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# THE TRIALS OF TENOFOVIR: Mediating the Ethics of Third World Research

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In 2004, Phnom Penh was on the front lines of debates over HIV research. Press coverage pitted the demands of a tenacious union of sex workers against the good intentions of international researchers funded, in part, by the Bill and Melinda Gates Foundation. The headlines reveal part of the story: “Key AIDS Study in Cambodia Now in Jeopardy.”<sup>1</sup> “Cambodia Stops Important Tenofovir Prevention Trial.”<sup>2</sup> “Hun Sen: Don’t Test Drugs on Cambodians.”<sup>3</sup> “Cambodian Leader Throws Novel Prevention Trial into Limbo.”<sup>4</sup> The drug at issue was tenofovir, a newer anti-retroviral commonly used to treat HIV infection. The research question was whether the drug could be used as an effective pre-exposure prophylaxis in high risk groups, such as commercial sex workers. The stakes are undeniably high. With a vaccine against HIV/AIDS still decades away,<sup>5</sup> attention must focus on intermediate strategies to slow the transmission of the disease, including pre-exposure prophylaxis.<sup>6</sup> Literally, tens of millions of lives hang in the balance.

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1 Marilyn Chase & Gautam Naik, *Key AIDS Study in Cambodia Now in Jeopardy*, WALL ST. J., Aug. 12, 2004, at B1.

2 John S. James, *Cambodia Stops Important Tenofovir Prevention Trial*, AIDS TREATMENT NEWS, July 23, 2004, at 4.

3 Corinne Purtill & Yun Samean, *Hun Sen: Don’t Test Drugs on Cambodians*, CAMBODIA DAILY, Aug. 4, 2004, at 1.

4 Jon Cohen, *Cambodian Leader Throws Novel Prevention Trial into Limbo*, 305 SCIENCE 1092 (2004).

5 The World Health Organization (WHO) notes that although “more than 30 candidate HIV vaccines” are in the pipeline, none is expected to be available for use in the immediate future. WORLD HEALTH ORG. [WHO], THE WORLD HEALTH REPORT 2004: CHANGING HISTORY, at xvi (2004) [hereinafter WHO, WORLD HEALTH REPORT], available at [http://www.who.int/whr/2004/en/report04\\_en.pdf](http://www.who.int/whr/2004/en/report04_en.pdf).

6 For a discussion of the importance of intermediate preventative measure, see Project Inform, *The World’s Most Important AIDS Research?*, PROJECT INFORM PERSP., Nov. 2004, <http://www.thebody.com/pinf/nov04/research.html>.

While the imperative for action is strong, so is the demand that medical research be undertaken in an ethical manner. The ethical problems raised by human experiments are complicated. They become even more complicated when the research subjects are vulnerable populations in an already resource-poor developing country. Exploitation is an ever-present risk. Safeguards must be in place to prevent the exportation of research to the Third World that would not meet basic ethical standards. This was not the problem in Cambodia. Instead, the Cambodian story illustrates the growing inability of First World medical ethics to address the demands of international research. The unfortunate result was that a well intentioned and well designed research proposal reached an impasse that led to its cancellation. How did two groups that should be allies in the battle against HIV/AIDS—sex workers and medical researchers—become pitted against each other as adversaries? It is important to understand what went wrong in Cambodia so similar problems can be avoided in the future.

This article proposes mediation as a framework to address the social and ethical tensions associated with Third World medical research. Section I examines the science behind the tenofovir trials, explaining the rationale for the study design and the logic for focusing on high risk populations. Section II details the social and political trials of tenofovir, looking at the conflicts culminating in the study's cancellation. Section III explores how the scientific and social concerns might be better mediated in light of emerging ethical principles guiding international research.

## **I The HIV/AIDS Crisis and the Science Underlying the Tenofovir Trials**

### **A. The HIV Crisis and the Importance of Prevention**

In discussing HIV/AIDS, a sense of urgency is unavoidable. As the World Health Organization (WHO) declares, “[t]ackling HIV/AIDS is the world’s most urgent public health challenge.”<sup>7</sup> HIV/AIDS is responsible for more than 20 million deaths in the last quarter century,<sup>8</sup> with five million new infections in 2003 alone.<sup>9</sup> “HIV/AIDS is now the leading cause of death and lost years of productive life for adults aged 15–59 years worldwide.”<sup>10</sup> While each new HIV infection is a tragedy for an individual and a family, the ravages of the virus go beyond its effects on personal health. “In many countries, the cumulative effects of the epidemic will have catastrophic consequences for long-term economic growth and seriously damage the prospects for poverty reduction.”<sup>11</sup> In addition, HIV infection promotes the spread of other communicable diseases, such as tuberculosis, to the

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7 WHO, WORLD HEALTH REPORT, *supra* note 5, at xi.

8 *Id.*

9 *Id.*

10 *Id.*

11 *Id.* at 9.

population as a whole. This places great stress on public health systems that are already overwhelmed and underfunded.

