



**BUILDING COLLABORATION  
TO ADVANCE HIV  
PREVENTION**

**GLOBAL CONSULTATION ON  
TENOFVIR PRE- EXPOSURE  
PROPHYLAXIS RESEARCH**

**SEPTEMBER 2005**

REPORT OF A CONSULTATION  
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AIDS SOCIETY ON BEHALF OF THE BILL  
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NATIONAL INSTITUTES OF HEALTH AND  
US CENTERS FOR DISEASE CONTROL  
AND PREVENTION

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# EXECUTIVE SUMMARY



**C**ontroversies surrounding human clinical trials of the antiretroviral drug tenofovir demonstrate the complexities involved in conducting HIV prevention research and the importance of trial sponsors, investigators, communities and activists working collaboratively to resolve concerns as they arise. Tenofovir, a drug now used in the treatment of HIV disease, shows promise as a new and potentially powerful tool for HIV prevention. Yet as of August 2005, two clinical trials testing the safety and efficacy levels of the drug as Pre-Exposure Prophylaxis (PREP) have been shut down, and other planned trials have been criticized. At issue are concerns about the way in which affected communities are engaged in tenofovir research and several significant questions regarding the rights and protections afforded trial participants. These debates point to broader issues in international health research generally.


In May 2005 the International AIDS Society convened a consultation to discuss ongoing concerns with tenofovir research. The meeting was convened on behalf of PREP trial sponsors: the Bill & Melinda Gates

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Foundation, the US Centers for Disease Control and Prevention, and the US National Institutes of Health. The meeting brought together over 50 stakeholders representing host communities and governments, advocacy groups, researchers, trial sponsors, and the product manufacturer.

The May consultation demonstrated the value of open and frank discussion and it laid the foundation for ongoing dialogue about PREP studies. Yet while better communication is crucial, the discussion made clear that the PREP research agenda depends upon resolution of serious and specific concerns. Each of these concerns must now be addressed collaboratively by researchers, sponsors, participating communities and advocates.

The consultation included presentations and group discussion on four key challenges that have emerged as particularly significant issues at tenofovir trial sites: provision of anti-retroviral therapy to trial participants who become infected with HIV during the course of a trial, delivery of proven effective HIV prevention interventions to participants, mechanisms to promote research literacy for host communities, and approaches to achieving meaningful community engagement in research.



**S**cientific rigor and broad stakeholder engagement must not be understood in opposition; each is crucial to successful HIV prevention research. Several investigators at the consultation acknowledged that while their research teams had made concerted efforts to meaningfully engage community members in research studies, these efforts sometimes fell short. Activists spoke to the importance of tenofovir research even as they pressed for specific changes in the conduct of trials.


As of August 2005 there are six ongoing or planned human clinical trials testing the use of tenofovir as PREP. At the consultation, study sponsors from each of the agencies running PREP trials provided overviews of their studies. They were followed by civil society representatives who called for engagement of communities earlier in the research process and increased investment in research literacy programs that can help people understand the process of clinical trials and key concepts in human clinical studies. Also needed are mechanisms for addressing concerns as they arise so disagreements and misunderstandings do not lead to interruptions in research.

While some questions of research ethics and participant protections remain unresolved on an international level, the dialogue on standards for ethical international health research has advanced rapidly in the last

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several years. In many ways, the key challenges addressed at the consultation can be seen as practical problems rather than raging ethical controversies.

Presentations on the issue of ARV provision centered on the mechanics of putting effective and long term delivery programs in place. The discussion on prevention interventions focused on risk reduction counseling, methadone maintenance programs and how to make clean needles readily available to injection drug users in tenofovir trials in spite of legal limitations from host and sponsor governments. Other presenters discussed models for meaningful community engagement and research literacy. Several people noted the importance of developing standards and guidelines for both activities. Other issues, including compensation for physical harm as a result of the study drug, and broad access to tenofovir if it should prove effective as PREP, were not addressed in-depth at the consultation and may need to be taken up in future discussions.



UNAIDS has recently held consultations to develop guidance on partnerships between civil society and researchers in HIV prevention research generally, and it is hoped that this work will help address some of the challenges encountered with tenofovir clinical trials.


Resolution of concerns with tenofovir research will require ongoing dialogue and specific actions at the country level. During the consultation, country-specific working groups focused on priority concerns in Botswana, Cameroon, Ghana, Malawi and Thailand. These groups offered recommendations to address local challenges, and several working groups made plans to follow up with their own consultations and stakeholder meetings. While country-specific dialogue was an important step in tackling some of the primary concerns with tenofovir research, the involvement of many different players at the country level will be needed in order to secure action on the recommendations.

No definitive definition of the word "community" emerged from the meeting but it became clear that, in the context of AIDS clinical trials, "community" means a wide range of stakeholders that includes potential participants, domestic and international activists, non-governmental organizations and human rights organizations. Successful research will depend on researchers consulting with a wide range of community members early in the research process.

## **MOVING FORWARD ON TENOFOVIR PRE-EXPOSURE PROPHYLAXIS RESEARCH**

In addition to recommendations from the country working groups, a variety of more general proposals were made at the consultation's closing session. These included:

- Establishing a global stakeholders group to move forward with the recommendations made at the meeting and to promote improved communication, coordination, and accountability as part of the tenofovir research effort.
- Developing standards of practice for community engagement that can be measured, monitored and adapted for use in different settings.
- Strengthening national ethics review boards in order to promote civil society engagement and ensure adherence to national and international ethical guidelines.



- Fostering community research literacy and capacity through expanded support for these efforts as well as a review of research literacy materials, and development of new materials if necessary.

- Building genuine partnerships between researchers in developed and developing countries and ensuring investigators in developing countries are not treated as "junior partners".

- More fully integrating clinical research into national treatment and prevention plans so that services provided through clinical studies become part of a country's comprehensive response to the epidemic.

