

# Will a Pill a Day Prevent HIV?

*Anticipating the Results of the Tenofovir "PREP" Trials*

A Special Publication of the AIDS Vaccine Advocacy Coalition (AVAC)

March, 2005

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# Will a Pill a Day Prevent HIV?

Research is currently taking place that could change the way we think about preventing HIV infection. Tenofovir, a drug that is now widely used in treatment of HIV and AIDS, is being tested in Africa, Asia, and the Americas for possible use as a product that HIV-negative people could take regularly to reduce their risk of HIV infection. This potential application of tenofovir is called pre-exposure prophylaxis – or “PREP”. No drug has yet been licensed for PREP.

With five million new HIV infections every year – almost 600 every hour – a biomedical tool to prevent HIV could have a profound effect on our ability to control the AIDS pandemic. Behavioral prevention interventions (like sex education in schools and community prevention campaigns) and access to current prevention tools (like condoms and clean needles) are proven to bring HIV infection rates down. But too often these powerful interventions are grossly underfunded and are undermined by political and social constraints that prevent honest discussion of HIV risk factors, including sex and drug use.

The world loves biomedical answers to complex social and personal problems. If tenofovir reduces the likelihood of HIV infection, it could be used by millions of people at elevated risk for HIV, including those who may have trouble insisting on condom use or other protective measures. But will it work, and will it keep working over time? Will there be side effects or other unintended consequences?

We need as many HIV prevention tools as possible, so research on vaccines, microbicides and other potential interventions must be accelerated. A vaccine might only have to be taken once or a few times – not regularly – and it might confer protection from HIV disease for years or a lifetime, and a microbicide could be used as needed and only be applied topically. But vaccines and microbicides may still be years away – tens of millions of people will likely be infected with HIV before these new technologies are available. If it is effective, tenofovir and other PREP drugs could conceivably prevent millions from becoming infected.

Research on tenofovir as a prophylactic has already stirred international controversy. New research results in monkeys have raised questions regarding the degree to which, and under what conditions, tenofovir may be effective.

*Researchers, policy makers and advocates need to take several steps now to ensure tenofovir PREP research meets the highest ethical standards and moves forward on an accelerated basis.*

This brochure will help you understand the basics about the research that is going on and some of the issues involved in the potential use of tenofovir as PREP.

## What is tenofovir?

Tenofovir (*tenofovir disoproxil fumarate*) is marketed under the name Viread™ for treatment of HIV and AIDS. It was licensed for HIV treatment by the U.S. Food

### The Key Points:

- Tenofovir, an antiviral drug that is now widely used to treat HIV disease, is being tested in several countries to determine whether it is safe and effective for use in prevention of HIV infection.
- This potential use of tenofovir is called pre-exposure prophylaxis – or “PREP”. If tenofovir (or another drug) is shown to be useful as PREP it could make an enormous contribution to HIV prevention when used in combination with current, proven effective, interventions like provision of condoms, clean needles and education.
- Research in animals indicates that tenofovir, used as PREP, may be effective in reducing the risk of HIV transmission. We should guard against over optimism: no one knows whether tenofovir will be appropriate for use as PREP.
- Even if it does reduce the risk of transmission, tenofovir PREP might be only partially effective, conferring protection well below 100% of the time.
- Greater coordination among PREP studies is needed to assess and fill gaps in the research effort. Larger studies (with greater statistical power) may be needed, and they should be planned and implemented without undue delay.
- Legitimate ethical concerns have been raised about tenofovir PREP trials, and these concerns need to be addressed thoroughly and speedily. PREP research is vitally important. People at risk of HIV cannot afford to have this research halted or delayed unnecessarily.

and Drug Administration in 2001 and is made by the company Gilead Sciences, Inc. in Foster City, California, USA. The drug is a nucleotide analog reverse transcriptase inhibitor (NRTI), which means that it blocks the functioning of HIV reverse transcriptase, an enzyme that HIV needs to multiply in the human body. Tenofovir is not a cure for HIV – there is no cure today – but it has been proven to reduce HIV viral load in many patients when used as part of combination therapy for HIV.

There are other drugs now used for HIV treatment that might be useful as PREP. Tenofovir was chosen as a promising agent for PREP for several reasons: it is taken once daily, can be taken without food, and also has a strong safety record, limited side effects, and a favorable resistance profile. Finally, research<sup>1-6</sup> has demonstrated the ability of tenofovir to reduce the risk of transmission of simian immunodeficiency virus (SIV) to monkeys. SIV is a virus commonly used in monkey research to model HIV infection in humans. Of course, humans may not respond in the same way.