One-fifth of the 34–46 million people living with HIV/AIDS worldwide are in Asia.<sup>12</sup> In Cambodia, estimates are that more than 1% of the adult population is infected with the virus that causes AIDS.<sup>13</sup> These figures highlight the need for thoughtful, creative and immediate action to diminish the spread of the virus. Appropriate interventions can make a difference, as the WHO reports. “Together, prevention, treatment and long-term care and support can reverse the seemingly inexorable progress of the HIV/AIDS epidemic, offering the worst-affected countries and populations their best hope of survival.”<sup>14</sup> Cambodia has made important progress in implementing a number of HIV prevention measures among sex workers. “In response to these programs, condom use between sex workers and clients rose to more than 90% and the number of men visiting sex workers was halved.”<sup>15</sup> It is estimated that these efforts have reduced HIV prevalence in the general population from predictions of 10–15% down to current projections as low as of 2–3%.<sup>16</sup> HIV prevalence among female sex workers is much higher, but even these numbers have been substantially reduced. A 1998 sentinel surveillance study found an HIV prevalence rate in sex workers of 42.6%, falling to 28.8% by 2002.<sup>17</sup>

Prevention is important, but there are serious limitations to traditional “safer sex” approaches. In many cases, as Sheila Davey found, “sex workers are unable to insist on condom use, especially if they are young, victims of trafficking, or migrants.”<sup>18</sup> In addition to encouraging condom use, prevention alternatives that empower women and bypass male involvement must also be developed. Approaches that can be controlled by the female partner, such as microbicides, or “anti-infective gels, creams, impregnated sponges and similar devices that women apply before sexual intercourse to prevent HIV transmission”<sup>19</sup> are particularly important. According to the WHO:

Epidemiological modeling based on the data from over 70 low-income countries suggests that even a partially effective microbicide is likely to have a significant impact on the epidemic: a product that is only 60% effective in protecting against HIV could avert 2.5 million new infections over a three-year period, even if it is used in only 50% of sex acts not protected by condoms, and assuming it is used by only 20% of people easily reached by existing health services.<sup>20</sup>

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12 *Id.* at xv.

13 *Id.* at 3.

14 *Id.* at xv.

15 *Id.* at 13.

16 *Id.* at 12. See also Jon Cohen, *Thailand & Cambodia: Two Hard Hit Countries Offer Rare Success Stories*, 301 SCIENCE 1658 (2003).

17 Cohen, *supra* note 16, at 1659.

18 Sheila Davey, *Sex and Drugs Fuel Simmering AIDS Crisis in Asia and Pacific*, 79 BULL. WORLD HEALTH ORG. 1000 (2001).

19 WHO, WORLD HEALTH REPORT, *supra* note 5, at 77.

20 *Id.*

Unfortunately, the use of microbicides is not without its own problems. Because waiting time is necessary between insertion and intercourse, they could cause irritation with frequent use, which may actually increase the probability of HIV transmission per sex act. Moreover, like vaccines, microbial agents are themselves still in clinical trials.

## B. Tenofovir as an HIV Prophylaxis

Other preventative strategies can give women greater control over their risk exposure. Anti-retroviral drugs are known to be effective in controlling HIV for persons already infected. Is it possible that antiviral treatment could reduce the risk of HIV transmission if taken before exposure to the virus as a form of prophylaxis? This is where the tenofovir story begins. Tenofovir is a long acting anti-retroviral drug of the reverse transcriptase inhibitor class that can be given once daily, with fewer side effects than many older agents. In a landmark study, scientists discovered that tenofovir given shortly after exposing monkeys to SIV, a simian virus similar to HIV, could prevent the monkeys from becoming infected.<sup>21</sup> This finding supported the theory that tenofovir could be used as a post-exposure prophylaxis for humans, and possibly as pre-exposure prophylaxis in high risk HIV-negative populations in order to prevent infection.

Substantial experience already exists with anti-retrovirals as post-exposure prophylaxis. In previous studies, the Centers for Disease Control and Prevention (CDC) determined that an older drug zidovudine (AZT) could reduce by 79% the risk of health care worker seroconversion after an occupational exposure to HIV, such as a needlestick.<sup>22</sup> Subsequently, the CDC recommended that health care workers sustaining exposures should receive prophylaxis with anti-retrovirals. The CDC monitors health care workers undergoing post-exposure prophylaxis. Although minor side effects such as nausea and fatigue are common, serious or lethal side effects are not.<sup>23</sup> The regimens in the CDC study included anti-retroviral cocktails of multiple classes of drugs,<sup>24</sup> increasing the potential for side effects above that of a single drug such as tenofovir. Moreover, with regard to potential side effects, tenofovir's safety profile is significantly more favorable than many of its treatment predecessors. Listed side effects for tenofovir include "nausea, vomiting, diarrhea, headache, asthenia, flatulence, and renal

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21 Roberta J. Black, *Animal Studies of Prophylaxis*, AM. J. MED., May 19, 1997, at 39. See also Che-Chung Tsai et al., *Effectiveness of Postinoculation (R)-9-(2-Phosphonylmethoxypropyl) Adenine Treatment for Prevention of Persistent Simian Immunodeficiency Virus Infection Depends Critically on Timing of Initiation and Duration of Treatment*, 72 J. VIROLOGY 4265 (1998).

22 Denise Cardo et al., *A Case-Control Study of HIV Seroconversion in Health Care Workers After Percutaneous Exposure*, 337 NEW ENG. J. MED. 1485 (1997).

23 Ctrs. for Disease Control & Prevention, U.S. Dep't of Health & Human Servs., *Anti-retroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services*, 54 MORBIDITY & MORTALITY WKLY. REP. 1, 4 (2005) [hereinafter CDC, *Postexposure Prophylaxis Report*].

24 *Id.*

impairment.”<sup>25</sup> In all but a few cases, side effects of anti-retrovirals are reversible once the drug is discontinued,<sup>26</sup> so the likelihood of permanent study drug-related side effects in this setting is remote.

