Preventing Prevention Trial Failures

A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia

Global Campaign FOR Microbicides

Acknowledgments

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Contents

Acronyms and abbreviations

AIDS	Acquired Immunodeficiency Syndrome
APNSW	Asia Pacific Network of Sex Workers
CAG	community advisory group
100% CUP	100% Condom Use Programme
FDA	US Food and Drug Administration
HIV	human immunodeficiency virus
NCHADS	Cambodian Ministry of Health National Centre for HIV/AIDS, Dermatology and STDs
NGO	nongovernmental organisation
NIH	US National Institutes of Health
PEPFAR	US President's Emergency Plan for AIDS Relief
PrEP	pre-exposure prophylaxis
STD	sexually transmitted disease
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WAC	Womyn's Agenda for Change
WHO	World Health Organisation
WNU	Women's Network for Unity

Introduction

In 2003, researchers from the University of California, San Francisco, and the University of New South Wales, together with the Cambodian Ministry of Health National Centre for HIV/AIDS, Dermatology

and STDs (NCHADS), began preparations to launch a clinical trial in Phnom Penh. The trial was to determine whether a drug called tenofovir disoproxil fumarate was safe and effective for use as a pre-exposure chemoprophylaxis to prevent HIV transmission. In August 2004, before the trial formally began, preparations for it were halted by the Cambodian government following protests led by the Women's Network for Unity (WNU), the union of Cambodian sex workers. This report reviews the events leading up to the cancellation of the trial in order to identify lessons that can be learnt from the process and consider how these problems can be avoided in future trials.

This report is based on interviews conducted in Cambodia and by telephone from mid-2006 through 2008 with key players in the events surrounding the trial.

Additional material for the report has been gathered from documents distributed by NCHADS and their research team. Copies of these documents were provided by nongovernmental organisations (NGOs) and medical professionals in Phnom Penh, as well as some former trial personnel. In addition, the WNU and Womyn's Agenda for Change (WAC) provided access to their internal documents about the trial. Supplementary material was collected from newspapers and online sources of public information.

There is no single version of events that constitutes the "real story" of the Cambodia tenofovir trial. The researchers, NGO staff, and WNU members interviewed presented different and sometimes incompatible accounts of the events surrounding the trial. Cambodian government employees involved in the trial declined to be interviewed, citing the "sensitivity" of issues surrounding the trial, as its termination had been a matter of government policy directed by the prime minister.

Given this reality, we focused on capturing as accurately as possible the political context and backdrop against which these events occurred by talking to key actors who were available for interview. These included members of the research team, members of the WNU, staff of WAC, staff of other local NGOs with sex worker programmes, sex workers who were unaffiliated with the WNU, and both local and foreign health professionals who participated in meetings about the trial. We could not capture and represent the views of those who did not or could not agree to be interviewed. Every historical account is, to some extent, biased in this way. Acknowledging this limitation, we hope that this report contributes to discussion on the lessons from this controversial episode in the history of HIV prevention research.

This analysis is divided into six sections. "Setting the stage" summarises the purpose of the trial and introduces the actors central to the events that unfolded from the trial's inception through its cancellation and the aftermath of that decision.

The second section, entitled "The political climate for Cambodian sex workers in 2003", reviews political changes occurring between 2000 and 2003 that had a direct impact on the lives of Cambodian sex workers. This background is essential to understanding the environment in which the sex worker advocacy groups and the NGOs serving sex workers were operating—and how it affected their interactions with trial staff.

The third section, "Chain of events, part I", recounts the steps taken in planning and preparing for the trial, including an overview of the formative research undertaken; the processes used for community consultation; and the responses of sex worker advocates to these events and approaches.

The fourth section, entitled "Context, communication, and ethical quandaries", interrupts the historical narrative to reflect on the dynamics underlying the events up to this point. The actions of groups involved in the trial are best understood by examining the contextual factors that shaped their respective priorities and then considering how this contributed to a breakdown of trust and the consequent failure of negotiations.

The fifth section, "Chain of events, part II", recalls what happened in the six months between March and August of 2004 when the trial was cancelled. It also highlights some important aspects of the aftermath as this decision played out on the larger global stage amongst funders, research institutions, and the broader HIV advocacy community.

"What do we learn from it all?" summarises the critical lessons that this experience offers. Some of the lessons are already being put into practice. Many research networks have taken steps to enhance and expand their community and stakeholder involvement strategies. "Good Community Practice Guidelines" and other relevant principles also have been developed in the last four years.

The final section of this report identifies some of the work that remains to be done to create an environment in which the conditions of the Cambodia pre-exposure prophylaxis trial will not be replicated.

I. Setting the stage

Why this trial?

Tenofovir is a nucleoside reverse transcriptase inhibitor drug marketed under the brand name Viread by Gilead Sciences, a US-based biopharmaceutical company. In 2002, when the Cambodia trial was initially planned, tenofovir had already been approved for use as a component of antiretroviral combination therapy for people with established HIV infection. The Cambodia trial was one of a series of pre-exposure prophylaxis (PrEP) trials launched in 2004. At that time (as now), it appeared that a major breakthrough in efforts to develop other new HIV prevention technologies—specifically vaccines or microbicides—was still several years in the future.[1]

Pre-exposure prophylaxis, or the practice of using treatment medications to prevent infection, is used to ward off many illnesses, including malaria and some forms of pneumonia. In the context of HIV and AIDS, evidence supporting the biological plausibility of tenofovir as a PrEP candidate came from its informal use for this purpose starting in the late 1980s. Tenofovir also is used as post-exposure prophylaxis to treat accidental HIV exposure amongst health care providers,[2] and to reduce the risk of perinatal transmission of HIV during childbirth.[3]

Tenofovir was chosen as a candidate for PrEP for two reasons. Preliminary research on tenofovir indicated that in the early to middle period of HIV infection, it may block the enzyme that causes HIV to replicate. Tests carried out by Gilead and the University of California, Davis, found that monkeys given tenofovir and then exposed to the simian immunodeficiency virus did not readily become infected.[4] Its preventive efficacy, however, may decrease after repeated viral exposures.[5]

The second reason tenofovir was chosen as a candidate for PrEP trials is that it had proven to be safe for widespread use amongst HIV-positive people. It not only produced fewer side effects than other antiretroviral medications but also was simple to use and HIV seemed to be less likely to develop resistance to it over time.[6]

By 2003, a great deal of scientific and medical interest had developed around the idea of PrEP, and optimistic expectations amassed around this possibility for doing "high-risk, high-reward" medical science. The PrEP trials (if successful) would not validate something already known, but rather, provide a first critical step in a new direction for HIV prevention. In 2003, *Science* writer Jon Cohen described the upcoming Cambodia trial as "a cutting-edge HIV prevention study that raises eye-popping possibilities".[7] The stakes were—and still are—very high for PrEP trials.

The purpose of the Cambodia trial was to test the efficacy and safety profile of tenofovir for human use by administering a daily oral dose of either tenofovir or a placebo to 960 sex workers over the course of one year. The trial was to involve healthy sex workers who had tested HIV negative at screening. Its outcome was to be determined by comparing the number of sex workers taking the oral tenofovir who seroconverted during the course of the trial to the number who seroconverted in the control group receiving the placebo.

Key players

The principal investigators for this trial were Dr. Kimberly Page Shafer, an epidemiologist working in HIV prevention research at the University of California, San Francisco, and Dr. John Kaldor, Deputy Director of the National Centre for HIV Epidemiology and Clinical Research at the University of New South Wales in Sydney. Dr. Ly Penh Sun of the Cambodian National Centre for HIV/AIDS, Dermatology and STDs (NCHADS) served as a co-principal investigator. Page Shafer relocated to Cambodia and was living there on and off during 2003–2004, and Kaldor worked on the trial from his base in Sydney.

1. Dunne R. Can HIV drugs protect against HIV? *BBC News*. 8 March 2004. Available at http://www.bbc.co.uk/2/hi/health/3525211.stm, accessed 3 March 2006.
2. New York State Department of Health. *HIV Prophylaxis Following Occupational Exposure*. New York, NY: New York State Department of Health; 2008. Available at http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=12568&nbr=6476.
3. Clayden P. CROI: Pregnancy and MTCT. Tenofovir plus FTC reduce NNRTI resistance following single dose nevirapine. *HIV Treatment Bulletin*. 2008;9(3/4). Available at http://www.i-base.info/htb/v9/htb9-3-4/Tenofovir.html.
4. Chase M. Trials will test whether AIDS drug can also prevent HIV. *Wall Street Journal*. 4 December 2003. Available at http://www.aegis.com/news/wsj/2003/WJ031202.html.
5. Subbarao S, Otten R, Ramos A, et al. Chemoprophylaxis with oral tenofovir disoproxil fumarate (TDF) delays but does not prevent infection in Rhesus Macaques given repeated rectal challenges of SHIV. Abstract presented at: 12th Conference on Retroviruses and Opportunistic Infections, February 2005; Boston, Massachusetts.
6. Irvin A, McGrory E. *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site*. Washington, DC: Global Campaign for Microbicides; 2009.
7. Cohen J. News focus special report: Can a drug provide some protection? *Science*. 2003;301:1660.

NCHADS was subcontracted by the University of California, San Francisco, and the University of New South Wales to conduct this trial. All trial staff, therefore, were technically employees of NCHADS and answerable to them. Various local and foreign staff at NCHADS played major roles in the trial design. Dr. Ly Penh Sun and Dr. Vonthanak Saphonn led the NCHADS trial team. As the director of NCHADS, Dr. Mean Chi Vun also was central to the trial's development.

Dr. Margery Lazarus, a medical anthropologist at the University of California's San Francisco campus, was employed to conduct the formative social research intended to inform the design of this trial.

The Women's Network for Unity (WNU) is a union of Cambodian sex workers that operates as an independently registered nongovernmental organisation (NGO). The organising efforts that led to its creation began in 1997 with mobilisation and capacity-building work to introduce the concept and build understanding of the need for, and potential benefits of, such an entity. The idea of unionization was not new in Cambodia, but the concept that sex workers could create and lead organised advocacy efforts on their own behalf was revolutionary. After three years of preparation, the WNU was launched in June 2000 by a group of sex workers for sex workers. As their materials explain, "It provides a foundation for support and builds solidarity and self empowerment among sex workers. Our network provides a space for women to come together, share ideas and discuss the collective challenges we face".[8] The WNU is run by an elected secretariat of seven sex workers, including Khao Ta and Sotheavy Sou. It has more than 5,000 general members from the sex worker community in Cambodia.

Womyn's Agenda for Change (WAC) is an NGO working toward the grassroots empowerment of Cambodian women. WAC was originally a programme of Oxfam Hong Kong, working in Cambodia. It became an independent NGO in mid-2004, though it continued to receive substantial funding from Oxfam Hong Kong and other members of the Oxfam network. WAC provides the WNU with technical support and assistance. In mid-2008, WAC was restructured, though its community support activities, including support for the WNU, continue. At the time of the trial, Rosanna Barbero was the director of WAC. Phoung Phally Pry was the coordinator of WAC's Sex Worker Programme.

8. Women's Network for Unity. *Background to WNU Press Conference on Tenofovir Trials in Cambodia on March 29, 2004*. Available at http://wnu.womynsagenda.org/documents/wnu29mar04.pdf.

II. The political climate for Cambodian sex workers in 2003

To fully understand the following events, it is important to outline the political upheaval that the Phnom Penh sex workers and their advocates experienced in the two years immediately before the trial's launch.

Prior to 2000, various nongovernmental organisations (NGOs) in Phnom Penh offered programmes for sex workers. Seven of the main NGOs working in this area joined forces in 2000 to support their sex worker groups' decision to create an independent union led and controlled by members of the sex worker community. This major step forward fostered greater sex worker autonomy; helped to build their capacity to implement their own community programmes; and encouraged sex workers to articulate their rights and needs. Thus, the Women's Network for Unity (WNU) was born.

Sex worker programmes flourished in a general upsurge of NGO attention to the links between human rights issues and HIV risk. In June 2001, the United Nations General Assembly Special Session on HIV/AIDS issued a Declaration of Commitment on HIV/AIDS. One highly publicised aspect of the debate amongst the Special Session conferees centred on how "those most vulnerable" to HIV infection would be defined. Some Muslim and Catholic nations were alarmed by calls to explicitly acknowledge the vulnerability of "men who have sex with men, sex workers and their clients, injecting drug users and their sexual partners" as well as refugees and children.[9] This phrase was dropped from the document in the final negotiation, but as one human rights expert pointed out, "It is worth noting that there are direct references to men having sex with men and to commercial sex workers in the national AIDS plans of many of the countries that actively rejected the inclusion of such references in the global consensus".[10]

The WNU celebrated its second anniversary on 8 July 2002 with an event illustrating that explicit political support for their work existed, at least in some quarters. Mrs. Men Sam On, a feminist leader and member of the Cambodian parliament, spoke at the event and was quoted in the press as saying, "You [sex workers] should enjoy the same rights as everyone else and no one should violate your rights. As a member of Parliament, I fully support the Women's Network for Unity and would like to appeal to other women to participate in this activity…to strengthen [women's] self-determination and improve problem-solving".[11]

This increased attention on the role of sex workers in HIV prevention was due, in large part, to Cambodia's 1998 adoption of a 100% Condom Use Programme (CUP) that mandated condoms as part of every commercial sexual encounter. According to Population Action International, consistent condom use more than doubled amongst brothel-based sex workers in Cambodia between 1997 and 2001, and their HIV infection rates declined.[12]

Amongst other things, the 100% CUP policy required sex workers to carry government identification cards documenting their regular check-ups for sexually transmitted infections. This had the effect of making it easier for the police to locate them, extort money from them, and abuse them—practices that were well-established before the 100% CUP and further facilitated by its implementation.