*It is important to guard against over optimism about tenofovir PREP. It is entirely possible it will not be effective or appropriate for wide use.*

Tenofovir is not perfect, and no one knows how safe it would be for HIV-negative people to use day after day for years. Among HIV positive people taking tenofovir in combination with other drugs, side effects have been relatively rare. In those who do report side effects, nausea, diarrhea, vomiting and intestinal gas are the most common complaints. There is some evidence that tenofovir may affect the liver or kidneys in people with HIV, or result in a small decrease in bone density in some patients. While tenofovir has some antiviral activity against hepatitis B, it is possible that stopping the drug abruptly may worsen liver disease caused by Hepatitis B virus in people who already have Hepatitis B. These and other potential side effects of tenofovir will need to be very carefully monitored as research continues.

## Don't try this at home!

The rumor is people in some cities are already popping a tenofovir before they head out for a high risk night. **That's a bad idea.** It is unknown whether they are getting any protection from the drug. And it is likely that because some people assume they are wearing a “biomedical condom” they are being careless about using prevention that definitely works: male latex condoms, female condoms and clean needles. It is quite possible tenofovir can do harm to some people, particularly when used repeatedly.

## How would PREP be used to prevent HIV infection?

Perhaps the closest precedent for PREP is provision of nevirapine, AZT, and/or other drugs to prevent mother-to-child-transmission (PMTCT) of HIV during pregnancy or childbirth. Post-exposure prophylaxis (PEP), in which antiretroviral drugs are initiated soon *after* possible exposure to HIV, is used in many health care settings.

What about a pill to stop HIV infection *before* it happens? The potential of such a drug is obvious. People at elevated risk of infection all over the world could take a pill daily and significantly reduce their risk. This might give individuals some level of protection even if they failed to use other protective measures (like wearing a condom) or if a condom broke. Using tenofovir as PREP would be particularly advantageous for people in serodiscordant relationships, or people who may feel unable to insist on condom use, including sex workers or people who feel relatively less powerful than their partners in sexual situations.

For all the talk about monogamy, the harsh reality is that many women in the world are infected with HIV by their male partners, even though the couple had agreed to be monogamous. Every year, millions of women are forced into sex. PREP (like vaccines and microbicides) would be a “female-initiated intervention” – it could protect women (and men) who are victims of sexual violence or coercion, or are afraid to insist that their partners use condoms.

PREP could also help streamline HIV prevention and treatment efforts by encouraging more people to come forward for testing (knowing that both prevention and treatment drugs were available) and helping health care personnel integrate prevention services into their medical practice.

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## Are there any concerns?

Yes. Though tenofovir has a good safety profile, no one knows what its effects will be on HIV negative people who take it for years. Even in people living with HIV, *the long-term effects of taking tenofovir are unknown.*

No vaccines or drugs work all the time. Tenofovir PREP might be only partially effective – in other words, it might provide protection well below 100% of the time. What if tenofovir fails to protect someone from infection, and they continue taking the drug for months before they get an HIV test and discontinue PREP? Between the time they are infected and the time they stop PREP, they would in effect be taking monotherapy (single drug therapy) for HIV infection, meaning they are on a treatment regimen that is not considered optimal against HIV disease and which runs the risk of making tenofovir ineffective as treatment later in the course of disease. Development of HIV resistance to tenofovir is possible, though slower than with other HIV drugs, raising the prospect of creating tenofovir-resistant HIV strains. Were this to happen on a wide scale, the overall effectiveness of tenofovir, and perhaps other antiviral treatments, could be reduced.

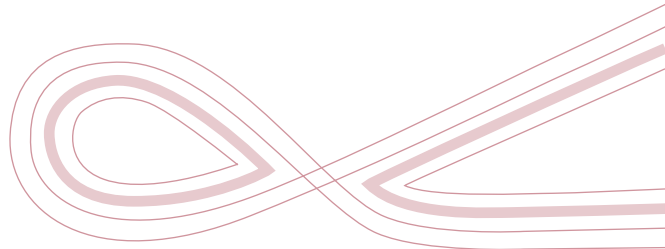
Data presented by the U.S. Centers for Disease Control and Prevention (CDC) in February 2005<sup>7</sup> have introduced new questions about the longevity of tenofovir's preventive effect, if there is one. Monkeys who were given tenofovir remained negative for SHIV infection for six weeks after being exposed to SHIV each week, indicating an initial protective effect of the drug. (SHIV is SIV modified with some components of human HIV-1). But after weeks of receiving tenofovir and repeated exposures to SIV, all the monkeys taking tenofovir eventually became infected. (This study only looked at rectal exposure; it is not known whether the results would have been similar or different with vaginal or intravenous exposure.) Did the protective effect of the drug wane with time or multiple SIV exposures? It is not clear what these data mean for humans, but they highlight the fact that the protective effect of tenofovir, and the longevity of an effect if there is one, are far from established.

