PHASE 2 TRIAL OF ORAL TENOFOVIR USE AS A CHEMOPROPHYLAXIS FOR HIV INFECTION IN NIGERIA: THE OUTCOME OF COMMUNITY INVOLVEMENT WITH THE SCIENTIFIC RESEARCH PROCESS

REPORT OF THE OUTCOME OF DIALOGUE BETWEEN THE COMMUNITY AND RESEARCHERS INVOLVED WITH THE PHASE 2 ORAL TENOFOVIR TRIAL IN NIGERIA

A REPORT BY THE NIGERIA HIV VACCINE AND MICROBICIDE ADVOCACY GROUP
Acronyms

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<th>Acronym</th>
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<td>AIDS</td>
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Acknowledgement

The report of the ongoing dialogue between stakeholders involved with the ongoing phase2/3 tenofovir trial in Nigeria cannot have been published at a much better time. The report hopefully would feed into the ongoing global discussion on defining ground rules for new HIV prevention technologies trials as well as feed into decision making processes on the global crisis related to TDF trials in general.

In Nigeria, there is a lot of renewed interest in research and clinical trials related to HIV/AIDS prevention and control. This had cumulated to significant prominence being given to issues on emerging HIV technologies in the newly developed five year National strategic plan on HIV/AIDS mitigation and control.

There are also increasing private initiatives and public institutional research on issues related to new HIV prevention technologies. The lessons learnt from the TDF trial in Nigeria would feed into processes for developing and implementing future research protocols. One of the highlights of the recommendations include the need for future research processes to focus on ensuring partnership with all stakeholders throughout the research process. Scientists can no longer assume the status of a reservoir of knowledge. This would ensure maximal utilization of limited resources such that end products are eventually taken up and not left on the shelves has had been the result of many past research efforts.

The Nigeria HIV Vaccine and Microbicide Advocacy Group (NHVMAG) would like to acknowledge the efforts and contributions of the following persons who made this report possible. They include Dr Ayo Arowojolu, the local principal investigator involved with the TDF trial going on in Nigeria; Kristin Perterson for reviewing the manuscript and making useful suggestions; Tubosun Obileye who made useful liaison contacts with the National Agency for Food and Drugs Administration and Control (NAFDAC); the members of the steering committee of NHVMAG who were instrumental in facilitating the discussion; and all stakeholders who made contributions to the discussion and dialogue process.

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Morenike Ukpong and Omololu Falobi
Forward

The design and conduct of clinical research has been a concern of AIDS activists since the beginning of the epidemic, particularly in North America and Western Europe. Last year, a controversy exploded about clinical trials of oral tenofovir to prevent HIV infection in Cambodia, with both local and international activists questioning the ethics of these studies. The controversy quickly spread to West Africa and elsewhere in Southeast Asia, where similar studies were being planned.

The issues raised by the tenofovir studies—the provision of care to trial participants who seroconvert during the course of the study, the involvement of the AIDS community in the design of the study, the nature of informed consent for vulnerable populations among many others—have implications for all clinical research in Africa, Asia, Latin America, the Caribbean, Eastern Europe and the Newly Independent States.

As more and more research is conducted in resource-poor countries, the need to confront these issues becomes a critical task for all people concerned about ending the AIDS epidemic. For without research, we will have no new treatments, vaccines, microbicides or behavioral interventions for HIV/AIDS and we will never learn how to best use the technologies we have now in settings where they are being newly, and often differently, deployed.

However, research is a partnership between scientists and people with AIDS and communities at risk. The "old-fashioned" view of PWLHAs or individuals at risk of HIV infection as objects of research experimented on by medical professionals ended with the birth of the AIDS activist movement in the 1980s. The Nigeria HIV Vaccine and Microbicide Advocacy Group's report on the dialogue between their community and researchers on the tenofovir trial is an important and groundbreaking document in the history of AIDS research.

What NHVMAG has done is to collect the concerns of all stakeholders in the tenofovir trial, synthesize them and develop a set of recommendations, which offer local solutions to the key challenges raised by the studies. The tone of the report is also remarkable. While some activists from around the world have loosely thrown around accusations of unethical conduct unnecessarily creating fear and suspicion about all AIDS research, NHVMAG has methodically and coolly analyzed the situation in Nigeria, pointing the way for activists across the globe as they deal with the challenges of AIDS research in their own countries.

Some of the dilemmas posed by the tenofovir studies will be difficult to solve, but they will only be solved if researchers, funding agencies, national governments, partner with the AIDS community in moving forward. NHVMAG has offered a roadmap for us to begin that journey together.

Gregg Gonsalves
Director of Treatment and Prevention Advocacy
Gay Men's Health Crisis
New York, NY
Summary

The document summarises the ongoing dialogue between community activists, researchers and other stakeholders involved with the phase2/3 tenofovir trial in Nigeria. Tenofovir, a drug used for the management of HIV infection is been tested for possible prophylactic effect against HIV infection in uninfected individuals.

Concerns raised by community activists about the trial include:

1. the need for the study design to ensure long term care for trial participants who become HIV positive while participating in the study
2. defining the criteria of success for the trial
3. explanation on why a phase 1 trial was skipped when no such study had been done on assessing TDF use in non infected individuals
4. the need for community preparedness before the trial begins
5. need for the establishment of a community Advisory Board to monitor the trial
6. addressing the issue of informed consent for trial participant
7. guaranteeing the long term care and safety of trial participants participating in a novel trial
8. defining the subject/community benefits from the trial especially in terms of ensuring access to the trial drug once proven effective
9. how does the trial ensure ‘patient confidentiality’
10. how the study is being monitored and evaluated independent of the study sponsors
11. how thorough was the review process done by the various review bodies in view of the limited understanding of issues related to new HIV prevention technologies
12. what was the depth of government’s involvement with this trial
13. how much community involvement was there in the design and implementation of the trial
14. the need for transparency and continued dialogue with the community on the outcome of the research

The report also summaries the outcome of the dialogue with the authorities of the University College Hospital, Ibadan as well as the recommendation made by NHVMAG on the research process.

It is however presently apparent that the researchers have not made significant changes to the research protocol despite the limited and cordial steps taken to institute a dialogue process. The phase2/3 TDF research process is still ongoing in Nigeria with recruitment of new clients who have limited understanding of the research process.

The next step ......................?
Justification for research and development of new HIV prevention technology

AIDS presents an unprecedented challenge. Recent figures released by UNAIDS and WHO show an estimated 37.8 million people now living with HIV worldwide. AIDS is the leading cause of death in sub-Saharan Africa, where the disease killed 2.3 million people in the year 2003 alone. AIDS poses a serious threat to the achievement of all key international development goals, not just those in health. In many countries, it is single-handedly reversing the hard-won development gains of the last 50 years.

Worldwide, it is recognised that the current AIDS prevention efforts – including HIV counselling and testing, promotion of abstinence, mutual fidelity, partner reduction, delay of sexual debut and condom use – must be sustained and increased, and new efforts to expand access to treatment are critical. At the same time, the rapid spread of the epidemic and its dire social, political and development ramifications highlight the urgent need to broaden the range of available prevention strategies and to see new prevention research in the context of a comprehensive AIDS control programme that includes prevention, care and treatment. This is in view of the fact that despite increased funding, political commitment and progress in scaling up presently available responses, the epidemic continues to outpace the global response.

While it is significantly important to scale up existing interventions so as to prevent new infections and save lives today, current responses will be limited even if fully implemented. Treatments can prolong life, but they are not a cure. Present prevention options can reduce rates of HIV incidence but will not end the epidemic. Without prevention options that can better meet the needs of people at risk of transmitting or contracting HIV, continued HIV incidence will place higher and higher demands on resources, making comprehensive programmes unsustainable.

In the long term, new prevention tools will play a critical role in ameliorating the effects of the AIDS epidemic especially in the settings that are hardest hit. In the same way that successful treatment regimens require triple and quadruple therapy, successful prevention requires multiple forms of intervention and complementary tools aimed at meeting the needs of different people. To meet this need, a growing array of public, commercial and non-profit entities are engaging in the search for new HIV prevention technologies one of which is the use of tenofovir as an oral prophylaxis to prevent HIV transmission.

TDF has been selected for investigation as a prophylaxis against HIV because of its unique pharmacological profile – it is an anti-HIV drug that works by inhibiting an important enzyme in the HIV life cycle, called nucleotide reverse transcriptase. By doing so, tenofovir stops HIV from invading cells that have not yet been infected with the virus. Studies in monkeys have also shown that it can prevent transmission of a virus that is similar to HIV, but it is not yet known if it has the same effect in humans. In addition to the convenience of being used as a once daily single tablet, its safety profile has been shown to be comparable to that of placebo among HIV infected persons. It had also been shown to have striking anti-HIV potency with a low potential for selection of resistance viruses. TDF is cleared from the body by the kidneys and is not metabolised by the liver therefore it has limited potential for pharmacological interactions with other hepatically metabolised drugs.

One of the strong points for exploring the possibility of the use of TDF as an oral prophylaxis against HIV infection includes the fact that condoms and potential vaginal microbicides would require correct
and consistent use during every coital act to be effective. This person-controlled use of products often interferes with the effectiveness of such products. An HIV vaccine, when produced, would eliminate this set back. However, the prospect for the development of an HIV vaccine is still far off in view of the many constraints and identified obstacles to its development. TDF, when shown to be effective in preventing HIV infection, could possibly then act as a stop gap and effective systemic control for HIV infection whilst the vaccine is being developed. Hopefully, it should be able to provide a wider range of protection from HIV infection unlike the condom and microbicide which only protects against sexually transmitted HIV infection.

Clinical trials are therefore presently being conducted in three African countries - Douala, Cameroon; Ibadan, Nigeria; and Tema, Ghana - to determine the safety and effectiveness of daily oral tenofovir to prevent HIV among heterosexual women at high risk of infection. It is also planned in a fourth African country - Lilongwe, Malawi - to determine whether tenofovir can safely and effectively prevent HIV among high-risk heterosexual men.

Family Health International, a research and service organization based in Research Triangle Park, North Carolina, is managing the trial and is responsible for all aspects of the study. The research is being supported by a grant awarded to Family Health International in 2002 by the Bill & Melinda Gates Foundation.

The local principal investigator on the trial in Nigeria, Dr A Arowojolu, gave an insight into the TDF trial in Nigeria. He wrote:

Nigeria was selected as one of several sites for the daily oral tenofovir (TDF) trial for several reasons. All sites were selected because their populations have high rates of HIV infection, which is an important factor for determining the effectiveness of possible HIV prevention drugs. By 2002, when the study was being planned, Nigeria’s HIV prevalence rate was reportedly 5% and rising, and prevalence of HIV infection among high-risk groups was 22% – 35%. In developing tools to fight the spread of HIV/AIDS, it is essential to bring the benefits of research to those groups that are most vulnerable to infection. One of the goals of the project is to stop the HIV epidemic and so the trials are slated where the epidemic is, while being sensitive to all the issues that make people vulnerable -- social, economic or gender-based. If tenofovir is shown to be safe and effective, HIV prevention programs that provide the drug can be established at the study sites. In addition, a pre-study site evaluation determined that the College of Medicine at the University of Ibadan has the appropriate infrastructure and staff capacity to enable it to handle logistics of the trial effectively.

The study also tried to incorporated community views and concerns right from the onset of its design after extensive consultation with local experts as well as community members. This consultative procedure also preceded selection of the site. Formative research conducted in preparation for the trial included: identification of areas where HIV-related risk activities are prevalent; development of relationships with local stakeholders, surveying their perspectives on trial-related issues; and developing recommendations for recruitment, informed consent, referrals to care, and for minimizing stigma. Potential trial volunteers, men and women at risk for HIV from the communities, people living with HIV/AIDS, and health care providers have all taken part in meetings, interviews, and focus group discussions, which have been invaluable in informing study design and implementation. The Formative Research Team continues to meet with stakeholders in the community to respond to their questions and concerns and to keep them informed about the study’s progress. They also continue to collect important data on the acceptability of oral TDF for HIV prevention, and of the trial itself, among participants, their partners, and the larger community. The Formative Research Team is independent of the clinical trial research team.

Volunteers eligible for the trial are HIV-uninfected women between the ages of 18 and 35 years who, by their sexual behavior, put themselves at the risk of acquiring HIV infection (average of three sexual acts per week and more than three different sexual partners per month). As outlined in the study protocol, the women also must be willing and able to give informed consent, to use the study product as directed and to participate in the study for up to 12 months. They must have adequate renal (kidney) and liver function,
be in general good health, and not be pregnant, breastfeeding or planning to become pregnant during the 12 months of study participation. The voluntary nature of the women’s participation is emphasized repeatedly in every interaction study personnel have with participants; all women are free not to participate in the study and may discontinue participation at any point.

Screening and enrollment for the trial began July 5, 2004, after approval of the protocol by the University of Ibadan’s ethics committee (UI/UCH IRC), the National Agency for Food and Drug Administration and Control (NAFDAC), and Family Health International (FHI)’s Institutional Review Board, completion of formative research, site-preparedness activities, training in the trial protocol and Good Clinical Practices for study personnel, close consultation with community members, and other preparatory steps.

The study entails participants being randomized to receive either tenofovir or a placebo once a day for the duration of the trial. All participants will receive HIV risk-reduction counseling, condoms, and treatment for symptomatic sexually transmitted infections during monthly clinic visits throughout the trial.

Screening and enrollment were temporarily suspended in November 2004 in order to address a few procedural and administrative irregularities – none of which entailed or caused any risk to participants’ health or well-being – that had been identified by an FHI review team. Such a step is not at all unusual in efforts to ensure the quality of clinical trials. Before the temporary enrollment suspension, 125 women had been enrolled and there was no interruption in their participation in the study at any point. In January, 2005, after additional on-site evaluation and training of study staff, screening and enrollment of new participants resumed while old participants are continuing to be followed up. The study will continue until 400 women have been enrolled.

As specified in the protocol, all study participants are followed for 12 months, during which they visit the study site once a month. At those visits, women are tested for HIV and receive HIV-risk-reduction counseling, condoms and treatment for symptomatic sexually transmitted infections. Every two to three months their liver and kidney functions are evaluated to identify possible reactions to the drug. Women who test HIV-positive during the course of the study receive enhanced referral to HIV care and support services, including antiretroviral drugs when necessary, at facilities identified by the University of Ibadan. Those who experience medical problems that are directly related to their participation in the trial will receive medical services for those problems free of charge. A health counselor has recently been employed to assist study participants who may develop complications or acquire HIV infection during the study. Their functions include the provision of support for such participants in the hospital and community.

Three independent participant advocates from Association for Reproductive and Family Health, Ikolaba, Ibadan, are working with the trial team. The role of the advocates is to ensure that participants’ rights are upheld throughout the informed consent sessions. Participants also have the right to refuse to use them. So that they can serve as true advocates on behalf of the participants, the advocates are not under our control and we do not pay their salaries.

Some of the discussants on the Nigeria eforum (www.nigeria-aids.org) discussion on the TDF trial debate noted some possible justification for the TDF trial:

.. it is certain that there is no known effective microbicide or vaccine for HIV prevention yet. It is unlikely that one will be available in the next 10 years. This is why all efforts should be intensified to encourage researches on other preventive measures that come into the picture. The ongoing TDF (tenofovir) study in Africa is one of such.

... Here in Africa, the CSW are very mobile and are only on the job for a few years. Most take on the job to gather enough money to start a business or support themselves in high institutions. They give fictitious names and address in order to hide their identities from health workers and researches. This is why it has been difficult to give a comprehensive health care to CSW in Africa. HIV positive CSW continue their business unabated and are reluctant to go for medical care due to their erroneous belief that they will be detained and handed over to the police or given lethal injections. Some men out of annoyance deliberately infect CSW in order to spread the disease. These men willingly burst their condoms with finger nails or pay a high price for a sexual act. These are reasons for continuous rise in prevalence of
HIV infection among sex workers. It is believed that if one stays long in the business one will acquire HIV.

This is why we need additional HIV preventive measures that are user controlled for the CSW, such as microbicides and TDF. However, it is doubtful if vaginal microbicides will be appropriate for someone who has many sexual acts in a day. After repeated applications the vagina will be so full that the microbicide will flow out to the embarrassment of the user.

This is likely to affect the acceptance and continuous use of microbicides by CSW. Microbicides will be more acceptable to other youths and elderly that will also benefit from its lubricating effect. TDF on the other hand, is a once daily pill just like oral contraceptive pill. It is independent of sexual act or the sexual partner and covers all other modes of HIV transmission. Just like all preventive measures, it has its limitations but we should not just discard it for selfish reasons.

The ongoing research in Africa will educate us and possibly help us to develop other preventive medications. (Posting 27 Appendix 1)

If found effective, the drug (TDF) will bridge the prevention gap created by the absence of a vaccine for HIV. It will be an additional choice for people with unmet HIV prophylactic needs (i.e. sexually active men and women who can not use condoms, microbicides or vaccines). Persons wanting temporary protection from HIV (e.g. long distant drivers, commercial sex workers, students etc) may also find the drug useful. (Posting 31 Appendix 1)

A number of concerns were however raised by community advocates during these discussion sessions. The subsequent pages presents these expressed concerns and made recommendations.
Phase 2/3 tenofovir trial in Nigeria: concerns

Study design and implementation

Many of the community AIDS and health activists expressed concerns and questions relating to the design and implementation of the study as well as the contents of the research protocol. NHVMAG’s Ethic and Scientific Committee extensively reviewed the protocol and noted issues of concern to the IRB of the University College Hospital, Ibadan, Nigeria where the trial was taking place (Appendix 4 Communication 2). During the dialogue on the listservs, many other issues and concerns were also expressed about the design and implementation of the protocol. These include the future implications for HIV management in trial volunteers who use TDF continuously or irregularly and get infected. Other concerns are those of future prospects for uptake of the drug if found effective in view of the poor drug ingestion culture of Africans, criteria for evaluating the success of the trial and more importantly, the fact that phase 1 trials were not conducted in HIV negative individuals. Below are some extracts of the discussions.

The concerns of many of the people who have raised issues so far are on the processes of the trial - NOT the names of trial volunteers or the list of those who will be given placebos or the real thing. Surely, discussions about the processes of a trial that involves human volunteers and has potential for major impact on the trend of the epidemic, should be in the public domain! (Posting 12 Appendix 1)

This trial is nothing like the microbicide and vaccine trials. We are talking about systemic intake. What happens to the volunteers who are on tenofovir, take it inconsistently and then get HIV infection? How would their future use and access to ARVs be affected? Secondly, for those who took tenofovir consistently and religiously during the trial and then discontinue once the trial stops but now get infected with HIV, what happens to them? HIV has no cure. The best we have now is ARV. We cannot jeopardise the chances of research participants to future access to this drug because they choose to be heroes - for me and you! (Posting 16 Appendix 1)

Finally, what benefit would the research be if at the end of this Phase II/III trial, tenofovir is found to be effective in preventing HIV infection when taking daily as an oral pill, yet studies show that people do not consistently take daily medications for various reasons (even for treatments how much more for prevention!). Not all trials have to be conducted; conducted trials have to be to the benefit of all. (Posting 16 Appendix 1)

What exactly is FHI's objective? A 30%, 50%, 80% success? What if tenofovir proves to be "half effective"? Is "half protected woman" better than nothing? To make it short: what are your criteria of success? How will you cope with the results if just "half good"? (Posting 17 Appendix 1)

You also said : We believe, as you do, that both individuals and communities need to participate actively in assessing the risks and benefits of trials. Talking about the risks... You mentioned very few (you did not mention any). Scientists usually make sure that risks are well understood and try to favor the most cautious attitudes towards engaging into a clinical trial. Is there a scientific evaluation of the effect of a long course daily dose of tenofovir on the future efficacy of treatments? While we know that Tenofovir can not be compared with Nevirapine in terms of its potential for selection of resistant virus, still we would love to learn from you that it is not an issue. If you have good reasons to think that there is NO such consequences, you should nonetheless present your arguments in the protocol and informed consent. (Posting 17 Appendix 1)

Has tenofovir been proven safe as a 12 months long MONOTHERAPY on HIV negative people? Not to my knowledge. I understand that this question is to be answered through this phase II/phase III trial. If FHI needs to further question the SAFETY, it means that there might be some risks that you don't fully control yet. I would like FHI to be more transparent about this. Clearly, running a "safety and efficacy" trial is, in its terms, questionable. (Posting 17 Appendix 1)
You have to take into account that testing hundreds of people will induce a high demand for care and support, and prophylactic treatments. How will FHI cope? (Posting 17 Appendix 1)

Again, how can you ensure safety when you did not fully test it first? How can you run a "safety AND efficacy trial" at once? I have never heard of such a thing before. Phase II and III are usually separated, and their design quite different to avoid putting huge numbers at risk. "safety" should have been tested on a small number of volunteers (not at risk). This is the STANDARD of science. (Posting 17 Appendix 1)

The College of Medicine believes that Tenofovir(TDF) is a safe drug for use as a chemo-prophylactic against HIV infection following the result of phase 1/II in literature. The provost particularly noted that a number of Phase 1 studies on TDF have been conducted in HIV negative participants, including studies on drug interaction, renal impairment and the drug's pharmacokinetics (studies GS 909, 914, 919, 930, 932, 943 and 1037). NHVMAG could not however find published peer reviewed reports on the study of tenofovir use in HIV sero-negative individuals during its literature search. We note that the phase I safety trial reported in the literature was done amongst HIV-positive people, not HIV-negative individuals. (Patricia Barditch-Crovo, Steven G. Deeks, Ann Collier, et al. Phase I/II Trial of the Pharmacokinetics, Safety, and Antiretroviral Activity of Tenofovir Disoproxil Fumarate in Human Immunodeficiency Virus-Infected Adults. Antimicrob Agents Chemother. 2001 October;45(10): 2733-2739). (Posting 31 Appendix 1)

Is this drug being tested for dosage? Duration? Frequency of use? Toxicity? (Exchange 1 Appendix 2)

FHI needs to be asked exactly how they will determine if the drug is working--what is the criteria for evaluation? (Exchange 1 Appendix 2)

Under "where will the study take place?": he mentions that if tenofovir is successful, it can be established as a prevention mechanism in the study sites, but how? does he mean that FHI will provide tenofovir for free? who will distribute? a very unclear promise. (Exchange 1 Appendix 2)

I just wondered why every new HIV prevention technology is promoted as a female controlled option. Yes, I do understand about microbicide but then, how does HIV vaccine and prophylactic use of tenofovir become a female controlled option as you rightly noted. (Exchange 2 Appendix 2)

Community preparedness

There are a number of reasons why communities need to be prepared for new preventive technologies research and clinical trials before they begin. Usually, new prevention technology research involves the recruitment of healthy subjects for research purposes. Most health researchers recruit participants from individuals or family members of those personally affected by a disease or condition, which is different from HIV prevention trials: non infected persons are the volunteers and statistical analysis is based on seroconversion. It is usually far more difficult to generate commitment among individuals who have not yet been personally touched by HIV. With HIV/AIDS related research, the stigma associated with HIV infection may make recruitment of health participants much more difficult.

Community preparedness efforts that are established prior to the execution of a clinical trial or the recruitment of the first volunteer, help to increase the community’s understanding of the research objectives, increases support for the research and research participants, and in the long run, ensure the demand for the product in the community. The trial is an opportunity to develop community understanding about AIDS and the tested product, and expand delivery of AIDS treatments and laboratory capacity at health centers.

