The Trials and Tribulations of Tenofovir: Ethics, Political Economy, and Clinical Research in Africa

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1. OVERVIEW

The clinical trial has long served as the primary medium for which clinical molecules have the potential to be transformed into marketed pharmaceutical products. As such, it is also a symbol of institutional and technological assemblages that mediate between information and global markets. While scholarly attention has been paid to social and cultural issues regarding informed consent and trial ethics, new shifts in the financing and industrialization of clinical trials combined with new technologies and legal reform, raise heretofore unforeseeable debates and dilemmas being newly raised in clinical research. As the number of clinical trials has increased almost exponentially in the last ten years, where experimental locales are shifting from the US public to private sectors as well as to overseas settings, two questions immediately present themselves. The first of these seeks to know the factors that account for such a proliferation of "outsourced" clinical trials and in light of these rapid and recent changes, the second inquires into the relationship between the very generation of human subjects and emergent ethical paradigms.

Capturing these concerns is best illustrated by a clinical trial that tested the efficacy of a marketed anti-retroviral drug, tenofovir, as a pre-exposure prophylaxis (PrEP, or HIV prevention technology) in Cambodia, Nigeria, Malawi, Ghana, and Cameroon. Funded by the Gates Foundation and carried out by Family Health International (FHI), four of the five trial sites prematurely shut down for different reasons. Upon close examination, the failure of the trial to complete presents an excellent case that illustrates 1) how differing forms of state privatization in both the US and African countries facilitate numerous and more rapid transnational flows of clinical molecules that 2) sets new precedents for the emergence of a science-humanitarian apparatus, which is subsidizing HIV related clinical trials while harnessing new kinds of capital and human mobility in the form of clinical molecules and human subjects; and 3) generates emergent debates throughout Africa that reflect radically different sets of ethics not simply at the level of researcher-human subject interactions but also at the level of representation, where scientific rationales, informed consent procedures, and study designs are consistent points of contention.

The study proposed here has two primary and several secondary research objectives:

1. <u>Political Economy of Clinical Trials.</u> The specific contributions include describing and analyzing how:

a. the co-evolution of new technologies, change in laws that create regulatory privatization, and the proliferation of "me-too" molecules in the US contribute to the rise of a new clinical trial industry and the subsequent outsourcing of clinical molecules for clinical research.

b. African state privatization via the International Monetary Fund's Structural Adjustment Program eliminated the capacity for African states to adequately regulate drugs and monitor clinical trials;

c. in the wake of a newly created porous channel that facilitates clinical molecules flowing more easily between US and African states, a new science-humanitarian consortium (clinical

research that is increasingly funded and administered by humanitarian, development, and social marketing firms) is coalescing to finance HIV-related clinical trials – increasingly prevention technologies including vaccines, chemoprophylaxis, and microbicides – generating otherwise absent subsidized markets engaged in the new business of experimentation.

2. Ethics and Scientific Rationales. Specific contributions to the literature include documenting and analyzing how:

a. new debates on clinical ethics in Africa represent a set of paradigms that are significantly different from Western biomedical practitioners and their institutional review boards;

b. study designs and scientific rationales are increasingly harnessed as a mode of ethical concern rooted in two critical factors: 1) inconclusive pre-clinical data and 2) the generation of human subjects for which a new category of personhood is constructed – HIV negative and at high risk to contract HIV – yet also at high risk due to the nature of the trial, which measures drug efficacy via sero-conversion.

c. ethics and scientific rationales are mobilized by both the less expensive technological designs of prevention research and the political economy of trials made to fit into the overall logic of privatization as well as capital and human mobility.

This ethnographic research project will take three years to complete and will be conducted in six countries representing the transnational nature of the trial. It will build on prior studies initiated by the PI focused primarily on democracy, AIDS, and drug politics and circulation in Nigeria. The study will result in conference presentations, journal articles and a book, and will contribute to existing literatures focused on multiple forms of therapeutic and pharmaceutical development, distribution, and ethics; on the co-evolution of scientific technologies and privatization/neo-liberal reforms; and on international political economies and drug geopolitics.

2. BACKGROUND AND SIGNIFICANCE

Little research in science and technology studies has examined knowledge production and technological work in post-colonial settings such as Nigeria and other parts of Sub-Saharan Africa. In such societies, weak regulatory institutions and different political configurations present a radically different context from North American and European settings in which knowledge about scientific authority, controversy, local and inter/national regimes of knowledge, the place of activism, and the interaction of technical and ethical issues is essentially produced.

