



# Ethics and HIV prevention research: An analysis of the early tenofovir PrEP trial in Nigeria

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## Abstract

In 2004, the first ever multi-sited clinical trials studied the prospect of HIV biomedical prevention (referred to as pre-exposure prophylaxis—'PrEP'). The trials were implemented at several international sites, but many officially closed down before they completed. At most sites, both scientists and community AIDS advocates raised concerns over the ethics and scientific rationales of the trial. Focusing on the Nigerian trial site, we detail the controversy that emerged among mostly Nigerian research scientists who scrutinized the research design and protocol. While some of the disputes, especially those pertaining to community engagement mechanisms, were ultimately resolved in international fora and implemented in later PrEP trials, concerns over science rationales and assumptions were never addressed. We argue that scientific rationales should be treated as ethical concerns and suggest that such concerns should be deliberated at host sites before the trial protocol is finalized.

## KEYWORDS

clinical trials, community engagement mechanisms, ethics, HIV prevention, Nigeria, PrEP, public private partnerships

## 1 | INTRODUCTION

In 2004, the first multi-sited clinical trial was conducted to determine if an anti-retroviral drug, tenofovir, could be taken to prevent HIV transmission—a biomedical technology known as pre-exposure prophylaxis (PrEP). Before the trial began, AIDS researchers characterized PrEP as a revolutionary breakthrough not just in pharmaceutical innovation but also in HIV prevention; they framed PrEP as a necessary humanitarianism for which researchers were ethically compelled to save the world's poorest from the AIDS epidemic.<sup>1</sup>

However, as soon as the trials began to recruit volunteers, controversy erupted at most PrEP trial sites, which were located at research institutions in Phnom Penh, Cambodia; Yaoundé, Cameroon; Accra, Ghana; Lilongwe, Malawi; Ibadan, Nigeria; and Bangkok, Thailand.<sup>2</sup>

<sup>1</sup>Kingori, P. (2015). When the science fails and the ethics works: 'Fail-safe' ethics in the FEM-PrEP study. *Anthropology & Medicine*, 22(3), 309–325.

<sup>2</sup>The Center for Disease Control (CDC), the National Institutes of Health (NIH), and UC San Francisco, among others, conducted the trials. FHI360, largely funded by the U.S. government, administered the trials. Gilead Sciences, the manufacturer, supplied tenofovir medication, and the Gates Foundation funded five research sites (\$6.5 million). The National Institutes of Health (NIH) awarded \$2.1 million to UC San Francisco to conduct a trial in Cambodia. The Center for Disease Control was awarded \$3.5 million to conduct the trial in Botswana, Thailand and the U.S.

Although reasons for disputes differed across locales, at stake for all sites were questions of ethics and scientific rationales outlined in the trial protocol.<sup>3</sup> Ultimately, three PrEP sites shut down and one refused Institutional Review Board (IRB) approval, which led to one of the biggest controversies that the world of AIDS research and activism experienced.

<sup>3</sup>Haire, B. G. (2011). Because we can: Clashes of perspective over researcher obligation in the failed PrEP trials. *Developing World Bioethics*, 11(2), 63–74; Peterson, K., Folayan, M. O., Chigwedere, E., & Nthete, E. (2015). Saying 'No' to PrEP in Malawi: What constitutes 'failure' in offshored HIV prevention research? *Anthropology & Medicine*, 22(3), 278–294; Ukpogon, M., & Peterson, K. (Eds.). (2009). *Oral tenofovir controversy II - Voices from the field*. Lagos: New HIV Vaccines and Microbicides Society. As Bridget Haire astutely points out, unresolved HIV clinical trial issues that emerged in the late 1990s re-emerged during the early tenofovir trials. In the 1990s, academics and researchers debated their obligations in HIV research – specifically regarding the use of a placebo in HIV antiretroviral therapy that tested mother-to-child HIV transmission after Lurie and Wolfe published their findings on the 076 AZT trials held in Uganda. See Lurie, P., & Wolfe, S. M. (1997). Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine*, 337(12), 853–856. According to Haire, some of the issues that arose in the 1990s trials are similar to those brought up in the 2004–2005 PrEP trials. These included unresolved logistics pertaining to care and support mechanisms as well as compensation to trial volunteers who seroconverted. However, the early HIV prevention trials raised new questions about assumptions and the production of scientific knowledge raised by African research scientists.

In this article we detail events that unfolded in Nigeria. We collected ethnographic interviews and conducted participant observation. We analyzed the activities of key organizations involved in the controversy: a bioethics and HIV-prevention-focused non-governmental organization (NGO), the New HIV/AIDS Vaccine and Microbicides Advocacy Society (NHVMAS), made up of Nigerian scientists, bioethicists, journalists and community advocates<sup>4</sup>; Family Health International, an international NGO and social marketing firm, now called FHI360, which designed the trial<sup>5</sup>; and FHI360's local research partners at the University College of Medicine at the University of Ibadan. We collected and examined four documented dialogues that took place between NHVMAS and the University College of Medicine ethics committee. We also analyzed an extended documented dialogue<sup>6</sup> that took place on a national Nigerian AIDS listserv—the *AIDS eforum*—that is run by the Lagos-based NGO, Journalists Against AIDS.<sup>7</sup> All of these actors—AIDS advocates, scientists, journalists, academics, FHI360, and NHVMAS—were subscribed members to the *AIDS eforum*. They followed and participated in PrEP dialogues and debates between August 30, 2004 and October 11, 2004. There was a total of 31 posts, which was the most ever made to this listserv on a single topic.