There are also concerns about how humans will behave if handed a bottle of pills that can protect from HIV infection. Some behavioral researchers believe that the advent of powerful combination therapy for HIV disease led to increased HIV infection rates in the United States as some people in higher risk groups became less concerned about HIV infection and less vigilant about protecting themselves. The same kind of “disinhibition” may also be a factor in use of PREP. If that happens, and if the drug does not confer 100% protection (a near certainty), or is taken irregularly, people could actually be putting themselves at increased risk of infection. Some people might refuse to use condoms if they learn their sexual partner is taking PREP and is thus theoretically “protected” from HIV. Individuals

may also engage in “disco dosing” – taking a pill just before going out for a big evening, and disregarding instructions on daily use, even though the efficacy of irregular use remains unknown.

PREP raises still broader social concerns. Development of a biomedical prevention tool could lead to “medicalizing prevention” to the point that effective behavioral interventions, as well as condoms and clean needles, receive even less funding and are implemented even less widely than they are today. Individuals taking the drug might be subject to stigma and discrimination because it would be assumed they are in a high risk group for HIV infection.

Efficacy of tenofovir as PREP, while an immediate boon to HIV prevention, might also make research on microbicides and vaccines much more complicated. If tenofovir is licensed for use as PREP by governments hosting clinical research, it will probably be provided to all people enrolled in trials of other prevention technologies in those countries, thus likely reducing infection rates among trial participants and requiring much larger numbers of volunteers in clinical trials and longer trials to get an answer. While this would be wonderful news from the standpoint of reducing infections today, vaccine and microbicide research would still need to continue.

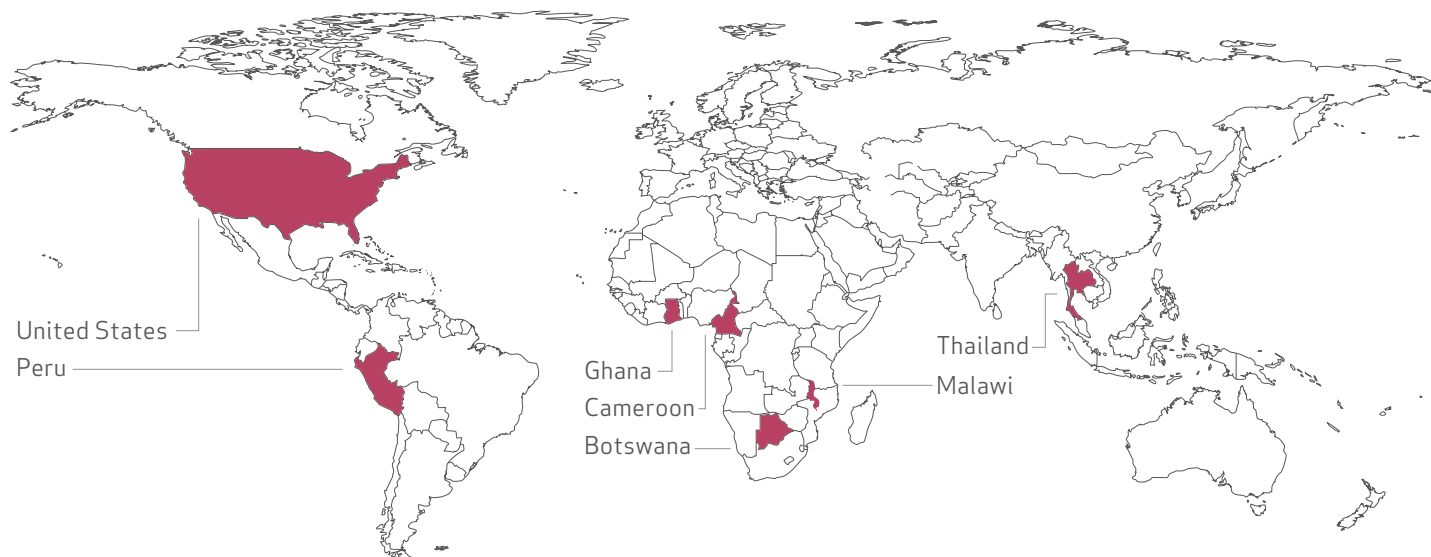


## What is the status of the research?

As of March 2005, there were six ongoing or planned human clinical trials of tenofovir as PREP. They are testing the drug in five different population groups in seven countries. Two of the trials are funded by the Bill & Melinda Gates Foundation and sponsored by Family Health International (FHI), three studies are sponsored by the CDC, and one is sponsored by the U.S. National