Community advocates raised concerns on the level of community preparedness for the TDF trial. Some of the discussions on this issue are quoted below.
First, it might be nice to explain clearly how the community was effectively prepared for this trial. This is an imperative for research processes and it may be nice to define this issue. (Posting 4 Appendix 1)

I guess the researchers are playing on the low level of awareness and on participants rights as regards new technologies (Posting 7 Appendix 1)

…. and propose that NGOs should actively commence processes of getting high risk groups and other potential cohorts for clinical trials adequately prepared to have full knowledge and understanding of the whole concepts of clinical trials and the extent of risk and benefits trials bring to both individual participants and the community as a whole. (Posting 8 Appendix 1)

At the end of the day, we firmly state that first thing must be done first and the Nigerian community as a whole need to be adequately prepared for clinical trials involving human subjects. (Posting 8 Appendix 1)

Establishment of a Community Advisory Board

In HIV research, the advisory process has traditionally been ensured through the creation of a Community Advisory Board (CAB). Respect for social and cultural structures of local communities has lead to the need for some site to develop alternative advisory structures to guarantee direct stakeholder input. Alternative advisory structures to CABs require that alternative methods for gathering input from the community must be guaranteed and opinions can be exchanged. These structures provide a formal channel for ongoing education, communication, advocacy, and problem solving among representatives of the community. It could also facilitate appropriate, timely, and ethical research efforts. The establishment of a CAB for any research in HIV/AIDS is essentially strengthened in its equity, scientific integrity, and practicality by the integral involvement of the HIV-infected and affected communities. It also fosters collaborative projects involving the community, which advances HIV identification, prevention, and treatment service efforts that are scientifically based, rigorously evaluated, acceptable and sustainable to and by the target communities.

Despite the various advantages identified in establishing a CAB, researchers involved with new HIV prevention technologies research have raised various concerns. They felt CAB members and the community could start making astringent demands from the researchers. But discussants felt that a well constituted and educated CAB would provide the critical linkage between science and the community and that such fears are unfounded. Below are extracts on discussions on the issue of establishing a CAB for the TDF trial.

We also need to hear from the Community Advisory Board (CAB) of the research project if actually it is in existence. As community advocates, we have learnt over the years through bitter experience not to trust the ethical committees/IRBs of institutions no matter how highly or lowly placed. Researchers all over the world have goals and milestones they are determined to achieve which can easily make them take decisions that might not ultimately benefit the study community. That is why even in the USA, an IRB approval is just the beginning of the process and can not under any circumstances substitute the roles of CAB and advocates in driving research agenda on the path of community friendliness. That is why all modern clinical trials of this magnitude must have a well represented CAB which acts as intermediaries between researchers and the study community to ensure that all the ethical provisions as approved by the IRB are actually implemented among the study subjects. (Posting 13 Appendix 1)

The provost (of college of Medicine, Ibadan) felt that establishing a CAB does not necessarily translate to community consultation and CAB has the potential for fuelling demands by some privileged members, which may not necessarily translate to community needs. While NHVMAG appreciates this concern, we believe that constitution of a genuinely-representative and functional CAB is a priority need. Aside from the fact that establishment of a CAB is a standard international requirement for any research study involving human subjects, NHVMAG believes that a CAB is necessary to provide the critical linkage
between science and community in a way that goes beyond the duties assigned to a single individual. We intend to continue to discuss with the study team on the need to put this important structure in place. (Posting 31 Appendix 1)

I am also of the opinion that the establishment of CAB is a necessity to serve as an interface between research and the community. Something similar to this or exactly like CAB needs to be setup by the UCH-medical team to further improve the data integrity of the study during and after the trial (Posting 15 Appendix 3)

However, I will like to caution on the setting up of this CAB issue. I shared the concern of the Provost at Ibadan. There is need to think over this especially on the constitution of such bodies, so that we wont have problems in our hands later on. Community awareness is a must, forming a board from them is delicate issue so that we don’t start having unnecessary demands in our hands. (Posting 17 Appendix 3)

I also feel that a CAB is definitely needed. This is almost a standard practice now. What is important is too ensure that the CAB is well constituted and that they fully understand their roles and responsibilities. NHVMAG has a role to play independent of the researchers. There are guidelines for CAB’s - the HIV Preventions Network have some, also last year a Southern African consultation was convened by the GCM to discuss the issue of community involvement in Microbicide research. (Posting 21 Appendix 3)

The CAB if properly constituted can help to dispel such rumours. I do hope though that this will not lead to coercion especially with the more disadvantaged sections of the community - this could happen when word get round that you can get free treatment for all ailments by enlisting in the study. The pros and cons need to be carefully considered and the push for the development of national standard of care guidelines is a move in the right direction. (Posting 24 Appendix 3)

Informed consent process/standard of informed consent

Informed consent is the process by which a fully informed trial participant can participate in a research process after fully comprehending the whole concept of the trial. It originates from the legal and ethical right the participant has to direct what happens to their body and from the ethical duty of the researcher to involve the individual in their health care. The most important goal of informed consent in trials is that the volunteer has an opportunity to make an informed choice to participate in the trial. It is generally accepted that complete informed consent includes a discussion of the following elements: the nature of the decision/procedure; reasonable alternatives to the proposed intervention; the relevant risks, benefits, and uncertainties related to each alternative; assessment of patient understanding and the acceptance of the intervention by the patient.

Although reputable researchers do not try to fool people or sign them up against their will, individuals sometimes have difficulty understanding the information about a trial before agreeing to participate. Individuals may not understand the medical terminology and/or clinical requirements of a study, and they should be encouraged to ask questions until they understand all aspects of treatment.

For the TDF trial, community advocates raised some specific issues as regarding the informed consent process especially with respect to informing the participants about the safety and possible side effects of the drugs to be taken. Some of the issues are highlighted below

What papers have the trial participants signed? (Posting 6 Appendix 1)

I guess toxicity has been tested before introducing TDF in the market as a treatment, but the conditions might have been different (ex: in triple combination, for several weeks only, on seropositive people only, etc.). We need to know exactly what still has to be tested, as far as safety is concerned. Otherwise there can’t be any fully "informed" consent, ie comparing risks and benefits. ? (Posting 17 Appendix 1)
Care of subjects

Long-standing fear, apprehension, and skepticism exist amongst the populations about medical research because of abuses that have happened in the past (e.g., the Pfizer meningitis study in Kano). Many feel that they do not want to give up rights or lose power in order to be "experimented on." Others may be skeptical about the quality of care that would be provided in a clinical trial. Some may find that trial recruitment strategies are not sensitive to their needs.

Usually, for participating in this study, participants incur costs such as opportunity costs for doctor visits, hospital stays and clinical laboratory tests. There are also extra care costs associated with clinical trial participation, such as transport and pay loss. These costs may or may not be covered by a participant's health plan where such health plans exist.

Where even health plans are to be taken up to cover participation in clinical trials, this may prove very difficult because of the reluctance of the novelty of the concept here in Nigeria and the general international notion that such care costs are high. This is more so when it has to do with a possibility of HIV infection diagnosis. Presently in Nigeria, it is extremely difficult to take a health insurance policy to cover HIV infected individuals.

For this TDF trial, some specific concerns raised by advocates include the quality of care for the trial participants. There were concerns about the reimbursement of costs expended by the participants for participating in the trial, management of complications and side effects of use of TDF, long term follow up of the trial participants, limitation of access of participants to only male condoms when female condoms could also be accessed and plan for support for HIV positive volunteers. These are noted below.

First, according to the Act Up report, Cameroonian sex workers participating in the trial are paid the equivalent of a taxi ride plus the amount of two sexual encounters. This is unheard of in a US-based clinical trial, yet typical of companies who are "out-sourcing" their trials to the "developing world." These kinds of concerns are further elaborated by SWOP. (Posting 2 Appendix 1)

FHI must be commended for attempting to bring possible solutions through product development but the reality of our situation is that we can not in good conscience afford to willingly allow even one other Nigerian join the list of PLWHA carelessly. (Posting 8 Appendix 1)

With the kind of access in the African countries where these trials are currently taking place, referral [for treatment of complications] means nothing but a death warrant. (Posting 9 Appendix 1)

Why are the research heroes going to have access to only male condoms, when female condoms exist? Why can't the participants have a choice of male or female condoms, knowing that male condom negotiation is an issue in Africa? (Posting 16 Appendix 1)

Another important issue: I assume that FHI will test people's serostatus first hand, before inclusion. What kind of psychosocial and medical follow up is in place for those people that will test positive and therefore be excluded from the trial? (Posting 17 Appendix 1)

How is the overall safety of the participants being protected during the study? In addition to counseling on HIV transmission and prevention, provision of condoms, and careful monitoring of any side effects, multiple safeguards are in place to protect the physical and psychological well-being of participants. (Posting 17 Appendix 1)

We will refer you for help if you are infected with HIV". Well that is a little short. To my knowledge, in trials looking at reducing mother to child transmission in developing countries, for example, no research agency would dare to completely get rid of that responsibility and transfer it to some unspecified local health center. Besides it is in full contradiction with the international ethical standards. (Posting 18 Appendix 1)
Clearly, FHI does not provide care and treatment to people getting infected in the course of the trial, nor to those who would fall sick for any other reason, and this is NOT ethics. People in FHI seem to consider that infections occurring during the trial are not part of their responsibility." If you are sick or have a health problem due to being in this research, you will not have to pay for visits to see the research doctor or clinic staff. (Posting 18 Appendix 1)

I took a look at the consent form, and some sentences are shocking. I do hope that this is an outdated version and things have changed with the help of that community dialogue. One part of the Cameroon document read: "you may experience anger and distress if you are positive for HIV. We do not provide treatment for HIV. (Posting 18 Appendix 1)

This is less that the minimum one can expect. That does not tell anything about the drugs that will be available, and other medical services that could be needed (exams, etc.). Who will pay for that? (Posting 18 Appendix 1)

"If you need more help, we will refer you to other clinics, where you may have to pay". This is unethical. And clearly the section about the risks is ridiculously short and imprecise. And please and please, donÂ’t promote abstinence in the informed consent form nor in the prevention cession when your whole study is based on the idea that female sex workers fail negotiating condoms. If you definitely think that they are not in a position to impose a condom, they will certainly not be able to ABSTAIN either. So avoid making them feel guilty above all. (Posting 18 Appendix 1)

Are the participants being counseled on HIV prevention? Women will be counseled monthly on safe sexual practices such as reducing their number of sexual partners and using condoms during every sexual act. Hmmm. Asking sex workers to reduce their number of sexual partners? Best way to do that is to find them another job! (Posting 18 Appendix 1)

Imagine someone simply saying if infected, you will be placed on ARV. 'Dash' HIV infection ... Just like that! I find this rather appalling. It is scary and gets me really worried about this trial. (Posting 22 Appendix 1)

I didn't realize until you pointed it out that they are distributing male rather than female condoms. I think this is because there is a higher chance of HIV exposure to the male rather than female condoms--again, this is better for data collection, but I am just speculating here. But you make an excellent point--the women should be able to choose what kind of protection they use. (Exchange 3 Appendix 2)

How many condoms do they get on these monthly visits? How far do the women live from the clinic and how are they getting monthly transport? (Exchange 1 Appendix 2)

I just wondered why every new HIV prevention technology is promoted as a female controlled option. Yes, I do understand about microbicide but then, how does HIV vaccine and prophylactic use of tenofovir become a female controlled option. (Exchange 2 Appendix 2)

My concern is where NHVMAG is asking for 'all ailments' of the participants are to be treated free of charge. One needs to be careful here. If for example a participant develops a hernia during the trial, is this the responsibility of the trial?? I do expect the trial coordinators to facilitate the management but not to cover all the costs. (Posting 21 Appendix 3)

**Access to ARV by trial participants**

All clinical research carries with it the obligation to ensure optimal therapy for participating patients such that the patients' participation is meaningful. While international discussions continue on the issue of standard of care to be provided for trial participants within the context of the country’s public health sector and the concept of inducement for trial participation, the various national HIV antiretroviral rollout programmes are beginning to pose ethical challenges to all investigators involved in HIV research.
Ethical conundrums with clinical trials include the provision of ARVs, which serve as an undue incentive for the participation of subjects in clinical trials. However, the OHVHR/UNAIDS publication on HIV/AIDS and human rights noted that such inducement may be found acceptable by local ethical review committees if participants choose to participate in a trial so as to access better care.

A number of comments during the discussion noted that it was a moral imperative for participants to have access to ARV drugs for the management of infection in view of the fact that exposure to the virus is highly important for assessment of trial outcome.

If the point of the trial is to measure the drug's effectiveness in preventing HIV, then I see some difficulty in recruiting sex workers who are practicing regular safe sex. In other words, the trial depends upon some level of UNPROTECTED sexual activity in order to get significant data/results. How has FHI managed the difficulty of creating a trial design that can get both good results and ensure high ethical standards and protections? And what will happen to those women who become positive during the trial? Will they get life-time treatment? (Posting 2 Appendix 1)

Thirdly - and that which I find most appalling - is to say that people who get infected in the course of the study would be referred to institutions for treatment. Which institutions? Is it UCH that runs a subsidised national ARV programme? I hope FHI is aware that each centre in the country already have their quotas exceeded and are not recruiting new clients. I hope that is not the referral point for persons who get infected on this trial. (Posting 4 Appendix 1)

If there's a trial to determine the effectiveness of a drug, the only way you can get results and assess the effectiveness of your trial is to expose people to the virus but have them use this drug. Simply put, what this means is that people would be exposed to HIV and then if they end up positive, they'll be referred to the already over stretched government-subsidized ARV centres. (Posting 6 Appendix 1)

I guess the researchers are playing on the low level of awareness and on participants rights as regards new technologies. If we cannot get a definite promise from FHI that they will do the humane thing of providing care + ARV for those infected in the course of this study, we need to start providing information for the appropriate authorities so as to stop this trial in Nigeria too. (Posting 7 Appendix 1)

For the Cameroun trial, all infected persons were given access to ARV by the research team after community advocacy efforts and drive. Is that known by IRB members in NAFDAC, FMOH and Ibadan? (Posting 16 Appendix 1)

What happens if a participant becomes infected with HIV? Those who do become infected will have enhanced referral to HIV care and support services, including antiretroviral drugs when necessary. Do you mean prophylactic treatment? A triple therapy during a month after getting at risk of infection? Or do you mean "in five to ten years from now, when the study will be over"? And FHI will be gone? Is everybody aware that people getting infected in this trial, ie under the responsibility of FHI, will need medical care and especially ARVs in years from now? How will FHI ensure the "sustainability" of this "referral" system put in place? In case they need to get access to the newest therapy because of a drug resistance problem, or just because it has become the new standard of care, will those infected women be in a position to ask FHI for a combination that might not be available in Nigeria by this time? (Posting 17 Appendix 1)

Subjects/community benefits

In clinical trials, subjects/communities are expected to have immediate and or late benefits from participating in clinical trials. Late benefits as noted by the article 30 of the Declaration of Helsinki and clarified by the World Medical Association during its 167th council session noted that such benefits should include post trial access by trial participants to such procedures as identified beneficial in the study.
Also, trials should provide an immediate public health benefit to communities, through health education or improved counselling or clinical treatment capacity. This is an important way of demonstrating commitment to the communities where clinical trials are carried out. It also ensures that a foundation is laid for subsequent delivery of proven products and leaves participating communities better off, irrespective of whether the candidate product is shown to be efficacious or not.

The forum discussion raised questions on how the trial highlighted possible subject/community benefit. One critical question that was asked was how the trial protocol ensured country benefits on the long run if TDF is proven effective in the prevention of HIV infection. Other concerns are noted below.

How will participants and other community members benefit from the study? Potential volunteers and other community members will benefit from increased awareness of HIV prevention because of their involvement in preparation for study initiation. In exchange of the risks linked to side effects and others (kidney problems) that you intend to measure, raised awareness is a bit cheap. Aren't there other ways to raise awareness? Can you certify that this one is not too costly for the human body when compared to other kinds of interventions? Frankly, if I were seronegative and a sex worker, I would not think that the benefits are higher than the costs. Let us be sincere here: there is NO direct benefit for the people in the trial nor the community around it. It is for the sake of science only. (Posting 17 Appendix 1)

We will refer you for help if you are infected with HIV". Well that is a little short. To my knowledge, in trials looking at reducing mother to child transmission in developing countries, for example, no research agency would dare to completely get rid of that responsibility and transfer it to some unspecified local health center. Besides it is in full contradiction with the international ethical standards. (Posting 18 Appendix 1)

My concern about the trials is that from the story that I read, this same Tenofovir was tried in Cambodia and it was rejected, so why Nigeria? What is the fate of those that have volunteered themselves for the trial? (Posting 29 Appendix 1)

What is being done to make tenofovir available for prevention, if proven safe and effective? (Exchange 1 Appendix 2)

…nothing about long term costs in case of adverse health effects (Exchange 1 Appendix 2)

… but even if this drug works and is provided at cost, will these women be able to afford it on a regular bases? Is the pill ultimately meant for them or for another target market? Gilead needs to be asked about its marketing strategy that they have designed for this drug. And FHI needs to be asked how it fits in. (Exchange 1 Appendix 2)

**Confidentiality**

Clinical research should be designed to keep the identity of participants confidential. The Institutional Review Board is responsible for overseeing any clinical trials that are performed in the specific healthcare institution and are to ensure that there are adequate provisions to protect the privacy of the participants. In addition, the informed consent form and the research staff should explain to participants how confidentiality will be guaranteed. Any possible times when confidentiality cannot be maintained should be described to the participant. Very few issues were raised on ensuring that information about trial participants are kept confidential during the discussion. One of this is noted below

Finally, I hope we won’t be given the ‘patient confidentiality’ clause excuse. I’m sure we can work this out in such a way that all parties would be protected and their confidentiality assured. (Posting 6 Appendix 1)
Study monitoring

All clinical research carries with it the obligation to ensure optimal conduct of the research. Accurate and timely knowledge of the progress made with each study is critical. The specific purposes of the monitoring program are to document the accuracy of data submitted, to verify investigator compliance with protocol and regulatory requirements, to ensure that the identity of participants is protected and to provide information to institution staff on good clinical practices related to data collection and data management.

Ideally, for any clinical trial, a sponsor designates one or more appropriately trained and qualified individuals to monitor the progress of a clinical investigation. In addition to the many duties of the monitor, s/he should ensure that the investigator’s obligations are being fulfilled and that the facilities used in the clinical investigation continue to be acceptable. This entails that the monitor or the sponsor should maintain a record of the findings, conclusions, and action taken to correct deficiencies for each on-site visit to an investigator.

Despite the much documentation on monitoring of clinical trials, the lack of trust between scientists and trial participants, wherein communities see researchers as using participants as guinea pigs has led to the increasing interest and advocacy for communities to organize to monitor trials themselves. There were concerns raised by advocates about the trial sponsor also paying for the monitoring of clinical trials.

Isn’t it funny how the same body carrying out the trial might be the same one recruiting and paying trial educators and supporters? Is there an independent body doing this? (Posting 6 Appendix 1)

Who is defending or monitoring the rights of the subjects? The donors and researchers? (Posting 11 Appendix 1)

Ethical review of proposal

Ethical committees evaluate clinical trials during the development and design of study protocols prior to the start of the trials. There are a number of issues that need to be assessed during protocol review as they are of significant ethical concerns. These include wash out period of non-trial medical products when conducting randomized placebo drug trials, and how informed consent is to be obtained. During trials, early termination of a trial and confidentiality of study data raise ethical concerns. For developing countries like Nigeria, the issue of patient safety, possible exploitation of patient and provision of the test drug for the trial participants after the trial are issues of ethical concern. Some other ethical questions that need to be assessed about the outcome of a trial include the actual need for the trial, the elimination of obvious bias and deception and the guarantee of the safety of the patients entering the clinical trial.

Discussants raised many of these issues especially about the competence and thoroughness of the ethical review process for the TDF trial in view of the limited understanding of ethics and New HIV prevention technologies in developing countries like Nigeria.

NAFDAC also needs to be asked about its own evaluation of pre-trial data. (Posting 2 Appendix 1)

Secondly, FHI may be pushing issues too far if they keep hammering on the fact that they received ethical approval from NAFDAC, Ministry of Health and the IRB of UCH, Ibadan, knowing very well what the ethics board and ethics approval process is like in African countries like Nigeria. The only approval that might apparently be reliable is that of the IRB in Ibadan because of its high standard of practice. But
then, everyone is new to the issues of new HIV prevention technology research and development in this area of the world. (Posting 4 Appendix 1)

Anyway, are they not lucky to be operating in a community with less information about new prevention technologies. In Nigeria, the first-ever Association on Ethics in Research was just launched this year! (Posting 7 Appendix 1)

I also agree that it is NOT enough to say that various ethics boards were commissioned to approve the trial. This is also what Pfizer said about the trial for Trovan conducted on children in Kano. After 11 children died and numerous more maimed, strong evidence emerged that Pfizer never got ethics board approval in Nigeria and actually falsified documents. Now Pfizer faces a class action suit in New York City filed by 11 different Nigerian families. My point is not to compare the ethics of the tenofovir to Trovan, but to emphasize that the lack of transparency has created a huge environment of mistrust. And in my opinion, the entire Pfizer scandal generated the ongoing denials (of state government officials in both Kaduna and Kano) of meningitis and measles epidemics and the refusal to get children vaccinated. So, here we have some very serious unintended consequences of denials and refusals to vaccinate that continue to negatively impact even after the companies and their drug testing are long gone. So, this is why I was very insistent that they show documentation. All of this means nothing until one sees and evaluates the documents. (Exchange 1 Appendix 2)

Depth of government involvement

The Government of any country is usually not directly involved in all clinical trials. However, all clinical trials conducted in the country are expected to comply with NAFDAC’s rules and regulations applying to the use of investigational drugs or devices. In addition, IRBs must review and approve any clinical trial protocol before its implementation. Institutional Review Boards are required by the government review research to insure the protection of research participants. NAFDAC and IRBs therefore act as the appropriate government arms of intervention to ensure good clinical practice. However, where the government watchdogs are not living up to expectations, the government’s direct intervention may be critical.

Many Nigerians expressed concerns over the non response of government officials and mouthpieces (NAFDAC, NACA, FMOH) on concerns raised over the ongoing controversies on the TDF trial. Ideally, NAFDAC essentially approves clinical trial protocols and should monitor and evaluate ongoing trials to ensure compliance with protocols. The FMOH further endorses clinical research protocols once NAFDAC has given an approval. NAFDAC therefore remains the key government watchdog for clinical research design and implementation. Many of the concerns raised are noted below.

Is NAFDAC clear on what is happening? Is NACA involved in this? Does FHI have the go-ahead from the Federal Ministry of Health or is this another PEPFAR-style program where the Nigerian authority is left out of the loop? (Posting 6 Appendix 1)

This is also a big challenge for the FMOH/NACA/NAFDAC to wake up to their responsibilities and sacred duty to provide fool proof mechanisms for research involving human subjects including vaccines and microbicides. NAFDAC especially must come to the full understanding that the scientific and political intrigues that go with product development of this nature are well beyond pure water and fake drug issues. (Posting 8 Appendix 1)

1. Is there a national process/committee for obtaining ethical approval for studies of this nature in Nigeria? 2. If such a process/committee exists, was this trial appropriately examined and approved? (Posting 9 Appendix 1)
Can somebody alert NACA/FMOH/NAFDAC. We need to hear from them. Or is it that they are not on this eForum? Somebody need to let them be aware of this controversy so that we can hear their own side of the story. (Posting 11 Appendix 1)

I want to pitch tent with other contributors that the relevant governmental bodies constitutionally charged with the responsibility of protecting the health of Nigerians to speak-out as a matter of urgency. (Posting 12 Appendix 1)

I stand to be corrected but I think it is high time NACA sat up their responsibilities including having a national or regional ethical committee to look at HIV and other diseases-related clinical trials in conjunction with local institutional review boards (IRBs). (Posting 25 Appendix 1)

(1) Who speaks for the Nigerian subjects of these trials?
(2) Who speaks for citizens like Frederick Adegboye?
(3) Above all, who speaks for Nigeria? (Posting 28 Appendix 1)

It is for the country ethics board and medicines control council (NAFDAC) to define what ‘standard of care’ they are satisfied with. If we as advocates feel that they will not do this well then we must agitate and advocate for change. (Posting 13 Appendix 3)

Community involvement in study design and implementation

The success of new prevention technologies research depends on the successful completion of human clinical trials in countries around the world. Tens of thousands of altruistic and courageous individuals will need to provide informed consent to participate in trials of experimental products, and millions of people in the communities where these trials take place will need to appreciate the importance of this research, have trust in ongoing research efforts, and support the research process.