If anti-retroviral drugs are effective as post-exposure prophylaxis, could their use be extended to certain high risk groups in a pre-exposure setting? Tenofovir is a good candidate for such a test. It has fewer side effects than other anti-retrovirals and can be taken in a once-daily dose. Researchers at the University of California at San Francisco (UCSF) and the University of New South Wales (UNSW) proposed to offer “960 HIV-uninfected female sex workers . . . either 300 mg of tenofovir or placebo daily for 1 year”<sup>27</sup>. The researchers would then assess, by comparing the two groups, whether tenofovir is effective as prophylaxis. Potential subjects would be tested upon enrolment to determine their HIV status. HIV-positive women would be screened out of the study at the beginning. Study participants would then be randomly assigned either to the tenofovir arm of the study and be given a daily dose of the drug for the following year, or to the placebo arm and be given a daily “sugar pill”. Neither the women nor the researchers would know who was receiving tenofovir and who was receiving the placebo. “At the beginning and once a month during the trial, study subjects will receive counseling to reduce risky behavior, free condoms, and free screening and treatment for sexually transmitted diseases.”<sup>28</sup> The experiences of patients receiving tenofovir versus those receiving placebo would be compared to assess safety and side effects. The United States National Institute of Allergy and Infectious Diseases (NIAID) and the Bill and Melinda Gates Foundation funded the study. The research was to be conducted in collaboration with the Kingdom of Cambodia Ministry of Health.

Studies of pre-exposure and post-exposure prophylaxis raise different ethical and medical questions. Risk of actual HIV exposure is typically higher in the post-exposure scenario. The course of post-exposure prophylactic treatment is relatively short, making side effects less likely. Moreover, alternatives such as behavioral change are not available in the post-exposure setting. In contrast, in the pre-exposure setting, the course of treatment can be much longer, with the drug potentially being taken for an indefinite period. This increases the risk of side effects. Counseling for behavior change may be an appropriate alternative in the pre-exposure setting. Similarly, the possibility that the pre-exposure prophylaxis might actually increase risky behavior must be seriously considered. In the end, whether the individual benefits of pre-exposure prophylaxis outweigh the

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25 *Id.* at 10.

26 *Id.* at 4.

27 Khabir Ahmad, *Trial of Anti-retroviral for HIV Prevention on Hold*, 4 LANCET INFECTIOUS DISEASES 597, 597 (2004).

28 *AIDS Prevention: Study Will Test Anti-retroviral Drug Tenofovir to Prevent HIV Infection*, DRUG WK., Oct. 10, 2003, at 9.

individual risks depends critically on the individual's level of likely HIV exposure. How high is the individual's high risk group?

HIV transmission rates affect individual cost benefit analysis. They also have important implications for study design. HIV transmission typically occurs through the exchange of blood and other bodily fluids during sexual intercourse. Despite the large numbers affected worldwide, the transmission risk from a single sexual encounter is low. The CDC estimates that the transmission rate for receptive penile-vaginal intercourse is one transmission per 1,000 acts and the risk for receptive anal intercourse is slightly higher—five transmissions per 1,000 acts.<sup>29</sup> This low sexual transmission rate raises challenges for scientific studies of preventative measures. With low transmission rates, studies must examine very large population groups, examine outcomes over a long period, or focus on high risk groups in order to determine statistically whether the proposed intervention is effective. A study design targeting high risk groups, such as sex workers, men who have sex with men or injection drug users is likely to be less costly and to generate statistically significant results in a shorter time.

These higher risk categories, however, also correspond to vulnerable social groups. While the economic and statistical desire to focus on high risk groups is understandable, testing the preventative efficacy of tenofovir on a group like Cambodian sex workers raises important ethical concerns. What medical treatment will be provided study participants for possible side effects of the drug during and after the study? What will happen to the women screened out at the beginning who learn for the first time that they are HIV-positive? What will happen to the women in either the tenofovir or placebo arm who become HIV-positive during the course of the study? Could participation in the study lead participants to engage in more risky behavior, a particularly important question for those in the placebo arm? Can one effectively recruit research subjects and obtain meaningful informed consent in a vulnerable population, such as Cambodian sex workers, where cultural, language, and socio-economic factors differ so dramatically from those applying to the people conducting the research?

## II The Social and Political Trials of Tenofovir

The Cambodian Women's Network for Unity (WNU) was at the center of the tenofovir dispute. Understanding the history and mission of the organization helps place the tenofovir controversy in perspective. WNU describes itself as a "grassroots representative collective of Phnom Penh based Sex Workers. The network seeks to promote the rights of Sex Workers to earn a living in a safe environment, free from exploitation and social stigma."<sup>30</sup> The organization was founded in 2000 and is reported

29 CDC, *Postexposure Prophylaxis Report*, *supra* note 23, at 7.

30 This background information is taken from the organization's website. Women's Network for Unity Home Page, <http://www.womynsagenda.org/Program/SWs/SWNU.html>

to have approximately 5,000 members. Notions of individual and group empowerment are central organizational themes. While the specter of HIV is ever present in the lives of Cambodian sex workers, there are dangers far more immediate, such as daily threats of violence and abuse from clients, the police and brothel owners.

Groups like WNU are on the front lines of efforts to improve condom use and introduce safer sexual practices. As WNU reports, demanding safer sexual practices begins with building the individual self esteem of its members:

The network has made significant achievements since its inception in 2000—sex workers have improved their attitudes to healthcare and approaches to HIV/AIDS prevention; improved their client negotiation skills; gained the courage to speak out about their problems; engaged in information sharing from workshops on HIV/AIDS and sex worker rights with their friends and peers. Together they have achieved solidarity and the collective strength that comes from one voice. They have an understanding of the value of their lives, and the importance of HIV/AIDS prevention.<sup>31</sup>

Preventative measures such as the promotion of condom use have been very effective in bringing down rates of HIV infection in Cambodia.<sup>32</sup> The participation of groups like WNU is central to the success of these efforts.

Exploitation is a daily fact of life for marginal groups in Cambodia. Trust is difficult to earn and skepticism is a necessary trait for survival. When rumors first started circulating about proposed medical research targeting Cambodian sex workers, the sex workers naturally turned to WNU. WNU adopted a proactive role. They pursued a negotiating position that sought to protect the rights and dignity of the sex workers as potential research subjects. WNU's specific concerns are outlined in a background statement issued in conjunction with a March 29, 2004 press conference.<sup>33</sup> These concerns reflect a sophisticated understanding of international ethical standards governing medical research in developing countries.