- Promoting better coordination of tenofovir research in order to advance this research rapidly and efficiently, and facilitate timely product labeling and distribution if tenofovir proves safe and effective as PREP.

- Following up on country-specific recommendations with periodic updates on country level actions to address recommendations made at the consultation.

- Holding forums on best practices in prevention research and on community engagement at the upcoming International AIDS Conference and other international meetings.

Discussions around tenofovir research are taking place in the context of a rapidly evolving global response to the AIDS epidemic. HIV treatment and prevention services are being scaled up in communities around the world.

***This is an opportunity to recognize the many potential links between tenofovir research and broader efforts to build health care infrastructure and civil society capacity.***

This is an opportunity to recognize the many potential links between tenofovir research -- and HIV prevention research more generally -- and broader efforts to build health care infrastructure and civil society capacity.



# INTRODUCTION

**T**enofovir (*tenofovir disoproxil fumarate*) is an antiretroviral drug made by Gilead Sciences, Inc. (Foster City, California, USA) that is currently used for treatment of HIV disease. Tenofovir is a nucleotide analog reverse transcriptase inhibitor (NRTI), a drug that blocks the functioning of HIV reverse transcriptase, an enzyme that HIV needs in order to multiply in the human body.

Tenofovir is now being studied to determine whether it is appropriate for use as pre-exposure prophylaxis (PREP) for the prevention of HIV infection. If tenofovir demonstrates safety and effectiveness in PREP studies, it could be a powerful new HIV prevention tool to be used in conjunction with existing HIV prevention interventions.

Other drugs now used for HIV treatment are also being considered for use as PREP. There are several reasons why tenofovir was selected for study for use in HIV prevention: it has a strong safety record, has limited side effects, is taken only once daily and can be taken without food. Research in lab animals has indicated that tenofovir may be able to reduce transmission of HIV, though the safety and efficacy of tenofovir as PREP has not been established in human trials.

Beginning in 2004, several tenofovir PREP trials encountered difficulties when host communities or advocacy groups raised concerns about what they perceived to be ethical shortfalls in trial design and implementation and inadequate consultation with the communities involved. To date, because of these difficulties, two tenofovir PREP trials have been closed. Another PREP study in Nigeria was stopped due to inability to meet protocol requirements.

“This meeting has been healing in a lot of ways. There was a great divide. We didn’t do everything right in these trials. Sometimes that’s really important to say.”  
*Researcher*

On the 19th and 20th of May 2005, the International AIDS Society (IAS) convened a meeting on behalf of the trial sponsors, the Bill & Melinda Gates Foundation, the US Centers for Disease Control and Prevention, and the US National Institutes of Health, in Seattle, Washington, USA with over 50 stakeholders representing the diverse communities participating in the tenofovir prophylactic trials, host governments from the respective countries, leading advocacy groups, senior researchers, all trial sponsors, and representation from Gilead.





The objectives of the meeting were to:

- Foster meaningful dialogue between key stakeholders engaged in tenofovir prophylactic research;
- Identify the ethical and operational challenges that obstruct existing research and work towards the resolution of these challenges;
- Identify strategies for ongoing problem management, including reporting of emerging challenges to individuals or agencies and mechanisms for resolving these.

This report is intended to capture the major issues raised and recommendations made during the consultation. Background information is also provided on several topics that were addressed at the meeting. Several people who were invited to the consultation but were unable to attend were contacted following the meeting, and their written input is incorporated in this report.



# WHERE THE RESEARCH STANDS: OVERVIEW OF CURRENT STUDIES AND PRINCIPAL ISSUES

As of July 2005 there were six ongoing or planned human clinical trials testing the use of tenofovir as PREP. Study sponsors from each of the three agencies running PREP trials provided overviews of their studies at the consultation. These presentations were followed by comments by civil society representatives, and then full group discussion about fundamental issues affecting past and future of tenofovir studies.

## STATUS OF TENOFOVIR PREP STUDIES

Mary Fanning of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) reviewed two tenofovir studies sponsored by the agency. The first, in Phnom Penh, Cambodia, was a Phase III trial involving 900 commercial sex workers. The study was intended to test the safety and efficacy of tenofovir, effects of the drug on bone mineral density, and safety issues related to tenofovir use in people with chronic Hepatitis B virus infection. The trial was stopped in August 2004 due to concerns raised by community members and the Cambodian government. Areas of concern included provision of care to address possible adverse events resulting

from the trial and treatment for participants who became infected with HIV during the course of the research.


“We know communities can understand complicated topics but we need to invest in research literacy, and that hasn’t happened yet.”

*Activist*

The second study in Lima and Iquitos, Peru will be a Phase III trial among 1400 men who have sex

with men. The study has the same objectives as the Cambodia trial. It is set to begin in September 2005 and run through January 2009. NIAID is also planning a lab study of specimens from tenofovir trials in Africa in order to better understand the effects of the drug.

Lynn Paxton of the U.S. Centers for Disease Control and Prevention (CDC) presented on three PREP clinical trials sponsored by her agency. One study, based in Atlanta and San Francisco in the United States, is designed to test the safety of tenofovir, as well as the adherence and acceptability of the drug in a population of 400 men who have sex with men. The study started in February 2005 and is expected to run 24 months.



CDC is also sponsoring Phase II/III studies in Botswana and Thailand that are designed to test the safety and efficacy of tenofovir as PREP. The Botswana study will involve 1200 heterosexual men and women and will start in August 2005. The Thai study which is recruiting 1600 male and female injection drug users began enrollment in June 2005.