## Current tenofovir PREP Studies

Study Location	Population Group	Sponsor	Study Goal	Expected Initial Results
Cameroon, Ghana	High-risk women 800 volunteers	FHI	Safety & efficacy	2007
Malawi	High-risk men 500 volunteers	FHI	Safety & efficacy	2007
Botswana	Young adults 1,200 volunteers	CDC	Safety & efficacy	2007
Thailand	Injection drug users 1,600 volunteers	CDC	Safety & efficacy	2007
United States	Men who have sex with men 400 volunteers	CDC	Safety	2007
Peru	Men who have sex with men 2,100 volunteers	NIH	Safety & efficacy	2008



Institutes of Health, Division of AIDS. The NIH's National Institute of Allergy and Infectious Diseases was supporting a seventh study among sex workers in Cambodia. That trial is on hold as of this writing. Gilead is not the sponsor of any of these studies. (Tenofovir is also being tested in other studies for possible use as a topical microbicide.)

### What will (and won't) the current research tell us?

The list above may look like a robust research effort, but in fact most of these studies have small sample sizes and may provide frustratingly limited information about the usefulness of tenofovir as a preventive tool. It is not yet clear when or how these data will be combined and what types of questions will remain unanswered. The only trial in the United States is testing the safety, but not the efficacy, of tenofovir as PREP (and only in men who have sex with men).

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All this means that when the study results start coming in they will not answer all the burning questions that communities and public health officials will be asking.

*More studies will likely be needed, and should be on the drawing board now.*

The current studies and their sponsors are to be commended for initiating research on PREP – a whole new area of HIV prevention science. It is now important for public health officials to tackle questions that may not be sufficiently addressed in the current studies, including:

- Whether the data from sub-populations in the current trials can be extrapolated to the general population in different countries and regions
- Long term (multi-year) safety of taking tenofovir daily
- Effects of combining tenofovir with other prescription and recreational drugs
- Effectiveness of irregular dosing (e.g. “disco dosing”)
- Appropriateness for use in adolescent populations and among women who may become pregnant
- Health effects on people living with Hepatitis B and other co-infection
- Behavior change (i.e. increased risk taking) among PREP users
- Effective risk reduction interventions tailored for PREP delivery
- Efficacy for different modes of transmission.

Tenofovir is licensed for use in many countries as an HIV treatment, so it can already be prescribed “off label” for HIV prevention. But no one knows if it can reduce HIV infection rates in HIV-negative people. If its efficacy as PREP is established, that could change everything in terms of willingness of doctors and public health workers to provide it, and consumers to demand it.

So one of the most important questions that has not been adequately answered is: *Is there a clear path to licensure and global use as a preventive tool?* In other words, if tenofovir shows safety and efficacy in one or more of the small trials listed above, what happens then? Can it be licensed for use as a preventive agent in those countries? What about in neighboring countries and other regions of the world? Should it be used in population groups different from those studied? Must there be additional, and larger, efficacy trials in many other countries in order to license the product globally, and who will conduct them?

What if studies demonstrate efficacy, but public health officials determine the data is insufficient to license or distribute tenofovir PREP? In that scenario, widespread misuse is a likely outcome.

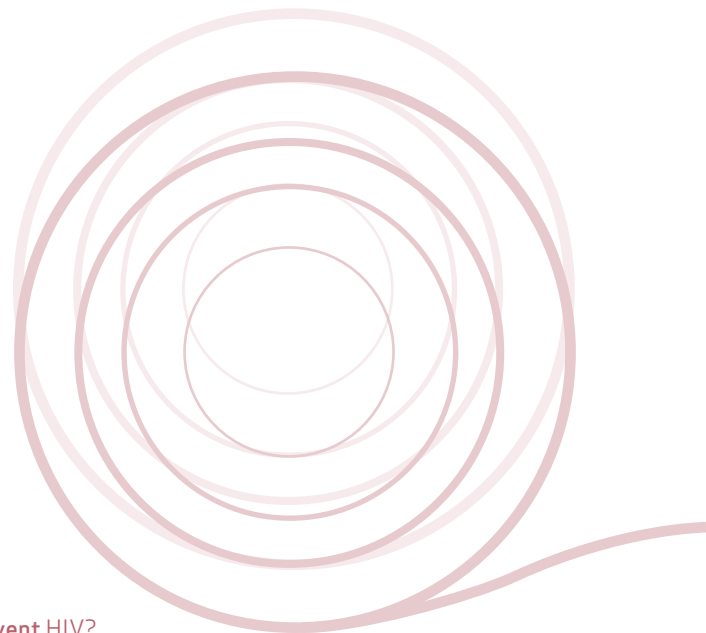
*Prudence* is perhaps the most important word in PREP research. No one wants to encourage millions of people to use a drug to prevent HIV if it is not safe and effective.

