# Anticipating the Results of PrEP Trials

*A powerful new HIV prevention tool may be on the horizon. Are we prepared?*

A publication from AVAC's *Anticipating and Understanding Results* series
August 2008

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AIDS Vaccine Advocacy Coalition

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*A powerful new HIV prevention tool may be on the horizon. Are we prepared?*

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*This report provides background on pre-exposure prophylaxis (PrEP) research, the status of current clinical trials, and issues concerning effective delivery should PrEP prove effective. It closes with a list of priority issues that need attention now from governments, global health institutions, donors, researchers, and advocates. This report is part of AVAC's "Anticipating and Understanding Results" series, which provides timely analysis of trials of new HIV prevention options. For other publications in this series, visit www.avac.org.*

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## A pill to prevent HIV?

Over the past two years, HIV prevention advocates have witnessed a series of disappointing results from clinical trials evaluating experimental biomedical approaches (vaccines, microbicides, cervical barrier methods and herpes treatment, for example) meant to reduce the risk of HIV acquisition. In spite of these disappointments, the search for new prevention interventions continues. These include novel biomedical approaches such as next-generation microbicides and vaccines as well as **pre-exposure prophylaxis, or PrEP**. Even though the results from initial PrEP trials are still a year or more away, it's time to start preparing for the news.

PrEP clinical trials are currently planned or underway in countries in Africa, Asia, Latin America and North America. These studies are looking at the safety and efficacy of PrEP, an unproven strategy in which HIV-negative people could take an antiretroviral drug (ARV), or a combination of ARVs, on a regular basis, in the hopes of reducing their risk of acquiring HIV.

Oral PrEP is one way that ARVs are being tested for use in HIV prevention. There are also studies underway looking at ARV-containing microbicides (applied topically to the vagina or rectum). One study, the VOICE trial in southern Africa, is testing both oral and vaginal delivery of ARVs to prevent HIV infection. While this document focuses on oral PrEP, there is broad attention to ARV-based prevention overall and it is useful to remember the multiple ways that this strategy is being investigated. When it comes to oral PrEP, clinical trials are now testing the drugs tenofovir (TDF) and a

combination of TDF and emtricitabine (FTC)—for use as PrEP.

It is important that communities and advocates weigh in on PrEP research: by the middle of 2009, more people will be enrolling in PrEP trials than in all HIV vaccine and microbicide efficacy trials combined.

*No one knows whether PrEP will work. Even if it does, it will need to be used in combination with current HIV prevention methods, including safer sex practices, use of male and female condoms, treatment of sexually transmitted infections, risk reduction counseling, clean needles, and male circumcision. PrEP will not be a silver bullet and will not replace any of these current strategies.*

*It is time for PrEP to be placed high on the AIDS advocacy and global health agendas.*

The evidence to date provides a strong rationale for exploring PrEP as a potential new tool for reducing the risk of HIV infection. The good news is that current trials can help determine whether PrEP is safe and effective. But we cannot sit back and wait for these answers—there is work to be done now.

***It is time for PrEP to be placed high on the AIDS advocacy and global health agendas.*** Public health leaders, advocates, policy makers and the diverse array of communities impacted by HIV/AIDS need to be better prepared for the results of PrEP trials than they are today.

This means supporting high-quality, accelerated research on PrEP ***and*** preparing for whatever results may come from PrEP trials, as soon as 2009.

## The Key Points

- PrEP is a potential new HIV prevention intervention that could have an important impact on HIV prevention globally.
- The ARV drugs tenofovir (TDF) and a combination of TDF and emtricitabine (FTC) are currently being tested in clinical trials for use as PrEP.
- Clinical research is taking longer than originally anticipated, but initial results from current PrEP efficacy trials may become available beginning as early as 2009.
- Current PrEP trials will leave important questions unanswered, requiring additional research.
- PrEP research is currently underfunded and deserves additional and sustained financial support.
- PrEP should be placed high on the AIDS advocacy and global health agendas. Action is needed now to:
    - o ensure current clinical trials have the best chance of producing decisive results
    - o identify and invest in additional research that is needed
    - o plan for optimal use of PrEP
    - o prepare for delivery of PrEP globally
    - o provide adequate funding for PrEP research.

## Why might PrEP work?

There is a good deal of excitement in the research community about the potential of PrEP. Scientists point to several examples from other areas of HIV treatment and prevention as reasons to think that taking ARVs may help protect HIV-negative people from HIV infection:

- Giving ARVs to pregnant mothers during labor and delivery, and to their newborn babies, both after delivery and during breastfeeding, has been shown to significantly reduce the likelihood of mother-to-child transmission of HIV.
- Though not definitive, studies of post-exposure prophylaxis (PEP) indicate that giving health care workers ARVs soon *after* occupational exposure to HIV may reduce the likelihood of infection.
- Studies done in non-human primates have found that pre-treatment with the ARVs TDF and TDF/FTC significantly reduces risk of infection by HIV-like viruses. These animal studies (done in a relatively small number of animals) have a number of limitations, but they do support the rationale for evaluating PrEP in humans.

While these points give reason for hope, it is entirely possible that drugs being tested now and in the future will not be found safe and effective for use as PrEP.