In line with a STS's longstanding interest in technological objects, there has been recent and increasing attention to ethics, pharmaceuticals and clinical trials (Petryna 2005, Fisher 2006, Sismondo 2004). This research project is very timely because it examines a pre-exposure prophylaxis (PrEP) clinical trial, among the many currently being conducted for the purpose of establishing a preventative strategy for HIV infection. The different classes of preventative trials include HIV vaccines and microbicides (and to a lesser extent, studies on the impact of male circumcision and the use of diaphrams on HIV prevention) yet chemoprophylaxis with antiretroviral agents, such as Gilead Sciences' tenofovir (brand name Viread) is being put forth as a promising new approach (Youle, 2003). This section details a) a brief history of ethics and HIV-related clinical trials in Sub-Saharan Africa, and b) a history

and political economy of the tenofovir PrEP trials, which are contextualized in c) state deregulation and the proliferation of clinical trials. This will be followed by section (d) that describes contributions to, and gaps in, the science and technology studies literature.

a. Ethics and HIV-related Clinical Trials in Sub-Saharan Africa

In terms of clinical treatment for HIV positive people, debates over research ethics and care of subjects have been ongoing over the last ten years. The now well-known AIDS Clinical Trials Group (ACTG) Study 076 established for the first time that the HIV antiretroviral zidovudine is an effective medical prevention of mother-to-child HIV transmission (Conner, et. al. 1994). However, the regimen itself was deemed to be too expensive in most countries, especially African, and uncertainty persisted over what research design to use to meet the needs of a less expensive regimen. In June 1994, a World Health Organization meeting convened to create a research agenda for perinatal HIV transmission. Scientists concluded that placebo controlled trials offer the best option for treatment assessment (Lurie and Wolfe 1997). This decision sparked an international and ethical debate over the use of a placebo and established standards of care in overseas clinical trials. Based upon this decision, subsequent trials took place to which Lurie and Wolfe claimed that 15 out of 16 reviewed were unethical, arguing that when it comes to the standard of care, alternative treatments or previous clinical data are not considered but rather that it is "an economically determined policy of governments that cannot afford the prices set by drug companies" (1997: 855). Since then a number of researchers have debated ethical standards in clinical research (Angell 1997, 2000; Bayer 1998; Benatar 2001; Botbol-Baum 2000; de Zulueta 2001; Lurie and Wolfe 1999; Shapiro and Meslin 2001; Schuklenk and Ashcroft 2000; Temple 2002; Varmus and Satcher 1997). On one side of the debate, these researchers argued that administering anything less than standard care to those on the placebo end of the study was ethically responsible, even if the standard of care medication was already known. On the other side of the debate, critics viewed the use of a placebo as highly unethical. They claimed that research carried out in overseas settings could be held to a standard that differs from requirement in "developed" countries. But nevertheless, the Helsinki Declaration was updated in 2000 that set a standard for ethical care equivalent to that of the country conducting the research as opposed to the host country. Just four years later, Kent et. al. (2004) found that out of all the HIV, tuberculosis and malaria-related clinical trials conducted between January 1998 and November 2003 in Sub-Saharan Africa, only 16% provided care that met guidelines to both intervention and control patients. Despite these claims, none of the international bodies setting guidelines on the ethics of clinical research agree on standardized ethical procedures in overseas trials.

This debate on the ethics of care within well-established treatment guidelines has not yet abated and continues alongside questions raised in HIV prevention trials. The difference between the two different kinds of research –prevention versus cure/alleviation – and the subject of ethical debate is the recruitment of human subjects who are HIV negative for prevention trials as opposed to those who are HIV positive for antiretroviral trials. Efficacy of a clinical product destined as a prevention technology is determined by the number of trial subjects who sero-convert from HIV negative to HIV positive throughout the duration of the trial. Anticipation of this ethical conundrum first emerged in the context of HIV vaccine possibilities. This earlier established literature, which appeared at first in the late 1980s (Christakis 1988) was concerned with reconciling community cultural norms (particularly African) with ethical paradigms of HIV vaccine experimentation (Ajayi 1980; Moodley 2002); and much of these concerns continue to be raised in existing trials (Beloqui 1998; Esparza 1991). More recently, problems with informed consent at the level of comprehension,

decision-making, and risk factors (Marshall 2006) as well as raising concerns for the difficulties in delivering regulatory approval and adequate oversight in developing countries (Berkley 2003) are the increasing subject of attention in clinical research.