Dr. Carol Jenkins documented the prevalence of abuse of sex workers by the police in a landmark study that used probability sampling to estimate the frequency of violence and theft perpetrated against Phnom Penh sex workers by police. Of the 500 brothel/mobile sex workers interviewed, 75 percent reported having been beaten by police within the last year; 91 percent had their money taken from them by police; 57 percent had been raped by a policeman acting alone; and 49 percent had been gang-raped by multiple policemen acting together within the last year. Jenkins noted that "[t]hese women are made significantly more vulnerable by the de facto arrangement between brothel managers and police, allowing the latter full access to brothel women whenever they want, in

9. United Nations. Declaration of Commitment on HIV/AIDS, Resolution S 26/2. Adopted at the UN General Assembly Special Session on HIV/AIDS, Agenda item 8, 27 June 2001. Available at http://data.unaids.org/publications/irc-pub03/aidsdeclaration_en.pdf.

10. Gruskin S. The UN General Assembly Special Session on HIV/AIDS: Were some lessons of the last 20 years ignored? *American Journal of Public Health*. 2002;92(3):337–8. Available at http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1447070.

11. Cambodian sex workers celebrate solidarity. *Phnom Penh Post*. 8 June 2002. Available at http://www.walnet.org/csis/news/world_2002/phonm-020708.html.

12. Chaya N. Cambodia and HIV: winning round two in a preventive fight. *Population Action International Research Commentary*. 2006;1(7). Available at http://www.populationaction.org/Publications/Research_Commentaries/Cambodia_and_HIV_Winning_Round_Two_in_a_Preventive_Fight/Cambodia_and_HIV.pdf.

any way they want. Further, when the pressures rise for brothel closure, the police have full power to torture, rape, and even kill sex workers with impunity".[13]

It is hardly surprising that the WNU and other sex worker advocates complained strenuously to the Cambodian National Centre for HIV/AIDS, Dermatology and STDs (NCHADS) about the fact that the 100% CUP policy further exacerbated their vulnerability, but NCHADS refused to address their concerns. A researcher based at the London School of Hygiene and Tropical Medicine's Centre for Population Studies validated Jenkins' findings as part of an ongoing pattern. She described the situation in 2006 as one in which an "unregulated military police force" placed the sex workers in Phnom Penh "at risk from both assault and arrest by police who supplemented their incomes by cracking down on the illegal trade and demanding bribes to release sex workers".[14]

The political climate took another sharp downward turn for sex workers in May 2003 when the US Congress passed the Global AIDS Act[15] to allocate US$15 billion over five years through an initiative known as the President's Emergency Plan for AIDS Relief (PEPFAR). Whilst PEPFAR was a step forward in terms of overall investment in HIV/AIDS work, the Global AIDS Act contains an insidious provision that became known as the "Prostitution Pledge".[16] The Act states that "[n]o funds…may be used to provide assistance to any group or organization that does not have a *policy explicitly opposing* prostitution and sex trafficking" [emphasis added].[17] All grantees also are required to refrain from activities that could be construed as condoning sex work in any way, even if the grantee pays for those activities with other funds.

The high priority that social conservatives, both inside and outside the US government, attached to this alleged strategy for eradicating prostitution and sex trafficking was illustrated by the US House of Representatives' 2004 passage of an expansive amendment on the subject known as the "Smith Amendment". It sought to require the US Department of State to collect, audit, and evaluate the organisational anti-prostitution policies of every PEPFAR grantee and subgrantee—foreign and domestic—and report back to Congress within 90 days of enactment of the legislation.[18] The Smith Amendment never became law because its companion version stalled in the US Senate. It is, nonetheless, a good indicator of the political climate at the time.

Not surprisingly, the Prostitution Pledge had an immediate impact on the sex worker community, the organisations engaging with them, and all subsequent attempts to cultivate dialogue with sex workers—including those made by trial staff. All of the NGOs running sex worker programmes in Phnom Penh in 2003 received US Agency for International Development (USAID) funding. Womyn's Agenda for Change chose not to sign the Pledge and to continue to support the WNU. The other six NGOs signed the Pledge and withdrew from their involvement with the WNU.

Practically overnight, the WNU went from being the focal point of sex worker programmes to being treated as a pariah by organisations fearful of jeopardising their funding. The NGOs that signed the Pledge shifted back to creating and supporting their own sex worker programmes, which led to competition and rivalries amongst NGOs working with the sex worker community. In Phnom Penh, many sex workers became deeply suspicious of the motivations of NGOs running sex worker programmes.

It was in this context that the trial team began consulting with local NGOs and asking for their help in recruiting trial participants. The ambient political upheaval caused confusion in two directions. Some of the NGO staff interviewed for this paper, for example, wrongly believed that the US-based pre-exposure prophylaxis trial researchers were connected to USAID and that the level of support they showed for the trial would directly affect their future USAID funding. Two years later, these NGOs agreed to be interviewed for this paper only on the condition of anonymity, stating that they were concerned about their funding relationship with USAID.[19]

The same presumed association between the researchers and USAID made some sex workers extremely suspicious of the motivations of the research team.

13. Jenkins C, Cambodian Prostitutes Union, Women's Network for Unity, Sainsbury C. *Violence and Exposure to HIV Among Sex Workers in Phnom Penh, Cambodia*. Washington, DC: US Agency for International Development; 2006. Available at http://www.researchforsexwork.org/downloads/Jenkins-CambodiaFinal.pdf.

14. Busza J. *Having the Rug Pulled from Under Your Feet: One Project's Experience of the US Policy Reversal on Sex Work*. United Kingdom: Oxford University Press, in association with the London School of Hygiene and Tropical Medicine Centre for Population Studies; 2006. Available at http://heapol.oxfordjournals.org/cgi/reprint/21/4/329.pdf.

15. *United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003*.

16. Masenior NF, Beyrer C. The US anti-prostitution pledge: First Amendment challenges and public health priorities. *PLoS Medicine*. 2007;4(7);e207:1158–61. Available at http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040207.

17. *United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003*, 22 U.S.C. § 7631(f).

18. Sexuality Information and Education Council of the United States. *US-Based Aid Groups Receive Ultimatum: Pledge Your Opposition to Prostitution and Sex Trafficking or Do Without Federal Funds*. July 2005. Available at http://www.siecus.org/index.cfm?fuseaction=Feature.showFeature&featureid=1263&pageid=483&parentid=478.

19. Interviews with four nongovernmental organisations, 22 June 2006.

III. Chain of events, part I (2002–May 2004)

Initially, the two universities involved (University of California, San Francisco, and University of New South Wales) had each planned its own pre-exposure prophylaxis (PrEP) trial. In 2002, Family Health

International received funding from the Bill & Melinda Gates Foundation to run the Asian site of a four-country PrEP study slated to include three African sites as well as one site in Asia. Dr. John Kaldor of the University of New South Wales in Sydney was given the responsibility of identifying and overseeing the Asian trial site.

Dr. Kimberly Page Shafer of the University of California, San Francisco, recalls that her epidemiological research kept pointing her toward the need for a new medical intervention in the fight against AIDS. She believed that PrEP could be such an option. She chose Cambodia as the trial site because she had successfully collaborated with the Cambodian National Centre for HIV/AIDS, Dermatology and STDs (NCHADS) in the past and knew that the Cambodian government had some significant successes with HIV interventions.

Kaldor and Page Shafer had done previous work together. When they discovered that they were both planning similar trials, they agreed to collaborate. This decision also responded to NCHADS' insistence that only one trial of this kind be conducted in Cambodia. Page Shafer visited Cambodia in late 2002 to do groundwork and background research, and a Cambodian researcher came to the United States to work on the protocol.

In early 2003, the US National Institutes of Health (NIH) approved funding for the University of California, San Francisco, to conduct the trial Page Shafer envisioned. In July 2003, the researchers signed a formal memorandum of understanding with the Cambodian Ministry of Health to conduct joint research and develop protocols for the trial.

Gilead Sciences did not provide any funding for the trial and was not involved in its planning or implementation. Their only contribution was to provide the medication and placebos to be used in the trial.

Cambodia had virtually no experience with clinical trials amongst highly vulnerable populations prior to the planning of the PrEP trial.[20] In 2003, the Cambodian Ministry of Health convened a National Ethics Committee to review the trial protocol. The University of California, San Francisco, worked with NCHADS to ensure that the Committee's composition and the training it received conformed to NIH standards, as outlined in an NIH policy adopted in 2000 called *Required Education in the Protection of Human Research Participants*.[21] The policy lays out specific training requirements that apply not only to institutions but to all NIH grant recipients. The University of California, San Francisco, provided a one-week biomedical ethics training course that was attended by stakeholders within the Ministry of Health as well as nongovernmental groups and sex workers. The course was conducted by Dr. Robert Grant and Page Shafer.

In March 2003, a preliminary protocol was submitted to the Cambodian Ethical Review Board and subsequently approved. With this provisional authorisation, the team was able to start formative research for the trial, and began hiring staff and building the clinic and laboratory capacity for the trial. The research team also began discussing the protocol in focus groups and interviews with stakeholders, including potential participants, brothel owners, police, and local government officials.

The draft protocol for the Cambodia PrEP trial included the following provisions:

- Participants would receive US$3 per month compensation for their participation in the trial for 12 months. (The monthly income of a rural female sex worker was documented in 2003 as US$14.50.[22])
- All volunteers would be screened for HIV in order to identify negative women eligible to enrol in the trial. Positive women who were identified during the trial screening process would be referred to the NCHADS HIV clinic but would not receive preferential access to clinic services or to other services from the trial.
- During the trial, participants were to receive counselling about risky behaviour, free condoms, and free screening and treatment of sexually transmitted infections.

20. Email communication from John Kaldor, 22 September 2008.

21. National Institutes of Health. *Required Education in the Protection of Human Research Participants*; adopted 5 June 2000. Available at http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

22. Sopheab H, Gorbach PM, Gloyd S, Leng HB. Rural sex work in Cambodia: work characteristics, risk behaviours, HIV, and syphilis. *Sexually Transmitted Infections*. 2003;79;e2. Available at http://sti.bmj.com/cgi/content/abstract/79/4/e2.

- Each participant was to receive an HIV test monthly. Participants who seroconverted during the trial would be given preferential access to free, comprehensive care and treatment at the NCHADS clinic, including access to antiretroviral therapy if medically indicated, in accordance with Cambodia's national treatment guidelines.
- Participants would receive treatment for side effects during the trial, but aside from the HIV care noted above, no treatment would be available for side effects or illnesses developed after the trial had finished.

Dr. Margery Lazarus began the social research phase of the trial by conducting a comprehensive assessment of the demographics, working conditions, risk behaviours, and sexual and economic networks of the female sex workers in Phnom Penh. She assembled a bilingual Cambodia staff selected for their communication and qualitative research skills. Working with them, she assessed possible locations for the clinic site, designed and assessed the comprehensibility of informed consent materials, and developed a participant recruitment strategy.

Informing the community and other stakeholders

In early 2003, draft information about the trial was distributed to stakeholders, including all nongovernmental organisations (NGOs) with sex worker programmes. Discussions with relevant individuals were initiated about the proposed participant recruitment strategy. In 2003 and early 2004, the research team held focus groups with sex workers and other members of the community, as well as larger consultative fora.

As part of the consultation process, the research team contacted local NGOs that engaged with sex workers in Phnom Penh, inviting them to attend meetings about the trial and relay the information they received to the women with whom they worked. Some of these NGO representatives also were invited to participate in the trial's community advisory group (CAG). Some of the meetings were conducted in English, with translators available as needed, whilst others were conducted in Khmer.

One NGO worker present at these meetings observed that some sex workers also were invited to participate in these community meetings, "but they generally didn't speak up very much".[23] She attributed this to the climate of intense distrust that had developed between many of the sex workers and the NGOs in the aftermath of the anti-prostitution pledge. Class, gender, and language differences also may have contributed to this reluctance.