If PrEP is shown to be safe and efficacious, it could be a useful tool to add to current prevention approaches.

One of the advantages of PrEP is that an individual could potentially use it without negotiation with his or her partner, so individuals who are unable to insist on condom use with their sex partners would still be able to increase their protection against HIV.

### Managing Expectations

The history of AIDS research is teeming with claims that a cure, vaccine, microbicide, or other needed scientific advance is just around the corner. It is possible that PrEP is just the latest false hope in an epidemic that continues to claim millions of lives a year.

We have to balance a sense of *urgency* about advancing PrEP research and preparing for PrEP delivery with a strong dose of *caution*, recognizing the very real possibility that PrEP will not work, will not work as well as some researchers hope, will not work for all who need new prevention options, or will turn out not to be completely safe.

*The world needs PrEP as soon as possible, but PrEP delivery would need to happen in the context of thoughtfully planned programs and clear safety and efficacy data from large-scale trials.*

## What might be the impact of PrEP?

Without data from trials, it's impossible to estimate what impact PrEP might have on HIV incidence rates. That will depend on the real-world effectiveness of PrEP (what level of risk reduction it provides), who gets access to PrEP, how long they use it, and whether people put themselves at increased risk of exposure to HIV because PrEP makes them feel protected.

While we have no definitive answers to any of these variables, a mathematical model published in 2007[i] predicted that in sub-Saharan Africa millions of HIV infections could be averted over a 10-year period if PrEP proves highly efficacious, is delivered to those at highest risk of HIV, and is used over an extended period.

PrEP involves a prescription drug, so it's likely that initial programs will be clinic-based. PrEP delivery would also require periodic HIV testing. In contrast to male circumcision—or hopefully one day, a vaccine—PrEP would require that people take a drug on an ongoing basis (daily or intermittently). Interest in PrEP could bring more individuals into the health clinic, where they would have access to HIV testing and other services, regardless of whether they chose to use PrEP.

# Why are TDF and TDF/FTC the first candidates for PrEP?

TDF (*tenofovir disoproxil fumarate*) and TDF/FTC (*tenofovir disoproxil fumarate* and *emtricitabine*) are in the nucleoside reverse transcriptase inhibitor (NRTI) class of drugs, and both are used in the treatment of HIV disease. They work by making it more difficult for HIV to replicate in the body, by interfering with an enzyme (reverse transcriptase) that the virus needs to reproduce itself. TDF was approved by the US Food and Drug Administration for use in HIV treatment in 2001, and the TDF/FTC combination was approved in 2004. TDF is marketed under the name *Viread*, and TDF/FTC is marketed under the name *Truvada*. *Truvada* and *Viread* are made by Gilead Sciences, Inc., based in Foster City, California, US. Generic versions of these drugs are being made by Indian drug manufacturers like Cipla and Matrix, and, at the time of this writing, Brazil was exploring manufacturing its own version of these drugs for treatment of HIV.

TDF and TDF/FTC have several characteristics that make them attractive for use in PrEP, including limited side effects and a strong safety profile among HIV-positive people, relatively long duration of action in the body, and less likelihood of promoting drug resistance than many other ARVs. The drugs are taken once daily and do not need to be taken with food, making them convenient for extended use.

## *Safety issues*

Because TDF and TDF/FTC have been used as treatment for people with HIV, a considerable amount of data exists from "real world" use and from clinical trials about the safety of these medications. Among HIV-positive people taking these drugs in combination with other treatments, side effects have been relatively rare. In those who do report side effects, nausea, diarrhea, vomiting and intestinal gas are the most common complaints.

As of August 2008, the most robust data on PrEP comes from a randomized controlled trial conducted by Family Health International (FHI) with African collaborators in three countries: Nigeria, Ghana and Cameroon. The Nigerian and Cameroonian sites did not complete the trial as planned (see our previous report, Will a Pill Day Prevent HIV? at http://www.avac.org/pdf/Pill_A_Day_Mar05.pdf), yet each site did contribute partial data.

Evidence from 859 women volunteers contributing information at these sites found no increase in safety problems or adverse events among participants who received TDF daily as compared with those who received placebo.[ii]

There is some evidence that TDF may affect liver or kidney function in people with HIV, or result in a small decrease in bone density in some patients. TDF and TDF/FTC have some antiviral activity against the hepatitis B virus. It is possible that there might be specific issues for people with undiagnosed or untreated hepatitis B who stop using PrEP for HIV prevention. While people are taking PrEP, it might help control hepatitis B. When they stop, symptoms could flare. The only data on this issue come from 22 participants in the trial noted above.[iii] Although there was no evidence of flaring in this group, more information will be needed including longer-term follow up in an expanded number of people.

If PrEP trials do show effectiveness, it will be critical to continue gathering additional data on safety and side effects as PrEP is used in larger and more diverse groups of people for periods longer than in clinical trials.

Looking at the sample of women who were enrolled at the three sites, it is not possible to make assessments about efficacy. Eight HIV infections occurred in the study: two in women taking PrEP and six in women taking placebo. (The study was double-blinded, meaning that neither the women nor the study staff knew who was receiving the experimental drug and who was receiving an empty pill, or placebo.) This difference between the two arms is not statistically significant and cannot be used as an argument that PrEP is effective.