Including community members at all stages and levels of the research process helps build trust and mutual understanding which helps to ensure that values and cultural differences among participants are respected. In addition, it ensures advocacy and education which is needed for political commitment, resource mobilisation, production, distribution, acceptance and delivery of products.

The TDF trial appears not to have adequately involved relevant communities in its design and implementation. This raised a lot of concerns by advocates.

I am also sure there are other NGOs that are working with Transactional Sex Workers (TSWs) and other vulnerable groups in Nigeria. Do they have insights into this study as representative of such communities? (Posting 11 Appendix 1)

Epidemics such as HIV/AIDS and tuberculosis have taught us that community engagement is as important - perhaps even more important than - science in driving a solution. Informed discussion on ethical conduct lies NOT only in the realm of science. But we accept that the conduct of science should remain true to the highest demands of sobriety, objectivity and integrity. (Posting 12 Appendix 1)

I also believe that this dialogue has gone on long enough for there to be an understanding that it is not only those carrying out the study that need to be interested in the protocol. Afterall, the outcomes are supposed to be of interest to the rest of us, in terms of impact. (Posting 24 Appendix 1)
….. we are not after ensuring that the trial stops BUT rather, that the community is mobilised to support research trial processes through constant communication. The voice of the community also needs to be heard and appreciated in the design of research protocols. That way we all (community and scientists) are together involved in developing products for our collective good. Research is no longer a hand down process - scientists do and community receives. Together (community and scientist) design, implement and take up products. (Posting 8 Appendix 3)

Transparency

The debate on the need for open access to clinical trial data has been on for a long time. Discussions have emphasized the need for interested stakeholders to have access to complete, accurate and unbiased medical information on drugs and medical devices. Therefore, it is paramount that pertinent clinical-trial data -- whether they are favorable, neutral or negative -- be available and readily accessible to all stakeholders. However, the inevitable concern is that any move that increases transparency could have negative consequences for the pharmaceutical industry and could lead to violation of IP rights with competitors gaining easier, deeper, and earlier insight on competitor activity; fewer new products entering development if increasing transparency leads to erosion of the value of differentiating factors; and more rigor in the design and conduct of clinical studies (thus increasing the cost of R&D) as the industry seeks to ameliorate risk. But then, clinical trial transparency promotes better, more robust, decision making.

For the TDF trial, information was not readily made available to interested parties making room for a lot of suspicion. Some of these concerns on the need for transparency and open communication at all stages of the clinical trial process are enumerated below:

So perhaps FHI and Gates can provide information on trial design and protocol, trial subject recruitment and evaluation criteria, approved human subjects protocols, ethics committee/board approvals, plans for care and support in the event of adverse effects and seroconversion that should be included in informed consent forms, and means and amount of remuneration. (Posting 2 Appendix 1)

And this leads to my third concern: tenofovir could potentially be a breakthrough in the AIDS crisis if it can successfully prevent HIV. Perhaps even more so than other trials, this one needs to be entirely transparent and in dialog with local experts. Without transparency, the trial runs the risk of a lack of trust, as well as the suspicion that some of the world’s most vulnerable people are viewed as not any more valuable than guinea pigs, as the SWOP analysis clearly states. (Posting 2 Appendix 1)

FHI must also note that at this stage of our community research all successful programs serve as templates for other interested groups so the processes must be open and transparent. (Posting 8 Appendix 1)

….. we believe that issues of scientific processes with impact on public health should be subjected to rigorous debate by interested public-minded stakeholders. The perception of science as a sacred masquerade whom only a restricted circle of anointed acolytes can view, is no longer acceptable. (Posting 12 Appendix 1)

This needs to start with the designers and funders making all relevant information available and open to ongoing feedback and dialog, ensuring high quality trial and post-trial care, and even being open to redesigning the trial if it is found to be unethical as Act Up Paris, SWOP and others claim. Many people’s lives are very much dependent upon a communicative, ethical, and transparent process. . (Posting 24 Appendix 1)

Yet the challenge for our country in this regard, but also as regards all our other endeavours is the need for transparency. Where there is no transparency, any action, especially including clinical trials will be assumed to be biased, incompetent and corrupt until proven otherwise. (Posting 24 Appendix 1)
I noticed that the microbicide trial in Lagos (on 6% cellulose sulphate) made significant changes to its protocol design following a better understanding of issues involved. The local partner moved for this and I was greatly impressed. So much so I feel proud and a part of the trial. All I expect is for our local partners to do the same with other protocols on the recognition of lapses rather than defend these lapses and then we can move on together. (Exchange 2 Appendix 2)
Addressing concerns and striking a balance

The TDF trial has raised a number of local and global concerns, which are applicable to all new research and development on HIV prevention technologies. Clinical trials of candidate HIV prevention products would entail the involvement of HIV negative individuals. The potency of these tested products would depend on their ability to prevent seroconversion. The ethical and moral obligations to trial participants therefore raise a number of concerns with increasing interest in new HIV prevention technology research.

Unfortunately, the public’s trust in scientists and the research process is low. Community concerns therefore need to be addressed while ensuring that scientifically and ethically sound researches progress. For Nigeria, a number of challenges were faced in trying to strike a balance between TDF researchers’ interest in making progress with the research and the community advocates concerns about the ethical issues raised on the design and implementation of the research protocol.

Challenges

1. Resistance from the research community: There was an initial resistance from the research community to institute dialogue with the community. Initial contacts with the local researcher met with a lot of rebuff and silence. The community views and perspectives were perceived as uninformed contributions and thus, concerns were treated with levity. Some of the comments in this respect include:

   "It is scientific misconduct to disclose information about ongoing trials to members of the public. The absence of information on public domain should however, in no way, be misconstrued to imply lack of transparency. We are prepared to entertain enquiries about this trial, but science is not and should not be conducted on the pages of newspaper or other related media." (Posting 10 Appendix 1)

The initial call for an open dialogue came up on August 30th 2004 after a number of informal enquiries about the trial. That posting read:

   "We believe that more information from the tenofovir research team at UCH is crucial in order to throw light on some of the concerns surrounding the trial. The lack of sufficient information on the tenofovir trial in Nigeria is not helping matters at all, and we strongly urge the study team at UCH to provide relevant information that would address the concerns about the trial." (Posting 1 Appendix 1)

No formal response from the trial site or researcher came till the 6th of September from the information department of FHI

2. Lack of trust of community by scientist: There apparently appears to be distrust of community advocates by researchers. Efforts to get information from the local partners on the ongoing TDF trial met with continued silence with the local researcher retorting on the need to get clearance from the international partners and sponsors before any issue on the trial could be discussed.

   "I should be able to give you clear details about the study in Ibadan once I clear things with the authorities concerned as soon as possible." (Posting 2 Appendix 3)

   "I have written Morenike about this study that there is nothing to hide because it is being carried out according to good clinical practice and ethical consideration. I have to clarify things from my sponsors before I make further comments." (Posting 10 Appendix 3)
Discussion on the need for the constitution of a CAB for the trial further shed light on the skepticism researchers have on relating directly with the community. The community is perceived as making unnecessary demands thereby exploiting the research team. Two postings noted these:

The provost (of the College of Medicine, Ibadan) felt that establishing a CAB does not necessarily translate to community consultation and CAB has the potential for fuelling demands by some privileged members, which may not necessarily translate to community needs. (Posting 31 Appendix 1)

However, I will like to caution on the setting up of this CAB issue. I shared the concern of the Provost at Ibadan. There is need to think over this especially on the constitution of such bodies, so that we wont have problems in our hands later on. Community awareness is a must, forming a board from them is delicate issue so that we don’t start having unnecessary demands in our hands. I will want you to think on the issue raised and agree on the way to handle it. (Posting 17 Appendix 3)

3. Funding:

There is a place for stakeholders meetings but like you noted, who bears the cost? This medium is more effective but then, this medium does not necessarily mean all stakeholders are on board for the discussion also. The open discussion allows for sentiments (which are equally welcome) and the sharing of objective facts may all be too difficult. (Exchange 2 Appendix 2).

When both parties agreed to come to a round table and discuss issues, the cost of funding the roundtable discussion became the obstacle to the dialogue process. Discussion stalled and communication between both parties was limited to the activities of NHVMAG acting as a liaison between interested community stakeholders and the researchers.

Funding was also an obstacle to ensuring possible independent monitoring of the research process by community activists as well as advocating for independent participant advocates for the trial participants who should not be funded by the research sponsor.

Constraints

1. Non existence of a National ethics review board: A National ethics review board could have acted up to address the various issues and concerns raised about the TDF trial if one existed in the country. A national ethics review board is a standardizing body which ensures that researches of national interest takes cognizance of issues of national concern in its design and implementation. Its non existence created a vacuum not just for addressing issues on the present TDF trial but also for past and future clinical trials.

2. Absence of a nationally defined standard of care for HIV prevention trials: The absence of a nationally defined standard of care for trial participants makes it difficult for researchers to design their protocol uniformly taking cognizance of the national interest as it affects the care of trial participants. This was noted by one of the contributors to the discussion (Posting 24 Appendix 3)

3. Poor community preparedness efforts: Poor community preparedness efforts make for poor understanding of research process and poor trust of scientific research. Most advocates and members of the community in which recruitment was to take place understood very little about the specifics of the trial. Absolute support and evaluation of research process was therefore poor.
4. **Poor understanding of ethical issues relating to New HIV prevention trials by IRB members:** Understanding the various debates and being kept updated about issues relating to HIV prevention trials around the world is quite important for members of any ethics board that would be evaluating research proposals on HIV prevention research. Members of the IRB in the country need to be kept updated about global events on new HIV prevention technology research and on current debates on ethical issues. This is in view of the fact that most phase III trials of these technologies would most likely take place in developing countries like Nigeria.

## Opportunities

**Existence of NHVMAG:** The existence of the coalition helps to facilitate discussions about issues related to clinical trials on new HIV prevention technologies. The coalition is an umbrella body for all stakeholders involved with new HIV prevention technology trials in the country and has an active listserv that enhances communication with all members. NHVMAG has so far helped to facilitate dialogue between the parties involved with this trial and has significantly helped to ensure that issues are well addressed and appropriately channeled.

## Successes

1. **The institution of a dialogue with the research institution and local research partner** was quite helpful. The dialogue which was instituted by NHVMAG facilitated the community’s understanding of peculiar issues related to the trial and how this may not fit in with the expectations of the community advocates. It also helped the community to understand the various processes instituted by the Research institution to ensure effective monitoring of the TDF research process and other HIV prevention technology researches ongoing in the institution. Presently, the research institution is working at organizing a national dialogue between community advocates and the local researchers involved with new HIV prevention technologies research efforts in the country.

2. **NACA and other relevant authorities (NAFDAC and FMOH) got interested** in new HIV prevention technology research going on in the country. In the past the focus of the national government and other relevant agencies had been on the development of an HIV vaccine. National structures had been put in place to facilitate national and collaborative research efforts in this respect. Little had been done in terms of other HIV prevention technologies research and development.

   The relevant national institutions were kept informed of the dialogue and processes involved with the TDF trial. Though no official statement was made by these government representatives, NACA got in touch with the research institution (UCH) and asked to be kept updated about the TDF research process. Also, NACA instituted contact with the FMOH on the need to review its ethical clearance process as well as train its relevant officials on ethical review processes for clinical trials. However, there is more expected from the government as they could examine the credibility of the evidences provided by the various bodies just as was done in Cambodia and Cameroon and take appropriate actions as deem fit. The continued silence on the issue is unhealthy.

3. **NAFDAC principal officers got interested in the trial.** A member of NHVMAG kept the principal officers informed about the dialogue and this got them to express their interest in being a part of
future dialogue processes. NAFDAC however has to do more than just becoming interested but get up and act especially with respect to monitoring trials. One of the mandate of NAFDAC as written up in their protocol is for the organisation to provide a monitor for clinical trials approved by them. The organisation therefore needs to be more alive to this responsibility.

4. UNAIDS has also shown interest in facilitating regional and international dialogues between community advocates and the research community. Expectedly, the dialogues should help with the defining of ‘ground rules for HIV prevention trials’.
Recommendations

1. Need for dialogue
As a first step towards addressing concerns, there is a need for a roundtable dialogue between stakeholders so as to ensure that all concerns are tabled and addressed appropriately. Every concern can then be heard and addressed appropriately thereby ensuring that the entire community work together to move the research agenda forward. While community advocates expressed interests in dialoguing with researchers no such dialogue had been instituted till date. The research institution (UCH) and NHVMAG are making concerted efforts to mobilize for funding for the process. Some progress is being made in this direction. Also, UCH had tried to institute a roundtable discussion with FHI, foreign partners on the trial with no success. Neither has relevant government agencies responded or instituted dialogue with relevant stakeholders who have expressed concerns over the trial. Some discussions which point to the need for this are enumerated below.

The ongoing professional dialogue probably is not in the best interest of the country, its development partners such as FHI and other stakeholders. The approach and methodology used is not designed in a problem solving manner. I still strongly believe that the issues are resolvable and we need to move on. I will encourage FHI to convene a consultation meeting through NACA with all the key stakeholders in participation with the aim of building consensus and providing appropriate policy and professional guidance to the intervention and resolve the way forward for the national response through this experience.

There is a place for stakeholders meetings but like you noted, who bears the cost? This medium is more effective but then, this medium does not necessarily mean all stakeholders are on board for the discussion also. The open discussion allows for sentiments (which is equally welcome) and the sharing of objective facts may all be too difficult. (Exchange 2 Appendix 2)

2. Need for NERB
The need for a National Ethics Review Board to ensure the standardisation of practice of all Institutional Review Boards in the country cannot be overemphasised. As noted by a discussant, ‘It is important that government lives up to its responsibility by setting clear structures and standards for ethical oversights of scientific research processes in the country. As a matter of urgency, the Federal Ministry of Health and the National Action Committee on AIDS need to set up a National Ethics Review Board…’

I stand to be corrected but I think it is high time NACA sat up their responsibilities including having a national or regional ethical committee to look at HIV and other diseases-related clinical trials in conjunction with local institutional review boards (IRBs).

3. Need for the nation to define standard of care for participants in future trial
The minimum standard of care required for participants in clinical trials conducted in resource-poor settings is a matter of controversy; international documents offer contradictory guidance. Though these international guidelines exist, the rates of adherence to established clinical guidelines of care in randomized clinical trials of HIV treatment is poor with standards for determining/defining clinical standards for trials in sub-Saharan Africa varying with researchers’ definition. It may therefore become highly necessary for countries, including Nigeria, to define its own minimum standard of care for trial participants involved with new HIV prevention technologies. This allows for uniformity of care...
provision for all trial participants and ensures that the participants/communities benefit from participating in the trial process. The document would need to define what constitutes an acceptable basic package of care to be provided to individuals who become HIV-positive during the course of a prevention trial. It would also answer questions like should this care also be made available to participants’ family members and the wider community? Do trial sponsors have an obligation to provide ARV to any or all of these groups? If so, does the obligation extend beyond the duration of the trial? Who should be expected to pay for care once a trial is finished? The document would be framed as a policy based on ethical aspirations, political commitment, and scientific rationale. Recommendations made for the TDF trial in Nigeria are enumerated below.

b. All participants must have access to both male and female condoms

c. All volunteers on the trial MUST be treated for ALL ailments they have during the trial, whether related to the trial or not. The treatment of these volunteers would take place at UCH at a cost to be borne by the research team

e. All participants with grade III or IV adverse events during the trial must be discontinued.

4. Need for updating of IRB members

Presently, the review and approval of all new HIV prevention technologies’ clinical research process rests almost exclusively within the domains of the institutional IRB and NAFDAC when the partnering institution/sponsor requires a NAFDAC approval. A national approval process is not spelt out for various research efforts except for HIV vaccine development.

There is therefore a need for a nationally defined clinical approval process for various new HIV prevention technologies and a need to update IRB members about this approval processes. In addition, the IRB members need to undergo various refresher trainings to ensure that they are kept updated on current issues relating to clinical trials on new HIV technologies.

5. Need for community involvement at the designing and implementation of research protocols

Community involvement represents on-the-ground implementation of science’s accountability to society, at the local as well as global level. Engaging a wide range of stakeholders as active and informed partners in decision-making about the research and its implementation enhances both the scientific validity and ethical integrity of clinical trials. There is a need for both trial sites and affected communities to be involved in conceptualizing and implementing a broader, more comprehensive scope of activities-- a mobilization framework-- that addresses the fundamental goals of community involvement: trial start-up, exchange of knowledge and information, maintaining scientific and ethical integrity of the trial, and community capacity-building. It is also a key factor in appropriate quality research. Supporting a community voice in the research process improves the likelihood that the research will be accurate, acceptable, and ethical.

6. Need for community preparedness activities

Community preparedness programmes are designed to disseminate information, raise awareness and promote human rights in relation to the development of new HIV technologies within communities. This would involve extensive information exchange via workshops, forums, lectures and seminars mainly to AIDS organisations, other non-governmental organisations and groups, and
interested stakeholders and sectors including government agencies, unions, youth groups and others. The preparedness training for government officials is crucial; they seem to be the least involved and least informed yet government plays a very crucial role in regulation. The aim of these sessions is to encourage the inclusion of relevant information on trials, ethics and human rights into generic AIDS training initiatives and programmes led by other organisations. Some issues raised by discussants are also enumerated below.

**Design and implementation of community preparedness activities at trial sites:** Community preparedness is a very important aspect of any research trial taking place within a human population. It includes community education and empowerment initiatives, sensitization programmes and identification of community needs relevant to the research effort. This will not only ensure support for the trial but would help increase the prospect of drug uptake in the future. Activities to ensure community preparedness for a trial is standard practice worldwide.

Community preparedness should however be integrated into the study if it has not been done. *(Appendix 18 Appendix 3)*

### 7. Need for continuous information exchange between community and researchers

Developing and implementing specific strategies to increase clinical trial enrollment presents unique challenges for all concerned. These challenges include maintaining public trust in the integrity of the research and building confidence in the treatments that result from clinical trials. Patient advocacy groups, professional organizations, pharmaceutical companies, and the federal government each play an indispensable role in educating the public about increasing participation in and support for research and clinical trials.

The public may not understand the potential benefits of participating in HIV prevention trials and that it is in everyone's best interest to become informed about these trials. People, including trial participants, frequently turn to patient advocacy groups as trusted sources of information. While many people hold a fundamental cynicism, often fueled by the media, about clinical trials, they seem to readily accept information about healthcare and healthcare options provided by advocacy groups. The credibility of advocacy groups is enhanced because they can provide patient and caregiver testimonials that relate people’s real-life experiences. This information is seen as both valuable and trusted. It is therefore advantageous to trial participants when advocacy groups work closely with the research community to ensure the messages to trial participants are in agreement.

### 8. Follow up care

Trial participants ideally should be informed about the long term follow up care that would be available to them. The informed consent form mentioned nothing about this despite its failure to also enumerate all the possible side effects associated with the use of the TDF. Discussants noted that in view of the possible strong side effect associated with the TDF, a minimum of 2 years follow up of all trial participants should be advocated for in the redesigning of the research protocol.

*I strongly believe that the concerns raised on the possible hepatocellular dysfunction associated with the use of Tenofovir would ensure that the PI and sponsor of this trial uphold the 2 year follow-up period to take care of any untoward reaction or even SAE after the trial. Advocacy should also continue to ensure that this pledge is not bridged.*
9. Changes to be made to trial protocol

Discussants made suggestions for changes to be made into the protocol, which would ensure that trial participants are better protected. These include the need for:

1. All participants diagnosed with HIV infection at screening and during the trial who require ARV should be enlisted in the PEPFAR treatment program at U.C.H.
2. All HIV testing should not only be based on the rapid test kits using saliva as planned by the investigators, but would also be done by the well-equipped virology laboratory at UCH
3. Effects of malaria infection on the efficacy of the drug as chemoprophylaxis for HIV infection should be evaluated
4. Trial volunteers will need to be followed for two years after the conclusion of the trial to monitor for possible long term complications that may arise from participating in the trial.
5. An independent clinical monitor will be appointed for the project. S/he will monitor and evaluate progress made on the research, ensure volunteer’s welfare as well as ensure that the researchers keep within the focus of the research design.

Recommendation made by NHVMAG

Based on the eforum discussion, NHVMAG summarized all issues and wrote a recommendation to the institution involved with the trial.

1. The need for trial participants to receive the BEST possible care in this research process. There should be no compromise.

2. The research protocol should also be amended to include:
   
a. Interventions to ensure community preparedness on the path of the researchers. Members of the community within the trial focus area should be adequately prepared for the trial (informed and kept updated about the research) so they can give their support for the process in view of stigma related to HIV infection. Where the community is not adequately prepared, there is a possibility of myths and misconceptions to develop about the trial. Trial participants’ retention may then be difficult. In a bid for researchers to then meet deadlines in view of funding constraints, compromises may then start to occur in the trial design and volunteer recruitment procedure.

   The Ibadan researchers could learn from the ongoing 6% cellulose sulphate (microbicide) trial at the Lagos University Teaching Hospital (LUTH). NHVMAG is actively supportive of that process because the local principal investigator has been responsive to community involvement and modified the protocol to include this despite the initial oversight. We are presently working together to design and implement community mobilization at the trial site. This University of Ibadan research team could benefit from dialoguing with Dr Sade Ogunsola who is leading the microbicide study at the Department of Microbiology, LUTH. The tenofovir trial could also learn from the community preparedness exercise of Prof Kayode Dada of the Department of Chemical Pathology, Ogun State University, Ago-Iwpye on their efforts during the phase 1 trial on 6% cellulose sulphate.

   b. Future dialogue should include interested community advocates. We do support the need for regular community meeting to review progress and problems, but please include community members who are vast on the issues on Board. NHVMAG suggests that the community should be represented on the Clinical Monitoring Team, the Safety Monitoring
Team, the Data Monitoring Committee and during the UCH IRB monitoring and review process. We would not want a compromise on this. This would ensure that that the community views, perspectives and concerns are addressed during deliberations and in the decision making process.

The community member would then report back to the community and such representatives would be our liaising arm of the project. The community could confidently relate to their reports.

c. The protocol should address the need to focus on participants’ health and not just the drug trial. As such, once the health of trial participants are compromised for whatever reasons, such participant should drop out of the trial process.

d. All recommendations should be reflected in the protocol an informed consent form that trial participants are to sign.

….. We believe that we are about reaching an end to this interesting discussion wherein the scientists and community work together in research efforts. The place for the community to participate in research design and implementation had long been identified as this facilitates the research process and the eventual uptake of the products.

The days of scientists doing things for ‘them’ (the community) is fast fading. We have to learn to do it together for ‘us’ and HIV/AIDS is teaching us how to do this properly.

Morenike Ukpong  
For the Steering Committee, NHVMAG
Email: info@nhvmag.org (Posting 30 Appendix 1)
NHVMAG: its role and place in Nigeria

Who is NHVMAG?

In 2003, a group of committed advocates and scientists came together to form the Nigeria HIV Vaccine and Microbicides Advocacy Group (NHVMAG) as a civil society response to address these imperatives. NHVMAG was formed to ensure the proactive participation of Nigeria and Nigerians in global efforts for the development of HIV vaccine and microbicides. It also recognises that there is an ethical imperative to seek, as urgently as possible, effective and accessible vaccine and microbicide products to complement other existing prevention strategies.