Other factors reported by some participants to have worked against the meetings being as productive as hoped included:

- Lack of research literacy: most participants needed basic, easily accessible information about clinical trials and how they are conducted. Without this, participants had no real context for the information they were receiving.
- Meetings that were described as long and tended to cover the same issues with very little forward motion or change. Several participant concerns were raised repeatedly, especially by the Women's Network for Unity (WNU), but never really addressed, and questions often went unanswered. This created the impression that the convenors had no real intention of modifying or adjusting the trial protocol in response to concerns and feedback received.
- Trial staff that were generally represented by researchers from the United States and Australia and one Cambodian government official who said very little.
- WNU leadership that tended to be vocal at the meetings. Other Cambodian and international NGOs working with sex workers also were invited, but some of these were simultaneously trying to engage sex workers in the trial whilst backing away from them in other contexts in order to meet the anti-prostitution pledge. This dissonance was inevitably counterproductive.

The primary concerns raised by participants at the meetings included:

1. How would informed consent be assured?
2. Why and how was Cambodia selected for this trial? Why hadn't they (the participating NGOs and sex workers) been asked if they wanted this trial to occur in their community?
3. How would future access to care, especially antiretrovirals, be assured to seroconverters?
4. What would happen when a trial participant fell pregnant during the trial and/or experienced drug side effects?
5. Would treatment and care be made available to trial participants who experienced drug side effects in both the short and long term after the trial had closed?

During this time period, Lazarus and a community education coordinator developed guidelines for how the study might structure and recruit members for an ongoing CAG. The 13-member CAG was a mix of representatives of local health NGOs, NGOs serving sex workers, multilateral and bilateral agencies, government health agencies, and one unaffiliated sex worker. It met in March and May of 2004.

23. Interview with Supriya Pillai, 31 January 2006.

The CAG process was new to both the researchers and most of the members. The researchers viewed it as a mechanism to raise and resolve a range of issues related to the trial. Several CAG members, however, reported feeling as though the researchers interpreted their questions and suggestions as indications that the member simply did not understand the issue raised. They responded by re-explaining the issue rather than by initiating discussion to explore the member's concern and consider how it might best be addressed.

NCHADS also formed an External Advisory Board for the trial that "brought together key governmental departments and international organisations with an interest in HIV and AIDS, including UNAIDS [Joint United Nations Programme on HIV/AIDS] and WHO [World Health Organisation]".[24] The board met in January and June 2004.

Women's Network for Unity responds to the trial

Womyn's Agenda for Change (WAC), a technical support organisation of the WNU, was amongst the stakeholders contacted with preliminary information about the proposed trial in early 2003. Members of the research team met with Rosanna Barbero, the director of WAC at the time of the trial. She recalls thinking then that WAC needed to learn more about the potential benefits and risks associated with clinical trials, in case the WNU was asked to become involved in the trial.[25] Two interns from the University of Michigan law school were working at WAC at the time, and Barbero asked them to do some research on clinical trials, including finding relevant case studies. Barbero and other WAC staff worked with the interns to compile information, particularly regarding the experiences of participants in past clinical trials so that, if asked, they could provide a balanced picture of what potential participants might expect if recruitment for the PrEP trial started in Cambodia.

Several months later, WAC received an invitation to attend one of the information sessions at NCHADS about the trial. Their sex worker programme coordinator, Phoung Phally Pry, invited members of the WNU to accompany her to the meeting. Several members of the WNU also attended focus groups conducted by Lazarus and her team around this time, and the trial quickly became a hot topic of discussion at WNU meetings.

The WNU Secretariat asked for WAC's assistance in providing additional information to answer their members' questions about both the positive and negative aspects of potential trial involvement. WAC agreed to provide the information it had collected and saw this support as one more step in empowering the WNU to define its own position regarding the trial. WAC had been providing this kind of technical assistance and capacity-building support to the WNU since the union's inception, a vital function given that none of the WNU Secretariat reads English. The ideological basis of both organisations is such, however, that WAC fully appreciated the WNU's autonomy and did its best to serve as an objective transmitter when meeting such information requests.

WAC staff and interns relayed their findings on clinical trials in a workshop for WNU members in early 2004. After the workshop, the WNU convened a membership meeting to discuss the new information and formulate their response. The members expressed particular concern about the risk of tenofovir side effects, noting that the trial materials cited bone density loss and kidney failure as possible serious side effects. It was at this meeting that sex workers, themselves, came up with the idea of asking for insurance.

At that time, no studies had been published on the possible safety consequences of ongoing tenofovir use amongst HIV-negative people,[26] so no real data existed with which to answer these concerns. Members were particularly concerned about their economic, as well as physical well-being. For many, their work provided the sole source of income for their children and other family members. Any side effects that rendered them unable to work (even briefly) could result in hunger and instability. Participation in the trial, therefore, could pose real and immediate risks to individuals and their families.

The members decided it was reasonable to ask that the risk taken by participants be offset by some kind of long-term insurance protection.[27] They decided to ask for health insurance for 20–30 years to cover medical expenses generated by the possible side effects of tenofovir (not general insurance for all medical problems, as has been misreported by some media sources). They also decided that US$3 per month was insufficient compensation for their involvement, since even the minor side effects listed in the trial materials, such as stomach aches or headaches, could reduce their ability to work and earn money.

24. Page Shafer K, Vonthanak S, Penh Sun L, et al. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *The Lancet*. 2005;366:1499–1503.

25. Telephone communication with Rosanna Barbero, 5 December 2008.

26. Thompson M. The experts speak. Studying the potential of tenofovir to prevent sexual transmission of HIV: first steps. *AIDS Patient Care and STDs*. 2005;19(1):1–4.

27. Group interview with Women's Network for Unity members, 23 June 2006.

According to the WNU Secretariat, members began explicitly asking in trial-convened focus groups and meetings that some kind of long-term insurance be provided to cover the possibility of long-term side effects. Sotheavy Sou from the WNU Secretariat recalls that after having raised these concerns repeatedly in focus groups and meetings, members became frustrated that their questions were not being adequately answered.[28] They viewed the researchers as unwilling to take seriously their concerns about the health of sex workers who were potential trial participants. They had observed that press conferences convened by other advocacy groups successfully drew public attention to concerns that were not being addressed and thought that the technique might work for them as well. The WNU decided to hold a press conference to bring the discussion to a head in a forum not convened by the research team.

The press conference was held on 29 March 2004.[29] Page Shafer described the conference as a "press bomb that was thrown into the trial development and consultation process".[30]

28. Interview with Sotheavy Sou, 21 June 2006.

29. Women's Network for Unity. *Background to WNU Press Conference on Tenofovir Trials in Cambodia on March 29, 2004*. Available at http://wnu.womynsagenda.org/documents/wnu29mar04.pdf.

30. Telephone interview with Kimberly Page Shafer, 3 October 2007.

IV. Context, communication, and ethical quandaries

This section explores how the various constituencies involved perceived the situation before them; how these differing perceptions led to sharply differing expectations and interpretations; and how these conflicting views—once made manifest in the form of decisions, statements, and actions—ultimately derailed the trial before it started. Perhaps the dominant lesson from this case study is the importance of researchers tailoring their attempts to address these disparities to the specific needs of the host community.

Understanding the complexities of prevention trials

The proposed study was a randomised, placebo-controlled trial to evaluate the extended safety and effectiveness of daily tenofovir in pill form as a means of reducing HIV acquisition amongst sex workers in Phnom Penh. Specific strategies are required to communicate the complexities of such a trial to people with no prior experience with clinical research. Two aspects of this kind of HIV prevention trial particularly tend to heighten anxiety, confusion, and concern amongst potential trial participants.

The first is the risk of drug side effects. HIV treatment trials enrol people who are already sick. Prevention trials, by contrast, recruit and follow healthy individuals to see whether the intervention reduces their risk of becoming HIV infected over time. Because HIV transmission is a relatively rare event, trials must enrol and follow large numbers of healthy people who are at extremely high risk of infection. This high rate of HIV seroincidence (new HIV infections) provides a backdrop against which it is possible to detect any difference between the infection rate amongst those individuals receiving the intervention (tenofovir, in this case) and those receiving the placebo.

Efficacy trials almost invariably take place amongst highly vulnerable populations, raising inevitable concerns about potential exploitation. Healthy individuals in a prevention trial likely use a very different risk/benefit calculus when considering possible side effects and other risks than people in a treatment trial who are already sick. People who are already sick may agree to tolerate drug side effects in the hope that the treatment will help prolong or save their lives. People who are healthy at the outset, however, may be less likely to accept substantial risk of side effects. This concern about side effects combined with the serious economic threat of being unable to work if the side effects are debilitating helps to explain the intensity of the sex workers' demand for insurance.

The second area of concern relates to HIV risk amongst trial participants. HIV prevention trials are based on the reality that some people will be unable or unwilling to use the provided prevention package (including free condoms and risk reduction counselling), and therefore, will become infected during the course of the trial. In the communities in which these trials take place, HIV risk is already high, and new infections are occurring regularly.

HIV prevention trials are ethically required to ensure that participants are aware of, given access to, and encouraged to use known preventative methods throughout the trial. As a result, trial participants often increase their level of condom use and actually have lower seroconversion rates than their peers who are not enrolled in the trial. Nevertheless, when a trial participant seroconverts, some people may "blame" the trial or question whether the trial did everything it could to help that participant avoid risk. This is understandable, given that HIV prevention trials cannot assess the impact of the test intervention unless a certain number of participants become HIV infected during the trial. This perceived conflict of interest is sometimes referred to as the "researcher's dilemma".

For some trial participants and others, this can become a source of ambivalence and even mistrust about the trial. As Sotheavy Sou from the Womens's Network for Unity (WNU) put it, "They told us that during the trial, if you have sex, you need to use condoms. When we first heard this, we didn't understand if you have an experiment why you need to use condoms. How can they test if the medicine is effective if we are all using condoms?"[31]

31. Interview with Sotheavy Sou, 21 June 2006.

Ethical challenges

The events surrounding the pre-exposure prophylaxis (PrEP) trials in Asia and Africa have fuelled ongoing debate about how medical and ethical standards are applied when trials take place in developing country contexts. The protocol for the Cambodia trial passed the ethical review processes that existed at the time in a number of different academic and national institutions. The fundamental question remaining, however, is whether those standards were sufficient to deal with a trial in the specific Cambodian context of the time.

As Rosanna Barbero, the director of Womyn's Agenda for Change (WAC) at the time of the trial, observed, "If you transport something that passes scrutiny in a western industrialised country and bring it to a country without the same legal mechanisms, health system, or level of education amongst participants, then you have to acknowledge the differences in the situation".[32]

With an annual gross domestic product of just US$441 per person in 2005, Cambodia is ranked 130 on the United Nations Development Programme Human Development Index. It is an extremely resource-poor country. Its health system is funded by international aid programmes and nongovernmental organisations (NGOs) and by charging user fees to patients. Access to health care is severely limited.

Health care access is further compromised by the stigma that Cambodian sex workers frequently face when using their health care systems. One function of the WNU is to assist sex workers who experience discriminatory treatment from medical staff when seeking treatment. This discrimination increased after implementation of the Global AIDS Act "Prostitution Pledge",[33] even in clinics specifically funded to work with sex workers. The WNU helps sex workers to overcome difficulties in accessing health services, including antiretrovirals.

These conditions posed major challenges to the goal of achieving the level of community understanding, engagement, and trust needed to ensure a well-accepted clinical trial. It also explains why the issue of access to health care for trial participants—and particularly the concern that women with serious side effects after the trial ended might be left stranded without health care—became a breaking point in researcher/community relations.

Informed consent

Informed consent issues also illustrated the depth and complexity of the communications challenges faced by this trial. Eng Van Eang from the HIV/AIDS Reproductive Health Association of Cambodia and Chhu Bun Eng, Director of Cambodian Women for Peace and Development, were two of many who expressed concerns about therapeutic misconceptions retained by some participants.[34] Concerns also were raised about whether sex workers felt intimidated by the officials administering the trial and thus refrained from asking questions during the informed consent process even though they did not fully understand the information.

Drs. Margery Lazarus and Kimberly Page Shafer and their staff understood the importance of ensuring truly informed consent and were working on methods for ensuring that participants were well-informed enough to give meaningful consent. Many of the medical terms related to the trial could not be directly translated into Khmer, so they worked to develop a lexicon for use by trial participants. They also were investigating table-top graphics and other methods of explaining concepts to participants. At the time the trial was cancelled, trial staff had already started testing comprehension of informed consent materials—first with community advisory group (CAG) members and then with sex workers during in-depth interviews.