Microbicides are another technology that are designed to block HIV infection by directly inactivating the virus. There are no surrogate markers or animal models known that can reliably predict whether microbicides will work in humans, and it is claimed that efficacy can only be assessed through large-scale clinical trials (Coplan et. al. 2004). Therefore, thousands of HIV-negative women deemed to be "high-risk" (usually sex workers), are currently being randomized to active or placebo microbicide groups and followed for several years to compare the rate of HIV infection. Indeed many calls have been made to expand clinical trial research in order to meet the needs of massive, wide-scale testing (Coplan et. al. 2004). Many social marketing firms and development agencies are sponsoring over 30 microbicide trials throughout Africa (Smart 2006). These relationships represent the increasing subsidization of clinical trials by social marketing firms as well as development and foundational agencies, which marks an unprecedented shift in African development agendas that have in the past almost exclusively funded health and not clinical research programs. As the search for more effective anti-HIV therapeutic technologies are put forth as a pressing objective in the AIDS crisis, these "partnerships" contribute to reductions on cost sharing, as well as put forth very attractive research programs that keep their programming afloat. Moreover, the Gates Foundation and others have provided a tremendous source of funding that generates new business possibilities for these agencies.

b. The History and Political Economy of the Tenofovir Trials

With all of the literature establishing the problems of reconciling ethics with clinical research, shutting down the tenofovir trials in four locations posed new questions, analysis, and demands that were never previously anticipated or experienced by clinical researchers. These included 1) questioning the relationship between "third world" experimental subjects and first world drug markets, 2) accusations of faulty trial designs, 3) disagreements over scientific rationales and the uses of particular technologies, 4) demands for long-term health insurance and other care of subjects issues that would require extraordinary costs, and 5) problems with African regulatory drug bodies, which were accused of not being able to properly regulate and oversee the trials. Confronted with these problems with the tenofovir trials, research scientists, especially Page-Schafer, et al. (2005) detailed the enormous amount of preparation put into educating communities, which nevertheless did not serve to deter criticism (Jintarkanon, et. al. 2005). This study will seek to understand and analyze the problem of apprehending different concerns among different institutions and organizations engaged in the tenofovir debates; it hypothesizes that the main problem for such misapprehensions includes the way that ethics are conceptualized. The tenofovir debates suggest a fundamental shift, which locate ethics not in the realm of exchanges between researchers and human subjects, but rather, in the realm of political economy. This sub-section provides a brief history of the trial combined with preliminary research that identifies gaps in the medical literature where the trial was vigorously discussed.

Tenofovir is used as both a first and second line drug for the treatment of HIV infection. But since 2004, the drug went into PrEP trials via the administration of several agencies including the Center for Disease Control (CDC), the National Institutes of Health (NIH), and Family Health International (FHI) in different countries throughout the world. This study examines the FHI-run trial, which was funded by the Bill and Melinda Gates Foundation, and administered at sites in Cambodia, Nigeria, Cameroon, Ghana and Malawi. HIV negative sex workers was the only social group selected for this trial due to perceived

high risk behavior. Since FHI initiated these clinical trials in 2004, four trial sites were shut down without being completed (Mills et. al. 2005b); Ghana was the only site that carried out the trial in full with inconclusive results. While the manufacturer, Gilead Sciences, supplied tenofovir medication for the trial, it did not contribute to financial costs or trial designs.

According to the medical literature and media reports, each site shut down for entirely different reasons. On August 11, 2004, Cambodia was the first to halt the trial even before it started. Page-Shafer, et. al. (2005) report on the process and shortcomings of setting up the trial in Phenon Phen, which included running focus groups and consulting with community organizations. But they did not acknowledge omitting dialoguing with a national sex workers union, Women for Unity, whose members would be ideal candidates for the trial. After reviewing the trial protocol and informed consent, the main point of contention of the Women for Unity was that there was no health insurance provided over the long term (thirty years were requested [James, 2004]) should the sex workers encounter negative effects or sero-convert. Their analysis was rooted in a claim that sex workers in the Third World are the experimental subjects for the eventual drug marketing and consumption practices in the West (James 2004). Such claims grounded in political economy were glossed over and instead only the clinical practices themselves were addressed. The Cambodian Minister of Health ultimately backed up the sex workers' claims and declared that the trial, indeed, was unethical; it withdrew prior government approval and ordered researchers not to proceed.

Shortly thereafter, the Cameroonian government ordered the suspension of the trial on February 3, 2005, where 400 sex workers had been enrolled since September 2004. Preliminary research indicates that AIDS activists in Douala and Paris (who were working closely together) as well as trial coordinators, agree that the media generated tremendous hype about the trial where some media reported that the trial was intentionally exposing sex workers to HIV (which Mills et. al. 2005a analyzed). Not reported in either the media, or the medical literature, was a dispute over remuneration and the referral process for treatment should trial subjects sero-convert. Both Cameroonians and Nigerians cited an historical lack of liability statements noted in trial protocols and informed consent documents in many current and former clinical trials in these countries.