The data available to date do tell us that further studies are warranted — and urgently needed.

## What are some of the concerns about PrEP?

### *Drug resistance*

What if PrEP fails to protect someone from HIV infection and she continues taking the drug for months before she gets an HIV test and learns she is HIV-positive? Between the time she is infected and the time she stops PrEP she would, in effect, be taking one or two drugs as treatment for HIV infection. Effective treatment for HIV involves three or more drugs in combination. Using one or two drugs is less effective. When HIV replicates in a person who is not on effective therapy, drug resistance can emerge. The drugs themselves do not *cause* the resistance: the virus copies itself and makes small, accidental mutations in its genetic code. Some of these accidental mutations improve the virus's ability to copy itself in the presence of one or two drugs. If the drug is present, these mutated, drug-resistant strains will copy themselves more efficiently, and will become more common in the blood stream. This is drug-resistant virus.

It is possible that if someone were taking PrEP and became HIV-infected and then continued taking PrEP for some time, he or she could develop HIV that is resistant to TDF and/or FTC. Although there would still be other drugs that the person could take, in triple combination, that would be effective treatment for the virus, this antiretroviral resistance may limit a person's treatment options. It is also possible that someone could transmit a drug resistant virus to someone else.

### *Partial effectiveness: a potentially challenging concept*

PrEP is not expected to provide 100 percent protection against HIV. It could reduce the risk of acquiring HIV, but condom use and other strategies would still be important to minimize risk of infection. For that reason, PrEP delivery will create challenges for public health agencies and community educators: they will need to inform people about the protective benefits of PrEP while stressing that no one taking the regimen should assume it provides full protection. In addition, it will be crucial to ensure access to HIV testing to minimize delay in identifying new infections among those taking PrEP.

### *Riskier behavior?*

There are concerns about how humans will behave if handed a bottle of pills that, along with condoms and/or clean syringes, may offer partial protection from HIV infection. Some behavioral research suggests that the advent of combination therapy for HIV disease led to increased HIV infection rates in the US as some people at elevated risk of infection became less concerned about HIV and less vigilant about protecting themselves. The same kind of "risk compensation" could also be a factor in use of PrEP. If PrEP proves partially effective and the people using it significantly increase their rates of risk behavior, then people could actually be putting themselves at *increased* risk of infection, since PrEP—like any other strategy—will not offer complete protection. Some people might refuse to use condoms if they learn their sexual partner is taking PrEP and is thus theoretically "protected" from HIV.

In the FHI study noted earlier, there did not seem to be increased risk-taking behavior among trial participants. Trial participants, who were provided with prevention counseling and condoms, reported that the number of their sex partners in the previous 30 days fell between enrollment screening and follow-up visits during the trial. In addition, self-reported condom use by trial participants increased between screening and follow-up. Of course, how people behave in a clinical trial may be very different from how they behave ordinarily. The behavioral data, as with most other HIV prevention studies, rely on self-reports of trial participants, some of whom may have told study staff what they thought the staff wanted to hear. *We cannot extrapolate from the FHI study data to know how people would react if PrEP were shown effective and distributed widely as protection against HIV.*

### *Social stigma*

Individuals using PrEP drugs might be subject to stigma and discrimination because others might assume that everyone taking PrEP is a member of a group at elevated risk for HIV infection. On the other hand, it is possible that PrEP might actually destigmatize HIV in some settings by highlighting that the disease comes from a viral infection rather than some moral failing.

## What is the status of PrEP research?

Seven PrEP trials are currently underway or in the planning stages. Taken together, these trials are designed to produce results in diverse populations—representing multiple routes of HIV transmission—including:

- injection drug users (IDUs) in a trial in Thailand
- gay men and other men who have sex with men (MSM) in trials in Brazil, Ecuador, Peru, Thailand, and the United States
- heterosexual men and women in a trial in Botswana
- sero-discordant heterosexual couples in a trial in Kenya and Uganda
- women (considered "high risk" or "sexually active" depending on the study) in trials in eastern and southern Africa

In addition, the NIH-funded Adolescent Trials Network in the US is now in the planning stages for a PrEP preparedness trial that will inform design of a possible future effectiveness and acceptability trial of PrEP in young gay men and other MSM.

If completed successfully, these trials will produce a wealth of information that would allow public health officials to make informed decisions about whether and how to use PrEP. But PrEP research is taking longer than expected. When AVAC published its first PrEP report in 2005, initial results from some of these studies were due in 2007 and 2008.