Barbero agreed on the critical need for informed consent but questioned how the necessary level of understanding could have been achieved in the time frame proposed by the trial. She reported that it took three years of slow, systematic community education and capacity-building to achieve a clear, shared understanding of the concepts involved in creating a sex workers' union. How then, she asked, can researchers expect to do the education needed to ensure that people clearly understand something as complex as the physical implications of enrolling in a clinical trial in less than a year?[35]

In the midst of the trial controversy in May 2004, a reporter from the *Cambodia Daily* (a local newspaper) wrote this about his interview with a sex worker who had participated in some of the trial's community meetings: "Sithi Ratana seems well informed until she began to explain that condoms could prevent liver and

32. Interview with Rosanna Barbero, 21 June 2006.

33. The Global AIDS Act states that "no funds. . .may be used to provide assistance to any group or organization that does not have a policy explicitly opposing prostitution and sex trafficking".

34. Collins J. Sex workers leery about HIV trial. *Cambodia Daily*. 30 March 2004.

35. Telephone communication with Rosanna Barbero, 5 December 2008.

kidney problems and that a cure for AIDS had already been found.... More importantly, she said that sex workers in another country had proven that after taking the drug they 'could become free of AIDS'."[36]

Handling ethical questions

The fact that medical trials can provide cash-strapped developing country governments with resources was raised as an issue of ethical concern by NGO health care workers in Cambodia at the time of the trial.[37] Free-floating suspicions and rumours were rampant before the trial closed. The situation raised persistent questions about how well the available ethical guidelines addressed the sharp financial and cultural disparities between the trial sponsors and institutions, on one hand, and the trial host community on the other.

One question of great importance to community advocates in Phnom Penh was whether the Cambodian sex worker community would ever benefit from the results of the trial if tenofovir turned out to be effective for HIV prevention. Developed by the World Medical Association as a statement of ethical principles to guide researchers and physicians, the Declaration of Helsinki states that "[m]edical research is only justified if there is a reasonable likelihood that the population in which the research is carried out stands to benefit from that research".[38]

Access to existing medications was, and is still, extremely limited for sex workers in Cambodia. Many cannot even afford to buy basic medicines for minor illnesses. Use of traditional medicines is common in part because "western" medicines tend to be available only in urban areas and are very expensive.[39] This question of future access to tenofovir was of sufficient concern to appear in the statement WNU distributed at their press conference in March 2004. It states "[i]f our members agree to take the risk, which may one day benefit people in richer countries and the drug company, then we deserve adequate protection for our future lives and our families. The high cost of this drug means that even if it is successful in preventing HIV/AIDS, Cambodian sex workers will most likely never be able to afford it".[40]

Whilst supporting this right to access, the researchers contended that their primary role was to generate new knowledge, not forge public policy. Nevertheless, the research team took steps to address the issue. They obtained an agreement with Gilead Sciences that participants in the trial would be offered free tenofovir for two years after the study if it proved successful.[41] Cambodia also was included on the list of countries eligible for Gilead's "Access Tenofovir" programme, created for the stated purpose of giving developing countries access to the medication at a price that covers only the cost of production and distribution.[42]

Unfortunately, the credibility of these good-faith efforts was damaged in the eyes of the community by Gilead's record and past conduct. In their research, WAC discovered that Médecins Sans Frontières (Doctors Without Borders) had already launched a campaign against Gilead for failing to live up to the promises made in their Access Tenofovir programme. Of the 97 countries announced to be eligible for the programme in 2002, only six had managed to complete the paperwork and other requirements for obtaining drug access at reduced prices.[43]

Gilead's credibility was further compromised because the WNU learnt that the US Food and Drug Administration (FDA) had, on multiple occasions, warned Gilead against misrepresenting the side effects associated with tenofovir. On 3 August 2003, the FDA posted a letter online regarding Gilead's promotion of the drug at a recent conference, noting that they had "minimized important risk information".[44] The letter states that this action "raises significant public health and safety concerns" and that Gilead had "previously

36. Doyle K, Naren K. The slippery ethics of third world drug trials. *Cambodia Daily*. 7 May 2004.

37. Collins J. Sex workers leery about HIV trial. *Cambodia Daily*. 30 March 2004.

38. World Medical Association Declaration of Helsinki. *Ethical Principals for Medical Research Involving Human Subjects*. Adopted by the 18th World Medical Association General Assembly, June 1964; Helsinki, Finland. Amended most recently in 2008. Available at http://www.wma.net/e/policy/b3.htm.

39. Wetzel L, Huong J. *Voices in the Cambodian Community*. Profile developed by the House Calls project, Harborview Hospital, Seattle, Washington. Available at http://www.ethnomed.org/ethnomed/voices/cambodia.html.

40. Women's Network for Unity. *Background to WNU Press Conference on Tenofovir Trials in Cambodia on March 29, 2004*. Available at http://wnu.womynsagenda.org/documents/wnu29mar04.pdf.

41. Collins J. Sex workers leery about HIV trial. *Cambodia Daily*. 30 March 2004.

42. Alcom K. Gilead to offer tenofovir at no profit to Africa. *AidsMap*. 17 December 2002. Available at http://www.aidsmap.com/news, accessed 4 June 2004.

43. Gilead's "Access Tenofovir" programme for developing countries: a case of false promises? Médecins Sans Frontières press release; 7 February 2006. Available at http://www.msfaccess.org/media-room/press-releases/press-elease-detail/?tx_ttnews%5Btt_news%5D=31&cHash=65d72b8994.

44. Letter from Thomas W. Abrams, Director, Division of Drug Marketing, Advertising, and Communications to John C. Martin, President and Chief Executive Officer, Gilead Sciences, Inc., Re: N11A 21-356, FDA Warning Letters, posted 3 August 2003. Available at http://pharmcast.com/WarningLetters/Yr2003/July2003/Gilead0703.htm.

been warned not to engage in such activities".[45] This information, located by WAC interns, heightened the sex workers' concerns about both the drug's potential side effects and Gilead's credibility generally.

Another ethical conundrum raised in this (and virtually every other) trial is the question of whether it is ever possible to fully prevent the phenomenon of therapeutic misconception—a situation that occurs when the participant does not fully grasp the difference between treatment and research. Although told repeatedly by the trial staff that the test product is not known to be effective (and may, in fact, be a placebo), a participant may still believe that she or he is receiving an effective medication. This kind of wishful thinking is particularly problematic in HIV prevention trials because participants may abandon condom use in the belief that they are protected by the trial-provided product.

At one of the WNU's group meetings, some members discussed their desire to participate in the trial so that they could earn more money by charging their clients the going rate for sex without condoms. These members said they felt certain that the drug must provide a good chance of protection if the researchers were willing to go to so much effort to conduct a trial.[46.] A related concern was that clients, knowing that some sex workers were participating in the trial, might resist using condoms[47] by arguing that condoms were not necessary for sex workers using the trial drug.

Even the best efforts to ensure and reinforce informed consent amongst trial participants, including efforts to dispel therapeutic misconception, are generally only partially effective.[48] Thus, the resulting risk (that participants may decrease their condom use) may arguably be construed as one of the trial-associated risks taken on by participants. This is one amongst many reasons used to argue that all seroconverters in a trial should receive guaranteed access to high-quality HIV treatment by the trial sponsors.

Another ethical issue—and one that is specific to this cohort of PrEP trials[49]—was the decision to expose vulnerable women to safety risks without first collecting safety data amongst HIV-negative individuals in far less vulnerable populations (in Europe or North America, for example). The Phase 3 trial proposed for Cambodia was constructed to evaluate both the "safety and efficacy of tenofovir in preventing HIV-1 infection",[50] despite the fact that a comprehensive safety profile had not yet been established through the conduct of safety trials in comparable populations.

This anomaly was flagged as an issue of concern as early as 2001, when the Bill & Melinda Gates Foundation convened a small, informal consultation on the ethics of the proposed tenofovir PrEP trials. Attended exclusively by researchers, ethicists, and advocates from the United States, the Gates Foundation meeting allowed for debate on potentially volatile issues such as the choice of study population, the need to ensure access to treatment for seroconverters, and the lack of safety data amongst HIV-negative individuals. Amongst the conclusions articulated at the end of the consultation were the following:

- Proceeding with a Phase 3 efficacy trial of oral tenofovir for prevention before doing Phase 2 safety trials amongst HIV-negative persons was not appropriate.
- Human safety trials of tenofovir in HIV-negative populations in the United States are appropriate and could be followed by efficacy studies in high-risk US populations and in similar populations in other countries. Ultimately, PrEP testing should involve a well-funded programme of multiple trials to evaluate the method amongst different users. This would ensure that the burdens and benefits of research were shared.
- The issues of access to HIV counselling, testing, and antiretroviral treatment could be addressed by conducting Phase 3 trials in developing country settings where such access either already existed or was being established, such as Botswana, Brazil, and/or Thailand. The consultation participants considered it extremely problematic to test an antiretroviral for prevention in settings where antiretrovirals for treatment were not yet available.[51]

45. Letter from Thomas W. Abrams, Director, Division of Drug Marketing, Advertising, and Communications to John C. Martin, President and Chief Executive Officer, Gilead Sciences, Inc., Re: N11A 21-356, FDA Warning Letters, posted 3 August 2003. Available at http://pharmcast.com/WarningLetters/Yr2003/July2003/Gilead0703.htm.

46. Interview with Phoung Phally Pry, 20 June 2006.

47. Doyle K, Naren K. The slippery ethics of third world drug trials. *Cambodia Daily*. 7 May 2004.

48. Lidz CW, Appelbaum PS, Grisso T, Renaud M. Therapeutic misconception and the appreciation of risks in clinical trials. *Social Science & Medicine*. 2004;58(9):1689–97.

49. Concern about the lack of pre-existing safety data regarding use by HIV-negative people was expressed in connection with the PrEP trials initiated in Cameroon, Ghana, and Nigeria around the same time as the trial in Cambodia.

50. Cambodia HIV Prevention Study: Summary Protocol Description, based on Protocol V1_Rev2 (approved by DAIDS MO 20 July 2004), provided by the US National Institutes of Health and Family Health International.

51. These conclusions are part of the public record only because Lori Heise, Director of the Global Campaign for Microbicides and the only advocate to participate in the consultation, wrote to Family Health International requesting a written update on whether and how Family Health International had taken into account the recommendations of the consultation.

Substantial discussion of these conclusions occurred amongst the trial sponsors and other entities. Ultimately, however, funding for the Cambodia and Cameroon PrEP trials proceeded without further external consultations.

Varying perceptions around the meanings and experience of "safety"

The sex workers interviewed for this paper understood the need to test the efficacy of tenofovir in a place where HIV infection rates are high enough to complete the trial in a reasonable amount of time and with a feasible sample size. They also understood that someone needed to test the drug on behalf of others and were willing to participate in research that might prove beneficial not only to their communities but to people in other countries.

Many, however, saw the decision to test safety amongst HIV-negative people for the first time in a developing country as an example of researchers from wealthy countries taking risks with their health. They argued that the drug's safety for use by HIV-negative people could and should have been tested first amongst participants who had access to good health care services and were better equipped to deal with any negative side effects that might occur in the short and long term. As noted above, for sex workers in Cambodia, even the remote possibility of being unable to work for a short period of time constituted an immediate threat.

The WNU connected the rejection of their call for long-term insurance against possible trial-related side effects with the fact that the impact of tenofovir on HIV-negative people, especially over the long term, was unknown. They saw the refusal to provide insurance as tacit admission that tenofovir might have serious and lasting health implications.[52] The WNU's press statement asks, "If the researchers are so sure that this drug is safe for HIV-negative women to take, in the short and long term, why won't they commit to insurance for us and our families? If we get sick or can't work it can be the difference between life and death for our families".[53]

Information presented at the first public meetings about the trial in Cambodia stated that tenofovir has very low rates of side effects and resistance[54] (compared to other possible PrEP candidates) and listed the possible side effects as dizziness, headaches, gas, nausea, vomiting, kidney damage, bone toxicity, and liver dysfunction. This led Soma Yu Norng, a WNU member, to observe, "I'm not sick now, but if I put myself in danger of sickness, if my kidney gets destroyed, where can I get the money to replace my kidney? If I fall sick, how can I earn the money to support my family and children?"[55]

Dr. John Kaldor pointed out that the trial included extensive safety assessment measures in part because no safety data were available on extended use of the drug by HIV-negative people. When questioned about the side effects in public discussions related to the trial, the researchers explained that serious side effects were very rare and noted that tenofovir had been found to be more easily tolerated and less toxic than most other AIDS drugs when used as part of antiretroviral combination therapy in people with HIV infection.

This interchange is a vivid example of miscommunication across sectors. Whilst the researchers saw the provision of all relevant information as a standard and ethically required practice, some members of the sex worker community saw the inclusion of information about serious possible side effects—in combination with assurances that suffering these effects was highly unlikely—as an attempt to dupe them into participating in a trial that might endanger their health. This fear grew when they heard some members of the focus groups suggest that the information about side effects be removed from trial materials because it was being misinterpreted.