The mission of NHVMAG is to halt the spread of HIV/AIDS in Nigeria by ensuring the availability of safe, effective, acceptable and affordable HIV vaccine and microbicide products for all Nigerians when developed.

Its Objectives are to:

1. Promote public understanding and support for the participation of Nigeria in the international HIV vaccine and microbicide development efforts
2. Promote early involvement of Nigeria in HIV vaccine and microbicide studies relevant to her HIV/AIDS control efforts
3. Mobilize active participation of Nigeria and her nationals in vaccine and microbicide research and development activities worldwide
4. Ensure access by all Nigerians to a safe, effective and affordable HIV vaccine and microbicides when developed
5. Collaborate with other institutions and organizations locally and internationally for the rapid development of a safe and effective HIV vaccine and microbicide for all humanity

NHVMAG works through four Operational Strategies:

1. Public Communication and Enlightenment: Through regular public communication programmes, NHVMAG promotes popular community support for the vaccine/microbicides development process. This may be through workshops and seminars, communication (press articles, TV/radio appearances, publications etc), advocacy visits, meetings, exhibitions, public speaking engagements etc.
2. Policy Advocacy: With HIV vaccine and microbicide research, the need to ensure political commitment is paramount. Through research and analyses, policy development, monitoring and implementation, we will ensure the creation and sustenance of a people-friendly policy environment for vaccine/microbicides research in Nigeria
3. Capacity building: Because vaccine/microbicides research and development are a highly intensive and high-capacity process, we will promote activities to build the capacity of Nigerian institutions and advocates, including facilitation of training opportunities, participation at international conferences and meetings, research assistance, sponsorship of scientific conferences and publication of scientific papers.
4. International collaboration: This involves building broad international support for the vaccine/microbicides development process in Nigeria and ensuring that our national interests are protected in vaccine/microbicides development worldwide.

NHVMAG is a popularly owned campaign, with its members, supporters and partners as the driving force. It works through five Thematic Groups (see below) with the following terms of reference:
Resource Mobilisation Committee
- Identify and harness human and material resources within and outside the country interested in funding and supporting HIV vaccine and microbicide research and development
- Engage in income generating activities to fund activities of the group and for the broader vaccine/microbicides development process in Nigeria

Scientific Committee
- Monitor and track issues related to HIV vaccine and microbicide development worldwide
- Create awareness on prospective research opportunities on HIV vaccine and microbicide research in the Nigerian scientific community
- Identify and support research and development activities by Nigerian institutions and nationals (locally or outside the country) on vaccine/microbicide development

Ethics, Law and Human Rights Committee
- Ensure that the process of HIV vaccine and Microbicide development conforms to national and international standards
- Keep scientists updated on various ethical issues related to HIV vaccine and microbicide research
- Liaise with and mobilise organisations working on ethical issues in the country to include HIV vaccine and microbicide as an issue in their agenda

Community Mobilisation Committee
- Ensure HIV vaccine and microbicide research and development is integrated into overall HIV prevention efforts
- Ensure popular community (CSO, CSO, private sector, media, religious sector etc) participation
- Ensure community preparedness for HIV vaccine and microbicide research and use

Public Communication Committee
- Ensure that all communities in Nigeria are brought on board and carried along in HIV vaccine and microbicide development
- Ensure public ownership, understanding and familiarity with HIV vaccine/microbicide issues
- Design and carry out a strategy for appropriate and accurate public communication of the vaccine/microbicide development process
- Liaise with media stakeholders and promote their full support and involvement in microbicide/ HIV vaccine advocacy

Role of NHVMAG
NHVMAG brings together stakeholders involved with HIV prevention trials and ensures their active participation in all processes that would facilitate new HIV prevention technologies’ research and development in Nigeria.

It also facilitates the country’s involvement in global research and development drive for new HIV prevention technologies. Its existence has enhances the commencement of community sensitization on HIV vaccine and microbicide research thereby filling a vacuum otherwise left by the national government.
Potentials of NHVMAG
NHVMAG is in a good position to prevent any problems that are often attributed to media – misconstruing and sensationalising issues – as the group has good media outreach and can conduct adequate training. They also have the opportunity to sensitise researchers on the appropriate language to use when dealing with media and the public as there would be an increasing need for researchers to relate with the community in which they work. A cross-training between media and scientists, and the scientists and community workers would facilitate these processes so that “everyone can see everyone’s issues” and possibly address this identified gap.
Conclusion

The ongoing TDF trial in Nigeria has acknowledged limited benefits. As reported in the Washington Post of the 2nd of December 2004, Craig Timberg in his article titled “Dose of prevention where HIV Thrives” noted that:

‘the drug raises a number of scientific and ethical questions, any one of which could prevent it from ever being widely administered’. There are questions and concerns being raised about the practically of its long term daily use by healthy persons especially in Africa where regular use of medicine is uncommon. Yet researchers note that taking the drug sporadically might provide only partial protection and could encourage mutant strains of HIV to develop’.

However, the concerns of the community on ethical issues involved with the trial need to be addressed to ensure that the rights of trial participants are protected, acceptability of the research outcome and possible uptake of the product when eventually developed for use. These concerns are growing with each passing day as recruitment for the trial in Nigeria continues without significant changes being made to the protocol to address concerns raised. Agitation continues on Cambodia and new agitations on the trial have started in Cameroon. In both countries, the expressed concerns are similar to those made by Nigerian advocates. These concerns are genuine as highlighted in the summary of the discussions. Other ethical questions that could be raised from the article of Emmanuel et al (What makes clinical research ethical? JAMA 2000; 283(20): 2701E11) include:

1. Why the use of sex workers when tenofovir would be use by the general populace (men and women) when found effective?
2. Why the use of sex workers who have NO LEGAL SATUS in the laws of the country? Why conduct a trial of national significance using persons with no legal status. This points to their possible use as guinea pigs.

There is always room to accommodate new learnings. Changes in ways of doing things are imminent. Changes are possible. Researchers need to learn that new demands are being made on research and research processes. We all need to make good room to accommodate these changes. HIV/AIDS is teaching us all new lessons. Lessons we all can learn from and improve our ways of doing things.

The Nigerian government may need to take definitive actions and make pronouncements about the ongoing trial - not just for now but also for the future – thereby safeguarding the health of the people.
Appendix 1
Postings about the oral tenofovir trial on the eforum

August 30, 2004
Subject: Tenofovir trials in Africa

Gilead, the company that makes tenofovir and which is part of a 6-nation study, has been told to stop its tests in Cambodia after protests about unethical practices related to the study (see article below). We'd like more information about Gilead's trials in Nigeria and elsewhere in Africa.

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Major HIV drug trial to be halted. The trial is set to run in seven other countries
http://news.bbc.co.uk/1/hi/health/3562704.stm

A major HIV drug trial in Cambodia has been shelved amid claims it violated people's human rights.

The trial was supposed to be one arm of an international study to see if Tenofovir, which is used to fight HIV, can also protect against the disease. But sex workers refused to participate unless they were given full medical insurance to protect them against any future illnesses.

Cambodian Prime Minister Hun Sen has now intervened to stop the trial. Earlier this month, he urged Cambodians to boycott the study, saying the country was not a test bed for "out-of-date" technologies. He also suggested that the drug should be tested on animals before any human trial was launched.

Can drugs protect against HIV?

Cambodian Health Minister Nuth Sokhom said the prime minister was worried the trial would contravene people's human rights. "He is worried that the drug testing will affect the health of Cambodian people, human values and rights," he said.

The decision was welcomed by the Cambodian Women's Network for Unity, which represents more than 5,000 sex workers. "We are very happy with this order as we don't want to take part in this drug test. There is no safety guarantee for us," said its director Kao Tha. "We are so poor that we don't have the money to pay for treatment if we fall sick after the test."

Claims rejected

Family Health International, the American organisation, is spearheading the trials and rejects claims that they violate human rights. "We strongly disagree," Dr Ward Cates of FHI told BBC News Online. He said the sex workers were offered good medical care. "The types of care being offered to any of the study participants was well beyond the standard of care offered in Cambodia and in other HIV prevention trials. "We are providing the participants with an enhanced standard of care." Dr Cates said he hoped the Cambodian government would reconsider its decision.

The Tenofovir trial has already started in Botswana, Ghana and Malawi. Plans are under way to test the drug on people in the United States, Thailand and Nigeria. The trial, which is expected to involve 8,000 people, will examine whether it is safe for healthy people to take the drug over a long period. Another trial will be needed before scientists will be able to say for certain if the drug does or does not protect against HIV. But Dr Cates is hopeful. "Tenofovir has great promise for further reducing risks of HIV in highly at risk groups," he said.
In response to the posting by Irene Ogbogu on Tenofovir trials in Africa, the Nigeria HIV Vaccine and Microbicide Advocacy Group (NHVMAG) is equally monitoring the situation with interest.

Tenofovir is already commonly used as an antiretroviral treatment for people living with HIV. NHVMAG got interested in the proposed phase II clinical trial of the use of oral tenofovir as a prophylaxis for the prevention of HIV infection in Nigeria when it was reported that it was a microbicide trial. The local (Nigerian) partner on the trial - based at the UCH, Ibadan - was then invited to discuss about the use of ARVs for the prevention of HIV infection during the National Advocates Meeting on New HIV Prevention Technologies in Nigeria, organized by NHVMAG at Valencia Hotel, Abuja on May 26-27 2004.

The presentation by the Nigerian investigator generated a lot of discussions and deliberations among participants, especially about the possible side effects of prolonged use of ARV in healthy subjects. The scientist (the local partner on the clinical trial) assured participants that findings of the phase I study showed good and promising results.

NHVMAG has since tried to get more information about the trial with no success. We therefore cannot make an objective statement on the planned (ongoing?) trial in Nigeria.

However, our analysis of the report from the terminated trial in Cambodia (circulated in the posting by Irene Ogbogu) showed that the reasons for the termination had to do with the proposed standard of care offered to trial participants. Sex workers, the prospective trial participants, were worried about the management of health complications that may arise from participating in the trial.

The research team in Nigeria will need to address this issue during their trial. The Scientific and Ethics Committees of NHVMAG are monitoring developments from the Cambodian trial and sites in other parts of the world (including Botswana, Ghana and Malawi) where the tenofovir studies are being carried out, especially since we believe the Nigerian study is modelled after the Cambodia trial. Based on our findings, we would issue a further statement on the standard of care provided for these trial participants at a later date. However, we are aware that NAFDAC and the Ethics Board of the local research institution would have looked critically into these issues - especially the issue of minimizing harm to the trial participants - before giving approval for the conduct of the trial in the country and in the institution.

We believe that more information from the tenofovir research team at UCH is crucial in order to throw light on some of the concerns surrounding the trial. The lack of sufficient information on the tenofovir trial in Nigeria is not helping matters at all, and we strongly urge the study team at UCH to provide relevant information that would address the concerns about the trial.

Morenike Ukpong
On behalf of NHVMAG steering committee
Email: info@nhvmsg.org

Hi all:
In Africa, the Gates Foundation gave Family Health International (FHI) $US 6.5 million to conduct the trials in Nigeria, Ghana, Cameroon and Malawi (other agencies and funding are also involved).

So perhaps FHI and Gates can provide information on trial design and protocol, trial subject recruitment and evaluation criteria, approved human subjects protocols, ethics committee/board approvals, plans for care and support in the event of adverse effects and seroconversion that should be included in informed consent forms, and means and amount of remuneration. (Contact information for these agencies are at the bottom of this message.) NAFDAC also needs to be asked about its own evaluation of pre-trial data.

I have three concerns over these trials after reading the Act Up Paris and SWOP (Sex Workers Outreach Project in Cambodia) evaluations (see links below). First, according to the Act Up report, Cameroonian sex workers participating in
the trial are paid the equivalent of a taxi ride plus the amount of two sexual encounters. This is unheard of in a US-based clinical trial, yet typical of companies who are "out-sourcing" their trials to the "developing world." These kinds of concerns are further elaborated by SWOP.

Second, the Act Up report also states that there is no access to female condoms (tenofovir does not prevent STIs or pregnancy). But the question that needs to be asked is whether condoms are entirely restricted in the trial. If the point of the trial is to measure the drug's effectiveness in preventing HIV, then I see some difficulty in recruiting sex workers who are practicing regular safe sex. In other words, the trial depends upon some level of unprotected sexual activity in order to get significant data/results. How has FHI managed the difficulty of creating a trial design that can get both good results and ensure high ethical standards and protections? And what will happen to those women who become positive during the trial? Will they get life-time treatment?

And this leads to my third concern: tenofovir could potentially be a breakthrough in the AIDS crisis if it can successfully prevent HIV. Perhaps even more so than other trials, this one needs to be entirely transparent and in dialog with local experts. Without transparency, the trial runs the risk of a lack of trust, as well as the suspicion that some of the world's most vulnerable people are viewed as not any more valuable than guinea pigs, as the SWOP analysis clearly states.

If members of SWOP refused the trial and the Cambodian Ministry of Health *actually backed them up*, then there is something terribly wrong in determining the value of human worth here by outside parties. These kinds of blunders can be avoided and should be for the future.

This needs to start with the designers and funders making all relevant information available and open to ongoing feedback and dialog, ensuring high quality trial and post-trial care, and even being open to redesigning the trial if it is found to be unethical as Act Up Paris, SWOP and others claim. Many people's lives are very much dependent upon a communicative, ethical, and transparent process.

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Date: September 6, 2004
Subject: Re: Tenofovir trials in Africa (3)

We have read the recent postings on Nigeria-AIDS and are happy to provide information on the oral tenofovir study. This is a different trial than the one some have referred to from Cambodia, with a different protocol and a different context. Family Health International believes that to defeat the HIV/AIDS epidemic, it is essential to develop new tools and technologies to stop HIV transmission. Ethical, scientifically sound clinical trials are the only way to make these kinds of research advances.

Family Health International (FHI) is involved in a clinical trial in three African countries to determine the safety and effectiveness of daily oral tenofovir to prevent HIV among heterosexual women at high risk of infection. The study is also being planned in a fourth African country to determine whether tenofovir can safely and effectively prevent HIV among high-risk heterosexual men. Local African researchers are conducting the trial. Ibadan, Nigeria, is one of the three study sites recruiting women. This study was designed according to the most rigorous international ethical standards. It has been reviewed by a special ethics committee devoted to protecting participants in human research, convened by Family Health International. The study has also been approved by Family Health International's institutional review board and by numerous ethics groups in Africa. In addition, it is supported by nongovernmental organizations, community groups, and the governments in the study countries.

What is tenofovir?
Tenofovir is an anti-HIV drug that works by inhibiting an important enzyme in the HIV life cycle, called nucleotide reverse transcriptase. By doing so, tenofovir stops HIV from invading cells that have not yet been infected with the virus. It is taken in the form of a pill, it is long lasting, it has relatively few side effects, and HIV is slow to develop resistance to it. Tenofovir is approved by regulatory agencies and already used in many countries as part of a drug combination to treat HIV. Studies in monkeys have also shown that it can prevent transmission of a virus that is similar to HIV, but it is not yet
known if it has the same effect in humans. Tenofovir is manufactured and being provided free of charge for the study by Gilead Sciences, located in Foster City, California.

What is this study testing?
This clinical trial is being conducted in three African countries to determine the safety and effectiveness of daily oral tenofovir to prevent HIV among heterosexual women at high risk of infection. It is also planned in a fourth African country to determine whether tenofovir can safely and effectively prevent HIV among high-risk heterosexual men. To do so, participants will be randomized to receive either tenofovir or a placebo once a day for the duration of the trial. All participants will receive HIV risk-reduction counseling, condoms, and treatment for symptomatic sexually transmitted infections during monthly clinic visits throughout the trial.

Why is this study important?
Current HIV prevention programs stress abstinence, being faithful to uninfected partners, and - if neither is possible - using condoms. Despite knowledge of these prevention strategies, it is estimated that some 14,000 people become infected with HIV each day. Moreover, many sexually active individuals, especially women, have difficulty negotiating condom use in their relationships, and additional prevention strategies are needed. If effective, tenofovir could be a promising addition to condoms because it is taken orally and would provide a constant level of protection against HIV, regardless of the timing of intercourse. It could also be a woman-controlled method, which could provide women with a choice for better protecting themselves against HIV.

Who is conducting the study?
Family Health International, a research and service organization based in Research Triangle Park, North Carolina, is managing the trial and is responsible for all aspects of the study. Local staff from the study sites in Africa are serving as the research investigators. The research is being supported by a grant awarded to Family Health International in 2002 by the Bill & Melinda Gates Foundation.

Where will the study take place?
The study is being conducted in the three African cities of Douala, Cameroon; Ibadan, Nigeria; and Tema, Ghana. The portion of the study to be conducted among men is being planned for Lilongwe, Malawi. These sites were selected because their populations have high rates of HIV infection, which is an important factor for determining the effectiveness of possible HIV prevention drugs. If tenofovir is shown to be safe and effective, HIV prevention programs that provide tenofovir can be established at these sites, so that these highly exposed individuals can be reached and can benefit from this intervention.

Are similar studies of tenofovir being conducted?
Four additional studies are being planned to test the ability of oral tenofovir to prevent HIV. The University of California at San Francisco and the University of New South Wales in Sydney, Australia, have designed a similar trial among high-risk women, to be conducted in either Cambodia or another country. The Centers for Disease Control and Prevention is also preparing to test tenofovir among diverse populations in three countries: injecting drug users in Bangkok, Thailand; heterosexual women at high risk of HIV infection in Gaborone and Francistown, Botswana; and men who have sex with men in Atlanta, Georgia, and San Francisco, California.

Who will participate in the study?
A total of 1,200 female volunteers from Ghana, Cameroon, and Nigeria will be recruited for the Family Health International study. To be eligible, all volunteers must be sexually active HIV-uninfected women between ages 18 and 35 years. Four hundred male volunteers are expected to be recruited in Malawi using similar eligibility criteria.

How long will the study last?
During this study to determine the safety and effectiveness of tenofovir for preventing HIV, volunteers will be recruited over a period of 6 months, and each individual will be enrolled in the study for 12 months.

How will participants be evaluated throughout the study?
They will be tested for HIV at a screening visit, an enrollment visit, and once a month during follow-up. With each HIV test, pre-test and post-test HIV prevention counseling will be provided. In addition, liver function and kidney function will be evaluated every two to three months to identify possible reactions to the drug.

Are the participants being counseled on HIV prevention?
Women will be counseled monthly on safe sexual practices such as reducing their number of sexual partners and using condoms during every sexual act. Male condoms will also be provided to them. A similar strategy will be developed for
male participants before the start of the trial in Malawi. As has been shown in previous studies by Family Health International and others, this should decrease the chances that the participants will become infected with HIV during the study. For example, results of a microbicide trial conducted by Family Health International in Cameroon, which used similar HIV prevention strategies, showed a 50 percent lower incidence of HIV among trial participants than among community members tested before the trial.

How are study participants being remunerated?
The level used for the Africa trials reflects ethical standards established for non-profit public health research. Reimbursement for time and transportation costs, and childcare (if necessary), have long been considered appropriate for both U.S.-based and international prevention research funded by NIH and CDC.

What about disinhibition of condom use?
Our formative data for the three West Africa sites indicates that while condom use rates may be high with sex work clients for some segments of the sex worker community, they are not universally used. Our focus groups and interviews with women indicate that negotiating or demanding condom use is complex and not always successful, and some women express skepticism about the effectiveness of condoms for preventing HIV infection. Also, women do not generally place the same importance on using condoms with boyfriends or regular clients. Our focus groups and interviews with men indicate significant resistance to condom use. These challenges to condom use are, in fact, the reason we need alternative forms of HIV prevention such as chemoprophylaxis.

What happens if a participant becomes infected with HIV?
Those who do become infected will have enhanced referral to HIV care and support services, including antiretroviral drugs when necessary. Local investigators have identified facilities within the study countries that offer HIV-related psychological, social, and medical services, and participants who become infected will be counseled and referred to those sites. Those who experience medical problems that are directly related to their participation in the trial will receive medical services for those problems free of charge.

How is the overall safety of the participants being protected during the study?
In addition to counseling on HIV transmission and prevention, provision of condoms, and careful monitoring of any side effects, multiple safeguards are in place to protect the physical and psychological well-being of participants. The study has already been approved by ethics committees at Family Health International and within the study countries. Members of these committees include ethicists, researchers, lawyers, and community representatives, among others. A detailed informed consent process is also being used to ensure that volunteers understand all risks and benefits of trial participation and know that they are not obligated to participate and can stop participating at any time. Throughout the trial, the investigators will also adhere to strict national and international procedures for monitoring and reporting any serious adverse experiences to the appropriate regulating agencies.

How has the community helped prepare for the study?
Evidence gained from in-depth social and behavioral research has been used to prepare the three West African trial sites for study initiation. Potential trial volunteers, high-risk men and women from the communities, people living with HIV/AIDS, and health care providers have all taken part. Through interviews and focus group discussions, these individuals provided information that helped determine from where volunteers should be recruited within the trial sites and identified appropriate medical resources available to trial volunteers who become infected with HIV. Similar processes are being used to prepare the Malawi site for study initiation. Continued research will also help identify barriers to and facilitators for establishing tenofovir HIV prevention programs, should the drug prove safe and effective.

What is being done to make tenofovir available for prevention, if proven safe and effective?
Family Health International will continue to conduct social and behavioral research during the trial to determine how acceptable tenofovir would be as an HIV prevention strategy among trial volunteers, their partners, and additional community members. It also plans to rapidly assess the study sites at the end of the trial to obtain additional data for determining the next steps in bringing tenofovir to the public, if warranted. Gilead Sciences will make tenofovir available at cost in the study countries and other resource-poor settings, if it is shown to safely and effectively prevent HIV infection.

How will participants and other community members benefit from the study?
Potential volunteers and other community members will benefit from increased awareness of HIV prevention because of their involvement in preparation for study initiation. Participants will also finish the trial with more in-depth knowledge and skills needed for HIV prevention. They will benefit from repeated counseling on issues of HIV transmission and prevention, free condoms, and free HIV testing and related pre-test and post-test counseling. Furthermore, because of the medical community's involvement in the trial and in identifying available HIV care and support facilities, some of those who
do become infected will have access to services that they might not have if they were not participating in the trial. Regardless of the outcome of the trial, its results will help guide other studies and future HIV prevention initiatives throughout the world.

Sincerely,
Elizabeth Robinson, Director, Information Programs, Institute for Family Health, Family Health International, PO Box 13950, Research Triangle Park, NC 27709 USA Email: media@fhi.org

Date: September 7, 2004
Subject: Re: Tenofovir trials in Africa (4)

I read with interest Kris Petersen’s rejoinder as well as the statement from FHI on the Tenofovir trial in Nigeria. FHI was involved with the Cambodia trial and their continuous stance was that they provided the best standard of care for prospective trial participants. Knowing and understanding the continuous controversies raging on ethical issues on standard of care for trial participants in African studies, it might just be nice for FHI to define the best standard of care offered to trial participants in this study.

First, it might be nice to explain clearly how the community was effectively prepared for this trial. This is an imperative for research processes and it may be nice to define this issue.

Secondly, FHI may be pushing issues too far if they keep hammering on the fact that they received ethical approval from NAFDAC, Ministry of Health and the IRB of UCH, Ibadan, knowing very well what the ethics board and ethics approval process is like in African countries like Nigeria. The only approval that might apparently be reliable is that of the IRB in Ibadan because of its high standard of practice. But then, everyone is new to the issues of new HIV prevention technology research and development in this area of the world.