Finally, Kate McQueen made a presentation on two Phase II studies sponsored by Family Health International (FHI), with funding from the Bill & Melinda Gates Foundation. The research will test drug safety and effectiveness, as well as factors affecting adherence, drug resistance, and potential effects on sexual risk taking. The first study in Douala, Cameroon; Tema, Ghana; and Ibadan, Nigeria began in July 2004 and was targeted to enroll 1200 women at elevated risk of HIV infection. The Nigerian study site was closed in February 2005 after enrolling 136 women due to inability to meet protocol requirements. Research at the Cameroon site was suspended in February 2005 due to concerns raised by the national government, community members and activists; 400 women were enrolled and in follow-up at the time of suspension. In Tema, research is ongoing with 400 women enrolled in the trial. The second study, in Lilongwe, Malawi, is expected to begin in the fall of 2005 and will enroll 500 men at high risk for HIV infection. Formative research for the study has already begun.

## CENTRAL ISSUES IN CURRENT STUDIES

Following the presentations by researchers, Marge Chigwanda of the University of Zimbabwe and Gregg Gonsalves of Gay Men's Health Crisis (GMHC) in New York, USA made comments from a civil society perspective. Ms. Chigwanda noted the importance of involving communities early in the research process, and taking time to prepare communities for research, rather than simply asking them to ratify a research plan that was prepared without their input. Otherwise, she said "You have come here with the ball and all the rules of the game, and asked us to kick the ball." Ms. Chigwanda also asked how civil society can become more involved in setting the research agenda for their communities.

***"You have come here with the ball and all the rules of the game, and asked us to kick the ball."***

Mr. Gonsalves noted the critical importance of tenofovir research and told the group that "clinical research saved my life". But he said the fact that tenofovir research is important does not absolve researchers from attending to the very legitimate concerns raised about

current trials. Mr. Gonsalves also emphasized the need to provide education to communities participating in studies. "We know communities can understand complicated topics," Mr. Gonsalves said, "but we need to




invest in research literacy, and that hasn't happened yet."

Discussions during and after these presentations indicated that both researchers and civil society representatives are grappling with complex and competing priorities in the context of tenofovir research. The issues raised involved both breakdowns in communications and disagreements about policies. Several researchers noted their efforts to engage in community consultation about their research, while acknowledging that inexperience, time constraints, and lack of clarity about how to define "community" stood in the way of more successful consultations. Civil society representatives spoke to the crucial nature of tenofovir research and HIV prevention research in general, while raising specific concerns about perceived shortfalls in both the community consultation processes and the rights and services provided to trial participants in PREP trials.

Each of the investigators talked about challenges they faced in attempting to consult with community groups. One investigator said that the research team "thought we had addressed the issues" raised by community members, only to hear from community groups that said they were not satisfied. Another investigator acknowledged that community awareness efforts did not receive sufficient attention because the research team was trying to move ahead quickly to launch the trial. A significant challenge for one investigator was trying to define who was in the "community" that needed to be consulted.

Lack of a clear standard for community consultation was a recurring issue in the discussion, and at least two civil society representatives called for a review and dissemination of best practices in the area. One member of civil society said that communities are typically not consulted until research is well underway, missing the opportunity for community input on trial design and informed consent, as well as delaying, and perhaps damaging, the process of building trust between researchers and community. Another civil society representative said that community involvement needs to start with discussion of the research design and continue for the life of the study.

There was no clear resolution on the question of what constitutes "community," but an ethicist at the meeting stressed the importance of coming to some definition of this concept and reviewing lessons learned on the issue from current and past trials. A wide variety of groups were identified as being important to the consultation process, including CAB members, trial participants, people in the study population, the media, and advocates on the local, national and international levels. One researcher described her team's efforts to reach out to a variety of groups perceived as stakeholders, including community groups, commercial sex workers, brothel owners, and others. Following these efforts it became clear that not all civil society groups had felt included, a fact that contributed to disruption of the trial.



The importance of researchers understanding the social context of the community emerged as another important theme. Some communities have little or no experience in clinical research and concerted efforts are necessary in order to provide training in research literacy in these communities. Stigma and discrimination is a dominant factor in many places, and these issues need to be addressed both in terms of community consultation, measures to protect participants, and tailored education programs. Many communities are struggling with a severe HIV epidemic and extremely limited access to health services. For them, securing treatment that can save lives may be the top priority even if they understand the critical importance of prevention research. "Prevention is important," one investigator said, "but in countries where HIV is widespread, communities see the immediate need for treatment."


**“Clinical trials saved my life.”**  
**Activist**

Some of the controversies surrounding tenofovir research appeared to be failures of communication, and several speakers stressed the importance of researchers learning to communicate effectively with local communities, the media and host governments. One investigator said that, "many researchers are quiet people but on sensitive issues like these, you have to talk". Researchers would benefit from training in discussion of complex research concepts with non-scientists.

Another investigator acknowledged that researchers need to examine their own feelings about the study populations and ensure they are not communicating negative attitudes about a group of already stigmatized individuals, such as sex workers or gay men. The chain of communication between sponsors and researchers on-the-ground is also crucial. One meeting participant said that, "The lesson for us as sponsors is when we ask researchers to do things like having a community advisory board and certain community discussions, we have to ensure that happens."

Community members also need tools to engage collaboratively in research design, including educational materials and trainings on clinical research concepts. Expanded efforts to provide research literacy was consistently identified as an important issue to promote community participation in, and acceptance of, research.

While better communication is a critical need, the discussion made clear that controversy over PREP studies also involves serious and specific concerns about what are perceived as inadequate services and protections for trial participants. These concerns include access to antiretroviral treatment for participants who become HIV infected during the course of the trial, treatment for physical harm, access to a comprehensive set of prevention interventions (including high quality prevention counseling and clean needles for injection drug users), and access to tenofovir after the study if it proves effective as PREP.



Several participants said that one crucial step towards successful PREP research is to acknowledge that trust has been damaged in several communities and that this damage has to be repaired. Part of the process should be willingness to discuss what went wrong, in addition to developing agreements for moving

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forward. One researcher commented that, "I learned that trust is one of the most important things".