Kaldor reflected that "[w]e had enough information to have a lot of confidence in the safety profile of tenofovir. The issue was about sharing that confidence in a way that is transparent and staged. It could come across as contradictory to say that a drug is likely to be safe and then ask people to be closely monitored for safety issues and sign consent forms about side effects".[56]

As discussed earlier, their history and prior experience with medical professionals did not predispose the sex workers to trust the information received from the research team. The Asia Pacific Network of Sex Workers (APNSW) works extensively with sex workers in the region, and Andrew Hunter, its policy director, understands that their scepticism regarding drugs and

52. Group interview with Women's Network for Unity members, 23 June 2006.

53. Women's Network for Unity protests drug trial recruitment tactics. WNU press statement; 15 June 2004. Available at http://www.wnu.womynsagenda.org/documents/wnu21june04.pdf.

54. NCHAD [Cambodian Ministry of Health National Centre for HIV/AIDS, Dermatology and STDS] HIV Prevention Study, Cambodia. PowerPoint handout; copy provided in 2006 by Womyn's Agenda for Change from their files.

55. Interview with Soma Yu Norng, 20 June 2006.

56. Interview with John Kaldor, 13 February 2007.

chemical agents is based on personal experience. He noted that "[i]f you look around with all the Agent Orange deformities, etc.,[57] it is easy to understand why. Nearly all Cambodians understand that so-called 'safe' agents can end up causing long-term health problems".[58]

Distrust of the research team also was generated by trial information stating that the preliminary data on the use of tenofovir for prevention were derived from simian trials. Khao Ta from the WNU Secretariat recounted this conversation in one meeting: "I said, 'You had a trial in your country, but you used apes. Here you want to use humans. Do you think we are apes?' We told them, 'First you try this medicine on one of your own sisters, and then you can come and give it to us.'"[59] The degree of offence taken at the mention of animal trials was generated, in part, by the fact that some of the words used to insult sex workers in Cambodia are animal names.

Cambodian National Centre for HIV/AIDS, Dermatology and STDs officials later explained that testing on animals was a common practice overseas, but this did not overcome the impression that the trial was equating the lives of sex workers to the lives of animals. Two protest slogans used throughout the campaign by the WNU and picked up by other members of APNSW were "We are not monkeys" and "We are not guinea pigs".

Another lesson from the Cambodia trial is that information about potential drug side effects must be presented at the outset in a way that is explicitly informed by the local context and community concerns. Once groups within the community formed a view that tenofovir might be unsafe, it was very difficult to ally these fears. More than two years after the trial was cancelled, women interviewed for this paper (both WNU members and non-members) expressed alarm about the possible short- or long-term damage to their health that the trial might have had, thus impacting their ability to work and support their families.[60]

Methods of communication and messaging

Meaningful, productive community engagement in a trial requires patient and well-constructed education efforts to familiarize people with the concepts, history, and functions of clinical research before starting to discuss the details of the trial at hand.

Most women in the sex worker community in Cambodia had no prior knowledge about the history or conduct of clinical trials, although some had experience with observational research. The Jenkins study mentioned earlier (on page 9) expanded the community's view of research somewhat. Using a participatory research model, Dr. Carol Jenkins engaged 33 sex workers selected by local sex worker organisations and provided them with two weeks of intensive training in February 2004 on research techniques and ethics, informed consent, and other topics. These peer interviewers then designed and pre-tested the questionnaires, and between mid-March and mid-May of 2004, they collected qualitative and quantitative data from more than 1,000 freelance and brothel-based sex workers.[61] It seems inevitable that Jenkins' study, with its high level of community involvement and participation, must have generated discussion amongst Phnom Penh sex workers regarding the widely contrasting styles of the two trials—the one being planned and the one underway—during the first half of 2004.

The trial staff reported that they used a variety of communication mechanisms and outreach at a range of levels to better engage with sex workers and organisations representing them. This multiplicity of approaches was perceived by some community members as confusing and failing to provide clear and consistent information. In some cases, it also fuelled suspicion and distrust of the researchers' motives.

In addition to difficulties inherent to the setting (including distrust of foreign institutions and absence of previous local experience with clinical research), the research team faced internal challenges. Most of the non-Cambodian staff had no prior experience working outside of the United States, did not speak Khmer, and had to communicate with trial participants and other community members and stakeholders through translators. Communication also was hindered by the stigmatising attitudes expressed by some of the Cambodian staff and other officials working with the trial. Lazarus observed that some found it hard to treat

57. Congenital deformities amongst at least 500,000 children and approximately two million cases of cancer in Southeast Asia are directly attributed to the toxic impact of Agent Orange and chemical defoliants used during the US/Vietnam war. More information is available online at http://www.independent.co.uk/news/world/asia/from-foe-to-friend-vietnam-and-the-legacy-of-war-424183.html and at http://www.agentorange.org.au/.

58. Email communication from Andrew Hunter, Policy Director, Asia Pacific Network of Sex Workers, 12 September 2008.

59. Group interview with Women's Network for Unity members, 23 June 2006.

60. A recurring theme amongst the potential trial candidates interviewed was this concern that the use of tenofovir could have caused short- or long-term damage to their health and thus jeopardised their ability to work and earn a living for their families.

61. Jenkins C, Cambodian Prostitutes Union, Women's Network for Unity, Sainsbury C. *Violence and Exposure to HIV Among Sex Workers in Phnom Penh, Cambodia*. Washington, DC: US Agency for International Development; 2006. Available at http://www.researchforsexwork.org/downloads/Jenkins-CambodiaFinal.pdf.

sex workers respectfully or regard their input as worthy of notice.

The trial's formative research team convened the focus groups and community meetings that were recorded, transcribed, and translated into English as needed for the research staff. They also conducted at least 45 informal informational interviews with community contacts (NGO leaders, bilateral and multilateral agency officials, government officials, health care officials, HIV programme donors, etc.), and established contact with four different groups of sex worker advocates.

The formative research indicated that to be successful, the study needed to place much greater emphasis on communication with multiple communities than had occurred to date. The team hired a full-time community education coordinator and a bilingual Cambodian doctor knowledgeable of trial procedures, educational techniques, and Cambodian culture. The principal investigators also approved a Communication Outreach Plan developed by the staff, which included production of an informational description sheet about the study and frequently asked questions about the study in English and Khmer.

Despite these efforts, the local atmosphere by April 2004 was rife with rumour, misinformation, and unfounded assurances from various sources. WNU member Sok Chea reported that "[t]he NGOs also tried to spread information in their areas. They said to tell the sex workers to join the trial and, if you do, there will be no problems with side effects but you will get $3 per month". WNU member Soma Yu Norng recalls that she attended a meeting at a local NGO where the sex workers were told that tenofovir had no side effects and that the sex workers should not be afraid to participate in the trial because it was being conducted by WAC or Oxfam Hong Kong.[62] WAC staffer Phoung Phally Pry said that some sex workers even came to the WAC office to check on information they had been given suggesting that WAC was producing the medicines used in the trial.[63]

Kaldor reported that he was accused at an international meeting of encouraging sex workers not to use condoms during the trial. The researchers had proposed to make the trial protocol publicly available to help dispel some of the most inaccurate claims that were circulating about it, but the US National Institutes of Health did not allow them to do this.

Misinformation in the media also contributed to the general climate of confusion. In an analysis of media reporting following the Cambodian and Cameroonian trial closures, Mills et al. noted that the "validity of the media reports of these trials are highly variable"[64] and that "[i]n no case did any [reporter] report interviewing those supporting the trials and those against the trials".[65]

Some of the media coverage said that WNU members were demanding general health insurance coverage when, in fact, the WNU clearly stated that it sought long-term insurance to cover problems emerging specifically from use of the trial product.[66] This media distortion of their position as a demand for "health insurance for life" also effectively lent support to those who were characterising the WNU's demand as unreasonable or unethical.

Massimo Ghidinelli of the World Health Organisation, who took up his posting in Cambodia after trial preparations were stopped, reflected on the trial aftermath with the following: "Human health needs a clear dialogue between all parties involved. The weak point in this process was that there were too many people involved—insufficient and unclear dialogue between the parties meant that there was too much space for discussions elsewhere."

Resolving community disagreement

Whilst the trial had clearly made efforts to engage the community, there were problems with both the clarity of their communication and the processes used for it. The research team conversed with sex worker groups in numerous forums and received a range of opinions from them on what they saw as suitable conditions for trial participation. All sides agreed that differences of opinion existed on several issues, not just insurance. Other hot topics included the amount of money paid to participants and how the trial would deal with participants who fell pregnant or became ineligible to continue for other reasons.

Khao Ta gave the following illustration of the process: "At one meeting, they asked how much money would

62. Group interview with Women's Network for Unity members, 23 June 2006.

63. Interview with Phoung Phally Pry, 20 June 2006.

64. Mills E, Rachlis B, Wu P, et al. Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights*. 2005;5:6;doi:10.1186/1472-698X-5-6. Available at www.biomedcentral.com/1472-698X/5/6.

65. Ibid.

66. Women's Network for Unity. *Background to WNU Press Conference on Tenofovir Trials in Cambodia on March 29, 2004*. Available at http://wnu.womynsagenda.org/documents/wnu29mar04.pdf.

be enough. Some said $10 was enough. But the sex workers who had been at previous meetings and knew about the side effects said that even if you give us $10, it won't be enough."[67]

Whilst the intention to collect input from a range of community stakeholders was laudable, the process of holding meetings and focus groups in different places and with a variety of invited audiences severely limited the opportunity for continuity and consensus-building.

When the WNU started asking for insurance at various meetings and forums organised by the research team, trial staff said they were not empowered to discuss this, but agreed to find the answers and respond. Several stakeholders interviewed concurred that questions went unanswered and that they knew of no transparent mechanism for getting responses to questions that could not be answered at the meetings.

This led the WNU to think that the researchers were avoiding their questions and not taking them seriously. In fact, the researchers were undertaking efforts "behind the scenes" to resolve the insurance issue, but this was not clearly communicated, and thus, was neither recognised nor appreciated.

No designated neutral space existed in which to resolve differences or clear up misunderstandings. It is possible that the level of conflict might have been reduced if space and time had been consciously provided to enable the sex worker community—prior to engaging in the negotiation process—to discuss these issues and work toward its own consensus on whether it was willing to endorse trial participation.

When the government or health authorities in a proposed trial site are not in a position to create these community spaces, it is in the best interests of the research team to look for ways to create them (perhaps in collaboration with a trusted NGO) so this intra-community dialog can occur. Such spaces must be clearly independent of the team's community education and outreach efforts in order to function effectively as venues for community deliberations, and hopefully, consensus-building.

The implementation of regular CAG meetings prior to finalising the trial protocol (to better take community stakeholders' insights and concerns into account) also might have helped to pinpoint and clarify issues of concern before they became inflamed. It must be acknowledged, however, that building consensus is sometimes impossible in highly charged situations, even when such efforts are made.

Who speaks for whom?

Given the complexity and diversity of thought that exists in virtually all communities, however they are defined, the question of who speaks for "the community" is a difficult one.

After the WNU called its press conference, members of the research team responded by publicly questioning whether the WNU actually represented the views of the broader sex worker community. In the *Cambodia Daily*, Page Shafer was quoted as saying, "I think it is one sex worker group and there are many in Cambodia".[68]

The WNU is a legally registered, independent organisation that defines itself as the only sex worker-run representative body in Cambodia. With a membership of more than 5,000 in Phnom Penh and surrounding provinces, it is by far the largest of any group working with sex workers in Cambodia. It saw leadership on this issue as an essential part of its mandate.

Public questions also were raised as to whether the WNU was demanding insurance solely on behalf of Cambodian sex workers or because they were being influenced by WAC or other external groups. The same *Cambodia Daily* article states that "Page Shafer made it clear that she didn't believe the network [WNU] was the sole driving force behind WNU's insurance demands and implied that one should look to Oxfam Hong Kong [WAC] which supports the network for answers".[69] Page Shafer repeated this in an interview for this paper, stating that the WNU was effectively the same group as WAC. She also said that the concerns raised by the WNU suggest that they had decided to oppose the trial on principle.

The idea that WAC was controlling the WNU was offensive to both organisations for two reasons:

1. They felt it implied that because the sex workers were relatively uneducated, they could not have identified the concerns they raised on their own, but only with the direction and guidance of outside activists.
2. It also suggested that because the WNU chose to access external assistance, they were not capable of acting independently. As discussed above, the WNU accesses technical support and assistance

67. Group interview with Women's Network for Unity members, 23 June 2006.

68. Doyle K, Naren K. The slippery ethics of third world drug trials. *Cambodia Daily*. 7 May 2004.

69. Ibid.

as needed from WAC. Because of the Global AIDS Act Prostitution Pledge, WAC was the only NGO still working with the WNU. Since none of the WNU Secretariat reads or speaks English, WAC staff translated trial information and provided translation services for WNU members at meetings. At the WNU's request, WAC also prepared a workshop to brief WNU members. As Barbero put it, "Sex workers should know their rights. In this situation, when the WNU asked us questions about the trial, we didn't have answers, so we did some research on their behalf".[70]

Barbero added: "We saw our job as helping the sex workers to decide whether they wanted to be part of this process or not. We talked about questions that the sex workers could ask the researchers so that they could be armed with information. We made sure that a WNU representative went with WAC staff to any meetings. We have an enormous responsibility to the WNU, and we take that responsibility seriously. If we were to present biased information to them, then we would be failing in our obligation to work towards sex worker empowerment."[71]

In interviews conducted for this paper, some Phnom Penh sex workers said that they felt that the WNU had taken too strong a line in their trial advocacy. However, all the sex workers interviewed (both WNU members and those unaffiliated with the WNU) said that they would have demanded some mechanism for treatment of long-term side effects as a condition of their participation, in any event.