We explain the controversy that arose as well as actions that different actors took over a six-month period. NHVMAS named many concerns in the protocol and requested that it be revised. FHI360 did not respond to requests, nor did it take action. Instead it shut down the trial, citing irregularities that it perhaps rightfully identified at the trial site. After sites across countries closed, the Gates Foundation and the United Nations Program on HIV/AIDS (UNAIDS) convened several international meetings in order to restart and move forward on future HIV prevention research. We analyze how the debate in Nigeria over the ethics of scientific rationales changed focus at the international meetings, which emphasized a new need to create 'effective partnerships' between host countries and global clinical trial consortiums. We discuss how this switch changed the future stakes of HIV prevention research and conclude by discussing the ethics and politics of producing scientific knowledge at overseas sites. We argue that debates between trial sponsors and overseas host community scientists should be considered ethical issues accounted for in future trial protocols.

## 2 | CLINICAL TRIAL HISTORIES AND THE INTRODUCTION OF PREP TO NIGERIA

In August 2004, the Cambodian Minister of Health ordered the closure of the Phnom Penh trial site—the first of all PrEP sites to shut down.<sup>8</sup> News of the closure reached AIDS advocacy listservs across the world, including in Nigeria. At that time, the national AIDS-eforum listserv had over 5,000 subscribers comprising NGO members, foreign donor communities, government health policy workers and HIV activists. In Nigeria, the news on this listserv immediately prompted questions about the status of the Nigeria trial site.

For the NGO NHVMAS, the news was not surprising. NHVMAS was formed in February 2003, a year prior to the Phnom Penh trial closure. It was interested in HIV prevention research and its potential to reduce HIV incidence. It was also concerned with the need to ensure ethical clinical trial conduct. The latter concern arises out of a history of clinical trials that were never officially registered, and therefore never regulated in Nigeria. As the lead clinical trial inspector at Nigeria's drug regulatory agency (NAFDAC) told us, an uncountable number of trials had been conducted in the country without proper registration. Most notable was Pfizer's 1996 unregistered Trovan study that sought to create new uses for an existing pharmaceutical product. It was marred by multiple ethics violations and the death of 11 children.<sup>9</sup> At that time, NAFDAC was newly established but it focused largely on eradicating fake drugs, and not on the regulation of clinical trial research. Moreover, there was no national health research ethics committee in place, and therefore clinical trial research had to gain IRB approval at partnering institutions.

Over the years, Nigeria's clinical trial history converged with healthcare system decline and regulatory gaps that generated a long-term vacuum. As a result, human clinical trial participants recruited for international studies were not adequately protected. These histories galvanized NHVMAS to act as an independent ethics review body that negotiates clinical trial protocols being implemented in Nigeria. Prior to the arrival of PrEP it had successfully renegotiated national and overseas trial protocols before they were implemented.<sup>10</sup>

On May 26–27, 2004, NHVMAS held the first National Advocates Meeting on New HIV Prevention Technologies in Nigeria in Abuja, Nigeria, three months prior to the initiation of the Nigerian PrEP trial site.<sup>11</sup> Attendees included HIV prevention researchers working in

<sup>4</sup>Formally known as the Nigeria HIV Vaccine and Microbicide Advocacy Group, referred to as NHVMAS throughout.

<sup>5</sup>Family Health International. (2004). Phase 2 study of tenofovir disoproxil fumarate (TDF) for prevention of HIV study 9780. Clinical Trial Protocol. <https://aidsinfo.nih.gov/clinical-trials/details/NCT00122486>

<sup>6</sup>NHVMAS. (n.d.). *Phase 2 trial of oral tenofovir use as a chemoprophylaxis for HIV infection in Nigeria: Report of the outcome of dialogue between the community and researchers*. Lagos: Author.

<sup>7</sup>Retrieved from [www.nigeria-aids.org](http://www.nigeria-aids.org). April 15, 2005.

<sup>8</sup>Sandy, L. (2012). International agendas and sex worker rights in Cambodia. In M. Forde (Ed.), *Social activism in South East Asia* (pp. 154–169). London: Routledge; Forbes, A., & Mudaliar, S. (2009). *Preventing prevention trial failures: A case study and lessons for future trials from the 2004 tenofovir trial in Cambodia*. Global Campaign for Microbicides. Retrieved from <https://www.global-campaign.org/clientfiles/Cambodia.pdf>. January 10, 2010.

<sup>9</sup>Khan, F. (2008). The human factor: Globalizing ethical standards in drug trials through market exclusion. *DePaul Law Review*, 57(4), 877–915.

<sup>10</sup>These included: renegotiation of the use of lime juice as a microbicide among female sex workers in Jos, Nigeria; renegotiation of community engagement and study participant recruitment protocol for cellulose sulphate microbicide trials conducted in Nigeria; and negotiations on the rationale, justification, and research result dissemination for the conduct of the SAVVY microbicide trial in Nigeria.

