals become available, CDC will evaluate the study findings and determine appropriate next steps for PrEP implementation among those populations.