Hunter summarised the WNU members' decision to demand insurance—and the reaction within parts of the research community—as follows: "What the sex workers actually wanted was protection against the possible health consequences of side effects. Insurance was how this was expressed in their campaigning. The researchers refused to accept that Cambodian sex workers had the information, knowledge, and personal empowerment to sit down and negotiate as equals. They wouldn't accept that the sex workers might have agency as a group."[72]

The WNU had accessed the technical assistance they needed from a group prepared to provide it to them. That action resulted in public allegations that the WNU was not acting independently, but rather, was being manipulated by other activists and used as a pawn to carry out someone else's agenda.

Barbero reflected on the situation with the comment, "Those who hold the view that the WNU's reaction was masterminded by radical anti-corporate activists can't possibly have ever spoken to the WNU directly. They fall just short of saying that the sex workers are stupid, illiterate, and uneducated and that therefore it must have been western activists who controlled their agenda".[73]

The WNU was aware that tenofovir might represent an important defence against the spread of HIV and that completion of the trial was ultimately in the interests of their community and other communities worldwide. As Sou observed, "If this trial is ethical, if it is a good trial—for example, if the researchers really supported the sex workers—then we aren't against the experiment. It was because they didn't support us, that was why we decided to oppose the trial".[74]

Respect for persons is one of the three major principles on which biomedical ethics is based. It requires that in the absence of evidence of diminished capacity, people must be treated as autonomous agents capable of considered opinions and choices. Similarly, groups (such as potential trial participants) must be seen as having agency and the right to use it. The trial's only ethical means of preventing differences of opinion from becoming conflicts is to build relationships within the trial communities and respond to the issues that are raised by community members.

70. Interview with Rosanna Barbero, 21 June 2006.

71. Ibid.

72. Interview with Andrew Hunter, 28 June 2006.

73. Interview with Rosanna Barbero, 21 June 2006.

74. Interview with Sotheavy Sou, 21 June 2006.

V. Chain of events, part II (June–August 2004 and the aftermath)

On 15 June, the Women's Network for Unity (WNU) held another press conference reiterating the demand for insurance and calling for the trial preparation process to be "better and more honest,

with sex workers not pressured or given wrong information about the drug".[75] The WNU also wrote a letter to Cambodian Prime Minister Hun Sen outlining its concerns about the trial. No response to this letter was received.

The next day, about 12 WNU members were invited to a focus group conducted in Khmer, during which they discussed their concerns and issues. The focus group was recorded and the issues documented in English.[76] Sotheavy Sou and Sok Chea from the WNU report being told at this meeting that insurance for participants was out of the question, and that if the WNU did not let go of the demand for insurance, then they would be bypassed in the recruitment of participants for the trial.

At about the same time, staff of the Cambodian Ministry of Health National Centre for HIV/AIDS, Dermatology and STDs contacted other local nongovernmental organisations (NGOs) working with sex workers and requested that they bring sex worker representatives to a meeting to discuss the terms of participation in the trial.

The WNU responded by stating that if the research team failed to provide insurance for participants, they would boycott the trial.[77] WNU members continued to attend public meetings and discussions about the trial held by the research team or NGOs to present their perspective.

The research team had explored possible mechanisms for responding to the demand for insurance and had put in place a mechanism for providing lump-sum compensation to participants whose health was seriously affected by trial participation. The US National Institutes of Health (NIH), however, disallowed that part of the protocol.[78]

NIH funding guidelines allow (but do not require) the use of NIH funds to pay for medical liability (malpractice) insurance and medical insurance to treat participants experiencing trial-related adverse events.[79] This insurance coverage, however, must end when the trial ends. NIH policy prohibits the use of its funds to provide post-trial treatment or financial compensation for long-term injury.

US policy in this area has been described by some ethicists as contravening accepted ethical guidance. Writing on behalf of the Network of Chairs of Human Health Research Ethics Committees in South Africa, for example, Peter Cleaton-Jones noted in *The Lancet*[80] that the South African Government expects trial sponsors to purchase insurance to cover the cost of trial-related injuries. This policy, he argues, conforms to both the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (developed by the US Department of Health, Education, and Welfare in 1979 and commonly known as the Belmont Principles[81]) and the Council for International Organisations of Medical Sciences 2002 ethical guidelines on biomedical research involving human subjects.[82] It is also the policy of many countries, including South Africa[83,84] and, significantly, Cambodia.[85]

75. Women's Network for Unity protests drug trial recruitment tactics. WNU press statement; 15 June 2004. Available at http://www.wnu.womynsagenda.org/documents/wnu21june04.pdf.

76. Email communication from Margery Lazarus, 15 September 2008.

77. Rith S. Sex workers stand firm on Bill Gates drug trial. *Phnom Penh Post*. 18 June 2004.

78. Email communication from John Kaldor, 22 December 2008.

79. National Institutes of Health Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards. Subpart A: General—File 3 of 5. December 2003. Available at http://www.grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part6.htm.

80. Cleaton-Jones P. Research injury in clinical trials in South Africa. *The Lancet*. 2006;367(9509):458–9.

81. National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Belmont Report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. 18 April 1979. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

82. Council for International Organisations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, CH: World Health Organisation; 2002. Available at http://www.cioms.ch/frame_guidelines_nov_2002.htm.

83. *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa*. Pretoria, South Africa: South Africa Department of Health; 2000. Available at http://www.doh.gov.za/docs/policy/trials/trials_04.html.

84. Medical Research Council of South Africa. Book 1: General Principles, including research on children, vulnerable groups, international collaboration and epidemiology, Section 10.6.1. In: *Guidelines on Ethics for Medical Research: General Principle*. Cape Town, South Africa: Medical Research Council of South Africa; 2006. Available at http://www.sahealthinfo.org/ethics/ethicsmonitoring.htm.

85. Cambodia Ministry of Health. *Ethical Guidelines for Health Research Involving Human Subjects*. Phnom Penh, Cambodia: Cambodian Government; 2002.

In July, some WNU members attended the 2004 International AIDS Conference held in Bangkok. At the conference, they were introduced for the first time to Act Up Paris. With the support of Act Up Paris and members of other sex worker advocacy organisations, the WNU staged a highly visible protest on 14 July against Gilead Sciences (the manufacturer of tenofovir) during a Gilead-sponsored satellite session on antiretrovirals.

Trial preparation stops

On 3 August 2004, at the groundbreaking ceremony for a new hospital, Prime Minister Hun Sen made the following statement: "Cambodia is not a trash bin country.... They should not conduct experiments with Cambodians. They should do it with animals."[86,87,88]

In Cambodia's highly volatile political environment, the prime minister's public statement had immediate consequences. The prime minister's language left little room for government officials to negotiate for the trial to be continued. It also sent a strong message to other countries where tenofovir trials were being initiated. As Sou recalls, "We were negotiating with the researchers when the government said that the trial should be cancelled. When that happened, we didn't want to oppose the government. The prime minister is like our father; when he says something is not good for us, then we must agree with him".[89]

On 13 August, all work on the Cambodia trial stopped.

Exactly why Prime Minister Hun Sen decided to make this statement and cancel the trial is unknown. The WNU received no communication from anyone in government about it. Some have suggested that the prime minister was concerned by the level of international press attention on Cambodia's sex industry. Others have speculated that he was using the controversy surrounding the trial to take an action that disadvantaged political adversaries who had supported the trial.

The aftermath

The sudden halt of the Cambodian trial preparations caught much of the research world by surprise. To the field as a whole, it constituted an abrupt and frightening precedent that immediately raised the stakes of the ongoing debate around appropriate levels of community and civil society involvement in HIV prevention research. It also ratcheted up tensions in Cameroon, where participant enrolment in the pre-exposure prophylaxis (PrEP) trial had started. A larger crisis appeared to be imminent, and HIV prevention researchers were concerned about its possible implications for their own work. Act Up Paris agreed to refrain from further action on tenofovir until December 2004 in order to allow time and space for negotiations to address the issues on the table. But no such dialogues were convened until 2005.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) volunteered to convene a meeting of all parties to discuss the obvious conflicts, but the major stakeholders had differing views about what should be addressed and accomplished at such a meeting. As a result, the UNAIDS meeting took on the larger agenda of "partnerships in trials" instead of addressing the specific concerns at issue in the tenofovir PrEP trials. With a selected handful of researchers and activists, UNAIDS organised three regional consultations in early 2005 to gather materials that fed into their larger consultation in June.

UNAIDS was not perceived as a neutral broker in this process by the members of the WNU, who reported that Gita Sethi, Cambodia's UNAIDS country director, was publicly critical of the WNU's position on the trial. The WNU also cited UNAIDS' reluctance to cover the cost of adequate translation[90] at the June meeting as indicative of their lack of impartiality.

Many participants at the UNAIDS June meeting were disappointed by the lack of clear-cut results and forward progress. The most visible output of the meeting was that at the recommendation of the meeting participants, UNAIDS and the AIDS Vaccine Advocacy Coalition subsequently worked with a number of other organisations to develop guidelines for "Good Participatory Practice".[91] Presented as a living document, these guidelines were first published in November 2007 and are subject to ongoing development.

86. Purtill C, Samean Y. Hun Sen: don't test drugs on Cambodians. *Cambodia Daily*. 4 August 2004.

87. *Cambodian Prime Minister Joins the Push to Boycott Drug Trials*. 3 August 2004. Available at http://www.thebody.com/content/art27148.html.

88. Major HIV drug trial to be halted. *BBC News*. 14 August 2004. Available at http://newsvote.bbc.co.uk/mpapps/pagetools/print/news.bbc.co.uk/1/hi/health/3562704.stm.

89. Interview with Sotheavy Sou, 21 June 2006.

90. Email communication from Andrew Hunter, Policy Director, Asian Pacific Network of Sex Workers, 12 September 2008.

91. Joint United Nations Programme on HIV/AIDS and AIDS Vaccine Advocacy Coalition. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf.

Meanwhile, the International AIDS Society and the Bill & Melinda Gates Foundation decided that another meeting to address the specific issues raised by the Cambodia and Cameroon trials was needed. This meeting occurred in May 2005 and was judged by its organisers to have been very productive.[92]

In 2004 and 2005, advocates had hoped for—and called for—the rapid creation of multi-sectoral opportunities to discuss the concerns that led to the trial preparations being halted in Cambodia, and later, the trial in Cameroon being suspended and eventually closed. This demand was a point of consensus amongst advocates who had otherwise widely differing views on the actions that led to the trial closures.

Andrew Hunter, Policy Director for the Asia Pacific Network of Sex Workers (APNSW), for example, posted an analysis of the situation on a sex work blog on 9 September 2004 that described the closure as a "stunning victory of the Women's Network for Unity and…Cambodian AIDS activists (who happen to be organized sex workers)". But Hunter concluded, "We would also like to work with researchers, donors and ethicists to try to come up with some ethical standards and monitoring for such trials that will allow valid research to proceed without harming the interests of the trial participants. This must include listening to the voices of potential participants and addressing valid health concerns".[93]

Gregg Gonsalves of New York's Gay Men's Health Crisis strongly disagreed with Hunter's characterisation of the closure as a "victory"—countering that the real victory "would have been to be able to craft a solution to the local study". Nevertheless, looking to the future, Gonsalves echoed Hunter in reminding activists online that "[w]e have to wrestle with the nuts-and-bolts mechanisms to address access to care and prevention interventions (among other issues), confronting the compromises and ethical choices that have to be made in partnership with researchers and other stakeholders. If we have to fight our way to the table to take part in these discussions, so be it—THAT is the fight, and we should make sure that the voices from communities in which these trials are taking place are front-and-center".[94]

Almost a year elapsed between the closure of the Cambodia trial and the UNAIDS meeting in June 2005 that yielded a collective agreement on the need for widely accepted standards for "involving the community" in clinical trial planning and implementation. The International AIDS Society/Gates Foundation and the UNAIDS meetings in May and June of 2005 occurred too late to prevent the suspension of the Cameroon trial in January 2005. Key actors on all sides have described this as a period of missed opportunities.