The WNU Statement raises three substantive concerns and two procedural objections. The substantive concerns will be addressed first. WNU was concerned about (1) the availability of medical treatment for side effects, both during and after the study period; (2) the access to tenofovir as a prophylaxis for sex workers in the future if the study proved the drug's efficacy in preventing HIV infection; and (3) the danger that the study may encourage higher risk practices, particularly for those in the placebo control group. While not specifically raised in the Statement,

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(last visited Oct. 7, 2005).

<sup>31</sup> *Id.*

<sup>32</sup> For a discussion of Cambodia's success in improving safe sex practices and reducing HIV transmission amongst sex workers, see *supra* notes 15-17 and accompanying text.

<sup>33</sup> Women's Network for Unity, Background to WNU Press Conference on Tenofovir Trials in Cambodia on March 29, 2004, <http://www.womynsagenda.org/Program/SWs/WNU/wnu29mar04.pdf> [hereinafter WNU Background Statement].



a natural concern also existed for the women who would be screened out of the study after learning that they are HIV positive and the women who become HIV positive during the course of the trials. As of 2004, access to anti-retroviral treatments in Cambodia for those infected with HIV was minimal to non-existent.<sup>34</sup>

Most media attention focused on WNU's demand for continuing medical coverage for potential adverse side effects. In the press, this was often portrayed as a demand for lifetime insurance, suggesting either the unreasonableness or the naïveté of the sex workers. This is not correct. The WNU demand for long term medical guarantees was limited to study-related side effects.

The Network wants insurance against possible side effects of Tenofovir for 30 years or more and not just health care for the duration of the trial. When the researchers are finished and leave Cambodia who will take responsibility for sex workers and their families who may be suffering longer term side effects?"<sup>35</sup>

The WNU demand resonates with ethical standards designed to govern international clinical research. CIOMS Guideline 19 addressing the "Right of injured subjects to treatment and compensation," provides as follows:

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.<sup>36</sup>

The ethical norm is clear: Researchers should be responsible for study-related side effects.

WNU's demands for insurance reveal a deeper psychological concern and underscore a basic breakdown in communication with study researchers. A demand for insurance is reflective of underlying conditions of uncertainty. There are ways to address uncertainty other than through the provision of insurance, such as providing credible information regarding the risks of future side effects. The WNU Statement reflects an incomplete understanding of the actual risk of side effects. It correctly notes that tenofovir as pre-exposure prophylaxis has only been tested in animals and

34 Hopefully, HIV therapies will be more widely available in the future. See WHO, "3 BY 5" PROGRESS REPORT 19 (2004), available at <http://www.who.int/3by5/ProgressReportfinal.pdf> (discussing efforts to increase availability of aviretroviral treatments in Cambodia).

35 WNU Background Statement, *supra* note 33.

36 See COUNCIL FOR INT'L ORGS. OF MED. SCIS., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, Guideline 19 (2002) [hereinafter CIOMS, Guidelines], available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm). See also World Med. Ass'n [WMA], *World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects*, princ. 29 (2004) [hereinafter WMA, *Declaration of Helsinki*], available at <http://www.wma.net/e/policy/pdf/17c.pdf>.

that the drug has not been tested on HIV-negative humans.<sup>37</sup> Similarly, the Statement correctly notes the known side effects of the drug, ranging from “diarrhea, nausea, [and] weakness to major liver and kidney failure and ‘brittle bone’ disease.”<sup>38</sup> Not acknowledged, however, is the fact that there is substantial clinical experience with tenofovir in HIV-positive persons and with post-exposure prophylaxis. The likelihood and severity of tenofovir’s side effects are known with some degree of certainty.

Recognizing this, the researchers likely felt that the chance of long term side effects was remote and, therefore, that insurance was not necessary. The question, however, is how could this sentiment be credibly conveyed to the women of WNU? In business, sellers with superior information will often extend warranties (a form of insurance) to convey their assurances of product safety and reliability. In the presence of asymmetric information, sellers who are unwilling to warrant their goods are rightly met with skepticism. From this perspective, the WNU demand for insurance for future side effects actually functioned as a test of the researchers’ veracity. WNU asked “If the researchers are so sure that this drug is safe for HIV-women to take, in the short and long term, why don’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.”<sup>39</sup>

This reasoning is sound from an economic perspective, but it is also a classic form of Cambodian logic—reasoning in the form of a question. If one focuses only on the question or the demand, one misses the basis of what is often a persuasive argument.<sup>40</sup> Dismissing the demand for insurance without providing credible alternative mechanisms to convey the actual likelihood of future risks simply added to WNU skepticism and distrust.

WNU’s second substantive demand was for access to tenofovir after the study, if the drug proved to be effective at preventing HIV infection.

If 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 to our future lives and 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.<sup>41</sup>

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37 WNU Background Statement, *supra* note 33.

38 *Id.*

39 *Id.* (quoting Kao Tha, President of Women’s Network for Unity).

40 A similar example of Cambodian logic can be found in the Press Release accompanying WNU’s June 15, 2004 Press Conference: “If they are so sure this drug is safe, why don’t they send their own sisters and daughters to test it? They have a lot more money than sex workers and have protection if the drug makes them sick. Also, if it was their sisters or daughters, they would be a lot more honest about the risks and side effects.” Press Release, Women’s Network for Unity, Women’s Network for Unity Protests Drug Trial Recruitment Tactics (June 21, 2004), <http://www.womynsagenda.org/Program/SWs/WNU/wnu21june04.pdf> [hereinafter June 21st Press Release].