<sup>11</sup>NHVMAS. (2005). *Situation report on new HIV prevention technologies in Nigeria*. Lagos: Author.

the country, ethicists, community advocates, policy makers, regulatory agency staff, and journalists. Also in attendance was the Nigerian primary investigator (PI) for the proposed tenofovir PrEP trial to be conducted by FHI360 and administered by the College of Medicine, University of Ibadan, in Ibadan, Nigeria.<sup>12</sup> The PI's presentation generated discussion on the use of existing antiretroviral drugs for HIV prevention, including questions about potential drug resistance. The PI assured meeting attendees that the findings of the Phase I study showed good and promising results. However, NHVMAS attempted to obtain more information without success.

With no trial protocol to evaluate, NHVMAS used the Nigeria-AIDS eforum to publicly ask the trial administrators and FHI360 for the trial protocol and the informed consent in order to review them. Three days later, on September 6, 2004, FHI360's Elizabeth Robinson<sup>13</sup> replied with a 'frequently asked questions' guide that did not get to the heart of the concerns being posted. Many listserv subscribers already knew the answers to questions such as 'what is tenofovir?' Moreover, FHI360 stated that the PrEP study 'was designed according to the most rigorous international ethical standards' and received institutional approval by FHI360 and African institutions. Also stated was that those who become HIV-positive on the trial would be referred to treatment sites.<sup>14</sup>

The responses to this post were instant, and many chronicled Nigeria's trial history. They included requests for more information pertaining to community preparedness, care of trial participants, study design/rationale and implementation, and informed consent. Subscribers described well-known healthcare referral problems. They also expressed little trust in most African ethics review boards as a result of past concerns over the quality of the trial protocol review. In one exemplary post, an internationally known Nigerian AIDS activist openly living with HIV, stated:

There have been too many drug trials where people from developing countries are used as guinea pigs and dumped. I was involved in a Roche/Swipha trial five years ago where I was made to pay [US \$1,000] to get on a six month ARV trial! There were consent forms but I never saw one let alone read or signed it. Roche claimed they never did a Nigerian trial, but [rather] Swipha, their Nigerian representatives [performed the trial]. Swipha said it wasn't a Roche trial but research [conducted] by some Nigerian doctors. I still have the labeled bottles and some of the pills today and it's very clear who 'sold' those research drugs ... [Regarding PrEP], I hope we won't be given the 'patient confidentiality' clause excuse [from research scientists]. I'm sure we can work this out in such a way that all parties would be protected and their confidentiality assured.<sup>15</sup>

<sup>12</sup>Ibid.

<sup>13</sup>Robinson, E. (2004). *Questions about tenofovir PrEP. Nigeria AIDS-Eforum*. www.nigeria-aids.org. September 6.

<sup>14</sup>Ibid.; see also NHVMAS, op. cit. note 6.

<sup>15</sup>NHVMAS, op. cit. note 6.

Thus, extended assurances of ethical conduct were met with continued demands for transparency and documentation. But the trial protocol and informed consent documents were not forthcoming. As soon as FHI360 posted to the AIDS eforum, it became a site of intense debate for the next six weeks.

### 3 | ANALYZING THE PROTOCOL: LOCAL EPIDEMIOLOGIES AND SCIENTIFIC RATIONALES

As the debate continued, a NHVMAS member reached out to colleagues at SIDACTION, a Paris-based NGO that at the time funded clinical research literacy training in African countries. SIDACTION did not have the protocol. It asked colleagues at REDS, an AIDS advocacy organization based in Cameroon, which was simultaneously investigating the PrEP site in Douala.<sup>16</sup> The Cameroonian colleagues supplied the protocol. After analyzing it, the scientists and ethicists at NHVMAS produced a list of concerns and informed the local PI and Health Research Ethics Committee at the University in Ibadan in October 2004.<sup>17</sup>

1. *Safety profiles.* The trial was technically a Phase 2b, referred to as a 'pivotal trial'. However, NHVMAS claimed that a Phase 2b trial was inappropriate because there were no substantive pre-clinical and Phase I trial data that evaluated the safety of tenofovir for use as PrEP. It also queried the safety of a systemic antiretroviral (in the form of pills) for HIV-negative persons. It advocated for a PrEP trial to evaluate safety in a less health-vulnerable population first.<sup>18</sup>
2. *Assumptions of tenofovir pills.* Trial officials conducted formative research prior to implementation and found that women who were interviewed were willing to use pills if found effective. But NHVMAS likened a daily tenofovir pill to contraceptive pills. It noted that Nigerian women frequently use injectable methods of contraceptives instead of pills. NHVMAS asserted that studying the use of contraceptive pills by women in the trial community would have provided better insight into the future use of a daily tenofovir pill.
3. *The adverse effects scale.* This scale is a categorized breakdown of low to high health problems (adverse effects) related and unrelated to the trial. It signals when a trial participant should withdraw from the study by defining specific adverse effects on a Grade 1-4 scale, Grade 4 being the worst health effects. The

<sup>16</sup>Akoa, Y. (2005). Clinical trials and fundamental rights: The tenofovir experience in Cameroon. *Interights Bulletin*, 15, 66-68; Yomgne, C. T. (2009). The Cameroon story. In M. Ukpong & K. Peterson (Eds.), *Oral tenofovir controversy II: Voices from the field* (pp. 20-29). Lagos: NVHMAS. Retrieved from <https://www.nhvm-as-ng.org/publication/TDF2.pdf>, December 2, 2009.

<sup>17</sup>NHVMAS, op. cit. note 6; see also FHI, op. cit. note 4.