Now that there is a growing PrEP trial portfolio, it's imperative that these trials be well-resourced and keep to their proposed timelines. In order to prepare this document, AVAC conducted interviews with a number of scientists and funders working in PrEP. Many emphasized that sufficient resources for trial volunteer recruitment

### Ongoing and Planned PrEP Trials as of August 2008

| Location | Sponsor/ Funder | Population (mode of exposure) | Intervention arms | PrEP strategy(ies) being tested | Status / Expected completion |
|---|---|---|---|---|---|
| United States | CDC | 400 gay men and other men who have sex with men (penile/rectal) | 1 | TDF | Fully enrolled – Ongoing / 2009 |
| Thailand | CDC | 2,400 injecting drug users (parenteral) | 1 | TDF | Enrolling / 2009 |
| Botswana | CDC | 1,200 heterosexual men and women penile and vaginal) | 1 | TDF/FTC (switched from TDF Q1 2007) | Enrolling / 2010 |
| Brazil, Ecuador, Peru, US, additional sites TBD (iPrEX Study) | NIH, BMGF | 3,000 gay men and other men who have sex with men (penile/rectal) | 1 | TDF/FTC | Enrolling / 2010 |
| Kenya, Uganda (Partners PrEP Study) | BMGF | 3,900 serodiscordant heterosexual couples (penile and vaginal) | 2 | TDF; TDF/FTC | Enrolling / 2012 |
| Kenya, Malawi, South Africa, Tanzania (FEMPrEP) | FHI, USAID | 3,900 high-risk women (vaginal) | 1 | TDF/FTC | Planning / 2012 Anticipated start Q3/2008 |
| Southern Africa; specific sites TBD (VOICE Study) | MTN, NIH | 4,200 sexually active women (vaginal) | 3 | TDF; TDF/FTC; TDF gel | Planning / 2012 Anticipated start Q1/2009 |

BMGF – Bill & Melinda Gates Foundation; CDC – US Centers for Disease Control; FHI – Family Health International; MTN – Microbicide Trials Network; NIH – US National Institutes of Health; USAID – United States Agency for International Development

and retention must be directed to the current studies to ensure that they are able to enroll at-risk populations in a timely manner, and generate clear answers to the study questions. Even after they have started, trials may often add sites, or expand their participant pool in order to meet trial goals. Such adjustments could be needed in the context of current PrEP trials, and *there should be full funding available for these and other activities*.

Ask researchers why PrEP clinical studies are taking longer than anticipated to launch, enroll, and complete, and you'll hear a variety of explanations. Some have faced challenges dealing with national Ministries of Health and local regulatory bodies. Researchers have set a high bar for determining the safety of PrEP drugs in HIV-negative people, and that essential caution requires substantial time spent gathering and analyzing data. And there are other challenges experienced in all HIV prevention research, including PrEP studies:

- *Longer than anticipated time to fully enroll studies:* Several trials are seeing enrollment take longer than expected. There could be many reasons, including that many HIV-negative people may not think of themselves as eligible for HIV-related research, or may not be highly motivated to participate in a study in which they have to take a pill every day.

- *Lower than anticipated HIV incidence:* Some PrEP trials are also seeing lower HIV incidence than originally expected. It's a very good thing that fewer people are getting infected. But when trials are planned assuming a certain incidence rate and that rate turns out to be substantially lower, it means the data produced by the research will be less likely to be statistically significant—less likely to produce definitive answers about PrEP safety and efficacy. Lower than expected incidence has already led at least one PrEP trial to expand enrollment and lengthen the timeline to report results.

- *Higher than expected pregnancy rates:* Several HIV prevention clinical trials are also seeing much higher pregnancy rates than anticipated. For example, in the FHI PrEP trial, over one in five of the women enrolled became pregnant. Trial volunteers who become pregnant are most often removed from product use, potentially leading to a significant loss of statistical power and undermining trial results. A recent report[iv] from the US Institute of Medicine (IOM) reviewed several challenges to HIV prevention trials, including high pregnancy rates, and recommended that regulatory agencies and investigators consider allowing pregnant women to continue participation in clinical research under some circumstances.

- *Concerns about low adherence levels:* In current PrEP trials, volunteers are asked to take the PrEP drug (or the placebo) once a day, but the evidence from other prevention studies suggests that many people do not use the product being tested as directed by the research team. Low adherence rates can undermine trial results and have been a major issue in previous HIV prevention trials, including clinical research on use of the diaphragm, at least one candidate microbicide, and at least one HSV-2 trial. (Researchers working on the FHI PrEP trial estimated that the study drug was used in no more than 68% of study days.)

## *Fuzzy answers…*

Even if all the current clinical trials do produce statistically significant data those results may be hard to interpret. The impact of the issues above (including HIV incidence, pregnancy, and adherence) could yield results that indicate PrEP is effective but within a wide range of possible efficacy levels—for example, somewhere between 10% effective and 80% effective—with no clear indication where the true efficacy level falls within this spread. This would make it difficult for public health planners to determine how to use PrEP most effectively and would complicate testing of second-generation drugs for use in PrEP. A premature conclusion that a particular compound is as effective as PrEP could damage prevention efforts and end development and testing of other prevention approaches.

Because the first few PrEP studies are in different population groups representing different routes of HIV transmission, statisticians will face challenges in pooling (or combining) data from studies scheduled to report results by 2010. This means that trials currently being run will lead to widespread acceptance of PrEP only if they demonstrate relatively high efficacy effects, and then perhaps only in the populations being studied.

### *…or startling results?*

It is also possible that despite all the challenges, PrEP turns out to be so efficacious that trials produce conclusive efficacy results sooner than anticipated. Each of the studies in the chart on page 7 is subject to interim analysis, which comes before all the data is in and the study is complete. Interim analysis of one of these studies could show clear effectiveness of PrEP, and the Data Safety and Monitoring Board (DSMB) reviewing the results could call for announcing the results early.