41 WNU Background Statement, *supra* note 33.

Again, this demand resonates with emerging international standards and expectations. CIOMS Guidelines 10 and 21 seek to ensure that the benefits of the research are made *reasonably available* to the populations supporting the research efforts. CIOMS Guideline 10 addresses “Research in populations and communities with limited resources”.

Before undertaking research in populations or communities with limited resources, the sponsor and the investigator must make every effort to ensure that: (1) the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and (2) *any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.*<sup>42</sup>

Similarly, CIOMS Guideline 21 “Ethical obligations of external sponsors to provide health care services”, states that “external sponsors are ethically obligated to ensure the availability of . . . services that are necessary as part of the commitment of a sponsor to make a beneficial intervention or product development as a result of the research *reasonably available to the population or community concerned.*”<sup>43</sup> The tenofovir researchers did little to respond to WNU’s demand.

WNU’s third substantive concern dealt with was the effects the trials might have on inducing high risk behavior. WNU warned that women involved in the trial would not know if they are taking the drug or a placebo and may mistakenly think that condom use is not necessary. Alternatively, they might take greater risks with clients in order to increase their income.

We believe that even if the experiment participants are given counseling or condoms many young women will still believe that they are safe from HIV infection as long as they are involved in the experiment. Condom use is our most effective and cheapest protection from HIV/AIDS and we are worried women will stop using them because they think they are protected by the drug.<sup>44</sup>

The possibility that a prophylaxis could undermine safe sexual practices is a serious concern and one under express examination in the tenofovir studies of gay men planned in San Francisco and Atlanta.<sup>45</sup> The problem of adverse behavior change amongst sex workers in Cambodia is even more complicated and the potential dangers more real. The women have

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42 CIOMS, GUIDELINES, *supra* note 36, Guideline 10 (emphasis added). See also WMA, *Declaration of Helsinki*, *supra* note 36, princ. 30 (“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”); Christine Grady, *The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment*, 5 YALE J. HEALTH POL’Y L. & ETHICS 425 (2005).

43 CIOMS, GUIDELINES, *supra* note 36, Guideline 21 (emphasis added).

44 WNU Background Statement, *supra* note 33.

45 Sabin Russell, *Antiviral Drug Used to Treat AIDS to be Tested as Vaccine*, S.F. CHRON., Dec. 1, 2004, at A9. In studies performed in the United States and Brazil among homosexual men, the availability of post-exposure prophylaxis did not appear to increase sexual risk-taking behaviors. See CDC, *Postexposure Prophylaxis Report*, *supra* note 23, at 4.

direct economic incentives to take risks because payment is often higher for unsafe services, such as intercourse without a condom. Moreover, WNU members are subject to the demands of pimps, brothel owners and clients in an environment where they have limited means of self protection. The type of education, counseling and oversight provided to both the tenofovir and the placebo arms of the study are critical aspects of ethical study design.<sup>46</sup>

Even more significant than WNU's substantive concerns may be the procedural objections raised by the organization. WNU demanded (1) the right to information and (2) that the researchers enter into a series of discussions with them as a legitimate stakeholder in the process. "WNU believes that all sex workers who participate in the trial have the right to ask questions and be fully informed about the risks and to demand better medical and financial protection."<sup>47</sup> "WNU plans to continue outreach activities to its members on this issue and have further meetings, workshops and press conferences to negotiate protection for its members' health and human rights."<sup>48</sup>

Information is critical to any notion of informed consent. Traditional research ethics envision a dyadic relationship between the researcher and the research subject. The research subject is typically viewed as an isolated, autonomous decision maker. This model is inadequate when addressing the ethical demands of research subjects who are vulnerable groups in developing countries. Study design should incorporate a broader community education component and aspire to a level of transparency that will facilitate the development of trust. In this process, space must be made at the table for other important stakeholders. In addition to informed consent, the ability to credibly convey information, such as the likelihood and severity of side effects, could have addressed substantive concerns like the need for long term insurance.

Unfortunately, healthy communication was lacking in Cambodia. The situation deteriorated even further as study implementation began. On June 15, 2004, the WNU held a press conference objecting to practices researchers were allegedly using to recruit sex workers into the study. "A number of sex workers have reported that when they were approached by recruiters, they refused to provide the name of the drug and would say

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46 A substantive concern not raised by WNU but deserving consideration is the possible promulgation of tenofovir resistance in those sex workers receiving the drug who go on to become HIV-positive. Resistance to most anti-retrovirals occurs rapidly if used as single drugs therapy in treating known positive patients. If widespread tenofovir resistance developed it would undermine the drug's use both as a prophylaxis and as a therapeutic treatment. It is true that utilizing a single drug therapy for prophylaxis would leave other classes of HIV drugs available for treatment of study participants who developed tenofovir-resistant HIV infection. This assumes, however, that these women would be lucky enough to have access to therapeutic treatment in the first place.

47 WNU Background Statement, *supra* note 33.

48 *Id.*

only that it is good for the sex workers and has no side effects.”<sup>49</sup> “Some sex workers have been told that the drug will prevent HIV and not being clear and honest that the drug is experimental and its effectiveness for HIV prevention and long-term side effects is not known.”<sup>50</sup> It is impossible to verify these claims using outside sources. There is no doubt that given cultural, linguistic and socio-economic barriers, obtaining legitimate “informed consent” in this setting presents a difficult challenge. It is interesting to observe, however, how closely WNU’s objections echo previous complaints by the US Food and Drug Administration against Gilead Sciences, Inc., the manufacturer of tenofovir. The FDA has warned that Gilead was making misleading and exaggerated claims regarding the efficacy of tenofovir and failing to properly warn patients about side effects in treating HIV/AIDS.<sup>51</sup> Illustrating WNU’s sophistication, as well as how much smaller the Internet can make the world, the FDA warnings were known by WNU and a copy of the Warning Letter was posted on their website. At a minimum, statements made during trial recruitment and their similarity to misstatements by the drug’s manufacturer in the United States added to the growing atmosphere of distrust.