<sup>18</sup>Research conducted by Mayer and colleagues established safety in HIV-negative individuals after the FHI360 PrEP protocols were designed and recruitment for human subjects began. However, the Mayer et al. study measured safety in (vaginal) gel form and not in pills. Mayer, K. H., Maslankowski, L. A., Gai, F., El-Sadr, W. M., Justman, J., Kwiecien, A., ... Rooney, J. F. (2006). Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. *AIDS*, 20(4), 543-551.

protocol mandated the following: the drug is withdrawn due to an unrelated event at Grade 3; when the participant reaches less than or equal to Grade 2 it is restarted. At Grade 4, the trial volunteer should be withdrawn permanently. Given the poor health profiles of the study population, NHVMAS argued that if a Grade 3 or 4 adverse event occurs, even if it is considered unrelated to the study drug, the drug should be discontinued.

4. *Drug resistance.* The resistant strain, K65R, linked to tenofovir was not monitored. NHVMAS expressed concerns over the fact that drug resistance was unknown among HIV-negative individuals (especially if they seroconvert during a clinical trial) and requested that drug resistance be monitored.<sup>19</sup>
5. *Malaria co-infection.* While one justification for conducting the study was to assess the impact of malaria infection on PrEP efficacy, the protocol did not outline a monitoring strategy on the relationship between malaria, malaria drugs, and tenofovir PrEP. NHVMAS argued that understanding the role of malaria and anti-malarial drugs was important,<sup>20</sup> and called for a preliminary Phase I trial to test tenofovir safety with malaria co-infection.<sup>21</sup>
6. *Care and support.* Individuals who test HIV-positive at recruitment or seroconvert during the trial would be given referrals to treatment sites. The AIDS eforum users asked for specific sites to be named and noted that the main HIV treatment program was at capacity. They argued that referrals often did not lead to actual care and treatment in Nigerian health systems. Therefore, NHVMAS advocated following up participants for two years after the trial completed.
7. *Community engagement.* NHVMAS requested that an independent clinical monitor and a community liaison officer be appointed for the study to serve as an interface between the trial sponsors and the AIDS NGO community. NHVMAS also advocated for the constitution of a community advisory board in order to facilitate a bi-directional relationship between the research team and the community that could address myths, misconceptions and concerns about the trial.

<sup>19</sup>The question of PrEP and drug resistance was posed by 2006 – two years after these early trials commenced. Derdelinckx, I., Wainberg, M. A., Lange, J. M. A., Hill, A., Halima, Y., & Boucher, C. A. B. (2006). Criteria for drugs used in pre-exposure prophylaxis trials against HIV infection. *PLOS Medicine*, 3(11), e454; Martinez, J., Coplan, P., & Wainberg, M. A. (2006). Is HIV drug resistance a limiting factor in the development of anti-HIV NNRTI and NRTI-based vaginal microbicide strategies? *Antiretroviral Research*, 71(2-3), 343-350; Subbarao, S., Otten, R. A., Ramos, A., Kim, C., Jackson, E., Monsour, M., ... Rendon, A. (2006). Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. *Journal of Infectious Disease*, 194, 904-911.

<sup>20</sup>At that time, research showed interactions between malaria infection and HIV infection. See French, N., Nakiyingi, J., Lugada, E., Watera, C., Whitworth, J. A. G., & Gilks, C. F. (2001). Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS*, 15, 899-906; Grimwade, K., French, N., Mbatha, D. D., Zungu, D. D., Dedicoat, M., & Gilks, C. F. (2004). HIV-infection as a co-factor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS*, 18, 547-554; Whitworth, J., Morgan, D., Quigley, M., Smith, A., Mayanja, B., Eotu, H. ... Ojwiya, A. (2000). Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: A cohort study. *Lancet*, 356, 1051-1056.

<sup>21</sup>At the end of the trial, 30% of trial participants had malaria infection. Peterson, L., Taylor, D., Roddy, R., Belai, G., Phillips, P., Nanda, K., ... Jaffe, H. S. (2007). Tenofovir disoproxil fumarate for prevention of HIV infection in women: A Phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clinical Trials*, 2(May), e27-e35.

8. Future access to PrEP. NHVMAS noted that there was no memo of understanding in place with the government of Nigeria, nor were there any discussions on future access if tenofovir was found to be safe and effective to use as PrEP.<sup>22</sup>

The letter from NHVMAS to the PI at University College Hospital (UCH), Ibadan stated that even though future HIV prevention trials were important and should be pursued, the tenofovir PrEP trial was *not necessary*. It argued that there was not strong enough justification and evidence to indicate that PrEP was appropriate for the trial community, nor was there potential for widespread implementation and use in Nigeria.

## 4 | RESPONSE TO THE NHVMAS LETTER

The PI at UCH responded to the letter by reiterating how much new technologies were urgently needed to break the HIV epidemic. The PI did not address most of the points listed by NHVMAS but went on to explain the meaning of HIV prophylaxis. He also accused the AIDS eforum of polarizing the debate. Certainly, he was correct about that. With many questions that received either vague answers or no response, the crescendo of anger on the listserv did appear polarizing.<sup>23</sup>

However, the University of Ibadan's health research ethics committee met on September 16, 2004 to reassess the PrEP protocol. It agreed to the following adjustments among others: those who seroconvert will be offered initial treatment at UCH, and active coordination with the PEPFAR<sup>24</sup> treatment program would take place. All participants will be followed up for two years after trial closure. An independent clinical monitor and community liaison officer will also be appointed.