*Urgency* has to be the other benchmark. With 600 new HIV infections per hour, it is imperative that PREP research be planned and coordinated to ensure the safest, most ethical, and accelerated research program achievable – one that can lead to global availability of this new prevention technology, if it is safe and effective, without unnecessary delay.

*Action is needed now – by researchers, policy makers, funders and activists – to ensure the questions above are addressed, research moves forward as rapidly as possible, and studies are designed and coordinated to enable global use without delay if safety and efficacy are found.*

## What is required to make sure the research is ethical?

At this writing a PREP trial has been stopped in Cambodia and a study in Cameroon was briefly on hold. Concerns have been raised about the study in Thailand. In all these cases, some advocates asserted that the studies were unethical on several 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.





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Some of the concerns raised are clearly legitimate, and deserve immediate attention. AVAC does not have enough information to assess in detail what really happened at these trial sites – thorough and unbiased investigation is needed.

**The primary lesson of these controversies is that communities must be meaningfully, productively engaged in research.** And we want to point out that if there are problems with these trials – all the concerns noted above are solvable – there is no need to abandon these trials. The problems should be identified, solutions developed in partnership with local communities, and then the trials should continue.

*PREP research is vitally important. People at risk of HIV cannot afford to have this research halted or delayed unnecessarily.*

But this is not just about one or two PREP trials. The underlying issue is that research must be done **with** (not **on**) communities. Researchers, communities and advocates have a responsibility to work together to improve and expedite the process of finding new prevention and treatment technologies. This controversy is an opportunity to engage communities in partnership and build community capacity to participate in clinical research.

## Who pays?

Trial volunteers are making an enormous personal investment by participating in PREP research. Researchers, in turn, must make investments in the future of these communities. But that does not mean sponsors, manufacturers or research institutions should bear the full burden of lifetime HIV treatment for trial volunteers. National governments need to take responsibility, with the help of aid organizations. In research settings where host governments now provide no ARV care, phased-in responsibility for AIDS treatment of trial volunteers should be negotiated in advance.

The following standards are consistent with international research ethical guidelines and emerging practice in clinical research and, we believe, should be applied in all PREP research:

- **All trial participants deserve high quality prevention counseling as well as ongoing access to condoms and, where applicable, clean needles.** (If needle distribution is prohibited by local law and IDUs are in the study group, researchers and non-governmental organizations should work together to find ways to ensure access to clean needles for participants.)
- **Trial participants who become infected with HIV during a trial should receive care, including provision of ARVs, when they need them, and on an ongoing basis.** Often, this will not be simple. In communities where health care infrastructure is limited and few people receive HIV treatment, how do you make a credible promise to provide ARV therapy decades after the trial ends? AIDS vaccine researchers, among others, are developing models that can be useful here, from creating special accounts to fund ARV purchases years in the future, to five year pledges for treatment until other funders take over, to alliances with local governments and research institutions that will stay in the community.
- **The informed consent process must be accurate, complete and designed with the involvement of community representatives.** Researchers should evaluate participants' comprehension of key issues involved in trial participation. Informed consent should be an on-going process, including assessments at follow-up visits to insure that participants retain comprehension of key issues such as the experimental nature of the research, the use of a placebo control, and the need to reduce HIV risk through behavioral means.
- **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 injuries.** A mechanism to ensure prompt and fair consideration of injury claims needs to be in place.
- **Local communities, advocates, and individuals from marginalized populations must be involved at every stage of the research process.** Ethics demands it, and so does long term community acceptance of the research.

Consensus on international ethical standards for prevention research is urgently needed and we are glad UNAIDS is leading an international consultation process to develop consensus guidelines.

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## If it is shown to reduce HIV infection, how does PREP get to people at risk?

If tenofovir or another drug regimen is shown to prevent HIV infection, expect to see it become the subject of speculation, misinformation, and internet-based opportunism. Expect a burgeoning black market from San Francisco to Abuja to Port Moresby, Papua New Guinea.