Ethical issues regarding the Cambodian tenofovir trials gained international attention at the July 2004 International AIDS Conference in Bangkok when ACT-UP Paris sprayed fake blood on Gilead posters and complained about the inadequacy of counseling and safe sex education being built into the trials.<sup>52</sup> To the surprise of all, Prime Minister Hun Sen called an end to the tenofovir trials on August 4, 2004.<sup>53</sup> “Cambodia is not a trash bin country,” the Prime Minister declared, stating that “[t]hey should not conduct experiments with Cambodians. They should do it with animals.”<sup>54</sup> Towards the end of the year, the focus shifted from Cambodia to Cameroon, where an identical study of tenofovir was underway. Similar ethical questions were raised, leading to a postponement of the African trials.<sup>55</sup> Those trials have been resumed and there is increasing pressure in Cambodia to restart the cancelled tenofovir study.<sup>56</sup> On March 4, 2005, WNU sent a letter to Prime Minister Hun Sen opposing efforts

49 June 21st Press Release, *supra* note 40.

50 *Id.*

51 Warning Letter from Thomas W. Abrams, Dir., Div. of Drug Mktg., Adver. & Comm’ns, U.S. Dep’t of Health & Human Servs., to John C. Martin, President & Chief Executive Officer, Gilead Scis., Inc. (July 29, 2003), available at <http://www.womynsagenda.org/Program/SWs/WNU/fda29july03.pdf>.

52 James, *supra* note 2, at 4.

53 Purtil & Samean, *supra* note 3, at 1.

54 *Id.*

55 U.N. Integrated Reg’l Info. Networks, *Cameroon: Clinical Trials of Anti-HIV Drug on Sex Workers in Question*, INTEGRATED REGIONAL INFO. NETWORKS, Jan. 27, 2005; see also U.N. Integrated Reg’l Info. Networks, *Cameroon: Government Suspends Trial of AIDS Drug*, INTEGRATED REGIONAL INFO. NETWORKS, Feb. 4, 2005.

56 Allen Myers, *Cambodia: Sex Workers Fight Proposed Drug Trial*, GREEN LEFT WKLY., Mar. 23, 2005, <http://www.greenleft.org.au/back/2005/620/620p18.htm> (“The Cambodian government is under pressure to allow a controversial trial of the anti-HIV drug tenofovir.”).

to restart the trials.<sup>57</sup> The letter continued to complain that researchers have not “provided information and documents related to the trial,” and asked, regardless of the fate of the tenofovir study, for the creation of “a community committee to supervise the ethics of any clinical trials” that might be conducted in the future.<sup>58</sup> Whether it is the trials of tenofovir or some other drug in some other country, the dilemmas of conducting medical research in developing countries are here to stay.

### III Mediating the Ethics of Third World Research

A dangerous misconception is that a study that meets the ethical strictures of the first world will necessarily satisfy the ethical needs of the third world. The reality is much more complex. A study protocol obtaining Institutional Review Board (IRB) approval in the U.S. or Australia cannot simply be exported to a country like Cambodia. Substantial differences in economic resources and prevailing medical standards between rich and poor countries create many obvious challenges. Less appreciated, however, is the fact that first world IRBs play a very specialized ethical function that is necessarily predicated upon a network of other social institutions capable of addressing ancillary social needs. This permits a complex division of labor, whereby certain social and medical concerns can be removed from the purview of “research ethics”. Comparable institutional networks do not exist in most developing countries. Consequently, the ancillary considerations that can be ignored in developed countries cannot be ignored in developing countries. Ethical third world research must therefore address a range of social and political issues not typically associated with the “ethics” of first world medical research. Furthermore, when addressing this broader range of social concerns, the very process of ethical review must itself take on more the characteristics of well functioning political processes, namely transparency, accountability and legitimacy.

What exactly does this mean? Research in the first world takes place against a backdrop of robust civic institutions and elaborate social systems dedicated to providing citizens comprehensive therapeutic care. This permits research ethics to perform a highly specialized institutional function and to do so in a realm that can legitimately ignore a range of difficult ancillary social and political questions. For example, whether a placebo design research protocol is ethical depends upon its incorporation of the prevailing standard of care. In the first world, determining the standard of care is largely a positive undertaking: what is the best alternative treatment a research subject would receive if they were not part of the study? The constraints determining the best alternative treatment in the developed world are largely matters of technology, not economics.

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57 See Letter from Kao Tha et al., Secretariat of Women’s Network for Unity, to Samdech Hun Sen, Prime Minister, Cambodia (Mar. 4, 2005), available at <http://archives.healthdev.net/sex-work/msg00556.html>.

58 *Id.*

When research is exported from the first to the third world, however, and when the prevailing standard of care is lower due to economic rather than medical constraints, defining the acceptable standard of care for research unavoidably takes on normative dimensions. Research ethics in this environment confronts issues that become increasingly social and political in nature.<sup>59</sup>

Once this is acknowledged, many mainstays of traditional medical ethics are called into question. Is it possible to address disparities in medical resources between first and third world standards of care in a responsible way without creating “undue inducements”? Similarly, it is well established in the developed world that researchers have no ethical obligation to treat non-study-caused medical problems, but merely refer such persons to existing clinical resources. This standard is defensible where medical services are generally available, but is far more contestable when no alternative treatment exists because of a lack of medical and financial resources. Even those who might continue to defend the absence of an affirmative duty to provide care as “ethical”, must feel uncomfortable about such a position in an HIV/AIDS prophylaxis study where those who become HIV positive during the course of research have no realistic access to care and anti-retrovirals. On the other hand, any effort to provide medical care for non-study-related problems would face the first world criticism that such care would be an unethical inducement, undermining the validity of participant informed consent. There are no easy answers, but these tensions highlight the shortcomings and inadequacies of existing ethical standards.