The WNU, working with APNSW, subsequently developed a code of practice for researchers, entitled "How to Work with Sex Workers: Code of Practice for Research and Questions for Researchers".[95] This document is an important effort to clarify specific issues of concern to sex workers and prevent recurrences of the problems that arose in Cambodia.

The publication by UNAIDS of *Ethical Considerations in Biomedical HIV Prevention Trials* also represents significant progress.[96] But, clearly, more work is needed to develop a normative framework of procedures for HIV prevention trials that, by its implementation, will inspire confidence in trial host communities and researchers about how successful communication and collaboration around trial implementation occurs.

92. Halima Y. Summary Meeting Update on Stakeholders Consultation to Address Issues Related to Tenofovir Prophylactic Research. PowerPoint presentation, July 2005; Rio de Janeiro, Brazil.

93. Hunter A. *Cambodian Sex Worker Victory: Unethical Tenofovir Trial Halted*. Posted to sex-work@eforums.healthdev.org, 9 September 2004.

94. Gonsalves G. Listserv posting on healthdev.org listserv, 5 February 2005.

95. Asia Pacific Network of Sex Workers. How to Work with Sex Workers: Code of Practice for Research and Questions for Researchers. In: *Making Sex Work Safe in Asia and the Pacific* (pages 23–24). Available at http://apnsw.org/apnsw.htm.

96. Joint United Nations Programme on HIV/AIDS. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007 Available at http://data.unaids.org/pub/Manual/2007/jc1349_ethics_2_11_07_en.pdf.

VI. What do we learn from it all?

The events in Cambodia highlight the importance of giving careful attention to the medical, political, and social context of a proposed trial site, including the usual level of access to treatment and care

available to potential trial participants. They also highlight the critical importance of researchers listening to the input received from community members, participants, and other stakeholders, and addressing their trial-related concerns.

It is clear that the research team for the Cambodian tenofovir trial made some sincere efforts in this direction:

- They held meetings and forums to talk with sex worker groups and other nongovernmental stakeholders and collect their input on suitable conditions for trial participation.
- They formed both a community advisory group and an external advisory group (although these did not meet until almost a year into the process).
- In response to concerns raised by the Women's Network for Unity (WNU), they sought alternative options for providing compensation to participants whose health was seriously affected by trial participation when their original proposal for meeting this need was vetoed by the US National Institutes of Health.

It is equally clear that a community hosting a clinical trial needs to be in a position to collectively engage with information about the clinical trials process, decide whether to participate, assess the appropriateness of the terms for trial participation, and negotiate these terms if they so choose. The host community must then have the opportunity to provide their input and recommendations and see the trial design reshaped by these community discussions. The Phnom Penh sex worker advocacy groups and nongovernmental organisations (NGOs) serving sex workers made sincere efforts to do this in the following ways:

- Womyn's Agenda for Change (WAC) and the WNU collected background information on clinical trials and presented it in accessible forms to help answer questions being raised by their members.
- Several NGOs, including the WNU and WAC, attended meetings and focus groups to learn more about the trial and present their questions and concerns.
- Even after the public events of the Bangkok conference, negotiations between WNU representatives and the researchers that might have resolved the areas of disagreement continued until the prime minister's announcement on 3 August effectively halted trial preparations. Both sides felt that the possibility of reaching an acceptable solution still existed at that time.

The fact that the situation deteriorated despite all of these efforts requires us to ask what else research teams need to do in setting up clinical trials with host communities. The *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, developed jointly by the Joint United Nations Programme on HIV/AIDS and the AIDS Vaccine Advocacy Coalition through a highly consultative process, seek to "provide systematic guidance on the *roles and responsibilities* of entities funding and conducting biomedical HIV prevention trials towards participants and their communities" [emphasis added].[97] The scope of the guidelines, both in terms of the global process used to create them and the fact that they address the whole research lifecycle, illustrates the importance the field has attached to answering the question, "What else is needed?"

As the Good Participatory Practice Guidelines point out, investing the time and effort required to engage the trial host community "through genuine, transparent, meaningful participatory processes" is not only an ethical responsibility, but also a vital contributor to the quality of the research. The HIV prevention field's incorporation of this lesson (learnt the hard way through the closures of the Cambodia and Cameroon pre-exposure prophylaxis [PrEP] trials in 2004–2005) is already evident.

Engagement of the host community generally needs to start with basic "research literacy" education. That is, researchers have to ensure that a baseline level of information about clinical trials (e.g., What is a clinical trial? Why are they conducted? Who funds them?) exists in the host community *before* they start talking about the specific trial they want to conduct. Typically, community-based advocacy groups like the WNU take it upon themselves to gather information about new initiatives affecting their constituencies and relay it in easily comprehensible forms. These efforts not only

97. Joint United Nations Programme on HIV/AIDS and AIDS Vaccine Advocacy Coalition. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf.

help diverse populations to become well-informed but also contribute substantially to ensuring that the information, when transmitted, explicitly addresses the host community's particular interests and is both *actually* reliable and *perceived as* reliable. NGOs or community-based organisations that are peer-led play a critical role and are important stakeholders in the trial process.

One example of preparatory work having been done well is provided by the work of a US Centers for Disease Control and Prevention-funded research team in Botswana led by Dr. Dawn Smith and Kata Chillag. Starting in 2001, the team spent 15 months on formative research prior to initiating a microbicides trial. Their process "built gradually from (1) informal, open-ended conversations with a range of civil society stakeholders to (2) more focused discussions of specific questions (where the trial site should be located, what it should be called) to (3) focus groups and structured interviews to document, compare, and assess responses formally.... Only after this was completed did the trial move to hiring community liaisons, convening a community advisory board, developing a 'reference group' to engage governmental agencies in trial decisions, etc."[98]

This level of investment in community education and engagement was unprecedented. According to Smith, it resulted in a strong base of support for the trial across stakeholder groups that has withstood substantial challenges—including unforeseen changes in trial design and study products. The substantial up-front effort to build mutual understanding, trust, and community ownership of the research ultimately allowed the site to proceed efficiently despite ever-evolving circumstances.

The pace and funding levels at which research is currently conducted preclude most research networks from having either the time or the resources to engage in capacity-building activities for this length of time prior to starting trial recruitment. Nevertheless, building the host community's research literacy (usually from the ground up) is essential to ensuring its ability to engage effectively with the research process. Rethinking the pace of clinical trial site development is, therefore, an essential step toward recognising the importance of thorough community work, especially at the early stages. It is also time to identify feasible alternatives to expecting that all of the necessary capacity-building work can or should be done by clinical trial staff.

In its 2008 report, the Microbicide Development Strategy's Civil Society Working Group noted that basic research literacy training might be most appropriately provided in trial host communities by the local NGOs serving those communities—as they are best equipped to embed it in the context of the community's existing knowledge and attitudes. The Working Group recognised, however, that most local NGOs do not currently have sufficient knowledge or experience to do such training, and added that "very limited support is available through foundations and other funders for HIV prevention advocacy, much less for [this] kind of capacity-building and foundational work".[99]

This led them to strongly recommend that research institutions and donors contract with national and international civil society entities specialising in providing this kind of training—funding them to build the knowledge base and expertise of local NGO staff and then provide them with the ongoing support and technical assistance needed to relay and reinforce this information effectively to their constituencies. It is vital that the institutions providing this training are completely impartial. The content they deliver about trials must focus on building local understanding of the mechanics of HIV prevention research so that community members, themselves, can weigh the pros and cons of trial participation and effectively assess the terms of their involvement.

These locally delivered trainings should *precede* the trial staff's provision of trial-specific information. They would not replace the need for the community education provided by research entities during their formative research. Instead, they would bolster its effectiveness by giving communities the time and space to absorb general research concepts before being asked to learn about a particular trial. This "train the trainer" approach also could help to obviate the suspicion that information about clinical trials is automatically biased because it is provided by researchers. Whether accurately or not, NGOs are generally viewed as being more objective educators than are clinical staff who have an interest in enabling a trial to move forward.

Many trials and trial networks have made real efforts to engage community groups and potential and actual trial participants. However, it is challenging to determine where these activities fit into the many overlapping steps required for trial implementation—including drafting and revising trial protocols, raising funds, and preparing infrastructure in trial settings. What is clear, however, is the critical importance of initiating a thorough

98. Forbes A, Sylla L, Yassky R. *The First 55 Steps: A Report of the Microbicide Development Strategy's Civil Society Working Group* (page 13). Washington, DC: Global Campaign for Microbicides; 2008. Available at http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-FinalReportFeb2008.pdf.

99. Forbes A, Sylla L, Yassky R. *The First 55 Steps: A Report of the Microbicide Development Strategy's Civil Society Working Group* (page 32). Washington, DC: Global Campaign for Microbicides; 2008.

and ongoing community consultation process whilst the community's input can still be factored into the conceptualisation and design of the trial.

In October 2007, for example, the Microbicide Trials Network co-hosted an Advocates Consultation in Johannesburg, South Africa, to collect the input of advocates and community stakeholders for the protocol they were developing for the VOICE trial.[100] This decision by a major research network mounting a large-scale HIV prevention trial to put its protocol out for community input prior to completion of the drafting process (whilst there is still time to make substantive changes) indicates movement toward fuller realisation of the need for civil society engagement.

Conducting an HIV prevention trial with minimal or late-stage civil society input is no longer acceptable—nor is it generally regarded as a wise or efficient approach. The three examples above (the Good Participatory Practice Guidelines, the Botswana experience, and the VOICE trial's inclusive approach to protocol drafting) mark the leading edge of change and illustrate that substantial evolution in the field is occurring.

A number of other research institutions also are visibly adapting to these new standards by engaging a wider array of stakeholders earlier in the process and better preparing investigators to understand the necessity for, and appreciate the benefits of, this approach. The following section provides a listing of specific requirements for the field derived through examination of the Cambodia and Cameroon PrEP trial experiences as case studies. Other guidelines and recommendations for this approach are articulated in other documents,[101,102,103,104] and need not be reiterated in full here.

The harsh realities, as we all know, are these: high background HIV seroincidence is required to gather evidence of effectiveness ethically in large-scale HIV prevention trials. High background HIV seroincidence exists most commonly in developing countries. HIV prevention research, at present, is predominantly funded and undertaken by institutions based in developed countries. Thus, enormous cultural, social, and economic disparities generally exist between the trial staff, planners, and sponsors on the one hand and the trial host communities on the other.

In asking a community to participate in a trial, researchers and research institutions assume responsibility for addressing this disparity. This includes explicitly acknowledging the disproportionate power they hold, and implementing measures—throughout the trial preparation and implementation stages—to enhance the community's ability to negotiate with them on as even a footing as possible. In-depth cross-cultural communication is also essential to ensure participants' capacity to give truly informed consent.

Governments, trial sponsors, and other civil society stakeholders (both inside and outside of trial host communities) also shape the "on-the-ground" context in which potential participant communities and researchers encounter each other. If they choose to do so, these actors can help mitigate the power differential somewhat and assist in creating an atmosphere of greater equality for these negotiations. Even when this work is done as well as possible, however, it does not create full parity amongst the negotiating parties.

We conclude with the two lessons that have emerged vividly from this particular case study.

The first is that—beyond practicality, political expediency, and research security—the obligation of researchers to engage effectively with the trial participants and host communities is a human rights issue. Dialogue between the community members and researchers around trial information must be reciprocal. Potential participants have a right to negotiate terms that they believe to be fair for their participation and to hear directly from the research team about the ethical constraints, financial limitations, and other issues that affect these terms. Explicit spaces, time, and mechanisms must be created for these dialogues, and senior members of the research team with the authority to advance those negotiations must be present. As the entity coming into the community, the research team must accept responsibility for ensuring the establishment of clear and transparent processes for this to occur and for bringing in external, trusted "third parties" to mediate the terms

100. The VOICE Study—Vaginal and Oral Interventions to Control the Epidemic—is being conducted by the Microbicide Trials Network to evaluate two different approaches to HIV prevention for women. For more information, please see the *MTN-003 (VOICE) Backgrounder* fact sheet available online at http://www.mtnstopshiv.org/node/347.

101. Joint United Nations Programme on HIV/AIDS and AIDS Vaccine Advocacy Coalition. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf.

102. Forbes A, Sylla L, Yassky R. *The First 55 Steps: A Report of the Microbicide Development Strategy's Civil Society Working Group*. Washington, DC: Global Campaign for Microbicides; 2008. Available at http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-FinalReportFeb2008.pdf.

103. Joint United Nations Programme on HIV/AIDS/World Health Organisation. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf.

104. Irvin A, McGrory E. *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site*. Washington, DC: Global Campaign for Microbicides; 2009.

of participation when necessary. The involvement at any level of staff or decision-makers who cannot respect the trial participants and potential participants is insupportable, as are actions that deny—or can be seen to deny—their agency.