## What will the impact be on future research?

Positive results from a PrEP trial could change the future of HIV prevention research. The combination of ARVs in TDF/FTC may make that compound more effective against HIV infection than TDF alone. But the first PrEP trial scheduled to report efficacy results (the Thai IDU study) is testing TDF, not TDF/FTC. If this study shows a high level of efficacy, would ethics require that trial participants in the placebo arms of other PrEP trials be offered TDF (even though the route of infection in the other trials is not the same as in the Thai trial)? If so, those participants would receive some protective benefit, but the expected reduction in HIV incidence and the alteration in study design in the middle of the TDF/FTC trials might make it impossible to complete clinical research on this potentially more promising combination product.

A positive result from any trial would also raise questions about the design of subsequent trials, particularly the question of what should be given to placebo group volunteers in other ongoing prevention trials. Would all studies (vaccine, microbicide, etc.) be required to offer volunteers PrEP if there is benefit in a trial in a specific population? What would ongoing PrEP trials need to do?

These types of challenges would be welcome: they would mean that the world would have additional prevention strategies to build into existing offerings. But they would also lead to difficult decisions about proceeding with other safety and efficacy studies.

Trial results from current trials, which are all testing daily use of PrEP, could also present serious challenges to future studies on intermittent PrEP dosing.

Demonstrating that intermittent dosing provides an equivalent level of protection to daily dosing will likely require substantially larger study sizes (than demonstrating that either intermittent or daily dosing is itself effective compared to placebo).

Guidance from UNAIDS and the World Health Organization (WHO), developed in collaboration with multiple stakeholder groups, will be crucial in supporting national policy-making and decisions on these questions. In the case of the male circumcision trials, when the first trial was stopped early based on positive efficacy results, researchers continued two other studies in order to confirm the efficacy findings.

The recent UNAIDS/WHO publication *Ethical Considerations in Biomedical HIV Prevention Trials*[v] says that introduction of new risk reduction methods into ongoing clinical trials should be "based on consultation among all research stakeholders including the community," and that mechanisms for negotiation among these parties should be outlined in the study protocol.

Waiting for confirmation, clarification and thorough data collection and analysis of PrEP results through two or more trials makes sense, as long as subsequent trials can be completed in a timely fashion. *The world needs additional HIV prevention strategies as soon as possible. With PrEP, as with any other experimental intervention, this urgency needs to be balanced with the need for confidence in the safety and efficacy of the intervention.*

## What are HIV prevention trials' obligations to their participants?

PrEP clinical trials have had a tumultuous history, with trials stopped in Cambodia and Cameroon based on concerns raised by participating communities. Some advocates in Thailand continue to be concerned about aspects of the PrEP IDU trial taking place in that country. In each of these cases, some advocates asserted that the trials were unethical on one or more counts, including inadequate provision of HIV prevention counseling for volunteers, lack of treatment for HIV infection acquired during the trial, an insufficient informed consent process, and limited involvement of communities in trial design.

One lesson of these controversies is that real disagreements can arise about whether communities, particularly those marginalized and criminalized groups whose human rights are already compromised in many settings, have been meaningfully and productively engaged in research. AVAC believes that for HIV prevention trials to be ethical and sustain the support of host communities, the following principles should be in place:

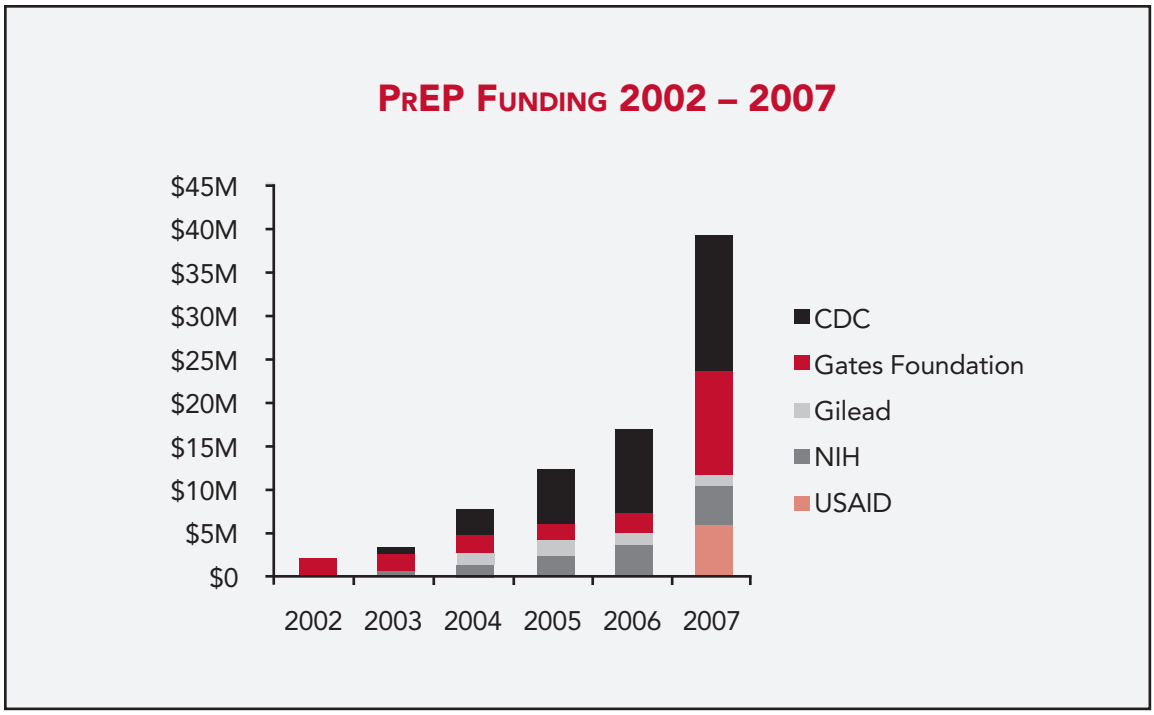
- All trial participants deserve comprehensive, medically accurate, and culturally relevant prevention counseling as well as ongoing access to male and female condoms, male circumcision, and, where needed by the study population, clean needles.
- Trial participants who become infected with HIV during a trial should receive care, including provision of ARVs, when they need it, and on an ongoing basis—ideally as part of national treatment programs that are accessible to the entire population. We are very happy to see the UNAIDS guidance, released in 2007, confirming that trial participants who become infected should receive HIV treatment regimens "from among those internationally recognized as optimal."[vi]
- Clinical trials should be used as opportunities to provide benefits to participating communities, such as building health clinics; training local health care personnel; and providing wider access to HIV testing, treatment, and prevention.
- Trial participants who become infected with HIV also need access to testing to determine whether the virus is susceptible to established first-line therapy. Participants need access to second– and third-line treatment as appropriate.
- The informed-consent process must be accurate, complete, and designed with the involvement of community representatives.
- People who are physically injured as a result of their participation in a trial must be compensated, as well as provided free treatment to address any physical harms that may occur.
- Local communities, advocates, and individuals from marginalized populations included in trials must be involved at every stage of the research process.

Researchers must also work to address special risks—including stigma and discrimination—that trial participants may encounter because of their involvement. One prominent example: the PrEP trial among IDUs in Thailand is taking place in the midst of a government-sponsored crackdown on drug users, potentially making trial participation perilous for some individuals.

*All trial participants deserve comprehensive, medically accurate, and culturally relevant prevention counselling.*

Two UNAIDS publications that can help guide ethical and sustainable implementation of HIV prevention clinical trials are *Ethical considerations in biomedical HIV prevention trials*[vii], developed in collaboration with WHO, and *Good participatory practice guidelines for biomedical HIV prevention trials*[viii], which was developed in collaboration with AVAC.

# Is PrEP research receiving the resources it needs?




Four funders provide the majority of financial support for PrEP research today: the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), the U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation. As the chart above shows, the Gates Foundation was the first to provide significant investments in PrEP, but CDC and NIH have become leading funders in the last several years. In 2007, USAID began to fund PrEP research. Gilead, the maker of TDF and TDF/FTC, has also provided significant financial and in-kind support for PrEP research. (Full disclosure: AVAC receives substantial financial support from the Gates Foundation.)

Global resources dedicated to PrEP in 2007 totaled US$39.5 million. It is difficult to compare this number to other fields, such as AIDS vaccine or microbicide development, since PrEP research costs do not include preclinical product design work—the drugs that are being tested in today's efficacy trials already exist and are licensed.

Still, it is fair to say that the funds for PrEP are limited and that there is little financing being directed at a PrEP pipeline of novel antiretrovirals that could be used. Given the promise of PrEP research, the numerous challenges confronting PrEP clinical researchers, and the additional PrEP research projects that are needed, there is no reason why this arena of AIDS prevention research should be short on funds.

*PrEP research is complex, expensive—and promising. It cannot be done on the cheap. It must become a priority in health-research funding.*

## What questions will remain after the current PrEP trials are completed?

All of the stakeholders involved hope that the current crop of PrEP trials will produce consistent, positive results on the safety, efficacy and effectiveness of PrEP. But, even if they do, ongoing research will be needed to learn more about the long-term safety and potential for drug resistance from taking PrEP. Current trials will also leave several other important questions unanswered:

- *"Intermittent dosing"*: All of today's PrEP studies are asking trial participants to take the study drug once each day, but a limited number of people may already be taking TDF or TDF/FTC intermittently, as in just before a sexual encounter. If intermittent or less-than-daily dosing were effective, it would certainly be easier, more affordable, and potentially safer than taking an ARV every day. *As of July 2008, there is no evidence that intermittent PrEP dosing will protect people from HIV infection.* A study published in February 2008 reported that intermittent dosing of TDF/FTC protected monkeys from an HIV-like virus at a rate comparable to that of daily PrEP dosing.[ix] But this is only one study, and monkeys are not people, and HIV-like viruses are not HIV, so the applicability of these results is far from clear.
- *Other drugs for PrEP*: Current studies will tell us about the safety and efficacy only of TDF and TDF/FTC, but researchers have suggested several other compounds that might be suitable for PrEP. It is important that the PrEP field begin now to consider a pipeline of products that is not dependent on TDF.
- *Additional populations*: Today's studies are not testing PrEP among pregnant women or adolescents (though, as noted above, a preparedness study in adolescents is in the planning stages). Many researchers believe that if PrEP is efficacious in adults enrolled in current trials, there is every reason to think it will also work in pregnant women and young people—but first it will be essential to determine whether PrEP is safe for these groups, and ongoing monitoring for safety and efficacy will be necessary. Women who want to become pregnant cannot always use condoms, so it would be particularly beneficial for them to have an additional HIV prevention option, such as PrEP. Preparation and planning are needed now to be ready to study PrEP in these populations as soon as efficacy data is available in other groups.