The trials of tenofovir are illustrative in this regard. The standard first world ethical position is articulated as follows:

Mary Fanning, associate director for clinical research at the National Institute of Allergy and Infectious Diseases, says offering volunteers 30 to 40 years of care, as the protest group demands, wouldn't pass an ethics test because it is an “undue inducement.” Incentives “so enormous” could entice volunteers to enroll in a study regardless of the risks, she says, tainting the informed consent process.<sup>60</sup>

The inadequacy of this reasoning is suggested by ethics blogger Stuart Rennie with a boxing analogy:

In this corner, the sex workers union demanding 30 to 40 years of medical care for sex workers in the study who acquire HIV. In that corner, Mary Fanning, associate director of clinical research at NIAID, countering that offering such compensation would be tantamount to undue inducement, would invalidate voluntary informed consent, and hence would be, um,

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<sup>59</sup> The commentary on Guideline 11: Choice of Controls in Clinical Trials of the INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS provides a window into these contentious issues. See CIOMS, GUIDELINES, *supra* note 36, Guideline 11 cmt.

<sup>60</sup> Chase & Naik, *supra* note 1, at B1. As should be clear from the earlier discussion, WNU was not demanding 30–40 years of free medical care, but simply assurances of long term post-study treatment of study induced side effects.

unethical. In this corner, ACT-UP Paris claiming that the \$3 offered to prospective participants already constitutes unethical inducement, and calling for the immediate termination of Viread [tenofovir] trials worldwide until participants were assured of effective HIV prevention education and resources, and received access to adequate treatment and care in the event of HIV infection. In that corner, Ward Cates of Family Health International (the North Carolina-based non-profit health organization overseeing the Cambodia and Cameroon trials) arguing that the human rights of study participants were respected, because the care being offered to them was well above the standard of care in Cambodia. Any reasonable sex worker, it seems, would be better off joining the trial than plying her trade outside it (but isn't that, um, undue inducement?).<sup>61</sup>

The WNU demands were not radical or irrational. The Union's demands reflected recognized standards of international medical ethics as articulated in the CIOMS Guidelines. As such, the impasse in Cambodia was not simply a failure of a team of first world researchers to take seriously the concerns of a union of sex workers. The trials of tenofovir illustrate the basic inability of existing research infrastructures to address a much broader range of contemporary ethical demands.

Under emerging international standards, researchers who choose to work in developing countries are called upon to take on new social responsibilities. For example, CIOMS Guidelines 10 and 21 require that future benefits derived from the research be made "reasonably available" to study participants.<sup>62</sup> Consistent with these standards, WNU sought assurances that if tenofovir were proven effective as an HIV/AIDS prophylaxis, sex workers in Cambodia would be assured future access to the drug. While perhaps originally grounded in ethical concerns, assuring future access also raises political and economic concerns. In this new environment, the lines between ethical, social and political responsibilities start to become blurred. Not surprisingly, therefore, asking even basic questions about how such ethical commitments are to be operationalized suggests how ill equipped traditional IRBs are to address these issues. These are social, as well as ethical concerns. Properly addressing these questions will require new processes that will increasingly take on characteristics that look more civic than ethical in nature.

The commentary to CIOMS Guideline 10, which deals with how the benefits of research are to be made *reasonably available* to the study community, is revealing in this regard.

When an investigational intervention has important potential for health care in the host country, *the negotiation* that the sponsor should undertake to determine the practical implications of "responsiveness," as well as the "reasonable availability," *should include representatives of stakeholders in the host country*; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, *as well as*

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61 Posting of Stuart Rennie to The Gilead Saga, American Journal of Bioethics Editors Blog, <http://blog.bioethics.net/2005/02/gilead-saga.html> (Feb. 18, 2005).

62 CIOMS, GUIDELINES, *supra* note 36, Guidelines 10, 21.



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*representatives of the communities for which subjects are drawn and non-governmental organizations such as health advocacy groups.*<sup>63</sup>

The lesson is clear. New institutional processes are necessary to work in conjunction with traditional ethical review boards to implement these responsibilities. These processes must be undertaken in a manner that openly acknowledges and accommodates their social and political dimensions.

Until more formal institutions are developed, it is natural to think of mediation as a framework to address these questions. It is also clear, however, that mediation will face a number of difficult challenges. Mediation is a process-oriented solution. This stands in sharp contrast to the substantively proscriptive nature of traditional ethical review. Identifying legitimate mediation partners, who can speak for the study subjects, and defining the rights and entitlements of the disparate stakeholders will be problematic. Beyond providing informed consent and agreeing to comply with the study protocol, research subjects are not traditionally viewed as “stakeholders” in the research process. Mediation will be more complicated, contentious and participatory than traditional ethical research review and approval. This can be difficult and unpredictable. Those who think that time and money will be saved by exporting research to the third world need to think again, at least if they are committed to conducting research in a responsible manner.

If mediation is to be successful, there are a number of prerequisites. To begin with, the relevant stakeholders must be identified and engaged. Participants in the process have to approach the exercise in good faith. Norms of healthy communication, mutual respect and full disclosure of information need to be encouraged. True understanding will require a willingness of participants to sympathetically engage the concerns of other stakeholders. Furthermore, mediating the more expressly social dimensions of third world research will require processes that serve more political and not scientific functions. To be effective, these mechanisms need to be modeled in accordance with the standards of well functioning civic institutions. Is the system open? Is the system accountable? Is the system legitimate?