A lot of people, rich and poor, are going to want to increase their defenses against HIV infection. The unknowns include: where will tenofovir be licensed for PREP, among what populations, and at what cost? Will you need a prescription to get it, or will community health workers be empowered to go into high-risk communities and make PREP easily available without fee?

Public health officials and people at risk of HIV infection may have different perspectives on these issues. Some public health officials may say PREP should be carefully controlled, and used only as a “second line” prevention intervention, where an individual is consistently failing to protect him or herself, or is clearly unable to insist on condom use. Many advocates will say that everyone at risk should have the right to access PREP regardless of their ability to pay. That means that governments, international agencies, donors, and manufacturers need to work together to meet demand among low income individuals.

These debates will take place (and, to some extent, be different) in countries around the world. But some things are certain already. First, ongoing, community-based behavioral interventions will be necessary to remind people that PREP is not fool-proof and that safe sex and clean needle use are still important. Individuals will also need help with adherence to their PREP regimen in order to minimize the number of people losing the (possible) protective effect of the drug. Phase IV (post-marketing) studies will be needed to gauge efficacy, toxicity, and effects in sub-populations.

Second, clear policies will be needed on HIV testing and monitoring of potential toxicities. Testing will be necessary on a regular basis, and public health authorities need to make testing available. The importance of developing testing infrastructure is one example of how PREP delivery could dovetail with overall HIV prevention and treatment scale up efforts and might be used to build public health capacity.

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*There is no time to waste in planning for global access.* The public and private sectors need to start talking about how PREP could and should be used, how tenofovir could be manufactured in sufficient quantity, how it would be distributed, and who would pay for it. As they make their plans, public health officials should remember that PREP could be a highly cost-effective prevention tool. According to an analysis by the Futures Group, if it has a high efficacy level and is priced at US\$0.14 per day (in poor countries), tenofovir PREP – as one component of a prevention package – could cost less per infection averted than many current HIV prevention interventions.

*But again, tenofovir may very well not work as PREP. On the issue of global access, delivery of existing HIV prevention and treatment technologies should be the top priority.*

Gilead has a right to make a reasonable profit on this drug. People at risk of HIV have a right to access all effective HIV prevention methods. These two concepts are not mutually exclusive if the public sector, multilaterals, donors, the company, and communities agree on access plans that include adequate purchase capacity and tiered pricing (lower prices for low and middle income countries and international health organizations).

*Gilead is to be commended for stating they will make tenofovir available at cost to people in poor countries. That is a first big step in a long walk to universal access.*

Generic manufacture of AIDS drugs has been the principal factor in steeply reduced AIDS drug prices, and it would likely make PREP more available. Like many advocates, we are very concerned about new trade agreements that may make it harder for generic producers to meet the desperate need for greater access to AIDS treatment and prevention.



## So what needs to happen now?

The prospect of PREP challenges all of us to be ready to do it right this time: if a new intervention to tackle HIV/AIDS is proven, it needs to be rapidly available around the world, especially in those communities hardest hit by the epidemic.

All of us need to challenge ourselves to be ready for positive (and negative) results from the current studies. **Greatly expanded delivery of HIV treatment and prevention are urgent priorities.** If tenofovir is effective as PREP, we should be fully prepared to incorporate it into comprehensive treatment and prevention scale up. There is a lot of work to be done:

- **The World Health Organization (WHO), UNAIDS, and trial sponsors** should ensure tenofovir PREP research is appropriately coordinated and progressing in an accelerated fashion. Statisticians, Principal Investigators, and trial sponsors should be convened on an ongoing basis to assess whether the statistical power of current studies is sufficient to move to licensure, and whether additional research (including bridging studies for use of tenofovir in populations not currently being studied) is needed.
- We urge **Gilead** to become increasingly engaged in talking with public health authorities and advocates about how tenofovir PREP can be more thoroughly tested for efficacy and, if it proves effective, can be made readily accessible.
- **WHO** and **UNAIDS** should identify the policies and planning required to ensure global access to tenofovir PREP. Demand estimates and modeling of use are needed. Manufacture, purchase capacity, and distribution issues must not be left until all the research is done.

## Why is a vaccine organization writing about tenofovir?

AVAC was founded in 1995 to advocate for the ethical development and global delivery of vaccines against AIDS. A decade later we are still committed to that cause. We are also not blind to the fact that other new prevention technologies are likely to arrive sooner than a vaccine. And we think many of the issues we work on – accelerated research, community involvement and education, research ethics, global access, and policy analysis – are highly relevant with PREP. In the coming years, AVAC will continue to work in partnership with other advocates to advance ethical prevention research and ensure that the benefits are shared globally.