Thirdly - and that which I find most appalling - is to say that people who get infected in the course of the study would be referred to institutions for treatment. Which institutions? Is it UCH that runs a subsidised national ARV programme? I hope FHI is aware that each centre in the country already has their quotas exceeded and are not recruiting new clients. I hope that is not the referral point for persons who get infected on this trial.

There is need for FHI to highlight more on this issue. How would participants who get infected during the trial get access to ARV treatment?

Morenike Ukpong
Email: mukpong2@yahoo.com

Date: September 7, 2004
Subject: Re: Tenofovir trials in Africa (5)

Dear All,
I read with great interest the on-going dialogue on the above subject matter and will advice NHVMAG, FHI, NACA and other stakeholders involved to create a forum of discussion as urgently as possible. The ongoing professional dialogue probably is not in the best interest of the country, its development partners such as FHI and other stakeholders. The approach and methodology used is not designed in a problem solving manner. I still strongly believe that the issues are resolvable and we need to move on. I will encourage FHI to convene a consultation meeting through NACA with all the key stakeholders in participation with the aim of building consensus and providing appropriate policy and professional guidance to the intervention and resolve the way forward for the national response through this experience. Let the meeting be guide with the principles of “lessons learnt to improve programming”. I will be glad to interface.

Regards.
Dr Michael Gboun
Monitoring and Evaluation Advisor
UNAIDS ICT/ESA
Email: gbounm@unaids.org
Report of dialogue between community advocates and researchers on Phase2/3 oral tenofovir trial in Nigeria

Date: September 8, 2004
Subject: Re: Tenofovir trials in Africa (6)

There have been too many drug trials where people from developing countries are used as guinea pigs and dumped. I was involved in a Roche/Swipha trial five years ago where I was made to pay N130,000 to get on a six month ARV trial! There were consent forms but I never saw one let alone read or sign it. Roche said they never did a Nigerian trial but to ask Swipha, their Nigerian representatives. Swipha said it wasn’t a Roche trial but a research by some Nigerian doctors. I still have the labelled bottles and some of the pills today and it's very clear who ‘sold’ those research drugs. I was told Roche would pay for 4 months and I should pay N65,000 a month for two months.

This debate about the Tenofovir trial is getting more interesting everyday. Please, let's call a spade a spade and be clear in what we say.

1. If there's a trial to determine the effectiveness of a drug, the only way you can get results and assess the effectiveness of your trial is to expose people to the virus but have them use this drug. Simply put, what this means is that people would be exposed to HIV and then if they end up positive, they'll be referred to the already over stretched government-subsidized ARV centres.

2. Is NAFDAC clear on what is happening? Is NACA involved in this? Does FHI have the go-ahead from the Federal Ministry of Health or is this another PEPFAR-style program where the Nigerian authority is left out of the loop?

3. What papers have the trial participants signed? Isn't it funny how the same body carrying out the trial might be the same one recruiting and paying trial educators and supporters? Is there an independent body doing this?

4. We want to be assured of the available referral sites and follow-up FHI talked about. We need to be sure these women know what papers they are signing or have signed. What 'informed consent' have they given? The Nigeria HIV Vaccine and Microbicide Action Group (NHVMAG), and other groups such as the Treatment Action Movement (TAM) should do an assessment and check with the trial participants if they truly understand what they're signing up for. NHVMAG and TAM have amongst their members, scientists, ethicists, journalists, lawyers and human right activists and we trust that since FHI is doing the ethical thing, they would not mind us double checking.

5. Finally, I hope we won't be given the 'patient confidentiality' clause excuse. I'm sure we can work this out in such a way that all parties would be protected and their confidentiality assured.

Morolake Odetoyinbo Nwagwu
Focal Person
Treatment Action Movement Nigeria
Email: tam@nigeria-aids.org

Date: September 8, 2004
Subject: Re: Tenofovir trials in Africa (7)

It is very unfortunate that we as Nigerians are part of this 'cover-up'. Reading FHI's 'prose' gave me a mixed feeling and brought back into memory what was done for the Cameroonians who were involved in the Nonoxynol-9 study. We were told that those who got infected during the trial were referred to local NGOs and Regional Medical Centers! We all know what happened to those unfortunate human beings. They had no care and most of them I believe are quiet in their grave and cannot remember what is called 'community preparedness', 'consent' or 'a New World Order'.

This FHI's "music" also gave a jazz reference and memory to Rakai studies in Uganda some few years ago (God forbid bad thing) where researchers from the North with the collaboration of our own African brothers were using Africans as "guinea pigs". We were later told that in the initial plan of the research, there was no plan to trace participants but they had their addresses and were informed not to tell their spouse about their status. I guess they were experimenting with HIV transmission and infectivity amongst humans...the "lesser" ones called Africans!
With the kind of access in the African countries where these trials are currently taking place, referral means nothing but a death warrant. This also underpins the insincerity of the researchers. Anyway, are they not lucky to be operating in a community with less information about new prevention technologies. In Nigeria, the first-ever Association on Ethics in Research was just launched this year! This was also a source of training for some of us researchers, scientists and community workers (Thanks for APIN-Harvard AIDS Institute who made that possible). I was one of the products of this kind of empowerment, and maybe that's why I can ask questions on justice and or 'benevolence'.

I guess the researchers are playing on the low level of awareness and on participants' rights as regards new technologies. If we cannot get a definite promise from FHI that they will do the humane thing of providing care + ARV for those infected in the course of this study, we need to start providing information for the appropriate authorities so as to stop this trial in Nigeria too.

If I were the Nigerian researcher involved in this study, I will begin to ask those that gave me drugs and direction some more information and sincere answers so that posterity will be lenient with my soul. It is true that new research and work will help to fight the virus, but we must not also voluntarily infect people who are voiceless, powerless and under-served in the name of searching for new innovative prevention methods for the whole world.

Bode-Law Faleyimu  
Coordinator  
Microbicide Advocacy Network(MAN)  
Email: caresblf@yahoo.com

Date: September 9, 2004  
Subject: Re: Tenofovir trials in Africa (8)

WHED as advocates of the rights and well being of CSWs and as an organization dedicated to getting communities adequately prepared for participation in clinical trials of this nature strongly believe that a lot more needs to be done in terms of getting the study participants adequately informed about what there are going into.

We totally agree with Rolake Nwagwu and Bode-Law Faleyimu and propose that NGOs should actively commence processes of getting high risk groups and other potential cohorts for clinical trials adequately prepared to have full knowledge and understanding of the whole concepts of clinical trials and the extent of risk and benefits trials bring to both individual participants and the community as a whole.

FHI must be commended for attempting to bring possible solutions through product development but the reality of our situation is that we can not in good conscience afford to willingly allow even one other Nigerian join the list of PLWHA carelessly. FHI must also note that at this stage of our community research all successful programs serve as templates for other interested groups so the processes must be open and transparent.

This is also a big challenge for the FMOH/NACA/NAFDAC to wake up to their responsibilities and sacred duty to provide fool proof mechanisms for research involving human subjects including vaccines and microbicides. NAFDAC especially must come to the full understanding that the scientific and political intrigues that go with product development of this nature are well beyond pure water and fake drug issues.

At the end of the day, we firmly state that first thing must be done first and the Nigerian community as a whole need to be adequately prepared for clinical trials involving human subjects.

Ali Johnson Onoja, PhD.  
Technical Consultant, Women's Health, Education and Development (WHED), Abuja, Nigeria

Date: September 9, 2004  
Subject: Re: Tenofovir trials in Africa (9)

Dear Colleagues,

This is a short reaction to Rolake Odetoynibo Nwagwu's very interesting and balanced piece in response to the above issue. I think the key issues here are that the need for research, involving clinical trials, which per definition will involve humans, is inevitable if we are to make any progress in controlling the HIV/AIDS pandemic.
Yet the challenge for our country in this regard, but also as regards all our other endeavours is the need for transparency. Where there is no transparency, any action, especially including clinical trials will be assumed to be biased, incompetent and corrupt until proven otherwise. So the key questions are (which also arose at the last National AIDS conference in Nigeria):

1. Is there a national process/committee for obtaining ethical approval for studies of this nature in Nigeria?

2. If such a process/committee exists, was this trial appropriately examined and approved?

3. If the answers to the above is yes...then the process should be made transparent and the issue closed, if not, WE ARE IN TROUBLE!

Chikwe Ihekweazu
Email: chikwe_ihekweazu@yahoo.de

September 10, 2004
Subject: Re: Tenofovir trials in Africa (10)
Dear Colleagues,

I have watched with keen interest, the on-going dialogue on the Tenofovir trial going on in Nigeria, and some selected African countries. The trial in Nigeria is being coordinated from the College of Medicine, University of Ibadan.

The trial has approval of the Institutional Review Committee of the COM/UCH, which reviewed both the science and the ethics of the trial. The IRC is the foremost of IRC's in this country and has a sound culture of good conduct. It is broad based in composition and all members are well trained.

It is scientific misconduct to disclose information about on going trials to members of the public. The absence of information on public domain should however, in no way, be misconstrued to imply lack of transparency. We are prepared to entertain enquiries about this trial, but science is not and should not be conducted on the pages of newspaper or other related media. We should also allow our Universities and Research Institutes to continue to develop a rich and credible tradition of inquiry so that they remain relevant to the society.

We assure all that College of Medicine, University of Ibadan will not abandon our commitment to protect and promote the health of our people.

Enquiries should be directed to:

Professor Isaac F. Adewole
Provost,College of Medicine, University of Ibadan, Ibadan, Nigeria, ifadewole@yahoo.co.uk

or

Professor Gladys Adeyinka Falusi
Chair,COM/UCH IRC, Protem Chair, Nigerian Bioethics Initiative (NIBIN), Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria, Te: 234-803-786-4468

Isaac Adewole
Email: fadewole@skannet.com

September 10, 2004
Subject: Re: Tenofovir trials in Africa (11)

Let me first of all thank all those who have reacted to this issue so that we can have a solution and move forward. Even FHI is beginning to understand that this dialogue is positive and all we are saying is respect for human beings.
Can somebody alert NACA/FMOH/NAFDAC. We need to hear from them. Or is it that they are not on this eForum? Somebody needs to let them be aware of this controversy so that we can hear their own side of the story. I am also sure there are other NGOs that are working with Transactional Sex Workers (TSWs) and other vulnerable groups in Nigeria. Do they have insights into this study as representative of such communities?

Who is defending or monitoring the rights of the subjects? The donors and researchers? The good thing about this is that we will all be better for it after we sort this out and FHI, the researchers, activists, communities etc will definitely leverage this and the gains will result in better process for future research and intervention.

Bode-Law Faleyimu
Microbicide Advocacy Network
Email: caresblf@yahoo.com

**Date:** September 10, 2004  
**Subject:** Re: Tenofovir trials in Africa (12)

Professor Isaac Adewole's offer of engagement on the controversy over the tenofovir trials is pleasing news! Even though it was slow in coming - the discussions on tenofovir has lasted on the eForum for two weeks without any word from the College of Medicine until now - his comments have demonstrated a willingness to engage with all various stakeholders with transparency and a sense of probity.

The Nigeria HIV Vaccine and Microbicide Advocacy Group (NHVMAG) will take up his offer to discuss and will be in touch with him very shortly. Our proposal is to work with the University of Ibadan College of Medicine in calling a roundtable at the earliest possible opportunity to discuss the various concerns raised about the trial and jointly ensure that the research study offers a rigorous ethical process and the best benefits to trial participants and the Nigerian public. NHVMAG will seek the partnership of other relevant stakeholders, including those who have made inputs to this discussion, such as the Treatment Access Movement and the Microbicides Advocacy Network, in facilitating the roundtable.

However, unlike Professor Adewole would have us accept, we believe that issues of scientific processes with impact on public health should be subjected to rigorous debate by interested public-minded stakeholders. The perception of science as a sacred masquerade whom only a restricted circle of anointed acolytes can view, is no longer acceptable.

Epidemics such as HIV/AIDS and tuberculosis have taught us that community engagement is as important - perhaps even more important than - science in driving a solution. Informed discussion on ethical conduct lies NOT only in the realm of science. But we accept that the conduct of science should remain true to the highest demands of sobriety, objectivity and integrity.

The concerns of many of the people who have raised issues so far are on the processes of the trial - NOT the names of trial volunteers or the list of those who will be given placebos or the real thing. Surely, discussions about the processes of a trial that involves human volunteers and has potential for major impact on the trend of the epidemic, should be in the public domain!

Omololu Falobi  
Member, Steering Committee, NHVMAG  
Email: info@nhvmag.org  
Website: www.nhvmag.org

**Date:** September 13, 2004  
**Subject:** Re: Tenofovir trials in Africa (13)

We also need to hear from the Community Advisory Board (CAB) of the research project if actually it is in existence. As community advocates, we have learnt over the years through bitter experience not to trust the ethical committees/IRBs of institutions no matter how highly or lowly placed.
Researchers all over the world have goals and milestones they are determined to achieve which can easily make them take decisions that might not ultimately benefit the study community. That is why even in the USA, an IRB approval is just the beginning of the process and can not under any circumstance substitutes the roles of CAB and advocates in driving research agenda on the path of community friendliness.

That is why all modern clinical trials of this magnitude must have a well represented CAB which act as intermediaries between researchers and the study community to ensure that all the ethical provisions as approved by the IRB are actually implemented among the study subjects.

We are glad to hear from the provost but we also need to hear from the Federal Ministry of Health (FMoH), National Agency for Food Drugs Administration and Control (NAFDAC) and the National Action Committee (NACA) on this very important issue to be sure that all the processes have been duly followed.

It should also be stated that the eForum is not a newspaper but a very reliable source of interactive discussions patronized by Nigerian researchers both at home and in diaspora.

Ali Johnson Onoja
Technical Consultant, WHED, Email: onojaali@yahoo.com

Date: September 13, 2004
Subject: Re: Tenofovir trials in Africa (14)

Dear colleagues,

We have read the many emails on the tenofovir study being conducted by researchers at the University of Ibadan College of Medicine and Family Health International. You touch on many important questions, so let me respond as best I can.

The tenofovir study is being conducted in the three African cities of Douala, Cameroon; Ibadan, Nigeria; and Tema, Ghana. The portion of the study to be conducted among men is being planned for Lilongwe, Malawi. These sites were selected because their populations have high rates of HIV infection, which is an important factor for determining the effectiveness of possible HIV prevention drugs. If tenofovir is shown to be safe and effective, HIV prevention programs that provide tenofovir can be established at these sites, so that these highly exposed individuals can be reached and can benefit from this intervention.

The well-being of study participants is Family Health International’s highest priority, as it is for our colleagues at the University of Ibadan. The study has been designed according to the most ethical international standards, and with stringent review within Nigeria, as Professor Adewole already described.

During each month of the study, participants will be counseled on safe sexual practices such as reducing sexual partners and using condoms, will be given condoms to use during every sexual act, and will be provided treatment for symptomatic sexually transmitted infections, if needed -- all of which have been shown to lower the risk of becoming infected with HIV.

All participants in the trial are volunteers. They will all be counseled before the trial starts to make sure they understand the potential risks and benefits of study participation and to know that they are not obligated to participate and may stop participating at any time. We are providing HIV prevention counseling using techniques that have been used successfully in previous research. (Results from recent trials of an HIV vaccine candidate in Thailand and the United States, for example, showed that risk behaviors were lower among participants than among non-participants because of the prevention interventions provided through the trials.) It is vital that potential participants understand that tenofovir is not yet known to prevent HIV and that half of the participants will receive a placebo, which contains no tenofovir. This concept is being stressed during the informed consent process.

Carefully designed ethical studies such as this one are the only way to accurately answer important research questions. Most of the drugs we use today to prevent and treat a variety of diseases, including the antiretroviral drugs used to treat HIV, have gone through the same types of studies. Tenofovir is not a new drug. It has been proven to be safe as a treatment for HIV and is one of 20 antiretroviral drugs already approved and used by thousands of individuals throughout the world to treat HIV infection.

We understand your interest in learning more about the processes followed in the trial, including informed consent. Dr. Morenike Ukpong, among others, has asked important questions about the standard of care offered to women willing to
participate in the trial. In the Nigeria tenofovir site, as in the other African sites, study participants who become infected with HIV will have enhanced referral to HIV care and support services, including antiretroviral drugs when necessary. FHI's colleagues at the University of Ibadan have identified facilities that offer HIV-related psychological, social, and medical services. Infected participants will be counseled and referred to those sites.

Like Dr. Onoja, we agree that successful programs can serve as templates for further research - whether on microbicides, vaccines or other HIV prevention strategies. We welcome your questions and commitment to helping educate communities to understand the concept of clinical trials. We believe, as you do, that both individuals and communities need to participate actively in assessing the risks and benefits of trials.

As Dr. Faleyimu says, open dialogue, respect, and a commitment to sorting out concerns is a positive thing, and the gains will result in better processes for future research and interventions.

Below, I am appending questions and answers about the tenofovir trial that Family Health International shared previously over NIGERIA-AIDS eForum, as some reading this email may not have had an opportunity to see it. New HIV prevention strategies are urgently needed, and we look forward to working together with you to make them a reality.

Sincerely,
Ms. Beth Robinson
Director, Information Programs, Family Health International, PO Box 13950, Research Triangle Park, NC 27709 USA
Email: brobinson@fhi.org, Media inquiries: media@fhi.org

Date: September 13, 2004
Subject: Re: Tenofovir trials in Africa (15)

Dear Colleagues,

My appreciation to all of you for your comments. I deliberately refrained from commenting because the debate initially focused on consent, preparedness and transparency. The most appropriate person to react is the Chair of the IRB who is on leave.

The initial publication by BBC on Cambodia contained remarks about Cambodia. The comments about human experimentation without animal tests were unscientific for this century. I had to come out to reassure all, because the discussion was getting off track. I am however disturbed that no one referred to the investigating institution by name. We have responsibility to our people and will respond to all enquiries made in good faith.

I look forward to a visit by Omololu Falobi or Bode-Law Faleyimu. I assure you all of our openness.

Professor Isaac F. Adewole
Provost, College of medicine

Date: September 13, 2004
Subject: Re: Tenofovir trials in Africa (16)

Like has been noted, it is nice to have some positive responses to the ongoing dialogue on the trial. I would like all interested parties to realise that no one is actually out to stop the trial. Rather, we ask for a review of the research protocol in the light of increased and better understanding of issues.

This same trial is also going on in Cameroon yet, FHI and the community dialogued and there were significant modifications made to the trial protocol.

I proudly acknowledge the works of Dr Sade Ogunsola, who is the local investigator for the microbicides trial in the Lagos University Teaching Hospital (LUTH). Continuous dialogue with community advocates and continued education led to reviews of the protocol. For one, community preparedness issues was introduced (which was not originally there).

Secondly, all those who become HIV positive on the trial would get guaranteed access to ARV through the PEPFAR programme. It was concerted efforts and determination that made her get those done.
This trial is nothing like the microbicide and vaccine trials. We are talking about systemic intake. What happens to the volunteers who are on tenofovir, take it inconsistently and then get HIV infection? How would their future use and access to ARVs be affected? Secondly, for those who took tenofovir consistently and religiously during the trial and then discontinue once the trial stops but now get infected with HIV, what happens to them? HIV has no cure. The best we have now is ARV. We cannot jeopardise the chances of research participants to future access to this drug because they choose to be heroes - for me and you!

Finally, what benefit would the research be if at the end of this Phase II/III trial, tenofovir is found to be effective in preventing HIV infection when taking daily as an oral pill, yet studies show that people do not consistently take daily medications for various reasons (even for treatments how much more for prevention!). Not all trials have to be conducted; conducted trials have to be to the benefit of all.

I believe in the efficiency of the IRB in Ibadan but we are all learning. All the IRB members are not experts on new HIV prevention technologies. There are more community advocates that are better informed and so there is a place for public debates.

For the Cameroun trial, all infected persons were given access to ARV by the research team after community advocacy efforts and drive. Is that known by IRB members in NAFDAC, FMOH and Ibadan? Why are the research heroes going to have access to only male condoms, when female condoms exist? Why can't the participants have a choice of male or female condoms, knowing that male condom negotiation is an issue in Africa?

I think we should move forward. All contributors on this forum have made significant and important points. They have ALL raised important critical issues that need to be considered. These should not be ignored but appropriately addressed. Prof Adewole could help see to that. Prompt action is needed before negative media information about the trial starts to be generated.

Like Omololu Falobi noted, I am sure NHVMAG, who definitely wants to see to prompt development of new prevention technologies, would want to speedily collaborate with Prof Adewole to work things out. Other stakeholders are TAM, WHED, MAN, JAAIDS, NAFDAC, FMOH, NABIN, and other scientists involved in the research and development of new prevention technologies in the country.

Morenike Ukpong
Email: mukpong2@yahoo.com

Date: September 15, 2004
Subject: Re: Tenofovir trials in Africa (17)

A few more questions to FHI.

First : New HIV prevention strategies are urgently needed, and we look forward to working together with you to make them a reality. What exactly is FHI's objective? A 30%, 50%, 80% success? What if tenofovir proves to be "half effective"? Is "half protected woman" better than nothing? To make it short: what are your criteria of success? How will you cope with the results if just "half good"?

I think this question is of extreme importance. What if men can then say "don't ask me to put a condom, you have this miracle pill that can almost protect you"? Scientific clinical research is normally considered as ethic with a condition: that it looks for better than the actual standard of care. We then need to know more about criteria and chances of success.

Are similar studies of tenofovir being conducted? The Centers for Disease Control and Prevention is also preparing to test tenofovir among diverse populations in three countries: I searched and could not find anything about this CDC trial being planned in US targeting men who have sex with men in Atlanta, Georgia, and SanFrancisco, California. I understand that they did not start enrolling yet. Still could you help us and find the protocol and informed consent form?

You also said : We believe, as you do, that both individuals and communities need to participate actively in assessing the risks and benefits of trials. Talking about the risks.... You mentioned very few (you did not mention any). Scientists usually make sure that risks are well understood and try to favor the most cautious attitudes towards engaging into a clinical trial. Is there a scientific evaluation of the effect of a long course daily dose of tenofovir on the future efficacy of treatments? While we know that Tenofovir can not be compared with Nevirapine in terms of its potential for selection of resistant virus,
still we would love to learn from you that it is not an issue. If you have good reasons to think that there is NO such consequences, you should nonetheless present your arguments in the protocol and informed consent.

Tenofovir has been proven to be safe as a treatment for HIV and is one of 20 antiretroviral drugs already approved and used by thousands of individuals throughout the world to treat HIV infection. Has tenofovir been proven safe as a 12 months long MONOTHERAPY on HIV negative people? Not to my knowledge. I understand that this question is to be answered through this phase II/phase III trial. If FHI needs to further question the SAFETY, it means that there might be some risks that you don't fully control yet. I would like FHI to be more transparent about this. Clearly, running a "safety and efficacy" trial is, in its terms, questionable.

Are the participants being counseled on HIV prevention? Women will be counseled monthly on safe sexual practices such as reducing their number of sexual partners and using condoms during every sexual act. Hmmm. Asking sex workers to reduce their number of sexual partners? Best way to do that is to find them another job! And if they failed negotiating a condom so far, you may like to try and counsel the men instead? :)

What happens if a participant becomes infected with HIV? Those who do become infected will have enhanced referral to HIV care and support services, including antiretroviral drugs when necessary. Do you mean prophylactic treatment? A triple therapy during a month after getting at risk of infection? ( :)) Or do you mean "in five to ten years from now, when the study will be over"? And FHI will be gone? Is everybody aware that people getting infected in this trial, ie under the responsibility of FHI, will need medical care and especially ARVs in years from now? How will FHI ensure the "sustainability" of this "referral" system put in place? In case they need to get access to the newest therapy because of a drug resistance problem, or just because it has become the new standard of care, will those infected women be in a position to ask FHI for a combination that might not be available in Nigeria by this time?