Judged by these standards, the failings of the Cambodian tenofovir trials become evident. The challenges were to prevent the exploitation of a vulnerable social group, to make adequate assurances for the medical treatment of study-related side effects, and to ensure future access to any treatment proven efficacious in the study. Addressing these concerns called for an effective mediation exercise. The CIOMS speaks of the need to include a wide range of stakeholders in these deliberations, including groups like WNU.<sup>64</sup> This is particularly true when the research subjects

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63 *Id.* Guideline 10 cmt. (emphasis added).

64 *Id.*

are vulnerable groups who are likely to be disenfranchised from existing political processes.<sup>65</sup> Even in developed countries with strong traditions of representative democracy, there is little reason to have faith that government ministries can effectively represent the interests of socially marginalized groups like sex workers, gay men and IV drug users.

It is impossible to appreciate fully from second hand press reports why the impasse between the researchers and the WNU could not be resolved. We can only offer some educated guesses. The researchers appeared to treat their mandate as a *fait accompli* and to view their previous IRB approval as a basis for not having to re-examine the ethical and social concerns raised by WNU. This mind set is probably representative of most medical researchers. IRB review in developed countries is a rigorous process. In the minds of the researchers, all of the important ethical questions had already been resolved. From this perspective, WNU was viewed as a potential public relations problem that had to be managed, but not as a group that had to be seriously engaged. This posture, however, fails to appreciate that there are important social and political dimensions to third world medical research that must be negotiated and resolved in the country where the research is to take place, not in the country of funding sponsorship. From this standpoint, the impasse leading to the cancellation of the study was nearly unavoidable. No mediation can be successful when one of the central stakeholders fails to acknowledge that there is anything that requires discussion and resolution.

Reflective of this denial was the failure of researchers to be forthcoming with information. The limited access to information is troubling even from the perspective of traditional informed consent. Informed consent presupposes the disclosure of appropriate information. Whether one is dealing with WNU as a group, or its individual members, prospective study participants have the right to ask fundamental questions about the study and to be given access to relevant information. This was not done in Cambodia. We believe it is fair for research subjects to ask for and be provided copies of the study protocol. We also believe that it is fair to ask for and receive copies of minutes of IRB meetings or summaries of IRB discussions that purportedly addressed and resolved "ethical" issues relating to the study. This level of transparency will make the first world IRB process more accountable as a civic institution, as well as provide the information needed to facilitate truly informed consent. Information

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65 It was not enough for the researchers to work collaboratively with the Cambodian Ministry of Health. Cambodia is at best a fledgling democracy, whose government institutions face daily struggles with corruption. See, e.g., *Rotten at the Core: Graft is Slowing Cambodia's Return to Better Health*, ECONOMIST, Feb. 17, 2005; *World Bank Warns Corruption Could Threaten Cambodian Economy*, THAI PRESS REPS., Feb. 16, 2005 ("World Bank President James Wolfensohn says the three greatest obstacles to Cambodia's growth are 'corruption, corruption, corruption.'"). As is true in many developing countries, the healthiest and most proactive forms of civic society are often found in the non-governmental organization (NGO) community.

and transparency are also essential for building the cooperation and trust necessary for successful mediation.

Groups like WNU cannot and should not be ignored. As the WHO recognizes in its “3 by 5” initiative, if progress is to be made in the war against AIDS, more, not less involvement of civil organizations will be required.<sup>66</sup> Civil organizations need to be able to advocate for vulnerable populations from which they draw their members, even if such advocacy challenges traditional ethical constructs and regulatory processes. WNU is not the first civic organization to challenge traditional research regimes. In the United States, organizations like ACT UP were responsible for accelerating the pace of change in AIDS research.<sup>67</sup> Researchers should view WNU’s participation as a stimulus that could help redefine considerations for ethical third world research, rather than as an impediment to study recruitment. In the future, this strategy would necessitate involving civil organizations like WNU at the early planning stages of the research. In accordance with CIOMS Guidelines, these groups should be engaged in discussions as to what type of care should be provided during the study and on what care is necessary on an ongoing basis to address study-related side effects. The end result would be to create allies rather than adversaries.

The goals of HIV researchers, sex workers and health care providers are the same. There is a collective need to take pragmatic steps to curtail the spread of the virus and to provide effective, compassionate medical care to those already infected with the disease. What happened to the tenofovir trials in Cambodia is regrettable. At the same time, the conflict helps focus much-needed attention on the political and social demands of third world research, demands that traditional research ethics and IRBs are ill equipped to address. It is not possible to know whether a mediation framework could have overcome the problems that led to the cancellation of the Cambodian research. The cancellation of the Cambodian study, however, suggests that future researchers must more effectively engage groups like WNU if important HIV/AIDS research is to succeed.

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66 WHO, WORLD HEALTH REPORT, *supra* note 5, at 26. The “3 by 5” initiative is a multidisciplinary partnership, the goal of which is to provide needed HIV treatment to 3 million HIV-infected individuals in the developing world by the end of 2005. *Id.* at xii. The program acknowledges that “[p]olitical commitment and national ownership of programmes are essential.” *Id.* at xiii. The program emphasizes the role that “associations of people living with HIV/AIDS and their advocates, faith-based organizations, and other groups such as trade unions” play in HIV/AIDS treatment and prevention strategies in developing countries, and welcomes their participation. *Id.* at 43.

67 The WORLD HEALTH REPORT states that “[g]roups such as the AIDS Coalition to Unleash Power (ACT UP), formed in the USA in 1987, combined a successful advocacy strategy with the building of a formidable scientific knowledge base, which enabled members to become informed participants in medical research and the policy-making process. During the 1980s and 1990s, these groups won increased funding for antiviral drug research, increased AIDS services budgets at federal, state and local levels, an accelerated testing process for drugs, and expanded access to experimental drugs for people not accepted into clinical trials.” *Id.* at 46.