### **UNAIDS Consultations on civil society and researcher partnerships in HIV prevention research**

UNAIDS has sponsored a series of consultations to promote effective partnerships between civil society and researchers in HIV prevention trials, including PREP trials. The meetings engaged multiple stakeholders, including researchers, funders, trial participants, civil society, activists, and government representatives.

In a presentation at the Seattle consultation, Dr. Cate Hankins of UNAIDS said that the project is intended to develop guidance on processes for reaching agreements on the design, conduct and oversight of HIV prevention trials in developing countries. Another goal is to build consensus on emerging issues in HIV prevention research and, hopefully, to develop norms and standards that can be used in this research.

Three regional workshops have been held as part of the project, each addressing what has worked and not worked in community-researcher partnerships, and discussing approaches to make these partnerships more successful. The workshops also addressed issues such as delivery of proven prevention methods (including condoms and clean needles) and provision of treatment to trial participants. The workshops led to development of regional platforms for community engagement and the selection of a delegation of regional representatives for an international consultation held in Geneva in June 2005.

Following the international consultation, UNAIDS hopes to support countries to develop national HIV prevention research plans and the agency will publish a guidance document based on its consultations.



# ADDRESSING KEY CHALLENGES IN TENOFOVIR CLINICAL RESEARCH

Sustained support for tenofovir research requires resolution of several specific issues relating to community involvement and rights and protections for trial participants. The consultation addressed four leading challenges that have surfaced thus far in PREP studies. Presentations and discussions on those topics are summarized below. Sidebars provide further background on some of the issues addressed at the meeting.

## PROVIDING TREATMENT AND CARE TO TRIAL PARTICIPANTS

The level of HIV treatment and care provided to PREP trial participants who become HIV infected during a trial has become a major concern at several tenofovir trial sites and in HIV prevention research more generally. At issue is whether trial sponsors are obligated to ensure all participants who become infected receive antiretroviral therapy and other HIV care for life. Talom Yomgne Calice of REDS in Cameroon, and Bob Grant of the University of California, San Francisco made presentations on the issue of treatment in tenofovir trials.

Mr. Calice commented on the services his organization provides to people who are considering enrollment in tenofovir research. He emphasized the need for trial sponsors, the Ministry of Health and the community to work together to define appropriate standards of care for trial participants. He suggested that in cases where this is not already happening, care and treatment services to be provided post trial should be formalized in a contract. It is important to pay attention to the quality of HIV treatment and care, Mr. Calice said, and the Health Ministry should ensure that treatment is carried out by competent providers during and after the trial. He stressed the importance of providing accurate information to prospective participants and said his organization "realized the need to have people readily

available who can explain the research to each participant".


Dr. Grant said that everyone in the room has the common goal of ensuring the well-being of

study participants and he identified several strategies to achieve this, including increasing the power of individuals to protect themselves, implementing a genuine informed consent process, providing HIV prevention services, treating HIV infection and other sexually transmitted infections, and providing treatment for side-effects related to the research study. Dr. Grant emphasized that HIV disease impacts already vulnerable populations and that it is important for research teams to identify ways to empower individuals involved in research.

On the question of treatment for HIV disease, Dr. Grant said the central questions have to do with logistics: how do you assure provision of treatment years after the

### *How do you assure provision of treatment years after the study concludes?*





study concludes? "We need to work through the mechanics of providing care...the details matter here," he said. Dr. Grant reviewed several approaches to health care provision, including options for medical insurance programs for trial participants in less developed countries. He said that co-payments are required in many insurance programs and that these are simply not affordable to a great many people. One approach would be for research sponsors to help develop treatment capacity in the public sector through provision of cash, equipment, training and other services. In exchange, the public sector would provide access to treatment facilities to study participants. (Two articles from the AIDS Vaccine Advocacy Coalition, whose Executive Director Mitchell Warren attended the consultation, discuss standards for community readiness and benefits for communities involved in clinical research. These articles are listed in References at the end of this paper.)


## Provision of ARVs for those who become infected during a trial

While there is not yet an international consensus as to whether trial participants who become infected with HIV should be guaranteed ART, the issue is steadily becoming a question of logistics and implementation rather than a hot topic for ethical debate. Several HIV prevention research networks have already made commitments to provide ARVs to their trial participants. For example, the International AIDS Vaccine Initiative (IAVI) has pledged to provide HIV care to participants who seroconvert and to make ARVs available to the participant for up to five years after ARV therapy is initiated. The HIV Vaccine Trials Network (HVTN), supported by the US National Institutes of Health, has also committed to providing ARVs and is creating a fund to support drug purchase.

Now the question is how to guarantee appropriate care years after a particular trial has concluded in areas that have very limited health care infrastructure. Several initiatives to address these logistical challenges are currently in the planning stages. IAVI is developing its program on a country-by-country basis. HVTN is planning to direct investigators at its sites to prepare ART treatment plans. Each site will be charged with identifying an administrator of its ARV program, most likely an NGO that currently provides services to PLWHIV and is able to ensure the confidentiality of client records.

Both networks see their ARV programs as a "bridge" to treatment, supporting therapy for individuals until they become eligible for a national ARV program in their country. IAVI's President Seth Berkley has written that, "In the end, only governments can provide long-term care guarantees. We need a development approach to strengthen their capacity to provide these services."






In response to a question, Dr. Grant said that treatment provision to people who are found to be infected with HIV at intake may be "the standard to shoot for". Two people in the audience questioned this, asking whether there should be preferential treatment for people who seek to participate in a trial, and noting that a guarantee of treatment for those who test positive at intake could provide an inappropriate inducement to volunteer for clinical studies.