These adjustments were relatively easy padded-on participant care and community engagement mechanisms. The issues pertaining to scientific rationales such as safety profiles, Phase II/III trial appropriateness, monitoring resistance, and testing the effects of malaria co-infection were not considered for revisions. Because the trial is multi-sited, the protocol must be identical at all sites in order to gather uniform data, which is a U.S. Food and Drug Administration (FDA) requirement for randomized clinical trials. The structure of a multi-sited trial that caters to U.S. drug approval requirements cannot always address the specificities of local health concerns.

<sup>22</sup>Médecins Sans Frontières noted that, despite Gilead's plan to make tenofovir available at cost, only a handful of countries had such drug approval contracts established at the time of the trials. These were designated as use for HIV treatment and not necessarily as PrEP. Médecins Sans Frontières. (2006). *Gilead's tenofovir 'Access Programme' for developing countries: A case of false promises?* February 7. Retrieved from <https://www.doctorswithoutborders.org/pr/2006/02-07-2006.cfm>. February 3, 2007.

<sup>23</sup>NHVMAS, op. cit. note 6.

<sup>24</sup>The U.S. President's Program for AIDS Relief – one of two primary programs offering free HIV treatment at that time (the other came from funds from the United Nations' Global Fund to Fight AIDS, Tuberculosis, and Malaria).

With minimal agreement on implementing care and support mechanisms, the UCH health research ethics committee stated to NHVMAS that it would confer with FHI360 on implementing new recommendations.<sup>25</sup> Unfortunately, FHI360 did not take action to revise the study protocol or hold dialogue with community members on the issues raised. It also offered no comments during this discussion between UCH and NHVMAS.

With no protocol modification, NHVMAS drafted a letter addressed to the Federal Ministry of Health and NAFDAC reiterating its concerns in March, 2005. In this letter, NHVMAS included details of the study by Subbarao and colleagues,<sup>26</sup> who tested tenofovir as a prevention technology in primates. They showed that the study drug only delayed SIV (the simian equivalent to HIV) onset for six weeks, referred to as 'partial protection'. All study animals were infected with SIV and died after 14 weeks despite the use of tenofovir. This was the first study that exposed HIV negative animals to HIV multiple times while on PrEP. Subbarao et al.'s model resembles the 2004 clinical trials, which relied upon consistent and frequent exposure to HIV (the rationale for recruiting sex workers) and daily treatment over time. The tenofovir Phase 2b trials were based on preclinical studies conducted earlier.<sup>27</sup> These studies showed good results but they exposed animals to HIV only once and not multiple times. NHVMAS did not find Subbarao's results promising for human clinical trials. Indeed, tenofovir alone as a prevention drug was deemed inefficacious several years later.<sup>28</sup>

Two days before the letter was sent to NAFDAC and the Federal Ministry of Health, FHI360 shut down the trial explaining that:

On March 11, 2005, FHI made the announcement that the Nigerian arm of the tenofovir PrEP trial will discontinue prematurely. FHI closed the trial voluntarily, because it determined that the study team was unable to comply with the required operational and laboratory procedures at the level necessary for conducting this study... More than 100 participants had been randomized. The announcement came as a disconcerting blow to the already fragile network of trials (Singh and Mills 2005).<sup>29</sup>

In August 2009, we interviewed one person working on the PrEP trial in Nigeria who concurred that there were several problems with

trial implementation. We consulted Nigerian regulatory officials to discuss their views on the science and ethics of the Nigeria PrEP trial. We were informed that FHI360 never submitted any documents on reasons for study closure. NAFDAC claims that during their three monitoring visits, no in-progress reports were submitted, leaving it unable to evaluate the trial. It is possible that FHI360 submitted documents to NAFDAC, which FHI's Ward Cates reiterated to us in emails. However, despite repeated requests, the final report submitted to NAFDAC was not shared with the authors.

## 5 | FROM ETHICS TO HUMANITARIANISM

The problems that Nigerian scientists found in the protocol were most likely not a surprise to those who constructed and financed the first PrEP trials. In 2001, three years before the trials commenced, the Gates Foundation held a meeting to discuss FHI360's proposal to initiate this PrEP study in human participants. In attendance were FHI360, Gilead Sciences, university researchers, and gender and development activists who started the Global Campaign for Microbicides (the first organization to conceptualize a biomedical technology for HIV prevention). Issues that were discussed at that meeting<sup>30</sup> were nearly identical to those identified by NHVMAS, and members of Nigeria's AIDS listserv three years later.

According to McGrory et al.,<sup>31</sup> the questions raised at the meeting revolved around the lack of data available on tenofovir safety in HIV-negative persons; the choice and form of the drug; choosing sites and study populations; and access to treatment and trial benefits. The 2001 Gates consultation concluded that it was not appropriate to conduct offshored trials without first establishing safety in HIV-negative individuals; that safety studies should first take place in the U.S. and then efficacy studies could follow 'in high-risk US populations and in similar populations in other countries' to 'ensure that the burdens and benefits of research were shared'<sup>32</sup>; that PrEP should be tested in countries where access to antiretroviral therapy existed; and that attention should be given to developing trial sites that would use a vaginal tenofovir form when Phase 1/2 studies were completed, if the results warranted such trials.<sup>33</sup>

Instead of following these suggestions, FHI360 chose to shift the stakes of its PrEP concerns from trial appropriateness to humanitarianism. For example, according to McGrory et al. FHI360 asked itself: 'Are the trials addressing a significant health risk that is a priority for the countries that would be hosting the research?' and 'Will the host-country populations benefit from the research

<sup>25</sup>NHVMAS, op. cit. note 11.