## If PrEP works, who will receive it?

On one level, the access and distribution issues involved in using the current PrEP candidates could be simpler than they would be with many other new prevention options. TDF and TDF/FTC are already licensed for use (as treatment) in countries around the world, so there would be far fewer regulatory hurdles than with a new vaccine or microbicide. In addition, these products are already being manufactured, limiting the lag time between the end of trials and scale-up of sufficient manufacturing capacity. Gilead, the maker of both TDF and TDF/FTC, has licensed TDF for generic production and says it expects that similar arrangements will be in place should TDF/FTC be proven effective for PrEP.

Of course, it is still not that easy. The efficacy of providing ARVs for prevention of mother-to-child-transmission (PMTCT) was established years ago, and today only about one in three HIV-positive pregnant women have access to PMTCT. Making PrEP widely available, particularly to people at greatest risk of HIV, will require significantly expanded access to HIV testing as well as PrEP, and take concerted planning and extensive new financing.

### *Delivery strategies to make PrEP effective and affordable*

Like male and female condoms, clean needles, male circumcision and other proven prevention strategies, the effectiveness of PrEP will be determined by the programs that deliver it—and the people who use it. There are a number of possible delivery scenarios for PrEP, such as targeted delivery to specific high-risk groups; widespread availability; or programs that offer PrEP as part of a combination package along with male circumcision, sexually transmitted infection (STI) treatment, and condoms.

PrEP delivery will likely involve some kind of ongoing medical consultation to monitor possible side effects, development of drug resistance, or other concerns. And it will require periodic HIV testing to ensure that people do not continue taking PrEP if they become HIV-positive. Effective PrEP delivery will depend on expanded opportunities for HIV testing and thorough training of health care personnel around the world.

Researchers are already starting to model the impact that PrEP could have, and to do cost-effectiveness analyses that take costs of TDF and TDF/FTC, levels of effectiveness, coverage, and other variables into consideration.[x, xi] At this stage, all these cost estimates are theoretical: we don't know the efficacy rate, what coverage level could be achieved, or the actual cost of these drugs if they are approved for use as PrEP. But modeling studies to date do suggest the importance of well-planned, targeted delivery of PrEP to those most at risk.

They tell us that *to make PrEP effective and affordable, public health leaders need to work well in advance with funders, providers, and communities to carefully plan delivery of PrEP so that it has maximum public-health impact. That will mean free access to the drug by those most at risk who are unable to pay for it, as well as programs to help people adhere to PrEP.*

## Preparing for PrEP: What is needed now?

It is too early to know whether PrEP will be proven safe and effective against HIV infection, but the preliminary evidence is strong enough to warrant a concerted research effort and to begin advance planning and preparations. Priorities for public health officials, researchers, donors, and advocates include:

**1. Ensure that current clinical trials have the best chance of producing decisive results.** Clinical trials now underway—in Thailand, Africa, Latin America and the U.S.—could establish the safety and effectiveness of PrEP, but only if these trials produce clear answers.

- *Make current studies successful:* The global health community should make the success of these trials a top priority by enthusiastically supporting recruitment, retention, staffing, community education and engagement, and other trial needs. Funding should be readily available to support expanded recruitment, additional trial sites or other measures where there are concerns about the statistical power of trials.
- *Modify studies as needed to accelerate possible adoption of PrEP:* National and regional regulatory agencies, including the US Food and Drug Administration, should clarify to the extent possible what data they will require to recommend compounds for use as PrEP. The regulatory pathway (or lack of need of one for PrEP) needs to be defined by regulatory agencies. This information should be used to inform potential modifications to current and future clinical trials, including expanded recruitment and harmonized reporting of work data.

### What is needed now?

1. Ensure that current clinical trials have the best chance of producing decisive results.
2. Identify and invest in additional research.
3. Plan *now* for optimal use of PrEP.
4. Prepare for global procurement and delivery of PrEP.
5. Provide adequate financing.

- *Be ready for the implications of trial results:* There is an urgent need to understand the safety and effectiveness of PrEP in the context of various modes of transmission including injection drug use and vaginal and anal sex. No single trial will provide results on all of these, so even if there is a positive initial finding from a single trial, other research will need to continue. This will necessitate clear and consistent communication on many levels: to governments, trial communities, policy makers, the media, activists and advocates. In order to prepare for this challenge, there is a need to start raising awareness of the issues now.