## STANDARD OF CARE FOR PREVENTION

It is widely accepted that participants in HIV research should receive HIV prevention counseling and condoms to protect themselves from infection. In fact, HIV clinical studies are an important opportunity to expand prevention resources in communities where research is conducted. Yet there is no detailed, widely accepted standard of care for HIV prevention interventions provided to trial participants. In the context of the tenofovir study in Thailand, provision of clean needles to injection drug users has emerged as a central issue. Thai law forbids researchers from providing clean needles to injection drug users (IDUs) and CDC, the funding agency for the trial, is also prohibited by U.S. law from providing needles to IDUs. In addition, Thai activists have raised several other concerns, including those noted below.

At the consultation, Karyn Kaplan of the Thai Drug Users Network and Mike Martin of the CDC made presentations on the issue of prevention standard of care with a focus on clean needle provision to IDUs. Ms. Kaplan noted that her organization and its partners are in full support of research to develop new HIV prevention tools and want to support research among IDUs. Community groups have raised concerns about the trial and want to be more involved in its planning, she said, but "we want to be a value added, not an extra burden, not something to shake off your foot". Ms. Kaplan raised several concerns about the planned tenofovir trial, including: lack of community involvement in design and development of the protocol, use of placebo without provision of clean injecting equipment (the "most effective tool for IDU HIV prevention"), lack of an adequate policy regarding provision of methadone maintenance to enrollees, and an "unclear" standard of care for sero-converters and HIV infected IDUs who are screened out at intake.

Dr. Martin, a member of the research team for the CDC trial in Thailand, said that "we did try to involve the community," though he acknowledged that these efforts could have been improved. He said the research team is committed to improving community consultation. Dr. Martin outlined the HIV prevention package to be provided to IDU trial enrollees. The package includes education about tenofovir and the tenofovir trial and a comprehension test to ensure enrollees understand this information, risk reduction counseling, drug use counseling, HIV voluntary counseling and testing, provision of condoms and bleach, and methadone treatment. Dr. Martin noted that Thai law prohibits the research team from distributing clean needles, but that in a survey done with IDUs at the site, 97% said they were able to access clean needles, usually at a pharmacy. Finally, Martin cited evidence from a previous trial of an AIDS vaccine candidate showing a reduction in risk behavior among enrollees over the life of the trial.




The discussion that followed focused on the status of clean needle access, legal prohibitions on provision of needles in Thailand, and options for making needles accessible. Ms. Kaplan questioned whether needles are as readily accessible as indicated in the survey Dr. Martin cited, and she and others noted that needle access needs to be understood in the context of an ongoing crackdown on drug users in Thailand. A third party non-profit provider has offered to make needles available to study participants, independent of the study protocol, and there was discussion about whether this approach would be workable in the local context. Several people acknowledged that U.S. restrictions on needle provision also have a significant influence on conduct in the CDC-Thai study.

A researcher at a trial site outside of Thailand questioned how heavy a burden should be placed on researchers. "To what extent are trials supposed to be addressing all the issues in a society that lead to HIV infection?" she asked. An ethicist at the meeting said the question is what is the appropriate standard for HIV prevention overall. "If despite your best efforts," he said, "you are not able to give needles out, is it ethical to proceed with the research, or should the study be stopped?"

## **RESEARCH LITERACY FOR INDIVIDUALS AND COMMUNITIES**

Basic understanding of research practices are essential if community members are to meaningfully participate in the design and implementation of clinical trials, and yet research literacy efforts often receive limited funding and no standards have been established for these programs. Emmanuel Trenado of AIDES in France, and Leigh Peterson of FHI both made presentations on research literacy efforts at the Douala, Cameroon tenofovir site and implications of these experiences going forward. Mr. Trenado's presentation was prepared in collaboration with Fabrice Pilorgé of Act Up-Paris.

Mr. Trenado outlined his experience with collaboration between European advocacy groups and organizations working at the Douala site. He said that community groups had encountered difficulties in trying to have constructive dialogue with the local research team and that some of the larger NGOs were not aware of the tenofovir trial. The local media also was not well informed about HIV or the trial specifically and held many misconceptions about the research. According to Mr. Trenado, northern activists attempted to work as facilitators between researchers and community but felt that ultimately they had limited impact. It appeared that concepts such as use of placebo were not well understood by prospective trial participants. Mr. Trenado asserted that the community also felt that they had not had adequate discussions about the possible behavioral impacts (i.e. reduced adherence to safer sex guidelines) of study participation.



Mr. Trenado noted that the lack of research literacy and inadequate communication strategies could compromise future HIV prevention trials. Product manufacturers and trial sponsors should attend to these issues, he said, as necessary steps to build trust and a sense of ownership among communities participating in clinical research. One thing that is needed, he said, is some consensus on how communities should be involved in research.

Dr. Peterson noted that there are many benefits to be gained from research and treatment literacy efforts, including improved implementation of the study and enabling community members to make greater contributions to the research. At the Douala site, Dr. Peterson said her team has recognized some miscommunication with the media and the need to improve that communication. She identified a variety of challenges to promoting research literacy, including multiple languages spoken in the community, overall low literacy levels, lack of familiarity with scientific concepts and terminology, and difficulty in distinguishing research goals from prevention goals.

The FHI research literacy program at the Douala site is directed to potential trial participants and the larger community. It covers several topics, including scientific methods, clinical research, HIV disease, basics of HIV prevention research, and information particular to the local study. Dr. Peterson said the program begins with formative research to identify the community's experience

**Researchers seem to believe that “Science is...a cult of the learned and they have the answers which the community must receive”.**


***Community representative and activist***

with research and knowledge of HIV/AIDS. Literacy training is provided through open community meetings and consultations, research advisory groups, and street outreach. Dr. Peterson stressed that informed consent is "an ongoing process, not a form to be read and signed".

The FHI study staff reviews elements of informed consent at participant follow-up visits. The research team has also established a Participant Advocates program. Advocates are recruited from an organization independent of the research team and charged with observing participant counseling throughout the study. The goal is to ensure participants have received appropriate counseling.