Please be more precise about FHI's commitment to care for and treat infected people.

Another important issue: I assume that FHI will test people's serostatus first hand, before inclusion. What kind of psychosocial and medical follow up is in place for those people that will test positive and therefore be excluded from the trial? You have to take into account that testing hundreds of people will induce a high demand for care and support, and prophylactic treatments. How will FHI cope? (other research agencies do cope with this important issue). How is the overall safety of the participants being protected during the study? In addition to counseling on HIV transmission and prevention, provision of condoms, and careful monitoring of any side effects, multiple safeguards are in place to protect the physical and psychological well-being of participants.

Again, how can you ensure safety when you did not fully test it first? How can you run a "safety AND efficacy trial" at once? I have never heard of such a thing before. Phase II and III are usually separated, and their design quite different to avoid putting huge numbers at risk. "safety" should have been tested on a small number of volunteers (not at risk). This is the STANDARD of science.

I guess toxicity has been tested before introducing TDF in the market as a treatment, but the conditions might have been different (ex: in triple combination, for several weeks only, on seropositive people only, etc.). We need to know exactly what still has to be tested, as far as safety is concerned. Otherwise there can't be any fully "informed" consent, ie comparing risks and benefits.

On benefits, you said : How will participants and other community members benefit from the study? Potential volunteers and other community members will benefit from increased awareness of HIV prevention because of their involvement in preparation for study initiation. In exchange of the risks linked to side effects and others (kidney problems. That you intend to measure), raised awareness is a bit cheap. Aren't there other ways to raise awareness? Can you certify that this one is not too costly for the human body when compared to other kinds of interventions? Frankly, if I were seronegative and a sex worker, I would not think that the benefits are higher than the costs. Let us be sincere here: there is NO direct benefit for the people in the trial nor the community around it. It is for the sake of science only.

What is being done to make tenofovir available for prevention, if proven safe and effective? Again, what do you mean by "effective"? And "safe"? That is a lot of questions.

thank you for your effort in answering them.
Marie de Cenival
Paris, France
Email: mdc@no-log.org

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Date: September 16, 2004
Subject: Re: Tenofovir trials in Africa (18)

In her contribution, Morenike Ukpong wrote: "This same trial is also going on in Cameroun, yet FHI and the community dialogued and there were significant modifications made to the trial protocol."

Can we have more information about those modifications? Is there a way we can access the Nigerian protocol (and consent form) and see what differs? Could FHI send us the documents? You can access a version of the Cameroon protocol and consent form at: http://trenado.free.fr/STUDY9780.pdf

I took a look at the consent form, and some sentences are shocking. I do hope that this is an outdated version and things have changed with the help of that community dialogue. One part of the Cameroon document read: "you may experience anger and distress if you are positive for HIV. We do not provide treatment for HIV. We will refer you for help if you are infected with HIV". Well that is a little short. To my knowledge, in trials looking at reducing mother to child transmission in developing countries, for example, no research agency would dare to completely get rid of that responsibility and transfer it to some unspecified local health center. Besides it is in full contradiction with the international ethical standards.

Clearly, FHI does not provide care and treatment to people getting infected in the course of the trial, nor to those who would fall sick for any other reason, and this is NOT ethics. People in FHI seem to consider that infections occurring during the trial are not part of their responsibility. If you are sick or have a health problem due to being in this research, you will not have to pay for visits to see the research doctor or clinic staff.

This is less that the minimum one can expect. That does not tell anything about the drugs that will be available, and other medical services that could be needed (exams, etc.). Who will pay for that?

"If you need more help, we will refer you to other clinics, where you may have to pay". This is unethical. And clearly the section about the risks is ridiculously short and imprecise. And please and please, donÂ’t promote abstinence in the informed consent form nor in the prevention cession when your whole study is based on the idea that female sex workers fail negotiating condoms. If you definitely think that they are not in a position to impose a condom, they will certainly not be able to ABSTAIN either. So avoid making them feel guilty above all.

Marie de Cenival
Paris, France
Email: mdc@no-log.org

Date: September 16, 2004
Subject: Re: Tenofovir trials in Africa (19)

Dear Colleagues,
The College of Medicine, University of Ibadan, organized a roundtable meeting today on the Tenofovir trial currently being conducted in Ibadan. We took into consideration the various issues raised at the eForum. We discussed extensively among others the following issues:

- Study design and implementation
- Community Preparedness
- Community Advisory Board
- Informed Consent Process
- Staff layout
- Best Clinical Practices
- Laboratory Practices
- Care of Subjects
- Subjects/Community Benefits
- Participants benefits
- Study monitoring

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Report of dialogue between community advocates and researchers on Phase 2/3 oral tenofovir trial in Nigeria

It might be pertinent to mention that College of Medicine, Ibadan is the foremost medical Institution in Nigeria. We are not new to drug trials, having conducted several trials in the area of communicable and non-communicable diseases in the past. We are still actively engaged.

We have supported, and facilitated the training of Nigerian Researchers in Bioethics. We also produced the working document for the National Guidelines on Ethics and have representation on the National Committee that is yet to be inaugurated.

At the end of the discuss, the roundtable concluded as follows:

1. The study is ethically designed and offers a tremendous opportunity for revolutionizing HIV/AIDS Care and support:
2. Irrespective of level of effectiveness, any increase is beneficial
3. The study will not expose participants to HIV infection but offer them valuable education and counseling on how to prevent HIV Infection
4. It has approval of the College of Medicine/University College Hospital Institutional Review Board
5. The study was preceded by formative research conducted by an independent researcher who demonstrated a clear need for a HIV Preventive pill
6. The conclusion of the research was: "We have a need for a pill to prevent HIV/AIDS and will use one if and when it is made available".
7. The formative research offered valuable opportunities for us to prepare the community

There are however, urgent needs to review certain aspects of the project implementation focusing on issues that were discussed at eForum and others that were highlighted during the roundtable meeting.

1. The roundtable recommended that all patients who tested positive during enrolment should be offered care and support.
2. Subjects who sero-convert during the trial will also be offered initial treatment and support
3. The two groups of subjects will be recruited into the ongoing PEPFAR trial as soon as new patients are being admitted
4. All subjects are to be followed up for a minimum period of 2 years after closure of trial
5. An independent clinical monitor will be appointed to ensure that participants are offered good care
6. A Community Liaison Officer will also be appointed to protect the interest of the community
7. Regular community meeting to review progress and problems will be conducted.
8. Female condoms should be provided to those who want it
9. All patients requiring care will be treated by the Project at the University College Hospital, Ibadan
10. We have decided to engage FHI in the process of implementing the above recommendations.

We shall gladly welcome for consideration other suggestions.

Professor Isaac Adewole
Provost, College of Medicine
University of Ibadan
Ibadan, Nigeria
Email: ifadewole@yahoo.co.uk
Date: September 20, 2004
Subject: Re: Tenofovir trials in Africa (20)

Major issues mentioned by Marie de Cenival is, if we are following the Cameroon protocol. Another question is: Who actually was at the round table called by the College of Medicine? I initially thought we may be worrying a bit much, but after reading for a while the comments and discussing the issues with others, I am honestly getting worried about this trial.

Dr Jennifer Anyanti
Email: janyanti@sfhnigeria.org

Date: September 22, 2004
Subject: Re: Tenofovir trials in Africa (21)

It's great to realize that Nigerians are no longer jumping at offers such as these.

In time past the trials would have been done in bureaucratic secrecy, leaving its wounds on people. All hands must be on deck to ensure that our people are not endangered the more.
NAFDAC, TAM, FMoH, JAAIDS, NEPWHAN, NACA and others should keep the pressure on so as to save the country form suffering further hicups in the fight against AIDS. We should not be stampeded into another drug trial. Our population should not be seen as a "guinea-pigging" us opportunity.

Jeph Oluwagbemiga
Jephking Consult, Lagos
Email: jeff_abiodun@yahoo.com

Date: September 22, 2004
Subject: RE: Tenofovir trials in Africa (22)

I have read with keen interest the dialogues that have transpired over the Tenofovir drug trial. It is important that we remind FHI and partners that 'Africa is come of age. How else can one explain a blatant disgust for human life particularly that of an African.

Imagine someone simply saying if infected, you will be placed on ARV. 'Dash' HIV infection ...Just like that! I find this rather appalling. It is scary and gets me really worried about this trial. I want to pitch tent with other contributors that the relevant governmental bodies constitutionally charged with the responsibility of protecting the health of Nigerians to speak-out as a matter of urgency.

Godspower Omorogie
Email: Gomoregie@sfhnigeria.org

Date: September 22, 2004
Subject: RE: Tenofovir trials in Africa (23)

I thank Dr. Enyanti for her comments. You did not however state the nature and form of your worry. We shall gladly take them into consideration when you put them across. We reviewed the Nigerian protocol and that is what is of interest to us.

The roundtable was attended by the underlisted:

Prof. Isaac F. Adewole - Chairman
Prof. F.A.A. Adeniyi
Prof. O.O.Akinwinka
Prof. O. Akinwale
Prof. A.O. Obiechina
Prof. O.O. Omotade
Prof. Gladys A. Falusi

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I believe that a roundtable that would be of interest to people in the field of public health would be more interdisciplinary in nature, than the list provided by Professor Adewole. Do forgive my ignorance if I'm wrong.

I don't have to be invited, but I'm sure even ignorant non-medical public health practitioners like myself would have appreciated having a group of people of known public health practitioners not - necessarily medical doctors - who could review and interpret the Nigerian protocol in a way that even the ignorant understand and can be satisfied with it.

I also believe that this dialogue has gone on long enough for there to be an understanding that it is not only those carrying out the study that needs to be interested in the protocol. After all, the outcomes are supposed to be of interest to the rest of us, in terms of impact.

Your colleagues did not raise concerns about the trials, but I'm sure your report of the review, when published or circulated would bridge that gap for us.

Edem Effiong
Email: edemeffiong@yahoo.co.uk

I have followed comments regarding the above trial with interest and I feel compelled give a reply to Professor Adewole's posting. It would have been nice to have the affiliations of the people who attended the College of Medicine round table. However, it is obvious from the titles and some of the names I can identify below that it was a meeting populated by academics in medicine and cannot by any stretch of imagination be described as a round table. There have been lots of worries expressed in this forum regarding ethical aspects of this study, subject/volunteer protection, standard of care/referrals for subjects who become infected, even the study aims, etc.

Who among the members at this round table represents people/persons living with HIV/AIDS (and we have quite a number of such organizations). What about the media, what about legal counsel, representatives of the FHI and NACA, etc.

In view of the lack of information regarding this trial that has generated so much furore, one would expect the college to have had a more embracing participation to iron out all the issues raised.

I stand to be corrected but I think it is high time NACA sat up their responsibilities including having a national or regional ethical committee to look at HIV and other diseases-related clinical trials in conjunction with local institutional review boards (IRBs). The Ethical Committees should be made up of clinicians, government representatives, representatives of PLWHAs (when appropriate), members of civil rights groups, etc. I know that there is something like that in place in The Gambia. This will reduce the incidence of controversies regarding trials that may actually be beneficial to the populace. Let's remember that there can be no effective research/trials without cooperating volunteers/subjects.

Thank you. Ifedayo Adetifa MD Email: ifedayo_tiffy@yahoo.com
September 26, 2004
Subject: Re: Tenofovir trials in Africa (27)

HIV infection is a scourge to humanity and all hands must be on deck to stop its spread. This is why a lot of researches are going on to find an effective preventive or curative remedy all over the world, including Africa.

I have read with interest about microbicide and vaccine trials in Africa and it is certain that there is no known effective microbicide or vaccine for HIV prevention yet. It is unlikely that one will be available in the next 10 years. This is why all efforts should be intensified to encourage researches on other preventive measures that come into the picture.

The ongoing TDF (tenofovir) study in Africa is one of such. I believe the TDF study was designed on sound ethical grounds otherwise all regulatory bodies in Africa would have stopped it before now. We cannot use the Cambodian experience to judge ourselves. In the first case, the commercial sex workers (CSW) in Cambodia have a union and are more organized than the ones here. They stay long on the job, their actions are well coordinated and they receive adequate medical care from the government. This is why the incidence of HIV infection in Cambodia is dropping.

Here in Africa, the CSW are very mobile and are only on the job for a few years. Most take on the job to gather enough money to start a business or support themselves in high institutions. They give fictitious names and address in order to hide their identities from health workers and researches. This is why it has been difficult to give a comprehensive health care to CSW in Africa. HIV positive CSW continue their business unabated and are reluctant to go for medical care due to their erroneous belief that they will be detained and handed over to the police or given lethal injections. Some men out of annoyance deliberately infect CSW in order to spread the disease. These men willingly burst their condoms with finger nails or pay a high price for a sexual act. These are reasons for continuous rise in prevalence of HIV infection among sex workers. It is believed that if one stays long in the business one will acquire HIV.

This is why we need additional HIV preventive measures that are user controlled for the CSW, such as microbicides and TDF. However, it is doubtful if vaginal microbicides will be appropriate for someone who has many sexual acts in a day. After repeated applications the vagina will be so full that the microbicide will flow out to the embarrassment of the user.

This is likely to affect the acceptance and continuous use of microbicides by CSW. Microbicides will be more acceptable to other youths and elderly that will also benefit from its lubricating effect. TDF on the other hand, is a once daily pill just like oral contraceptive pill. It is independent of sexual act or the sexual partner and covers all other modes of HIV transmission. Just like all preventive measures, it has its limitations but we should not just discard it for selfish reasons.

The ongoing research in Africa will educate us and possibly help us to develop other preventive medications. The reactions of the microbicide advocacy group raise a lot of questions. Are they being sponsored to discredit TDF research because of the fear that oral ARV may do to microbicides what oral contraceptive pills did to spermicidal jellies and creams? No matter how we look at it the reasons why Cambodian stopped TDF research applies to all drug researches, especially microbicides and vaccines. If we do not take care we may be unable to perform any research on ARVs again in Africa because of the need to insure the participants against complications.

Evelyn Chuckwuemeka
Email: evelynchucks@hotmail.com

September 26, 2004
Subject: Re: Tenofovir trials in Africa (28)

Like other concerned Africans, I have followed the lengthy discussion on the controversial Tenofovir trial in Nigeria with keen interest. First, I must congratulate Nigerians not only upon their concern for the welfare of their fellow Nigerians, but also on their vigilance and boldness in asking tough questions about this important issue. It is gratifying to know that Nigerians are no longer content to be unwitting and docile consumers of products just because academicians with impressive and envious titles endorse them. More grease to their collective elbows.

With the possible exception of Morenike Ukpong, Kristin Peterson and Irene Ogbogu’s reference to Tenofovir trial in Cambodia and the controversy surrounding it, the discussion on this forum appears to ignore the captivating drama it has caused in that Southeast Asian country. It is significant to note that the Prime Minister of Cambodia, Hun Sen stopped the Tenofovir trial in his country after the Cambodian Women Network for Unity (an organization of sex workers) protested.
against the trial. Tenofovir trial was to start there in June 2004, but it was halted when the Women's Network for Unity claimed:

(1) that Tenofovir DF had only been tried on monkeys and not on human beings, and therefore, they were not about to become the first group of human beings subjected to undergo Tenofovir trial.

(2) that their population was very likely chosen because it was among the poorest in a poor country.

(3) that the trial subjects were asked to take Tenofovir pills in exchange for free medical services, counseling and $3 per month during the trial period, whereas the manufacturers of Tenofovir stand to rake in millions of dollars if the efficacy of the drug is proven, based on these trials.

(4) that the drug side effects includes “diarrhea, nausea, weakness to liver, kidney failure and "brittle bone" disease”, yet there was no provision for insurance for trial subjects.

The fascinating aspect of this saga is Cambodian Health Minister, Nuth Sokhom’s statement that the Prime Minister ordered the trial stopped because it would affect his people’s health, contravene their human value and rights.

My questions are:

(1) Who speaks for the Nigerian subjects of these trials?
(2) Who speaks for citizens like Frederick Adegboye?
(3) Above all, who speaks for Nigeria?

Dr. Atta A. Ubokudom
Email: uboknasia@comcast.net

September 26, 2004
Subject: Re: Tenofovir trials in Africa (29)

I read from a national daily which gave me an insight into the Tenofovir trials in Nigeria. I quite agree with what others have said so far about the trials especially the views of Dr Morenike Ukpong.

My concern about the trials is that from the story that I read, this same Tenofovir was tried in Cambodia and it was rejected, so why Nigeria? What is the fate of those that have volunteered themselves for the trial?

Akintimi Clement
Email: clemsakintimi@yahoo.com

September 26, 2004
Subject: Re: Tenofovir trials in Africa (30)

NHVMAG notes with concern and deep respect the various issues that continue to be raised and discussed on the tenofovir trial. Like NHVMAG promised, its Ethics and Scientific Committee took time to study the trial protocol and sort information about the trial from colleagues in other parts of the world.

Our suggestions for possible further review of the research protocol have been officially forwarded to the Provost of the College of Medicine, University of Ibadan.

Recommendations made include:
1. The need for trial participants to receive the BEST possible care in this research process. There should be no compromise.

2. The research protocol should also be amended to include:
   a. Interventions to ensure community preparedness on the path of the researchers. Members of the community within the trial focus area should be adequately prepared for the trial (informed and kept updated about the research) so they can
give their support for the process in view of stigma related to HIV infection. Where the community is not adequately prepared, there is a possibility of myths and misconceptions to develop about the trial. Trial participants’ retention may then be difficult. In a bid for researchers to then meet deadlines in view of funding constraints, compromises may then start to occur in the trial design and volunteer recruitment procedure.

The Ibadan researchers could learn from the ongoing 6% cellulose sulphate (microbicide) trial at the Lagos University Teaching Hospital (LUTH). NHVMAG is actively supportive of that process because the local principal investigator has been responsive to community involvement and modified the protocol to include this despite the initial oversight. We are presently working together to design and implement community mobilization at the trial site. This University of Ibadan research team could benefit from dialoguing with Dr Sade Ogunsola who is leading the microbicide study at the Department of Microbiology, LUTH. The tenofovir trial could also learn from the community preparedness exercise of Prof Kayode Dada of the Department of Chemical Pathology, Ogun State University, Ago-Iwoye on their efforts during the phase 1 trial on 6% cellulose sulphate.

b. Future dialogue should include interested community advocates. We do support the need for regular community meeting to review progress and problems, but please include community members who are vast on the issues on Board. NHVMAG suggests that the community should be represented on the Clinical Monitoring Team, the Safety Monitoring Team, the Data Monitoring Committee and during the UCH IRB monitoring and review process. We would not want a compromise on this. This would ensure that that the community views, perspectives and concerns are addressed during deliberations and in the decision making process.

The community member would then report back to the community and such representatives would be our liaising arm of the project. The community could confidently relate to their reports.

d. The protocol should address the need to focus on participants’ health and not just the drug trial. As such, once the health of trial participants are compromised for whatever reasons, such participant should drop out of the trial process.

e. All recommendations should be reflected in the protocol an informed consent form that trial participants are to sign.

Please note that the summaries and document the dialogue on an off the eForum, including recommendations made and actions taken. This document would be sent to all relevant stakeholders for information and future actions as this process has been quite educative and NHVMAG considers it a process to be learnt from.

We believe that we are about reaching an end to this interesting discussion wherein the scientists and community work together in research efforts. The place for the community to participate in research design and implementation had long been identified as this facilitates the research process and the eventual uptake of the products.

The days of scientists doing things for ‘them’ (the community) is fast fading. We have to learn to do it together for ‘us’ and HIV/AIDS is teaching us how to do this properly.

Morenike Ukpong
For the Steering Committee, NHVMAG
Email: info@nhmag.org

October 11, 2004

Subject: Re: Tenofovir trials in Africa (31)

Over the past three weeks, NHVMAG - the acronym for the Nigeria HIV Vaccine and Microbicide Advocacy Group - has been engaged in consultations with different stakeholders involved in the ongoing phase 2b study on oral Tenofovir (TDF) for the prevention of HIV, being undertaken at the College of Medicine, University of Ibadan, Nigeria.

The consultations sought to explore and carry forward the very engaging discussions on the trial that have taken place on the eForum over the past month or so now. Subsequent to the eForum discussions, NHVMAG initiated direct contact with both the College of Medicine and Family Health International (FHI). We communicated directly with Professor Isaac Adewole, Provost of the College of Medicine and Ms. Elizabeth Robinson of FHI. We also networked with partners local and international to garner information that are relevant to the trial in Nigeria, especially TDF studies held, planned or ongoing in Cambodia, Cameroon, the United States and elsewhere.
Following are summaries of the discussions and conclusions reached:

1. The College of Medicine believes that Tenofovir (TDF) is a safe drug for use as a chemo-prophylactic against HIV infection following the result of phase 1/II in literature. The provost particularly noted that a number of Phase 1 studies on TDF have been conducted in HIV negative participants, including studies on drug interaction, renal impairment and the drug's pharmacokinetics (studies GS 909, 914, 919, 930, 932, 943 and 1037). The studies noted that abnormalities, including elevated creatinine phosphokinase and liver functions tests. However, these were resolved with or without drug discontinuation and without sequelae. To detect these changes for the present research, blood samples would be taken from the participants at screening, enrolment and at follow-up. Abnormal liver and kidney tests form part of the exclusion criteria and information about the possibility for these side effects has been included in the screening and enrolment consents to be given to the participants.

NHVMAG could not however find published peer reviewed reports on the study of tenofovir use in HIV sero-negative individuals during its literature search. We note that the phase I safety trial reported in the literature was done amongst HIV-positive people, not HIV-negative individuals. (Patricia Barditch-Crovo, Steven G. Deeks, Ann Collier, et al. Phase I/II Trial of the Pharmacokinetics, Safety, and Antiretroviral Activity of Tenofovir Disoproxil Fumarate in Human Immunodeficiency Virus-Infected Adults. Antimicrob Agents Chemother. 2001 October;45 (10): 2733-2739).

2. If found effective, the drug (TDF) will bridge the prevention gap created by the absence of a vaccine for HIV. It will be an additional choice for people with unmet HIV prophylactic needs (i.e. sexually active men and women who can not use condoms, microbicides or vaccines). Persons wanting temporary protection from HIV (e.g. long distant drivers, commercial sex workers, students etc) may also find the drug useful.

3. The College of Medicine has held two roundtable consultations with members of the university community (which included 8 medics and 8 non-medics; a professor with a degree in bioethics and a former program manager with WHO). Following the consultations, it was agreed that the FHI-led study team MUST make the followings changes to the trial protocol so as to ensure maximal benefit to trial participants:
   a. All participants diagnosed with HIV infection at screening and during the trial who require ARV should be enlisted in the PEPFAR treatment program at U.C.H.
   b. All participants must have access to both male and female condoms
   c. All volunteers on the trial MUST be treated for ALL ailments they have during the trial, whether related to the trial or not.
   d. All HIV testing should not only be based on the rapid test kits using saliva as planned by the investigators, but would also be done by the well-equipped virology laboratory at UCH
   e. All participants with grade III or IV adverse events during the trial must be discontinued.
   f. An independent clinical monitor will be appointed for the project. S/he will monitor and evaluate progress made on the research, ensure volunteer's welfare as well as ensure that the researchers keep within the focus of the research design. A community liaison officer has been appointed for the project. His appointment was made with the ratification of the Network of People with HIV/AIDS in Nigeria (NEPWHAN). He will liaise with the researchers and the general public on progress made on the ongoing trial
   g. Effects of malaria infection on the efficacy of the drug as chemoprophylaxis for HIV infection will be evaluated.

4. Concerns were raised about the long term consequences of the use of TDF. The provost noted that the results of clinical studies show that TDF clears from the system within 36 hours of use thereby reducing the chances of developing resistant HIV strains, even if infection is acquired during the trial. Nevertheless, trial volunteers will be followed for two years after the conclusion of the trial to monitor for possible long term complications that may arise from participating in the trial.