<sup>26</sup>Ibid. NHVMAS only had access to the conference proceedings. The 2005 citation represents the full publication.

<sup>27</sup>Tsai, C.-C., Follis, K. E., Sabo, A., Beck, T. W., Grant, R. F., Bischofberger, N. ... Black, R. (1995). Prevention of SIV infection in macaques by (R)-9-(Phosphonylmethoxypropyl) adenine. *Science*, 270, 1197-1199; Van Rompay, K. K. A., McChesney, M. B., Aguirre, N. L., Schmidt, K. A., Bischofberger, N., & Marthas, M. L. (2001). Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. *The Journal of Infectious Diseases*, 184, 429-438.

<sup>28</sup>Tenofovir was ultimately found not to be effective as PrEP on its own, but in 2012 a combination drug, truvada (emtricitabine/tenofovir), was the first to be approved by the FDA as PrEP.

<sup>29</sup>Singh, J. A., & Mills, E. J. (2005). The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? *PLoS Medicine*, 2(9), e234. <https://doi.org/10.1371/journal.pmed.0020234>

<sup>30</sup>McGrory, E., Irvin, A., & Heise, L. (2009). *Research Rashomon: Lessons from the Cameroon pre-exposure prophylaxis trial site*. Washington, DC: Global Campaign for Microbicides - PATH: 27. Retrieved from [http://www.global\\_campaign.org/clientfiles/Cameroon.pdf](http://www.global_campaign.org/clientfiles/Cameroon.pdf). March 28, 2010.

<sup>31</sup>Ibid.

<sup>32</sup>Ibid, p. 13.

<sup>33</sup>Ibid, p. 13.



results?<sup>34</sup> That is, if a country is viewed as highly burdened with HIV infection, and FHI360 could play a role to mitigate that problem, then FHI360 prioritized its own idea of a broader humanitarian impetus. The concerns regarding trial management were made to fit within this clinical-humanitarian approach. FHI360's humanitarian claim was countered by NHVMAS, which asserted that there were potential human hazards associated with the tenofovir PrEP trial itself.

Instead of reflecting on the scientific rationales raised by its own consultations (and then later by Nigerian scientists), FHI360 shifted attention to the minutiae of clinical interactions. These were informed by FHI360's humanitarian imperatives such as 'supporting sustainable improvements in local access to care' and 'minimizing the potential for stigmatization of trial participants.'<sup>35</sup> It conducted formative research to understand the most efficient ways to administer informed consent and reduce potential risk among PrEP trial volunteers. Ultimately *an ethics of trial efficiencies drew attention away from an ethics of science rationales*. An ethics of trial efficiencies is an abstraction of broader ethical questions, and implementing good clinical practices is imagined as serving broader humanitarian values. An ethics of scientific rationales recognizes the unevenness of scientific knowledge and health expertise that trial coordinators and host communities possess; and that differences should be actively understood and not assumed. These different ideas of ethics are at the root of the PrEP debates and unexpected trial controversies.

## 6 | INTERNATIONAL DIALOGUES: ERASING SCIENCE RATIONALES

After three trial closures (Cambodia, Cameroon and Nigeria), a refused IRB approval (Malawi),<sup>36</sup> and a trial marred by claims of serious ethics violations (Thailand),<sup>37</sup> the Gates Foundation, UNAIDS, and FHI360 became concerned about future HIV prevention research. In May 2005, UNAIDS organized a series of 'regional consultations' in Abuja, Nigeria; Pattaya, Thailand; and Durban, South Africa. Gates and the International AIDS Society held follow-up international consultative meetings in Geneva, Switzerland, and Seattle, Washington, U.S.A. Researchers, ethicists, government officials, and community members (AIDS activists, and potential trial participants such as sex workers, men who have sex with men, and injection drug-users)

attended these meetings. We attended the Nigeria meeting and analyzed reports from the other meetings.<sup>38</sup>

The meetings' objectives were to learn more about trial failure, local community concerns, and ways to move forward on future research. The discussions circled around 'what happened?' at each of the sites. All actors had their views, their regrets, their insights, and newly acquired education.<sup>39</sup> At the Nigeria meeting, there was agreement between international and local actors to implement community engagement mechanisms that would provide HIV clinical education to trial communities and their advocates. Certainly, community engagement helps to insure the successful completion of a PrEP trial. Nigerian scientists and AIDS advocates additionally made calls to negotiate the trial design at the moment it is conceptualized by foreign researchers, which was not convincing to foreign actors in the room, including the meeting's moderator. Certainly, a negotiation like this does not guarantee the successful completion of a trial. There exists the potential for a host community to deem it unnecessary, which happened at the Nigeria and Malawi<sup>40</sup> trial sites.