Dr. Peterson said the research team had learned many lessons thus far, including the need for improved community input and representation, better bridges between the research team and international advocacy groups, earlier development of a communications plan, and more active demonstration of the research team's commitment to research ethics and community partnerships.

In the discussion that followed, a civil society representative suggested that literacy is needed for the wider community in proximity to the trial, not just participants and advocates. A specific concern was raised about a trial site where, according to the speaker, study staff have high recruitment targets sometimes ask prospective trial participants to sign an informed consent



document without providing adequate information about the trial. Individuals often seek to enroll in the trial, it was claimed, in order to get the physical exam that is promised, even though they know do not meet enrollment criteria.

## **MECHANISMS FOR COMMUNITY INVOLVEMENT IN TRIAL DESIGN AND CONDUCT**

While there was consensus at the meeting that community involvement is essential to successful tenofovir research, there was also wide acknowledgement that no standard exists for engaging community or even defining the community that needs to be engaged. Dawn Smith of the CDC, who is the Principal Investigator at the Botswana PREP site, made a presentation on community engagement efforts in that trial. Morenike Ukpong of The Nigeria HIV Vaccine and Microbicide Advocacy Group (NHVMAG) had been invited to make a presentation on civil society perspectives, but she was unable to attend the meeting. (Dr. Ukpong's PowerPoint presentation, as well as follow up communications with her, was used as a basis for the summary of her comments. Her PowerPoint slides were distributed to meeting participants in lieu of her attendance.)

Dr. Smith started her presentation by saying that in a small country like Botswana "the community is everyone," but that study staff use different approaches to reach distinct parts of the community. The investigators strive to hear directly from community members, and not rely solely on messages filtered through organizations or governments. On the question of who defines the research agenda in a community, Dr. Smith said that "we don't ask 'what research should we do' but we did ask the community if they thought tenofovir research was a good idea". Community is, she said, involved at every stage of the research and the study team aims for "consultation" over "confrontation" in its interaction with civil society.

### **One framework for community engagement**

A Global Campaign for Microbicides report suggests that the research team work with community members to develop a strategic community involvement plan. The plan might include creation of a community advisory board or another kind of advisory group, funding for a community advocate or ombudsperson position, or providing grants to local NGOs to promote community engagement. The GCM report also suggests the research team do outreach in the community to a range of stakeholders in addition to the "official" leadership, collaborate with non-governmental and community based organizations, and sponsor comprehensive health and community education programs to help community members put the planned research in context.

One of Dr. Smith's slides showed the partnership model her staff uses, detailing different ways that various stakeholders are included in community consultation. Site researchers do community preparedness research, hire community liaison officers, prepare informed consent documents, and present their research plans for review by ethics committees. Community members participate in CABs, serve on government "reference groups," and participate in periodic surveys and focus groups that help develop recruitment messages. Trial participants themselves can join a Participant Advisory Group, attend special meetings for study volunteers, and complete exit questionnaires that ask about their experiences in the trial. Study staff also do qualitative interviews with a subset of trial participants to learn about their attitudes and experiences in the trial.

***"The community is everyone..."***

## **Community engagement: a view from Ghana**


"Community engagement...should be done in a culturally appropriate context and one that does not conflict with our systems of governance ...nor compromises the confidentiality of study participants... For example, in Ghana, at the village level, the traditional authorities have to be informed of research issues..."

At the national level, the Ethical Review Committee (ERC) by its diverse composition (professionals and individuals from a cross-section of society) is expected to represent the views of the community and its concerns. In this study, the ERC has played a monitoring role by demanding regular reports from the study site, visiting the site and providing feedback to the latter regularly..."

An important lesson ... is that countries in which trials are to be carried out need to have sustainable systems in place comprising ethical review committees and other regulatory authorities as well as guidelines for engaging communities."

*Ministry of Health, Ghana*

Dr. Smith said that requirements for successful partnership between the community and researchers include a sense of joint ownership over the research, respect for each other's contributions, transparency about decision making, and collective efforts to keep "eyes on the prize" - namely, health research that can benefit the community. She said that while all participants in the process need to be honest with each other, this honesty should be expressed with a degree of "humility" that shows respect for other perspectives. Dr. Smith said that one area needing more exploration is how to involve the international community in the discussion about local research, noting the tension between hearing international perspectives and respecting the autonomy of local communities.



In her prepared slide presentation, Dr. Ukpong emphasized the importance of building real partnerships between researchers and community. She said that she felt that the consultation process had not been adequate in the (now discontinued) tenofovir trial in Nigeria. (Staff with FHI later said that the consultation process at the Nigeria site is on-going and is an important part of the exit process. The agency expects valuable lessons may be learned from this process.) Dr. Ukpong identified several barriers to successful partnership, including miscommunication, mistrust, and resistance on the part of researchers to work with community because, she said, "non-scientists are often seen as disruptive or incapable of understanding research concepts". She described the attitude as, "Science is indeed a cult of the learned and they [researchers] have the answers which the community must receive".

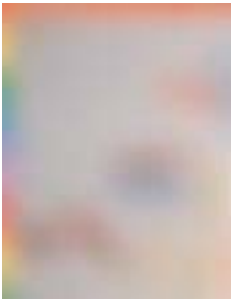
Dr. Ukpong also made a variety of suggestions for building and sustaining genuine partnerships to advance health research. One is for community and researchers to understand themselves as part of one community, rather than two. She wrote that, "The local researcher must learn to view himself/herself as a part of the community he/she works with...Researchers are not helping 'them'. It is about us". She wrote that more dialogue is needed between researchers and members of civil society, and that both sides need to overcome a sense of "mutual mistrust" and begin to see each other as true partners.

Other specific recommendations offered by Dr. Ukpong included making the research process more open and transparent, ensuring research findings are translated expeditiously into policy and practice, creating partnerships with the national government, and establishing independent bodies that can monitor the trials and maintain close contact with communities.