**2. Identify and invest in additional research.** Whatever the results of current clinical trials, additional PrEP research will be necessary. A plan for launching these studies is needed now, and this critical research will require adequate funding. Needed additional studies include:

- Safety and efficacy studies on intermittent PrEP dosing
- Bridging studies to test safety in pregnant women, adolescents, and others
- Safety and efficacy studies of other PrEP candidates
- Implementation research to test several aspects of product delivery, including marketing, communications, adherence support, delivery in combination with other prevention, distribution, human resources training, and community-level impact

**3. Plan *now* for optimal use of PrEP.** In a July 2007 paper[xii] in *The Lancet*, Lynn Paxton (of the CDC) and colleagues called for public health leaders to, "begin planning for [PrEP] implementation as soon as possible." The authors laid out a series of issues that require attention now, including assessment of:

- Which settings are appropriate for PrEP
- What level of PrEP efficacy would warrant widespread delivery
- Which populations would benefit most from PrEP
- Where targeted vs. more generalized delivery is most appropriate

The article also suggested that mathematical modeling be used to help consider the "risks, benefits and costs of different implementation strategies."

▶ *Plan and model multiple delivery strategies now:* UNAIDS, WHO, the CDC and major global health funders should immediately follow up on the recommendations in the above-cited article, outlining a plan of action to assess how PrEP can be used for maximum public health impact.

**4. Prepare for global procurement and delivery of PrEP.** While Gilead and others have said that manufacturing, regulatory processes, and intellectual property concerns will not be major challenges in making PrEP available, we at AVAC remain nervous. AIDS treatment only began to reach significant numbers of people in need when drug prices plummeted and the WHO took a leadership stand calling for rapid treatment scale-up. *We will need that kind of leadership on PrEP.*

▶ *Declare a well-planned and resourced campaign to deliver PrEP:* UNAIDS and WHO should lay the groundwork for a global PrEP delivery program designed to make a major impact on HIV incidence using targeted delivery of PrEP. This may start with relatively small-scale delivery projects designed to inform larger programs later. Once sufficient efficacy and safety data are available, national governments and major public and private funders, along with UN agencies, should set global and national PrEP goals for strategic and targeted delivery of PrEP, backed by significant resources, appropriate technical support, and effective coordination.

▶ *Figure out who will pay globally:* The Global Fund, PEPFAR, and other major funders of AIDS services need to have plans in place to make PrEP rapidly available globally. Global Fund financing should be available as soon as normative guidance on PrEP is issued by WHO and UNAIDS.

▶ *Figure out who will pay in rich countries:* Rich countries also need to determine how PrEP access will be financed. This is particularly important in countries like the United States, in which there is no universal health coverage and private health insurers might balk at financing PrEP or discriminate against clients who identify themselves as needing PrEP.

▶ *Prepare now for rollout:* UNAIDS, WHO and major global health funders should not wait for clinical trial results to be available, but should promptly set up regional and national consultations, prepare efficient technical support systems, create public health decision making tools, and help countries prepare to integrate PrEP into their national strategies. Different national epidemics will require different delivery strategies, and work on national rollout plans should begin soon. At the same time, public health officials need to send the clear message that the effectiveness of PrEP is not yet established.

▶ *Develop guidance and supports:* UNAIDS, WHO, the Global Fund, PEPFAR and major AIDS services organizations should be prepared for the possibility that PrEP will demonstrate a high level of efficacy. These data could come before the anticipated trial end date. Just as WHO/UNAIDS have done with male circumcision, there is a need for these and other normative agencies to prepare to provide guidance on a range of issues including community consultations, integration of PrEP into HIV prevention services, communications strategies and health care worker training modules.

- Monitor delivery: UNAIDS and other global health organizations need a plan for Phase IV (post-marketing) research that can provide needed information on long-term safety, toxicity, drug resistance, adherence, behavioral impacts, delivery strategies, and other critical issues. UNAIDS, WHO and other global health leaders need an implementation research strategy and learning initiative for PrEP delivery.

**5. Provide adequate financing.** The PrEP research enterprise today is reminiscent of the inadequate financing levels for AIDS vaccines and microbicides in the early 1990s. Serious underinvestment in PrEP is hampering progress and must be corrected.

- *More funding now:* Governments of wealthy countries and private donors committed to global health must make investments in PrEP commensurate with the substantial challenges and considerable promise of this research.

PrEP may prove ineffective. Or it may turn out to be a unique and important new opportunity for the world to reduce HIV infection and change the course of the epidemic. People at risk of HIV cannot afford unnecessary delay in PrEP research. Nor can we wait for definitive results before laying plans to utilize PrEP to maximum public health impact against the pandemic.

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## About AVAC

Founded in 1995, AVAC is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and global delivery of new HIV prevention options.


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For more information about AVAC, please contact us at

Physical:
119 West 24th Street, 7th Floor
New York, NY 10011, USA

Mailing:
101 West 23rd Street, Suite 2227
New York, NY 10011, USA

Phone: +1-212-367-1279 Fax: +1-646-365-3452
E-mail: **avac@avac.org**

Internet: **www.avac.org** and **www.prepwatch.org**


**AIDS Vaccine Advocacy Coalition**
101 West 23rd Street, No. 2227 • New York, NY 10011 • USA
**Phone:** +1 212-367-1279 • **Fax:** +1 646-365-3452 • **Email:** avac@avac.org • **Internet:** www.avac.org