The second lesson is that mechanisms must be in place to ensure that communities have a general knowledge of clinical trials and access to processes that enable them to engage in well-informed discussion and negotiation about a specific trial. Communications strategies should be designed with the primary intent of building up a common understanding between researchers and communities, each of which may have sharply differing expectations and interpretations. These strategies must explicitly recognise that scientific language is not always the "right" way to talk about research and that a lower level of education does not, in any way, imply inability to comprehend and critique scientific processes.

Smith described the formative research phase of the Botswana trial as "learning to talk about the topic".[105] The labour-intensive work of developing if not a common understanding, at least a recognition of the differences in perception—and an ability to talk through such differences explicitly—is an essential basis for meaningful negotiation and comprehension. Thus, it must be the first work undertaken by a trial staff when entering a setting in which sharp financial and cultural disparities exist between the researchers and the trial host community.

No one wins when a trial is stopped for non-scientific reasons. But the only way to prevent this is to invest the time and resources needed to build the kind of mutual trust on which collaborative partnerships can be based.

105. Forbes A, Sylla L, Yassky R. *The First 55 Steps: A Report of the Microbicide Development Strategy's Civil Society Working Group* (page 13). Washington, DC: Global Campaign for Microbicides; 2008. Available at http://www.global-campaign.org/clientfiles/GCM-MDS-CSWG-FinalReportFeb2008.pdf.

VII. Requirements for future prevention trials

The following list of "requirements for future prevention trials" was originally developed to accompany *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site*, a case study

written for the Global Campaign for Microbicides by other authors. We are reprinting them here, with very slight modification, because we believe this is a useful statement of general principles and responds to many of the lessons that can be drawn from this case study. To see these "requirements" in their original form, please go to the Global Campaign for Microbicides website, www.global-campaign.org, and search on *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site*.

Study design and process

- Research protocols or other formal trial-related documents must include a clear rationale for selecting the trial site. Such documents can be important communication tools and ultimately serve to protect the trial and the researchers. Researchers and advocates should develop a joint process to develop guidelines for site selection that consider social and political factors as well as scientific ones.
- The urgency of HIV prevention research—as compelling as that may be—needs to be constantly disciplined by the false economy of proceeding too quickly. HIV prevention trials demand substantial and prolonged engagement with the community and national stakeholders prior to the initiation of a trial.
- Outreach efforts must go beyond the trial's immediate geographic setting and include both provincial and national stakeholders. Whilst important, formative research should not substitute for an open process of consultation that is recognised as linked to the trial.
- Trial processes should include an explicit "conflict resolution" plan and consider designating a community ombudsperson that can receive and elevate concerns.

Research culture

- Social science research and researchers must be accorded higher status within the structure of clinical trials, including shared authority in decision-making around protocol design. This is especially important in trials evaluating user-controlled interventions such as pre-exposure prophylaxis or microbicides because these trials in effect include behavioural components in addition to new technologies.
- Country-level researchers should be more centrally involved in designing trials as well as implementing them. This will allow the trial to draw on their knowledge of local realities and help rectify the historic power imbalance between Northern and Southern researchers.

Norms and standards

- Investment in building basic HIV and research literacy in communities where trials will be conducted is essential to ensuring community members' ability to engage effectively and equitably with the research process. Whilst no "one size fits all" process for this can be required, steps to build community understanding of the mechanics of HIV prevention research should precede the trial staff's provision of trial-specific information in order to give communities the time and space to absorb general research concepts before being asked to consider information about a particular trial.
- Researchers, advocates, and governments must forge a shared framework of expectations, accepted norms, and practical approaches to community involvement. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the AIDS Vaccine Advocacy Coalition, are a good first step in this direction. Efforts should continue to determine if these guidelines can be made normative for HIV prevention trials.
- International ethics bodies and researchers should develop guidelines specific to HIV prevention trials, such as standard of care for trial participants, approaches to risk reduction counselling, and the burden of proof of safety data needed to progress to efficacy testing. Important progress in this regard has been made with the publication by UNAIDS of *Ethical Considerations in Biomedical HIV Prevention Trials*.
- Operational guidance is needed within the community on treatment and long-term care for individuals who seroconvert during clinical trials.
- Governments must develop and enforce clear national guidelines on issues such as participant

remuneration, standard of care for trial participants and those screened out, community participation and other consultative processes, and post-trial access to products.

Research management

- Research networks and partnerships must anticipate and plan for "adverse political events" as routinely and concretely as they do now for adverse clinical events. This includes proactive communications planning and investment in mechanisms to build relationships with local allies.
- Onsite researchers and staff need to develop communication skills, as well as in-depth understanding of the rationale, design, and implementation approaches of the trial. Trials need to clearly articulate what entities and individuals are ultimately responsible for what.
- Trials need a specified process and mechanism for handling questions, inquiries, and complaints—ideally, a highly informed neutral actor well-armed with facts, documentation, and access; for example, a community advisory board, an ombudsperson, or a community liaison.
- Provisions must be made for post-trial access to products and interventions by trial participants, communities, and host countries; for example, preferential pricing, registering the drug in the host country, and determining who is responsible for delivering and following up on what to whom.

Communication and language

- Skilled communications professionals as well as the researchers themselves should proactively reach out to civil society, medical professionals, and the national and international media on the rationale, plans, and progress of trials.
- Challenges, difficulties, and setbacks should be dealt with in an honest and straightforward way. Responsiveness and respect should infuse all communication.

Advocacy and activism

- Activists should work toward devising clear goals and using strategies that correspond with those goals. Certain strategy choices, such as going to the press or staging public protests, are effective tools that have led to many important scientific, health, and human rights gains. These strategies also can be difficult to control or have unintended consequences that need to be considered in taking on this course of action.
- Advocates need to judge themselves and each other by the accuracy of their facts. Advocates as well as researchers should be held accountable to standards of evidence and responsible behaviour.
- Advocates should caution themselves and each other against overstated claims to represent constituencies such as "the community" or "women" without a clear basis for such assertions.

Annex 1. Timeline of Oral Tenofovir Trial: Cambodia

2000	**June :** Women's Network for Unity (WNU) established
2001	**26 October:** US Food and Drug Administration (FDA) approves tenofovir for treating people living with HIV/AIDS
	27 November: Bill & Melinda Gates Foundation holds ethical consultation on Family Health International proposal to test oral tenofovir in Phase 3 trials in four countries, including Cambodia
2002	**8 July:** WNU celebrates second anniversary with public support from at least one Cambodian parliamentarian
	28 October: Gates Foundation approves US$6.5 million grant for multi-national trials to evaluate the safety and efficacy of tenofovir for reducing the risk of HIV infection in high-risk sexually active adults
	2 December: At the request of Global Campaign for Microbicides Director, Lori Heise, Family Health International sends out memo on how they responded to recommendations of 2001 ethical consultation
	December: Gilead Sciences announces its "Access Tenofovir" programme to make tenofovir available at nonprofit cost, if effective, in 68 developing countries
2003	**January:** Dr. Kimberly Page Shafer, of the University of California, San Francisco, and Dr. John Kaldor, of the University of New South Wales, agree to collaborate on Cambodia trial
	20–24 January: University of California, San Francisco, provides a one-week training, "Ethical Issues in Research: Human Subjects", attended by Ministry of Health stakeholders, Cambodian Ethical Review Board members, nongovernmental groups, and some sex workers
	28 February: University of California, San Francisco, Committee on Human Research Institutional Review Board approves protocol (Year 1)
	Early 2003: US National Institutes of Health approves funding for the University of California, San Francisco, to conduct pre-exposure prophylaxis trial proposed by Page Shafer
	March: Preliminary trial protocol (Year 1) is submitted to the Cambodian Ethical Review Board
	Early 2003: Trial staff start meeting with stakeholders, including Womyn's Agenda for Change (WAC) and other nongovernmental organisations (NGOs) with sex worker programmes, which inspires WAC to start gathering information on clinical trials and potential impacts on participants
	May: US Congress passes the Global AIDS Act, including "Prostitution Pledge" language
	1 July: Cambodian Ethical Review Board approves preliminary protocol (Year 1)
	July: Kaldor and Page Shafer sign memorandum of understanding with Cambodian Ministry of Health to conduct joint research and develop protocols for the trial
	23 July: Trial staff hold first community information session about the trial
	3 August: FDA posts letter online regarding Gilead's promotion of tenofovir, noting that they had "minimized important risk information" and had been "previously warned not to engage in such activities"
	1 September: Formative research team starts mapping, focus group work, and key informant interviews with sex workers and other members of the community
	31 October: University of New South Wales Institutional Review Board approves Year 1 trial plan

2004	**Early 2004:** WAC provides workshop on research case studies to WNU members, and members decide to focus advocacy around insurance demand
	15 January: Cambodian Ministry of Health National Centre for HIV/AIDS, Dermatology and STDs convenes first meeting of its External Advisory Board comprised of key government departments and international organisations, including the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO)
	February: Dr. Carol Jenkins (of the study on violence and HIV risk amongst sex workers in Phnom Penh) provides two-week training on research ethics and participatory research methods to 33 sex workers who become peer interviewers collecting data for the study
	4 March: Trial staff hold second Cambodia Community Advisory Forum
	March–May: Qualitative and quantitative data are collected from 1,000 sex workers for Jenkins study
	23 March: First meeting of 13-member community advisory group is convened for trial, comprised of representatives of local health NGOs, NGOs serving sex workers, multilateral and bilateral agencies, government health agencies, and one unaffiliated sex worker
	29 March: First WNU press conference is held
	14 May: Second meeting of community advisory group is held
	15 June: WNU holds second press conference criticising the trial
	24 June: Second Cambodia External Advisory Board meeting is held
	11–16 July: XV International AIDS Conference is held in Bangkok
	14 July: WNU, the Asia Pacific Network of Sex Workers (APNSW), and Act Up Paris stage protest at Gilead's symposium at the AIDS conference
	16 July: APNSW and Act Up Paris publish press release denouncing the tenofovir trials
	3 August: Cambodian Prime Minister Hun Sen makes public comments about trial in which he states that "Cambodia is not a trash bin country"
	13 August: Trial preparations stop
	29 September: Conference call takes place amongst AIDS, sex worker, and microbicides NGO activists and advocates about their issues with the trial
	25 October: Conference call of donors, researchers, and activists takes place regarding the issues with the trial
2005	**January:** Cameroon tenofovir trial is cancelled, also for political reasons
	Early 2005: UNAIDS organises three regional consultations to gather materials to inform agenda of larger meeting in June
	19–20 May: International AIDS Society and the Gates Foundation hold meeting to address the specific issues raised by the Cambodia and Cameroon trials
	20–21 June: UNAIDS convenes consultation to discuss the larger agenda of "partnerships in trials"
	June: APNSW publishes *Making Sex Work Safe in Asia and the Pacific*, which includes "How to Work with Sex Workers: Code of Practice for Research and Questions for Researchers"
2007	**July:** UNAIDS/WHO publishes *Ethical Considerations in Biomedical HIV Prevention Trials*
	November: UNAIDS and the AIDS Vaccine Advocacy Coalition publish guidelines for "Good Participatory Practice", developed at the recommendation of the UNAIDS 2005 consultation

Annex 2. People Interviewed for the Cambodia Tenofovir Pre-exposure Prophylaxis Trial Case Study

Organisational affiliations stated were as of 2004, not necessarily as of the date of this printing.

Individual interviews:

Anonymous representative, nongovernmental organisation (NGO) 1*

Anonymous representative, NGO 2*

Anonymous representative, NGO 3*

Anonymous representative, NGO 4*

Rosanna Barbero, Womyn's Agenda for Change

Sok Chea, Women's Network for Unity member

Frédéric Bourdier, Institute de recherche pour le developpment Cambodia

Melissa Hope Ditmore, Network of Sex Work Projects

Massimo Ghidinelli, World Health Organisation

Andrew Hunter, Asia Pacific Network of Sex Workers

John Kaldor, University of New South Wales

Margery Lazarus, University of California, San Francisco

Soma Yu Norng, Women's Network for Unity Secretariat

Kimberly Page Shafer, University of California, San Francisco

Phoung Phally Pry, Women's Network for Unity member

Supriya Pillai, PSI/Cambodia

Sotheavy Sou, Women's Network for Unity Secretariat

Khao Ta, Women's Network for Unity Secretariat

Maurits Van Pelt, MoPoTsyo Patient Information Centre

Group interviews:

Pra Yu Vorng, Sam Sothi Ratana, Prak Nak, and Heang Srey Pouu, Sex Worker Programme members, Urban Sectors Group

Women's Network for Unity members (regular members who comprise the public face of the network, not members of the Secretariat; they requested not to be identified by name)

* These four NGOs operate sex worker programmes in Phnom Penh. They agreed to be interviewed for this paper only on the condition of anonymity, stating that they were concerned about jeopardising their funding from the US Agency for International Development (see "The political climate for Cambodian sex workers in 2003".

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