## From advising to mobilizing

In 2003, the Global Campaign for Microbicides (GCM) worked with the South African Microbicide Research Initiative to convene a meeting on community involvement in clinical trials. A report based on the meeting defines community involvement as "activities in which communities work collaboratively with the research team in decision-making, problem-solving, and project implementation". Community involvement can be largely advisory - "community representatives provide input into specific areas of the study as requested by the research team". It can be collaborative - "representatives and the research team cooperate in developing and implementing the research process". The report suggests that community involvement can also be understood as a process of broader social and community mobilization in which, "engagement in the research process strengthens community capacity to analyze and address its own health and development priorities".





# RECOMMENDATIONS FROM COUNTRY WORKING GROUPS

During the consultation, participants broke into working groups to discuss the key challenge areas and other concerns in specific research settings. There were break out groups focusing on issues in Botswana, Cameroon, Ghana, Malawi and Thailand. Recommendations were developed to address priority issues in each setting. While not binding on any party, these recommendations represent a positive step towards addressing some of the concerns with tenofovir research. Even so, several people at the consultation cautioned that those in attendance are not able to put all the recommendations into effect themselves. What is needed is ongoing dialogue and collaborative efforts on the country and international levels to follow through on the recommendations.

## TREATMENT AND CARE

The Cameroon group recommended that individuals who are found to be HIV-infected at intake be referred to the National AIDS Program and that laboratory tests needed to qualify for the Program be paid for by the research study. The group also recommended that trial volunteers be provided with Prevention of Mother to Child Transmission (PMTCT) services, and treatment for Hepatitis B and Hepatitis C virus co-infection. Treatment for HIV infection, including appropriate care for those with viral resistance to tenofovir, was also recommended. Those who experience adverse events from use of tenofovir should receive treatment for these events. The group recommended that the services noted above should be guaranteed for five years, and in the case of ARV therapy for HIV infection, five years from the time this treatment is initiated. If tenofovir proves effective, the group recommended that all study participants be provided with the drug for five years after completion of the trial.

**“Research is often designed in Europe or America. An impatient colleague arrives and looks impatiently for a co-researcher in the host country.”**  
*Researcher*

The Thai working group recommended that available linkages to care be more clearly articulated to participants and that information on accessing needed care be disseminated more widely. They also requested clarification of the registration status, availability and price of tenofovir for prevention and treatment in Thailand. The representative from Gilead confirmed that in many of the countries where these studies are taking place tenofovir is already being made available at cost - that is, at no profit. In countries where intellectual property protection does not apply, generic drug manufacturers are free to produce generic versions of tenofovir. As one activist pointed out, "at cost" pricing does not ensure affordability to all populations. A variety of measures will be necessary to accomplish widespread access to tenofovir, should it be approved for use as PREP.



## **STANDARD OF CARE FOR PREVENTION INTERVENTIONS**

The Thai group recommended exploring ways to provide trial participants with information about HIV prevention and treatment services that are not available through the trial sites. It also recommended examining options for ensuring high quality and culturally sensitive counseling, and implementing quality assurance programs to monitor counseling services.

## **RESEARCH LITERACY FOR INDIVIDUALS AND COMMUNITIES**

The Botswana group recommended that when educational materials are created for clinical trials they should be made in a variety of formats and languages in order to appeal to different groups and improve research literacy among participants and community members.. The group also said that researchers need literacy training about the community, and it recommended creation of training programs for researchers and protocol reviewers in order to improve their communication with the community and the media. (*Note: The Botswana Working group made general recommendations for clinical trials that were not meant to be specific to the Botswana study. The group did commit to bring these recommendations back for local discussion and implementation as deemed appropriate by local institutions and the community.*)

The Cameroon group recommended strengthening research literacy services for everyone, including health care workers, participants, and the whole country.

## **COMMUNITY INVOLVEMENT IN TRIAL DESIGN AND CONDUCT**

The Botswana working group defined "community" as everyone in the country, and recommended that some element of the community needs to be involved in each stage of the research process. The group recommended development of guidelines on community involvement in clinical research. The group noted that all stakeholders should be involved in developing the guidelines. It also recommended building community knowledge and understanding of research ethics. The working group called for the creation of feedback and communication mechanisms in clinical trials to identify and address concerns if and when they arise. In instances when these mechanisms are not successful in resolving issues, the group noted the need for a conflict resolution mechanism. The group recommended building ethics review capacity as well.





The Cameroon working group noted that trust between the community and researchers has been damaged and that regular meetings with multiple stakeholders would be one important step to rebuilding trust. The group also recommended strengthened efforts on ethical conduct of research and the informed consent process.

“We have to look at human resource development in less developed countries. It is unacceptable that we are still sending [immunological] samples from Africa to the North. We need to support training institutions so more work can be started and finished locally.”  
**Researcher**

Group members felt that many of the concerns with tenofovir research could be addressed by making sure there is a very thorough country-specific research protocol, assuming that protocol is reviewed and discussed with civil society.

The Thai working group recommended exploring opportunities for both community and stakeholder input to the trial, and approaches for researchers and community to work collaboratively in promoting the safety of trial participants and the rights of drug users.

## NEXT STEPS ON RECOMMENDATIONS

Several country working groups discussed specific follow-through plans. The Thai group agreed to explore issues of concern at a series of community forums and to address trial participant safety (especially for injecting drug users and commercial sex workers) at meetings in the coming months. The Cameroon group planned a two-day stakeholder meeting to be held in the country within the next few months.



# MOVING FORWARD ON TENOFVIR RESEARCH

At the closing session there was a strong sense that the consultation had been an important step in addressing the polarization that has characterized some tenofovir research, and in establishing an ongoing dialogue among stakeholders. Professor Bernard Lo, a bioethicist from University of California San Francisco said, "This meeting has given us the much needed opportunity to take a step back in order that we may take several strides forward."