The meetings in Geneva and Seattle were geared toward developing 'effective partnerships' in order to implement community engagement mechanisms. Effective partnerships were imagined to take place between *communities* defined as AIDS activists, sex workers, and their advocates, and *researchers*, defined only as PrEP researchers and not African scientists residing outside of research partnerships. (For the Nigerian site, these categorizations were inaccurate, especially given that Nigerian research scientists in NHVMAS identified themselves as part of the broader AIDS 'community'.) The organizers assumed that communities were uninformed about HIV clinical science and were in need of further education by PrEP researchers.

While it was probably the first time in clinical research history that multiple actors reflected on trial problems together, the quick move to effective partnerships omitted several issues. There was little discussion over the assumptions built into the protocol in terms of how they map on to the reality of women's health in resource-constrained settings. There were no deliberations regarding the pre-clinical data that NHVMAS found to be problematic; no follow up on the impact of malaria co-infection; little discussion about the exact terms of future access; and no reflection on the logics of marketing PrEP in places where little antiretroviral treatment is available. In other words, community engagement and effective partnerships

<sup>34</sup>It additionally asked: 'Can appropriate steps be taken to minimise all medical, social, and psychological risks associated with the research? Is the research unnecessarily burdening vulnerable populations?' Ibid, p. 14.

<sup>35</sup>Ibid, p. 14.

<sup>36</sup>Peterson, K., et al., op. cit. note 3.

<sup>37</sup>Kaplan, K. (2009). 'The Thailand Response'. In M. Ukpong and K. Peterson (Eds.), *Oral Tenofovir Controversy II: Voices from the field* (pp. 36–41). Lagos, Nigeria: New HIV Vaccine and Microbicide Advocacy Society.

<sup>38</sup>Collins, C. (2005). *Gaps and inconsistencies in ethical guidance for HIV prevention research: Background paper prepared for UNAIDS*. Geneva: UNAIDS; June 2005; International AIDS Society (IAS). (2005). *Building collaboration to advance HIV prevention - Global consultation on tenofovir pre-exposure prophylaxis research: Report of a consultation convened by the International AIDS Society on behalf of the Bill and Melinda Gates Foundation*. Atlanta, GA: U.S. National Institutes of Health and U.S. Centers for Disease Control; Mellors, S. (2013). *Towards creating effective partnerships for the conduct of HIV prevention trials: Perspectives from regional consultations held in Southern Africa, Western and Eastern Africa and South East Asia*. Geneva: UNAIDS; UNAIDS. (2006). *Good participatory practice guidelines for biomedical HIV Prevention Trials*. Geneva: Author.

<sup>39</sup>International AIDS Society, op. cit. note 37.

<sup>40</sup>Peterson, K. et al., op. cit. note 3.

were imagined to pertain only to implementing an already-existing trial protocol. The consultative meetings did not explore how mechanisms could be created to negotiate trial designs. The scientists in Nigeria who critiqued the protocol exist outside of international PrEP research partnerships. They were not imagined to be part of this landscape, and their concerns were not entirely legible to these dialogues.

These dichotomies of researchers versus communities not only erased multiple scientific concerns but they also led to a prominent discourse that explained the reasons for trial closure. During our participant observation at conference sites, we witnessed PrEP scientists arguing that 'uninformed AIDS activists' residing outside of the sites rallied to shut down the trials. ACT UP Paris was especially singled out as major Global North instigator that instructed their presumed 'lesser-educated' colleagues in the Global South to revolt. Stories such as this one was so powerful that it overshadowed actual events happening on the ground, including the long and arduous attempts made at most sites to re-negotiate the trial protocol. This discourse effectively erased African scientists' concerns out of the debate.

## 7 | CONCLUSION

Scholarly discussions on overseas HIV clinical trials have focused on a number of critical issues such as informed consent, the inappropriate use of a placebo, trial participant remuneration, among others.<sup>41</sup> That is, the practices that routinely take place in clinical trials are evaluated in ethical terms. The usual background to these evaluations is the uneven relationships found between international research scientists and their host scientific and trial communities.<sup>42</sup> Such disparities include the radical power differences found in salary, global and local mobility, human security, research resources, publishing access, political and research networks, who controls data, media access, and much more. In fact, at the time that the early PrEP trials were closing across sites, reports in the international media and in the most highly ranked medical journals about 'what went wrong' were made by the trial coordinators and not by scientists in the host communities located outside of the trial network.<sup>43</sup>

<sup>41</sup>Kingori, op. cit. note 1; Molyneux, S., & Wenzel, G. P. (2008). Ethics and the ethnography of medical research in Africa. *Social Science & Medicine*, 67(5), 685–695; Michael, M., & Rosengarten, M. (2013). *Innovation and biomedicine: Ethics, evidence and expectation in HIV*. Basingstoke: Palgrave Macmillan.

<sup>42</sup>Crane, J. (2013). *Scrambling for Africa: AIDS, expertise, and the rise of American global health science*. Ithaca, NY: Cornell University Press; Elliott, D. (2014). Imagining 'Atlanta': The politics and poetics of space and marginality in medical research in East Africa. *Cultural Studies Review*, 20(1), 276–301; Fairhead, J., Leach, M., & Small, M. (2006). Where techno-science meets poverty: Medical research and the economy of blood in the Gambia, West Africa. *Social Science & Medicine*, 63(4), 1109–1120; Farmer, P. (2002). Can transnational research be ethical in the developing world? *The Lancet*, 360(9342), 1266.