- **WHO and UNAIDS** should anticipate training needs for health care workers, clarify questions of research ethics, and engage communities, industry, and governments in participatory planning for PREP delivery. Also needed is an improved system for reporting adverse events from PREP use.
- **WHO, UNAIDS, and trial sponsors** or another organization should develop a communications strategy to prepare for announcement of PREP results and potential delivery of PREP.
- Research **fundors, policy makers and the public** must recognize tenofovir PREP as just one (far from proven) component of what must be a comprehensive AIDS research agenda. Better HIV treatments are needed, including pediatric medications. Vaccine and microbicide research still holds great potential and must be accelerated. And other antiviral drugs should be tested for their potential usefulness as PREP.
- **All of us** have a responsibility to advocate for PREP research that proceeds rapidly and ethically.

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## Close

The world needs combination HIV therapy and combination HIV prevention. If PREP is found effective with tenofovir, it will become a powerful tool, but it will need to be delivered alongside behavioral interventions, condoms, clean needles, HIV testing, and access to HIV treatment.

Finding a new pill will not mean politicians and providers have an excuse to dodge the difficult issues involved in this pandemic, including stigma, the inequality of women in most societies, the sexuality of young people, drug use, homophobia, and the sex industry. PREP may one day be important in the response to AIDS, but that response will never be equitable nor ultimately effective unless societies confront the inequality that drives HIV and impedes access to HIV prevention and treatment.

## Where can I get more information and get involved?

For more information, contact us at AVAC at +1 212.367.1279 or [avac@avac.org](mailto:avac@avac.org)

*You can also get more information on the internet:*

"Thai Activists Speak Out on Tenofovir Trial in IDUs," December 8, 2004  
<http://www.aidsinfonyc.org/tag/activism/thaiTenofovir.html>

US Centers for Disease Control and Prevention background paper:  
[www.cdc.gov/hiv/PUBS/TenofovirFactSheet.htm](http://www.cdc.gov/hiv/PUBS/TenofovirFactSheet.htm)

Family Health International background paper:  
<http://www.fhi.org/NR/Shared/enFHI/PrinterFriendly.asp>

Family Health International press release on delay of Cameroon study:  
<http://www.fhi.org/en/AboutFHI/Media/Releases/Feb42005FHItenofovirStudy.htm>

Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians, Center for HIV Identification, Prevention, and Treatment Services (CHIPTS) <http://www.aidspartnershipca.org/pubs.html>

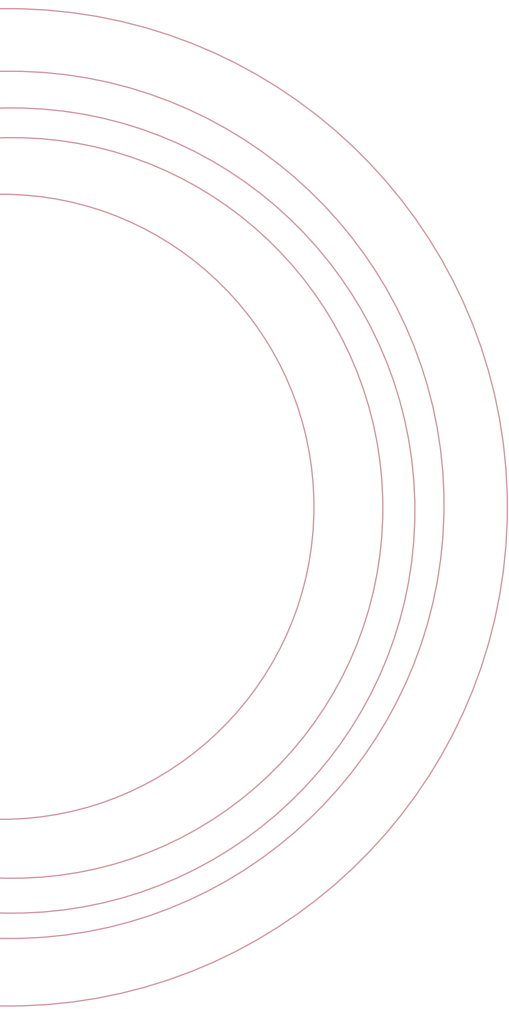
Gilead  
<http://www.gilead.com/wt/home>