5. In addition, NHVMAG made the following recommendations to the provost:

   a) Establishment of a Community Advisory Board (CAB): The provost felt that establishing a CAB does not necessarily translate to community consultation and CAB has the potential for fuelling demands by some privileged members, which may not necessarily translate to community needs. While NHVMAG appreciates this concern, we believe that constitution of a genuinely-representative and functional CAB is a priority need. Aside from the fact that establishment of a CAB is a standard international requirement for any research study involving human subjects, NHVMAG believes that a CAB is necessary to provide the critical linkage between science and community in a way that goes beyond the duties assigned to a single individual. We intend to continue to discuss with the study team on the need to put this important structure in place.
b) Design and implementation of community preparedness activities at trial sites: Community preparedness is a very important aspect of any research trial taking place within a human population. It includes community education and empowerment initiatives, sensitization programmes and identification of community needs relevant to the research effort. This will not only ensure support for the trial but would help increase the prospect of drug uptake in the future. Activities to ensure community preparedness for a trial is standard practice worldwide.

The Provost of the College of Medicine observed that the TDF study was preceded by formative research which included:

a. Consultations with community members.
b. Discussions on the informed consent forms/process with potential participants
c. Identification of concerns of care givers on the use of Tenofovir
d. Determination of the impact of participation on stigma and other social harms

While we genuinely appreciate these steps, NHVMAG stresses that community preparedness, as internationally practised, is much wider than what the provost outlined, and remains a priority need.

6. It is important that government lives up to its responsibility by setting clear structures and standards for ethical oversights of scientific research processes in the country. As a matter of urgency, the Federal Ministry of Health and the National Action Committee on AIDS needs to:

a. Set up a National Ethics Review Board
b. Urgently define the standard of care for clinical trial participants.

NHVMAG is already working with NACA and the FMOH in convening a national consultative meeting to deliberate on these issues. We will continue to monitor issues on the trial as well as other microbicide trials going on in the country and ensure compliance with internationally recognised ethical standards for clinical trials.

NHVMAG appreciates the various contributors to the discussions on the tenofovir trials, on the Nigeria-AIDS eForum and other communication channels. The discussions have been quite enriching, and have contributed to strengthening our common resolve to ensure that our nation benefits optimally from the important work of science in finding new options for HIV prevention and control.

A summary of lessons learnt from this process will be documented, and made available to all stakeholders as soon as the consultations are concluded.

On behalf of Steering Committee, NHVMAG

Morenike Ukpong
Omololu Falobi
We: www.nhvmag.org
Email: info@nhvmag.org
Appendix 2
Communications amongst concerned community members

Wed, 8 Sep 2004 11:29:41 -0500
rolakenwagwu@yahoo.co.uk, mukpong2@yahoo.com
Kristin Peterson" <krisap@umich.edu>
tenoforiv side bar (1)

Hi Morenike and Rolake:

I just wanted to add some more comments on FHI.

Comments on FHI: "the most rigorous international standards." Well, there is a very big global controversy in bioethics communities over which standards count as rigorous. As Morenike states, these need to be absolutely defined. I also agree that it is NOT enough to say that various ethics boards were commissioned to approve the trial. This is also what Pfizer said about the trial for Trovan conducted on children in Kano. After 11 children died and numerous more maimed, strong evidence emerged that Pfizer never got ethics board approval in Nigeria and actually falsified documents. Now Pfizer faces a class action suit in New York City filed by 11 different Nigerian families. My point is not to compare the ethics of the tenoforiv to Trovan, but to emphasize that the lack of transparency has created a huge environment of mistrust. And in my opinion, the entire Pfizer scandal generated the ongoing denials (of state government officials in both Kaduna and Kano) of meningitis and measles epidemics and the refusal to get children vaccinated. So, here we have some very serious unintended consequences of denials and refusals to vaccinate that continue to negatively impact even after the companies and their drug testing are long gone. So, this is why I was very insistent that they should documentation. All of this means nothing until one sees and evaluates the documents.

Under "What is tenoforiv?": The SWOP report states that tenoforiv was never tested on healthy human subjects (this is the first stage of any clinical trial). This needs to be explored bc I am not sure about this. I do know that Tenofovir must have been tested at one time as an antiretroviral because it is used in an ARV drug combo. But SWOP could be correct on one issue. If a drug is being tested for a new use, it may need to be tested once again on healthy subjects before moving to the target population. But the thing here is that if tenoforiv has not been tested on healthy subjects, Gilead and FHI may have argued that HIV neg sex workers make up two stages of a drug trial--the healthy subjects and the target population. I'm really only speculating here and it would be very good to see NAFDAC's pre-trial data evaluation--there should be some answers on this issue there. Also, tenoforiv, like other ARVs is toxic--I see no comments on side effects. Is this drug being tested for dosage? Duration? Frequency of use? Toxicity?

This is also a double blind study it seems. Some women are getting placebo and others are getting the drug--no one will be told what they are receiving. I would want to look at the official informed consent forms here. If some women think they are taking a preventative drug and they are actually getting a "sugar pill" it could be disastrous. Also, who is doing the counseling? What are they told? How many condoms do they get on these monthly visits? How far do the women live from the clinic and how are they getting monthly transport?

Also, I was very suspicious of the claim that they are distributing condoms. This still needs to be explored: how many? How often? By whom exactly? The reason why I was suspicious was because if a woman remains negative throughout the duration of the trial, does the trial deciper whether it was the drug that was working or the condom that were working? This is where the placebo comes in. I imagine it works like this: the trial deciphers if the drug is working only if the group of women taking the drug all remain negative, and at least some members of the placebo group become positive. If members of both groups become positive, then the drug is not working. Any of the women who end up in the placebo group have a very strong chance of becoming positive. The only way the trial can determine if the drug is working is to count the number of people who become positive. So, FHI needs to be asked exactly how they will determine if the drug is working--what is the criteria for evaluation?

(I should add that there is a huge debate in the bioethics community worldwide over the use of placebo--whether it is...
ethical or not. I don't care what the official stance is, there is still a debate and it is highly controversial. So whenever you hear someone say that "everything falls within international guidelines" they might be right, but there is still a move to question almost all of the international guidelines. This is why I think it was absolutely critical that Morenike asked for details.)

This trial seems to be counting on the disempowerment of women and condom negotiation to fail—they almost come out and say that directly, but they say it in the context of women needing to take control of their own lives by using a pill alternative. I agree that there needs to be more options other than condoms, but even if this drug works and is provided at cost, will these women be able to afford it on a regular bases? Is the pill ultimately meant for them or for another target market? Gilead needs to be asked about its marketing strategy that they have designed for this drug. And FHI needs to be asked how it fits in.

Perhaps interviewing the women themselves as they progress throughout the trial might be a good idea. Center for the Right to Health (CRH) in Lagos did a study on the HIV cure claim trials run by NIPRD where they interviewed nearly all participants—they are excellent researchers, they run support groups and are in contact with sex workers, and could perhaps get on board here.

Under "where will the study take place?": he mentions that if tenofovir is successful, it can be established as a prevention mechanism in the study sites. But how? Does he mean that FHI will provide tenofovir for free? Who will distribute? A very unclear promise.

Remuneration: no numbers here. Nothing about long term costs in case of adverse health effects. Nothing on how they are ensuring that the women have enough to feed, which has been enough reason for trial drop-out in the past.

"What is being done to make tenofovir available for prevention, if proven safe and effective?": if this is true that the drug will be provided at cost, it may be very affordable and a first. But I want to see the contract to sell at cost and who will distribute in country. Given the history of clinical trials in Nigeria and the climate of mistrust, I really think that it is necessary to keep asking these questions publicly. And I think they should be asked in a way that does not seem adversarial, but rather always geared toward a greater public interest and greater public good.

Anyway, I will watch this very carefully

Peace, Kris

Kristin Peterson
DuBois-Mandela-Rodney Post-doctoral Fellow, Center for Afroamerican and African Studies
University of Michigan, 505 South State Street, 4700 Haven Hall, #4663, Ann Arbor, MI 48109-1045
Email: krnap@umich.edu

Assistant Professor, Department of Anthropology, Michigan State University, 354 Baker Hall
East Lansing, MI 48824

Exchange 2

Dear Kris,

Thanks for this lengthy mail and support. A point of correction, there are a number of people that think so about the issue of caring for research participants. Many are just not vocal or think it is important to openly discuss their opinions.

Really, I think the protocol design for the study is alright. We were informed by the local partner that there was a phase 1 trial and that side effects in relation to the drug use are minimal in healthy subjects. I must confess that I have not seen any data and would be only too glad to read up data on this.

Like you noted, I just wondered why every new HIV prevention technology is promoted as a female controlled option. Yes, I do understand about microbicide but then, how does HIV vaccine and prophylactic use of tenofovir become a female controlled option as you rightly noted.

If the trial is that gender sensitive, why not promote the use of female condom. Knowing fully well that sex negotiation is difficult for women in developing countries. At least, the trial would have helped to promote female condom here in Nigeria for one. Secondly, it would further reduce the chances of not using the condom. At worst, let the trial participants have the
option of choosing between the male and female condom.

An open discuss like that on the eforum is quite helpful and contributory. I have encouraged the moderator to have a summary of the discuss presented to the necessary authorities as this can help inform the development of future guidelines for such research protocols. There is a place for stakeholders meetings but like you noted, who bears the cost? This medium is more effective but then, this medium does not necessarily mean all stakeholders are on board for the discussion also. The open discussion allows for sentiments (which are equally welcome) and the sharing of objective facts may all be too difficult.

I really think the discussion can lead to a change in the defective system if it is effectively and properly moderated and IF we have a sensitive and responsive government. It does not necessarily mean the end of the trial (as it happened in Cambodia) but rather, an improvement in the protocol design for the study.

I noticed that the microbicide trial in Lagos (on 6% cellulose sulphate) made significant changes to its protocol design following a better understanding of issues involved. The local partner moved for this and I was greatly impressed. So much so I feel proud and a part of the trial. All I expect is for our local partners to do the same with other protocols on the recognition of lapses rather than defend these lapses and then we can move on together.

I guess this is extensive enough. Awaiting your response

Morenike

Exchange 3
Morenike Ukpong mukpong2@yahoo.com
Kristin Peterson krisap@umich.edu
Re: tenofovir side bar (3)
rolakenwagwu@yahoo.co.uk, omololu@nigeria-aids.org, sagwale@yahoo.com, bofa@chevrontexaco.com

Dear Morenike and Rolake:

I think so far the posts have been very good and really shows that people don't forget how they have been treated in the past and the climate of mistrust in the present EE thanks Rolake for this (I was also a clinical trial subject years ago and I have not forgotten...).

Morenike: I didn't realize until you pointed it out that they are distributing male rather than female condoms. I think this is because there is a higher chance of HIV exposure to the male rather than female condoms EE again, this is better for data collection, but I am just speculating here. But you make an excellent point EE the women should be able to choose what kind of protection they use.

If the stakeholders meeting ever materializes, I hope you both can really steer the direction of it and count others in who have had experience as clinical trial subjects and have science/research backgrounds. There certainly needs to be some demands to scrutinize all the documents.

As you point out below, Morenike, significant changes can happen with an open dialogue. Perhaps you could share that experience with the eforum. Right now, I think tempers are high, which I certainly feel is the most normal response here. But, I think alongside the anger and mistrust, is room for demonstrating the power of openness and transparency. It might even inspire UNAIDS to pay for all meeting expenses. Wouldn't that be nice? Keep me involved however you see fit.
Take care and peace, kp

(Exchange 4)
Dear all,
I have posted a huge PDG file on my web site (15MB). The file contains:
- screening informed consent
- informed consent
- trial protocol
of the ongoing trial in Cameroun
If you have high speed internet access, download would take you 15 minutes http://trenado.free.fr/STUDY9780.pdf

Overall, AIDES believes that volunteers who become infected or are found already infected during new preventive technologies trials should receive long-term antiretroviral treatment for the following reasons:

1. Provision of antiretrovirals is now feasible. Substantial advances have been made in the availability of these drugs in developing countries: reductions in prices; publication of WHO guidelines for antiretroviral provision in resource-poor settings; and the launch of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Furthermore, sponsors of international new preventive technology trials have increased capacity by building and equipping clinical facilities and training clinicians and local laboratory staff.

2. Ethics guidance has improved. The 2002 Council for International Organizations of Medical Sciences (CIOMS) guidelines state that provision of services beyond those necessary for research, including treatment of an infectious disease contracted during trial of a vaccine (a preventive technology) against that disease, is not required, but is "morally praiseworthy". UNAIDS advises that sponsors should seek "at a minimum" to ensure access to the highest level of care and treatment attainable in the host country. Both sets of guidelines encourage establishment of a care package before starting research.

3. Trials could face significant opposition and suspicion if the HIV infected volunteers are left without care and therefore delay enrolment of urgently needed future trials.

4. Finally, we need to evaluate the efficacy of ARV treatment for those who become infected after being exposed to ARV pre exposure prophylaxis.

AIDES asks the sponsors of study 9780 to modify the design of the protocol to make ARV treatment available to anyone who participates in the trial including those who are screened out because they are already HIV infected.

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Director, International Programs
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Agenda en ligne (on line agenda):
http://trenado.free.fr
Appendix 3
Discussion on NHVMAG e-group

From: "mukpong2" <mukpong2@yahoo.com>
Date: Tue Aug 31, 2004  8:31 am
Subject: NHVMAG stance and the planned tenofovir trial in Nigeria (1)
Dear advocates,

for those of us that attended the 1st national advocates meeting that held in Abuja in May 2004, we would remember the discussion and issues raised over the presentation on the study on the use of tenofovir, an antiretroviral drug, as a prophylaxis for the prevention of HIV infection (a summary of the meeting is posted on the website. A full report could be obtained on request).

There has been a lot of international discussion about this study following the termination of a similar study in cambodia. NHVMAG has had to write a rejoinder on our understanding of issues related to the trial. We have written a rejoinder just to ensure that readers have an objective assessment of the situation and hopefully, the report would not negatively impact on other planned researches in the country. If you visit the eforum (www.nigeria-aids.org) you would be able to read up on the cambodia trial as well as get to read NHVMAG's rejoinder later today or tomorrow.

Keep informed
Steering Committee

From: Ayodele Arowojolu <ayo_arowojolu@yahoo.com>
Date: Thu Sep 2, 2004  5:42 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (2)
Morenike, I should be able to give you clear details about the study in Ibadan once I clear things with the authorities concerned as soon as possible. THERE IS NOTHING TO HIDE ABOUT THE STUDY. You can be rest assured that all regulatory authorities were duly informed before the study was started.
Ayo

From: Morenike Ukpong <mukpong2@yahoo.com>
Date: Thu Sep 2, 2004  6:31 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (3)
Thanks Dr Arowojolu,

All we are worried about is the need to clear any sentiments and ensure the wrong signals are not sent around. That matters so that as to avoid any negative impact on research processes in the country. This was moreso as the posting came from WHED, a body which works actively with sex workers, the main group of people that many researches on new HIV prevention technologies would focus on. Once again, thanks for your prompt response

Morenike

From: Okanlawon Odusoga <lawonodusoga@yahoo.co.uk>
Date: Fri Sep 3, 2004  10:44 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (4)
Hello Ayo
I'm aware all is well about the study. What you need to do is to assure all advocates that the rights of all participants in the study are well taken care of.

How is everybody
Lawon.
From: alliance rights <all_aidsng@yahoo.co.uk>
Date: Fri Sep 3, 2004 1:36 pm
Subject: Re: [NHVMAG] Re: Tenofovir trials in Africa - Statement by NHVMAG (5)

Dear Friends,
If the answers to concerns raised are not forthcoming, as is mostly the case in these parts of the Global village, Do not we then disregard whatever results the researches say they elicit? Abi?.
Dare Odumuye.

From: "LifelinePlus Foundaton." <lifelineplusfoundation@yahoo.com>
Date: Sat Sep 4, 2004 9:03 am
Subject: Re: [NHVMAG] Re: Tenofovir trials in Africa - Statement by NHVMAG (6)

Dare ,
You are right and what Omololu did by posting NHVMAG resolve after the advocacy meeting is in the right direction. The issue now is raising a lot of questions and suspicion too. We will keep on keeping on More grease to all of you.
Ijeoma nnaji

From: adebowale ayobade <ayobade2000@yahoo.com>
Date: Sat Sep 4, 2004 9:58 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (7)

Morenike, I went through all responses with keen interest and contribution about the tenofovir application to Nigeria trial participants should be given serious thought because it will be tested on women that are discriminated against. Secondly, are the researchers women if not, are the male researchers gender sensitive. Thirdly the ethics committee should issue a statement telling us about the short and long term of tenofovir effects as a preventive treatment for HIV/AIDS on the trial participant.
Thanks Debo Ayobade

From: Morenike Ukpong <mukpong2@yahoo.com>
Date: Mon Sep 6, 2004 3:21 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (8)

Dear Advocates,
I read with joy Dr Arowojolu's (the local partner on the tenofovir trial) response. I am sure sooner than later, they would be issuing a statement on the standard of care offered to trial participants in Nigeria.

We cannot just ignore the result of the trial like Dare and Ijeoma suggested; it is important that care and support given to trial participants must be optimal.

Like the steering committee noted, we are not after ensuring that the trial stops BUT rather, that the community is mobilised to support research trial processes through constant communication. The voice of the community also needs to be heard and appreciated in the design of research protocols. That way we all (community and scientists) are together involved in developing products for our collective good. Research is no longer a hand down process - scientists do and community receive. Together (community and scientist) design, implement and take up products.

We all wait for Dr Arowojolu's response. In the meantime, the heads of the scientific and ethics committee are working on reports of the trial.

Morenike

From: alliance rights <all_aidsng@yahoo.co.uk>
Date: Mon Sep 6, 2004 3:39 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (9)

Point of correction! I said, if the researchers do not respond to our concerns, before trials are concluded and then come up with results and expect us to eat and digest, then we disregard such results. Because, as you pointed out, the active
input of the community is very crucial in the research process, from design to the final conclusions. As far as MSM are concerned, any interventions, trials, research etc, etc, must as a rule include MSM themselves from start to finish, anything less is unacceptable to our community. I hope I am understood. I also assume I speak the mind of Ijeoma.

Regards,
Dare Odumuye.

From: Ayodele Arowojolu <ayo_arowojolu@yahoo.com>
Date: Mon Sep 6, 2004 8:29 am
Subject: Re: [NHVMAG] NHVMAG stance and the planned tenofovir trial in Nigeria (10)
Dear Lawon,
I have written Morenike about this study that there is nothing to hide because it is being carried out according to good clinical practice and ethical consideration. I have to clarify things from my sponsors before I make further comments. After all the study was approved by NAFDAC, UCH/UI IRB and MOH.

Cheers
Ayo

From: "LifelinePlus Foundation." <lifelineplusfoundation@yahoo.com>
Date: Thu Sep 9, 2004 12:20 am
Subject: Re: [NHVMAG] Re: Tenofovir trials in Africa (11)
I must congratulate NHVMAG members on the work they are doing. People are beginning to appreciate what the group is doing with the other treatment advocates. You guys are doing a marvelous work. They are still Nigerians who are still touched in their inner most heart on the plight of PLWHAs and other persons who are not privileged to know their sero-status. It is good that these FEW [without] conscience are checked, as the little stipend they take to sell their conscience and mortgage the children's future will ever hang on their throat. I do hope that the ETHICAL COMMITTEE is doing what is necessary to check these people. We are talking about LIFE let us not only write through the net alone.
IJEOMA NNAJI

From: augusta akparanta-emenogu <augusta1010@yahoo.co.uk>
Date: Wed Sep 8, 2004 9:02 am
Subject: Re: [NHVMAG] Re: Tenofovir trials in Africa (12)
Well said my sister. Anything short of what you have listed is not worth even considering. Pls let us unite to ensure the right thing is done.
Augusta Akparanta-Emenogu

From: "Kim Dickson" <k-dickson@dfid.gov.uk>
Date: Mon Sep 13, 2004 3:47 am
Subject: [NHVMAG] Re: Tenofovir trials in Africa (13)
This is an excellent discussion you are having on Tenofovir. I congratulate NHVMAG on facilitating this.

The role of groups such as NHVMAG is to work to ensure that are people do not get used as 'guinea pigs'. I am sure that we will all agree that clinical trials are definitely needed and therefore we all need to actively support and if possible participate in them. We must not let previous bad experience cloud our judgments or stop the trials but rather work to prevent exploitation.

Let us clearly articulate what are issues are so that NHVMAG can take them forward with FHI.

It is for the country ethics board and medicines control council (NAFDAC) to define what 'standard of care' they are satisfied with. If we as advocates feel that they will not do this well then we must agitate and advocate for change.

There has been much debate over standard of care and no international conclusions have been reached. I know SA stated in vaccine/microbicides trials that they want ARV's to be provided to those that get infected. The question was for how long?? I am not sure what the final decision was. This can be investigated and Nigeria have a national discussion on this issue.

Morenike can the NHVMAG ethics group review this in detail?

Dr. Kim Eva Dickson
HIV/AIDS Advisor, DFID Nigeria, Plot 607, Bobo St (Off Gana), Maitama, Abuja
From: Morenike Ukpong <mukpong2@yahoo.com>
Date: Mon Sep 13, 2004 5:04 am
Subject: Re: [NHVMAG] Re: Tenofovir trials in Africa (14)

Thanks for this encouraging discussion Kim,

there has been a lot of posting on this on the eforum (www.nigeria-aids.org). There are presently 12 postings and I would encourage all NHVMAG members to keep constantly informed on the issues.

The heads of the ethics and scientific committee are working quite hard on the issue. I must sincerely say the Dr Agwale (the head of the scientific committee) has really made significant moves to facilitate processes to address the ongoing dialogue. Omololu, Rolake and myself have also kept ourselves continually informed not just about what is happening in the country but also about what is happening at other trial sites. The steering committee members are updated about the entire issue and we are working upfront.

Recently, the Provost of the College of Medicine, UCH posted a discussion and plans to facilitate a meeting to help out with the discuss (posting 10 on the eforum). This was also posted on the form by Dr Ayo Arowojolu. We hope to work with him on this.

I personally believe that things would move forward but with improved care offered to participant trials.

Nice reading from you on the forum kim

Morenike

NHVMAG@yahooogroups.com

BAMIDELE IWALOKUN" bamwal@yahoo.com (15)

NHVMAG,
The outcomes of your consultation and discussion with all the stakeholders involved in Tenofovir clinical trial research plan has further demonstrated the indispensability of advocacy and its elements in promoting proper health care for people at risk and those living with HIV/AIDS. I strongly believe that the concerns raised on the possible hepatocellular dysfunction associated with the use of Tenofovir would ensure that the PI and sponsor of this trial uphold the 2 year follow-up period to take care of any untoward reaction or even SAE after the trial. Advocacy should also continue to ensure that this pledge is not bridged. I am also of the opinion that the establishment of CAB is a necessity to serve as an interface between research and the community. Something similar to this or exactly like CAB needs to be setup by the UCH-medical team to further improve the data integrity of the study during and after the trial

Iwalokun

NHVMAG@yahooogroups.com

kayode dada" dadacrrh@yahoo.co.uk (16)
Tue, 12 Oct 2004 00:05:54 +0100 (BST) (16)

Dear Morenike and Omololu

I am delighted to note the successful outcome of the consultation over the Tenofovir trial on-going at the UCH Ibadan and want to congratulate all who were involved in this detailed review process. The conclusions reached are magnificent. There is no doubt that many lessons have been learnt not only by scientists and researchers but also by community activists including NHVMAG members. The ultimate triumph of course, will be the disappearance of the 'us' and 'them' in considerations of these issues and the current exercise has rightly drawn our attention to this fact.. All of us in health research are indeed activists for the promotion of health and should be seen to conform to the highest ethical standards.