*"This meeting has given us the much needed opportunity to take a step back in order that we may take several strides forward."*

The ultimate success of tenofovir PREP research depends upon follow through on the recommendations made at the consultation and ongoing dialogue and collaboration to address remaining concerns and new issues as they arise.

Several constructive recommendations for next steps were made at the closing session. These included:

**Establish a global stakeholders group.** There was broad support for creation of a stakeholders group to move forward with the recommendations at the meeting and to promote improved communication, coordination, and accountability as part of the tenofovir research effort. All the trial sponsors present at the consultation expressed willingness to consider financial support for meetings of the stakeholders group. The goal would not be to create a superstructure that takes autonomy from trials, but to establish a forum that can help maintain dialogue and take other actions to advance ethical and widely supported tenofovir research.

**Foster community research literacy and capacity.** Trial sponsors were encouraged to provide more support for research literacy and to identify dedicated funds in research budgets for this purpose. Also needed is a review of available research literacy materials, and development of new materials if necessary. Community members themselves should have a central role in developing and reviewing research literacy materials. In addition, support to community-based organizations playing a role PREP research will enhance civil society involvement in the research.

**Build true partnerships.** Local capacity development also means building genuine partnerships between researchers in developed and developing countries. Investigators in less developed countries often feel like "junior partners".



**Develop standards of practice for community engagement.**

Though community engagement activities will differ in each community, development of guidelines and minimum standards for engagement efforts, as well as approaches to measuring and monitoring engagement, would be extremely useful. Guidance coming from the UNAIDS HIV Prevention consultations may be helpful in suggesting standards in this area.

**Hold forums on best practices in community consultation.**

There was broad support for holding forums at the upcoming International AIDS Conference in Toronto, and other regional and international meetings, on models for community consultation

**Promote coordination of tenofovir research.**

Tenofovir PREP research is sponsored by several different organizations. The overall research effort is not coordinated through a trials network and no global research plan has been developed. "There is no network for tenofovir trials," one sponsor said, "these have been like orphan trials". Much greater collaboration, planning and coordination is needed among tenofovir researchers and sponsors in order to advance this research rapidly and efficiently, and facilitate timely product licensure and distribution if tenofovir proves safe and effective as PREP.

**Strengthen national ethics review boards.**

These organizations can play a crucial role at promoting civil society engagement and ensuring adherence to ethical guidelines.

**Integrating research into a comprehensive response.**

Clinical research should be more fully integrated into national treatment and prevention plans so that services provided through clinical studies become part of a country's comprehensive response to the epidemic. Donor governments and institutions can do a great deal to promote and support better integration of research, prevention, care and treatment.

**Follow up on recommendations.**

Periodic updates on country level follow-through will be an important mechanism for maintaining the momentum generated at the consultation.

The consultation was characterized by a broad acknowledgement of the importance of tenofovir research and recognition of the need to work more collaboratively to address current and future concerns with PREP trials. HIV prevention research is at an early stage in many resource-limited countries, and already numerous important lessons have been learned. The challenge for researchers, sponsors, advocates, communities and governments is to apply these lessons in a way that will advance ethical, widely supported, and urgently needed HIV prevention research.



## REFERENCES

AIDS Vaccine Advocacy Coalition (AVAC), "Correlates of Readiness," and "Vaccine Trials: Leaving communities better off," in AIDS Vaccine Trials; Getting the global house in order, AVAC, New York, May 2004

Berkley S, Thorny issues in the ethics of AIDS vaccine trials, Lancet 2003; 362(9388):992

Fitzgerald DW, Pape JW, Wasserheit JN, Counts GW, Counts GW, Corey L. Provision of treatment in HIV-1 vaccine trials in developing countries. Lancet 2003; 362(9388):993-994

Global Campaign for Microbicides, Rethinking the ethical roadmap for clinical testing of microbicides, report on an international consultation, Global Campaign for Microbicides Washington, D.C., May 2005

Global Campaign for Microbicides, Mobilization for community involvement in microbicide trials, Report from a dialogue in Southern Africa, Global Campaign for Microbicides Washington, D.C., 2004

***This report was written by Chris Collins under the direction of Yasmin Halima, International AIDS Society.***

# APPENDIX

## MEETING PARTICIPANTS

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Abdelkader Bacha	AfriCASO	Senegal
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Marjorie Chaponda	UNC-HIVNET Project	Malawi
Marge Chigwanda	CONNECT, University of Zimbabwe-UCSF	Zimbabwe
Katchit Choopanya	Taksin Hospital	Thailand
Rutt Chuachoo Wong	Ministry of Health	Thailand
Edith Clarke	Ministry of Health	Ghana
Chris Collins	IAS	Switzerland
Grace Ebum	Delano Assoc. for Reproductive & Family Health	Nigeria
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Helene Gayle	Gates Foundation	USA
Katy Godfrey	NIH	USA
Gregg Gonsalves	GMHC	USA
Bob Grant	UCSF	USA
Alan Greenberg	CDC	USA

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Cate Hankins	UNAIDS	Switzerland
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Howard Jaffe	Gilead	USA
Karyn Kaplan	Thai Drug Users Network	Thailand
Kristi Kenyon	Bonela	Botswana
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Mitchell Warren	AVAC	USA
Angela Wassuna	The Hastings Center	USA
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Pierre Ongolo Zogo	Ministry of Health	Cameroon

## INVITED BUT UNABLE TO ATTEND

Morenike Ukpong*	Nigeria Vaccine and Microbicide Advocacy Group	Nigeria
James Clovis Kayo	Cameroon Network of Association of PLWHA	Cameroon
Daniel Okpanul*	Goodwill AID	Ghana
John Gyapong*	Ministry of Health	Ghana
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Themba Moeti	Ministry of Health	Botswana
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\* Submitted comments following the meeting