- <sup>1</sup> Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, Benveniste RE, Black R. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science*. 1995 Nov 17;270(5239):1197-9.
- <sup>2</sup> Van Rompay, KKA, CJ Berardi, NL Aguirre, N Bischofberger, PS Lietman, NC Pedersen and ML Marthas. 1998. Two doses of PMPA protect newborn macaques against oral simian immunodeficiency virus infection. *AIDS* 12:F79-F83.
- <sup>3</sup> Van Rompay, KKA, ML Marthas, JD Lifson, CJ Berardi, GM Vasquez, E Agatep, ZA Dehqanzada, KC Cundy, N Bischofberger, and NC Pedersen. 1998. Administration of 9-[2-(phosphonomethoxy)propyl] adenine (PMPA) for prevention of perinatal simian immunodeficiency virus infection in rhesus macaques. *AIDS Res. Hum. Retroviruses* 14:761-773.
- <sup>4</sup> Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, Lifson JD, Morton WR. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV<sub>mac</sub> infection depends critically on timing of initiation and duration of treatment. *J Virol*. 1998 May;72(5):4265-73.
- <sup>5</sup> Van Rompay KK, McChesney MB, Aguirre NL, Schmidt KA, Bischofberger N, Marthas ML. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. *J Infect Dis*. 2001 Aug 15; 184(4):429-438. Epub 2001 Jul 16.
- <sup>6</sup> Van Rompay KK, Lawson J, Colon R, Bischofberger N, Marthas M, Oral tenofovir DF protects infant macaques against infection following repeated low-dose oral exposure to virulent simian immunodeficiency virus, July 2004, abstract at XV International AIDS Conference.
- <sup>7</sup> Subbarao S, Otten R, Ramos A, Jackson E, Adams D, Kim C, Bashirian S, Johnson J, Monsour M, Janssen R, Paxton L, Greenberg A, Folks T, Chemoprophylaxis with oral tenofovir disoproxil fumarate (TDF) delays but does not prevent infection in Rhesus Macaques given repeated rectal challenges of SHIV, February 2005, abstract at 12th Conference on Retroviruses and Opportunistic Infections.



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AVAC gratefully acknowledges the researchers and community representatives directly involved with tenofovir PREP studies, as well as many friends and colleagues in government, industry, and the advocacy community, for their expertise and advice as we prepared this report.



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## The AIDS Vaccine Advocacy Coalition (AVAC)

Founded in 1995, the AIDS Vaccine Advocacy Coalition (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 vaccines against HIV/AIDS.

This special report and AVAC's continuous policy analysis, advocacy, education and outreach work are made possible by the dedicated labor of AVAC advocates and support from the Bill & Melinda Gates Foundation, Broadway Cares/Equity Fights AIDS, the Ford Foundation, the Gill Foundation, the International AIDS Vaccine Initiative, the Overbrook Foundation, Until There's a Cure Foundation, the WHO-UNAIDS HIV Vaccine Initiative, and many generous individuals who have become AVAC Members. AVAC is an IRS-certified 501(c)3 tax exempt organization, and donations are tax deductible.

### For more information

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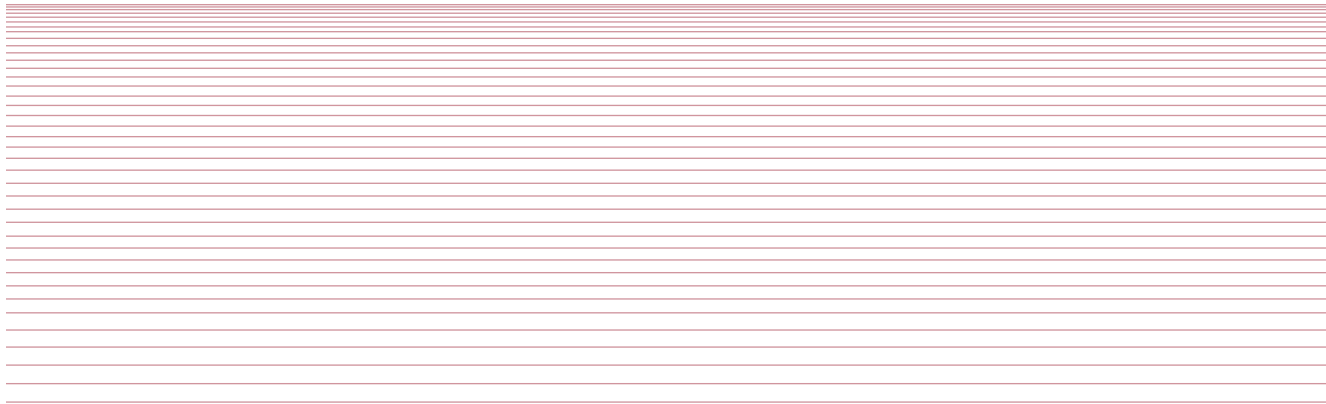
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