I applaud too your initiatives with NACA and FMOH on the constitution of a National Ethics Review Board. I hope that these two bodies will involve other stakeholders in the composition and operations of the Board.

The 'Ethics debate' - and many ethical issues are truly controversial - is one in which all researchers must participate. Training in the ethics of health care and health research should be incorporated in the curriculum of postgraduate programmes in our biomedical institutions. Kayode Dada
Dear Morenike and Omololu,

I must highly commend the efforts you are making to make microbicide trial to survive in this country. Your effort on the TDF trial is a case in point. However, I will like to caution on the setting up of this CAB issue. I shared the concern of the Provost at Ibadan. There is need to think over this especially on the constitution of such bodies, so that we wont have problems in our hands later on. Community awareness is a must, forming a board from them is delicate issue so that we don’t start having unnecessary demands in our hands. I will want you to think on the issue raised and agree on the way to handle it.

ADEIGA

Morenike

I would like to use this opportunity to publicly thank you for your personal contributions in moving the microbicide agenda forward. Your personal contributions and efforts have helped NHVMAG move its agenda forward positively.

As per the issue of CAB that you raise; it is NHVMAG's concern. The discussion is open for us all. NHVMAG is bigger than Omololu, Morenike and the steering committee. What we wrote as summary was the consensus reached after prolonged deliberations by on the eforum and outside the eforum by various stakeholders. You only need to know how much interest the international community had in this issue. They were not Omololu and Morenike’s suggestions.

We would strongly welcome suggestions about the composition and operations of the proposed CAB from everyone as the dialogue with UCH is still open and consultative meetings are still being held.

Morenike

I commend your efforts and those of other advocates on the way the TDF study problem in the country has been resolved thus far. It is in our interest to see the study go on because of the various advantages but at the same time we must ensure a good standard of care for the study participants. The words of the Provost of the College of Medicine, Ibadan, and the willingness of the investigators to modify the standard of care are very reassuring.

I agree with Adeiga and the Provost on the issue of CAB. Formation of this board will not add anything to the standard of care but would complicate issues especially on unending demands by the study participants. I will suggest we do not push demand for CAB any further. Community preparedness should however be integrated into the study if it has not been done.

Your idea about involving NACA and FMOH in ethical reviews is also most welcome. In order however to prevent unnecessary bottle necks that could result from centralising study approvals in the country, these bodies may need to train, give broad guidelines to and monitor the activities of the various ethical review boards in the country.

Yours

Lawon.
Dear Dr Odusoga,
Thanks for your continuous useful suggestions and contributions. I would also like to use this medium to intimate members that NACA is working positively towards the establishment and inauguration of a National Ethics Review Board (NERB). The whole process is in the pipeline. All that is delaying things are administrative bottlenecks.

In turn, NHVMAG and NERB are equally working together to do a step down training for all IRB in the country on ethical issues involved with New HIV Prevention Technology Research. As these unfold, every NHVMAG member would get to learn more.

I also want to thank everyone for your participation and useful suggestions. Please do keep rolling in more suggestions on what we all can do together to ensure that our objectives are achieved.

Morenike

Abimbola Titilopemi™ atitilopemi@yahoo.com
Tue, 12 Oct 2004 08:53:08 -0700 (PDT) (20)

Dear Researcher,
Pls, how will the effectiveness of Tenofovir be evaluated when participants have been counselled to use condom as a prevention method against HIV/AIDS?

Bimbo Fashoyin

NHVMAG@yahooogroups.com
Kim Dickson™ k-dickson@dfid.gov.uk
Wed, 13 Oct 2004 08:19:37 +0100 (21)

I would like to add my congratulations to NHVMAG, you/we are truly playing a critical role in microbicides and vaccines advocacy.

I also feel that a CAB is definitely needed. This is almost a standard practice now. What is important is too ensure that the CAB is well constituted and that they fully understand their roles and responsibilities. NHVMAG has a role to play independent of the researchers. There are guidelines for CAB’s - the HIV Preventions Network have some, also last year a Southern African consultation was convened by the GCM to discuss the issue of community involvement in Microbicide research.

My concern is where NHVMAG is asking for 'all ailments' of the participants are to be treated free of charge. One needs to be careful here. If for example a participant develops a hernia during the trial, is this the responsibility of the trial?? I do expect the trial coordinators to facilitate the management but not to cover all the costs.

All the above issues clearly illustrate to me the need to have national standard of care and trial ethics guidelines, I hope we can facilitate this process.

Kim

NHVMAG@yahooogroups.com
Morenike Ukpong™ mukpong2@yahoo.com

Dear Kim,
Thanks for acknowledging that WE are all a part of this ongoing process. As NHVMAG facilitate things, we would extensively deliberate on the issue of the CAB and ensure that the CAB is well constituted and that members fully
understand their roles and responsibilities. I would be forwarding all mails on the suggestions so far to the Provost. I am aware that Dr Arowojolu would read all these on the forum.

The suggestion about the treatment was a result of the fallout from the roundtable discussion and this was taking the peculiarity of the study site into consideration. The Provost explained that knowing the community, participants would attribute all their ailments to the research and so if not treated there may be negative reports about the study circulating in the community. Efforts therefore have to be made to preserve the image of UCH, which would still be serving the community and doing research long after the study and the research process.

I would ask the Provost if he wants to enlist with NHVMAG and then he could also possibly contribute to this process in turn

Morenike

NHVMAG@yahooogroups.com
Kim Dickson k-dickson@dfid.gov.uk
Wed, 13 Oct 2004 08:19:37 +0100 (23)

Dear Morenike

The Provost raises an important point. The CAB if properly constituted can help to dispel such rumours. I do hope though that this will not lead to coercion especially with the more disadvantaged sections of the community - this could happen when word get round that you can get free treatment for all ailments by enlisting in the study. The pros and cons need to be carefully considered and the push for the development of national standard of care guidelines is a move in the right direction.

Kim
Appendix 4
Correspondence with the trial institution

1. Communication with Prof Adewole, Provost UCH, Ibadan

Dear Prof Adewole,

Interested community members read with joy your actions on the tenofovir trial in response to the concerns raised. NHVMAG is particularly proud of the way you have risen up to the situation and we look forward to working with you on a long term basis.

For one, the issue of treating infected participants with ARV is a welcome development. That is about the only physically tangible benefit the community benefits from this trial. It also helps to compliment the 3x5 WHO initiative. We are very proud of this move.

In addition, the introduction of the female condom into the study was highly welcome as this would further help to promote its use amongst women in the Nigerian community. This would also be a positive fallout of the trial for the community.

NHVMAG (the acronym for the Nigeria HIV vaccine and Microbicide Advocacy Group) have taken time to conscientiously study issues that have arisen out of concerns. The Scientific and Ethical Committee had taken time to read through the Protocol for the trial (That revised on the 17th of December 2002 and that revised on the 22nd of August 2003) and we would like to note the following:

1. The trial is NOT a necessity. This is for the following reasons.
   a. If the trial enrolment made all we discussants (advocates and academia) eligible for the trial, would we volunteer? – NO. Why? – Because we understand the issues of ARV toxicity. Who then volunteers? – the poorly informed who sell sex and would possibly benefit monetarily and psychologically from participating in the trial.

   Although the research protocol highlighted the merits of TDF, all findings related to HIV negativity had been limited to animal studies. There are no phase I studies to highlight the merits of the trial in HIV negative individuals. This we believe is significant and a great oversight. The protocol might do better to explain why the phase I trial was skipped.

   b. When the trial ends and tenofovir is found effective, who would use them as preventive drugs? – None. Why? – Because we stakeholders would not take ARV everyday just to prevent HIV infection because of the toxicity. Secondly, the community of trial participants would not likely be able to afford the tenofovir since there is no IPR transfer presently signed.

   While the protocol highlighted the clinical endpoint of the trial as well as discussed the effectiveness outcome of the drug trial there are no social science study to justify and support uptake of the drug.

   Compliance with ARV intake by PLWHA in Africa is higher than what occurs in developed countries because of the so many associated social factors such as poor prospects for drug switch and associated stigma with the infection. These social factors reduces daily drug compliance in Europe and USA because they are not present and social support exist.

   Furthermore, the protocol justified the need for the research in view of what oral contraceptive pills achieved with pregnancy prevention. The study did not consider the use of the pills in the study community (Nigeria) and compare its uptake with that of other barrier methods. Many women use injectable methods of contraceptives frequently because of the need for REDUCED need for compliance as is expected for pills. Pills also have time related limited use and does not necessarily have to used continuously all year round. This study implies a much longer use of TDF and therefore its comparison with oral pills may not be exact in view of the absence of social science based articles to support this stance (Read page 10, paragraph 2 under section 1.2 on rationale).
The result of the formative research was likely studying directly (through a focus group discussion) the possibility of uptake of the drugs. The study of the use of contraceptive pills would be more objective and conclusive than a direct focus group discussion about TDF. No one knows about the TDF use and so responses are only anticipatory and subjective. Study of the use of contraceptive pills by women would give a better insight into the prospect of using the oral tenofovir daily.

In addition, the protocol does not define the ‘good faith effort Gilead would be providing for public health use of the drug’. (Read page 10, paragraph 1 under section 1.2 on rationale). Defining this clause is VERY important and a NECESSITY as the Federal Government can hold unto this in future to ensure the drug availability and accessibility to its citizens. NVHMAG is drawing up an action plan with NAFDAC and the Federal Government to ensure that policy structures are put in place to ensure that these new HIV prevention technologies are available to all citizens as soon as they are developed and licensed for use. This clause is therefore of paramount important and SHOULD be defined PROPERLY.

c. Other drugs are presently been developed like tenofovir which are less likely to develop viral resistance than tenofovir. These drugs are also been planned for trials. When they undergo trial, what happens to tenofovir?

d. Unlike HIV vaccine and microbicide, this trial ONLY takes place in Africa. Why? Because this protocol would not go past EMEA in Europe and the FDA in America. It would pass without stress in Africa. This becomes more apparent to be on reading through the protocol because one of the justifications for the study was the need to ‘establish the safety profile for healthy, uninfected persons or the infected persons with conditions such as malaria’ (Read page 10, paragraph 2).

NOTHING in the methodology and data collection and analysis discussed about assessing for the status of malaria in the trial participants. From the beginning to the end of the research design, nothing highlighted this issue. One then wonders if the malaria issue is just a mask for the trial to hold and a point to justify why it can hold in Africa and Asia.

In addition, if truly one need to answer the question of the role of malaria infection in the efficacy of drug therapy, then a phase 1 study is HIGHLY justifiable just like a phase 1 study to show the efficacy of TDF in the prevention of HIV infection is HIGHLY necessarily. All studies demonstrating this are animal model study and this does not translate to human results.

2. But then, if the trial should go on in view of the invested capital and resources, participants must have the BEST. No compromise. We would also want to suggest the following amendments to the protocol.

a. There is a sincere need for community preparedness efforts on the path of the researchers. Members of the community within the trial focus area should be adequately prepared for the trial (informed about the research) so they can give their support for the process in view of stigma related to HIV infection. Where the community is not adequately prepared, there is a possibility of myths and misconceptions to develop about the trial. Trial participants and participants’ retention may then be difficult. In a bid for researchers to then meet deadlines in view of funding constraints, compromises may then start to occur in the trial design and volunteer recruitment procedure.

The researchers could learn from the ongoing 6% cellulose sulphate trial going on in LUTH. NHVMAG is actively supportive of that process because the local PI was responsive to community involvement and modified the protocol to include this despite the initial oversight. We are presently working together to design and implement community mobilization at the trial site. This research could benefit from dialoguing with Dr Ogunsola of the Department of Microbiology, LUTH. The trial could also learn from the community preparedness exercise of Prof Dada of the Department of Chemical Pathology, Ogun State University on their efforts during the phase 1 trial on 6% cellulose sulphate

b. Future dialogue should include interested community advocates. We do support the need for regular community meeting to review progress and problems but please include community members who are vast on the issues on Board. NHVMAG would willingly suggest possible members if consulted. We have as members 91 individuals and a number of organizations amongst whom are Professors, scientists all actively involved with researches into new HIV prevention technologies, 3 members of the National Ethics Board, enlightened media men, youths, informed members of the public, PLWHA, prominent government officials who are directly involved with decision making processes in the federal ministries, academicians and a host of others. These are men of timber and caliber. Our recommendations would be without bias.
NHVMAG suggests that the community should be represented on the Clinical Monitoring Team, the Safety Monitoring Team, the Data Monitoring Committee and during the UCH IRB monitoring and review process. We would not want a compromise on this.

The provost would well recognize that what we ask for is not out of order as the IRB composition should include a layman so as to ensure that the community views, perspectives and concerns are addressed during deliberations and in the decision making process.

The community member would then report back to the community and such representatives would be our liaising arm of the project. The community could confidently relate to their reports.

c. Also, why did Gilead Science modify the NIAID common toxicity scale? What was modified on that scale and were the toxicity values modified upwards or downwards (Appendix 1, pages 39-48)

d. For appendix 2 on the management of clinical and lab adverse events, (pages 49-50), we would advice that when participants are identified to have grade 3 adverse events, and the grade3 or 4 recurrence is considered UNRELATED TO THE STUDY DRUG, please the researchers should still DISCONTINUE STUDY DRUG. The trial is about the patient and not about the drug. This we consider HIGHLY important.

e. All recommendations should be reflected in the protocol an informed consent form that trial participants are to sign.

We would like to know – how much are trial participants being paid as transport cost?

Please note that NHVMAG would summarise and document the dialogue on an off the eforum including recommendations made and actions taken. This document would be sent to all relevant stakeholders for information and future actions as this process has been quite educative and NHVMAG considers it a process to be learnt from.

The forum moderator did not post all discussions so as not to generate unnecessary controversy on the trial. These postings would however, be included in the compiled document.

There were also discussions on the issue on the NHVMAG listserv. This would also be included in the compiled document.

We believe that we are about reaching an end to this interesting discussion wherein the scientists and community work together in research efforts. The place for the community to participate in research design and implementation had long been identified as this facilitates the research process and the eventual uptake of the products. The days of scientists doing things for ‘them’ (the community) is fast fading. We have to learn to do it together for ‘us’ and HIV/AIDS is teaching us how to do this properly.

NHVMAG would post a mild summary of this dialogue of the eforum. It also hopes to post the eventual outcome of its findings by the Scientific and Ethics committee and our dialogue with you on the forum (we promised to do this very early in the discussion).

Thanks for your anticipated cooperation and continued dialogue.

Morenike Ukpong
For the Steering Committee, NHVMAG

2. Response

Dear Morenike,

RE: TENOFOVIR TRIAL
I wish to thank you once again for your four-page comment on the TDF trial currently being implemented in Ibadan. I initially thought it was a memo sent to me but copied to the listed addresses. I however discovered after my reply to you,
that it is actually flagged on the e-forum. I also wish to take the liberty to use this opportunity to address issues raised by Edem Effiong, Ifedayo Adetifa, Jeff Oluwagbenga, and Godspower Omeregie.

For those who have just recently entered the discussion, I would like to again point out that to defeat the HIV/AIDS epidemic, it is essential to identify ways to stop HIV transmission. Ethical, scientifically sound clinical trials are the only way to make these kinds of research advances. The College of Medicine of the University of Ibadan is proud to be conducting a trial to find out whether oral tenofovir, used in conjunction with other prevention strategies such as condoms, is effective in preventing HIV infection. If found effective to prevent HIV, it could substantially reduce the number of Nigerians who become infected.

Investigators with the University of Ibadan have worked closely with the community, and met or discussed with many stakeholders at Local, State and Federal to elicit input, concerns and recommendations. In short, we respect your concerns, take your questions seriously, and are committed to community involvement, transparency and the ethical conduct of research.

GENERAL COMMENTS

I had indicated that I would reply your mail after consultation because an advisory panel set up by the College of Medicine would meet on Monday, 27th September at 1000 Hours. I am however sufficiently disturbed by the contents of the submissions on the e-forum that I felt an urgent reply is needed. Although you indicated that “the forum did not post all discussions so as not to generate unnecessary controversy on the trial”, in fact, the forum is polarizing a discussion in ways that are counterproductive to solutions to the very real problem of HIV/AIDS in Nigeria. It reflects mental laziness that no one till now has visited to conduct an inquiry of this study in order to post a report on the e-forum. What we have are half truths, falsehoods and insinuations. Perpetuating misinformation does not help anyone, rather undermines the creation of an atmosphere of collaboration where concerns can be genuinely explored, and where groups working to prevent AIDS – including NHVMAG, Treatment Action Movement Nigeria, the Microbicide Advocacy Network, the Federal Ministry of Health, and universities such as the University of Ibadan – can find the best ways to attack this killer disease. The moderator of the e-forum owes the nation a sacred duty to ensure that ONLY serious and truthful comments are posted on the forum.

SPECIFIC COMMENTS

1. THE COLLEGE OF MEDICINE ROUNDTABLE.

I submitted the list of participants at the roundtable following a request by Jennifer Anyanti (janyanti@sfhnigeria.org). She has refrained from commenting on the participants. Some have questioned the credentials of the members. This is in order. It is however disturbing that anyone in the 21st century would suggest that Professors are all medical people. Nineteen (10 non-medics vs 9 medics) highly qualified and respected Nigerians were invited to the roundtable and 16 (8 non-medics vs 8 medics) attended. I can pardon those who do not know but find it difficult to appreciate those who did not make efforts to know. Among the participants were:

- Emeritus Professor E.O. Akande: Former Program Manager WHO (Geneva) and currently Chair, WHO (Afro) Advisory Board on Reproductive Health. He is also an adviser to the Federal Ministry of health.
- Emeritus Professor M.A. Olatuawura: He is a foremost Psychiatrist and former Chief Medical Director, UCH. He is also an adviser to the Federal Ministry of Health.
- Professor Laolu Akinyele: Non medic and current Dean, Faculty of Public Health, University of Ibadan.
- Mrs. Elizabeth Etteh: Seasoned Administrator
- Professor O Omotade: He is a member of the YET TO BE INAUGURATED National Ethics Board. Professor Omotade has a Postgraduate degree in Bio-ethics and wrote the first draft of the National Guidelines on Ethics.

The major assignment of the roundtable was to consider comments made by individuals and groups, review the protocol, the IRB approval, and recommend review. An advisory panel was also constituted to assist the Principal Investigator.

2. THE UI/UCH INSTITUTIONAL REVIEW BOARD.

This is the organ that reviewed the protocol. I do not want to engage in a running battle with my colleagues but wish to submit that this is the most sensitive and balanced IRB in Nigeria. We have a lawyer, teacher, lay members and other non-medics on the IRB. The Chair is Professor Gladys Adeyinka Falusi (She is a non-medical) She is also the Protem Chair of the Nigeria Bioethics Initiative.
3. THE PROTOCOL.

You made extensive comments on the original protocol that Family Health International, which is responsible for tenofovir studies in four countries, provided to you as it has to anyone who has asked. The version you have was last revised on August 22, 2003. I am however disturbed that you did not consider it fit and proper to consult me or request for the protocol. Direct communication is an essential component of trust and partnership. What I have and what we are using is the version 2.0 Protocol study 9780 with a revision date of June 24, 2004.

4. THE DRUG TENOFOVIR (TDF)

You have also created a wrong impression that we are testing a new drug. THIS IS FALSE. The drug Tenofovir is one of the best anti-retroviral drugs ever made. It is currently in use in the USA and EUROPE. It was licensed by Food and Drug Administration (FDA) of USA in 2001. There are more than 11 published multicenter studies that used Tenofovir for treatment of HIV since the registration of the drug. What is novel about the drug is the concept of using it for prevention. This is called CHEMOPROPHYLAXIS. A medication can only be tested for prevention where there is risk of infection hence the need for trial in developing countries. I order not to expose our women to risk of infection; we are giving condoms to all of them.

The Hypothesis we are testing is: IF A WOMAN IS ON CONDOM AND TAKES THE DRUG, TENOFOVIR, SHE IS BETTER PROTECTED THAN IF SHE IS ON CONDOM ONLY.

The answer can only be one of two:

1. YES, SHE IS BETTER PROTECTED or
2. NO, SHE IS NOT BETTER PROTECTED

The answer can never be: IT EXPOSES HER TO HIV.

5. DO WE NEED THIS TRIAL?

This is a very important question. We are dealing with the greatest biological threat to human survival. This virus is unlike what we have ever seen. It is rapidly evolving and new HIV prevention strategies are urgently needed. A novel approach including prevention with a daily dose of tenofovir could substantially reduce the number of HIV cases worldwide, if proven effective, especially when combined with other effective strategies such as correct and consistent condom use. This is a very important trial that could help millions of people avoid HIV infection. This is very important when we take into consideration the very slow progress we have made in the development of a vaccine or microbicide. A focus on HIV/AIDS written by RONKE OLAWALE in the Daily Guardian of yesterday (24 September, 2004) suggested that a vaccine may take several decades to emerge, if at all it emerges.

Seven countries, including the United States, are now testing or will soon test the oral form of tenofovir as an HIV prevention approach. Tenofovir is uniquely suited for this study because it comes in the form of a pill, it only needs to be taken once a day, and HIV is slow to develop resistance to it. When tested as a treatment for HIV in infected men and women, it had a safety profile similar to that of a placebo and was associated with relatively few side effects.

6. WHO WILL USE THE DRUG

I find this question rather strange. As the site Coordinator of the PMTCT Program and Co-Principal Investigator of the APIN Plus (Pepfar) Program, I certainly know of husbands and wives of HIV positive partners who are looking for additional protections. These are needed to stabilize marriages of sero-discordant couples that are crumbling.

7. CONDUCT OF THE TRIAL:

I wish to re-affirm that all our subjects are VOLUNTEERS. The sites and potential subjects were well prepared though a dynamic process of community consultation which was preceded by focus group discussions. Community members, including potential study participants, have provided information that helped identify areas where potential participants may be found. They have also been pivotal in identifying available local services offering HIV care and support, which will enhance referral of participants who become infected with HIV and those who test positive for HIV during screening. Mechanisms have also been created so that a variety of stakeholders can provide feedback on the trial and advise on how to effectively implement research results to support HIV prevention and treatment in the local community.

I am unable to respond to the comments of Godspower Omorogie because they simply do not exist in any of our documents. The informed consent documents were revised on May 3, 2004. They were carefully prepared and represent one of the best around. The roundtable suggested care for those picked up at screening and those who seroconvert
during the trial. We have followed this up with the Country Director of the PEPFAR Program who without any pressure agreed that they be registered into the treatment and care program.

7. INFORMATION ABOUT THE TRIAL

This is major assignment to be undertaken by JAAIDS. We shall provide information on all researches/service delivery being undertaken at the University of Ibadan and the University College Hospital. It is the responsibility of the PI to provide responses to enquiries but the Office of the Provost can provide additional information on request. We also encourage our members to share knowledge at the local and International Knowledge Economic Fronts.

8. OUR RESPONSIBILITY:

Our responsibility is to continue to scrutinize the postings on the e-forum. We shall take into consideration factual comments and genuine criticisms. The College of Medicine WILL not operate on rumours and falsehoods.

As a practitioner and researcher in the field of Sexual and Reproductive Health and Rights, I consider my College of Medicine to be fortunate at this point in time. I am conversant with the issues and have an enduring relationship with the NGO community and Network of People Living with HIV/AIDS. I am also alive as a unionist having been President of the National Association of Resident Doctors of Nigeria (NARD) and Secretary General of the Nigerian medical association (NMA). My invitation to anyone who is honestly concerned about the implementation of this trial stands.

I look forward to meeting with you soon.

With very warm and sincere affection,

Prof. Isaac F. Adewole
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