<sup>43</sup>Grant, R. M., Buchbinder, S., Cates, W., Clarke, E., Coates, T., Cohen, M. S., ... Harrington, M. (2005). Promote HIV chemoprophylaxis research, don't prevent it. *Science*, 309, 2170–2171; Mills, E. J., Singh, S., Singh, J. A., Orbinski, J. J., Warren, M., & Upshur, R. E. (2005). Designing research in vulnerable populations: Lessons from HIV prevention trials that stopped early. *British Medical Journal*, 331, 1403–1406; cf. Jintarakanon, S., Nakapiew, S., Tiendum, N., Suwannawong, P. et al. (2005). Unethical clinical trials in Thailand: A community response. *The Lancet*, 365(9471), 1617–1618.

We argue that these unequal structural conditions should not be considered as background or context, but their effects should be located in the realm of ethics. It has long been assumed that the structural inequality of overseas trials results in skewed material outcomes. Yet, the stakes are also epistemological. That is, trial structural divides have the potential to affect struggles over who assumes, controls, and produces scientific knowledge.

An exemplary artifact of scientific knowledge is the trial protocol. It reflects unchallenged assumptions (correct or incorrect) about local community health and the utility of possible future drug products. These potentials and promises are, moreover, politically obliged to institutions that have a great deal of global influence at the level of HIV funding and policy, such as the Gates Foundation, U.S. governmental institutions and UNAIDS. As such, the protocol was not imagined as unsettled or open for debate. One could argue that this is a problem of the multi-sited clinical trial whose protocol must be uniform across sites in order for trial products to be considered for eventual FDA approval. While this certainly is the case, such an explanation does not elucidate why debates were ignored and why many questions about scientific rationales and protocol design went unanswered. One problem is that such dynamics between the trial researchers and the host community are not often imagined as even possible among IRBs located in the Global North.

After decades of African AIDS activism that has taken ownership of epidemiological, social and material knowledge of HIV, the Nigerian trial site imagined itself to be entitled to debate scientific knowledge embedded in the PrEP trial protocol. But the fact that the protocol *belonged* to FHI360 (in that it was not open to negotiation or revision) is a result of structural inequalities, which has implications for ethics.

When scientists and advocates at the Nigerian regional consultative meeting suggested that trial conceptualization and design be considered as part of a new community engagement paradigm, they were making an ethical argument: that the scientific knowledge should be fairly deliberated, distributed and shared. Unfortunately, the introduction of such an ethical practice into global HIV prevention research did not take place.

In 2014–2015, similar debates emerged during the West Africa Ebola epidemic. However, unlike the events of the early PrEP trials, African researchers, bioethicists and scientists successfully advocated for the use of alternative rather than randomized clinical trial designs that tested Ebola vaccines and treatment therapies<sup>44</sup> as well as compassionate access to untested drugs.<sup>45</sup> For these African researchers, randomized control trials that use a placebo were not considered appropriate as a clinical trial design during a high-mortality emergency epidemic. This was due to the fact that Ebola had no known standard of care, compassionate

<sup>44</sup>Adebamowo, C., Bah-Sow, O., Binka, F., Bruzzone, R., Caplan, A., Delfraissy, J.-F., ... Olliaro, P. (2014). Randomised controlled trials for Ebola: Practical and ethical issues. *The Lancet*, 384(9952), 1423–1424.

<sup>45</sup>Folayan, M. O., Brown, B., Yakubu, A., Peterson, K., & Haire, B. (2014). Compassionate use of experimental interventions in the Ebola outbreak. *The Lancet*, 384(9957), 1843–1844.

access to therapy was feasible, and clinicians and communities made joint decisions over life and death. Moreover, African scientists advocated for trial implementations to respect the communitarian nature of societies,<sup>46</sup> and the history, politics and social dimensions of effected areas.<sup>47</sup> These stances produced alternative trial designs, including the Suffit Ebola vaccine trial<sup>48</sup> and the Favipiravir treatment trial.<sup>49</sup>

During the early PrEP trials, needed community engagement mechanisms were difficult to conceptualize but over time they have been successfully implemented. As with the Ebola trials described above, community engagement should apply to an HIV prevention protocol where host scientific communities of overseas research are invited to deliberate over the assumed scientific understandings of community health, local biologies, scientific knowledge, and the future output of HIV trial outcomes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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<sup>46</sup>Folayan M. O., & Haire, B. (2016a). Communitarian societies and public engagement in public health: A commentary. *Critical Public Health*, 27(1), 6–13.

<sup>47</sup>Folayan, M. O., & Haire, B. (2016b). History, culture and social norms: Implications for Ebola drug and vaccine clinical trials in affected regions. In N. G. Evans, T. C. Smith, & M.S. Majumder (Eds.), *Ebola's message: Public health and medicine in the 21st century* (pp. 201–216). Cambridge, MA: MIT Press.

<sup>48</sup>Camacho, A., Carroll, M. W., Dean, N. E., Doumbia, M., Edmunds, W. J., Egger, M., ... Keita, S. (2015). The ring vaccination trial: A novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. *BMJ*, 351, h3740.

<sup>49</sup>Sissoko, D., Laouenan, C., Folkesson, E., M'lebing, A.-B., Beavogui, A.-H., Baize, S., ... Carazo, S. (2016). Experimental treatment with favipiravir for Ebola virus disease (the JIKI trial): A historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Medicine*, 13(3), e1001967.