Five weeks later, on March 14, 2005, FHI, on its own initiative, shut down the trial in Nigeria citing technical problems with the trial administration located at the University of Ibadan, at University College Hospital. Acutely different from all other sites and not reported in the media or the medical literature was a national and public debate taking place over a Nigerian AIDS listserv on the ethics and science of the tenofovir trial, lead by the Nigerian HIV Vaccine and Microbicides Advocacy Group (NHVMAG). This was a debate that lasted for several months and is the only established written record on the ethics and science of a clinical trial. NHVMAG is a Community Advocacy Board (CAB) that advocates for new technologies while and also negotiates between trial coordinators and trial subjects for high ethical standards when regulatory agencies in Africa are perceived to fail. Some members of NHVMAG were enrolled in HIV related clinical trials during the 1990s, all of whom reported to me during previous research that they received either no informed consent, dosage counseling, or expired drugs. These experiences prompted them to develop more thorough scientific understandings of clinical trials; and by the time that tenofovir and so many other trials emerged in Nigeria by the 2000s, many of these former trial subjects became literate in international clinical trial standards and protocols. The ethical concerns cited by the Nigerian advocates included a lack of information in the informed consent on side effects; how management of medical conditions of potential co-infections, such as malaria would be handled; cost reimbursement; and lack of official referral process for those who sero-convert.

In addition to ethics, the science and scientific rationales were also cited as problematic. The claims made by advocates included a lack of malaria co-infection safety profiles; future prospects for uptake of pills which fare as badly as contraceptives in developing countries; lack of information on the exact evaluation criteria of the drug's efficacy as a prevention technology; unexplained modification of the National Institute of Allergy and Infectious Diseases (NIAID) toxicity scale; disagreement over the management of clinical and laboratory adverse events as defined in the protocol; and contentions over how data in animal models were interpreted [referring specifically to Tsai (1995), van Rompay (2000, 2002), and Subbarao (2005)]. A number of issues prevented these concerns from being answered or worked out including initial unwillingness of the trial coordinators to establish a meeting despite their claims of the essential need for Community Advocacy Boards in setting up trials (Grant, 2005). However, NVHMAG ultimately stopped a meeting from proceeding, claiming to possess a lack of funds for transport and per diem.

Lastly, in October 2005, the Malawian government halted the trial due to concerns that safety was not tested in HIV positive individuals, including the concern that the drug could give rise to tenofovir-resistant HIV. Nothing beyond this has been reported in the media or the medical journals.

Following these discussions were a series of consultations that were facilitated by The Joint United Nations Programme on HIV/AIDS-UNAIDS (in Durban April 2005 and Abuja June 2005, and Geneva in August 2006) and by the International AIDS Society in May 2005 in Seattle to get a better understanding of the breakdown and to facilitate a dialogue among so-called "stakeholders." These dialogues revealed problems such as ethics in care of subjects linked more explicitly to in-country infrastructure and financial barriers. These meetings established a new precedent for current and ongoing organized debates and cooperation among all actors involved.

The international and in-country discussions were important because they signal emergent debates on overseas experimentation. Most of the bioethics and medical literature on these topics treat ethics as a didactic interactive problem between researchers and human subjects, focusing more often on human subjects' misapprehensions of informed consent and the ethics of placebo and standard of care. The tenofovir debates suggest a fundamental shift, which locate ethics not in the realm of exchanges between researchers and human subjects but rather, in the realm of political economy. This is indexed by the disparate positioning between third world subjects and first world markets; and drug regulatory systems that are dependent upon national economic performance and state agendas, both of which ultimately shape the way that trials are designed and implemented. Indeed, one informant elaborated to me on the relationship between clinical trial protocol approvals and "national interests."

Moreover, the demand for high standards of care directly influences new anti-HIV technological designs, driven by cost-saving reasoning—a reasoning that contributes to overseas outsourcing. As Kent et. al (2005) claim, "(c)omparing the effects of new interventions intended for resource poor settings against the 'best current method' from well resourced settings may be of little value if that method is ordinarily unavailable. That is, using a universal standard of care would proscribe a whole category of research of potential import to resource poor settings, namely the study of inexpensive 'intermediate' interventions that might be effective and feasible, even if considerably less effective than the best standard" (2004:241). These "inexpensive intermediate interventions" already comprise some of the most predominant research being carried out and financed by science-humanitarian collaborations.

An ethnographic rendering of these political and economic dynamics does not yet exist, but is absolutely essential in understanding the making and rise of the clinical trial

industry and the accompanying ethical conundrums. Preliminary research in Nigeria shows that activism around clinical trials only began once a) so many prevention technologies began being tested and b) activists themselves began receiving international funding for their prevention technology advocacy work and scrutiny of clinical trials. In some cases, both funding sources overlap. The combination of advocacy, of HIV clinical trial histories, and a great increase in the current number of trials being conducted were the three crucial factors that made these ethical debates even possible. Therefore, the study will establish the precise relationship between emergent ethical debates, the proliferation of clinical trials, and international research and development/humanitarian consortiums.

c. State Deregulation and the Proliferation of Clinical Trials

This study hypothesizes that the major thematic shift in ethical clinical trial debates is directly linked to the dramatic increase in clinical trials since the legal and financial reorganization of the Federal Drug Administration in 1992 and the already existing structural adjustment induced decline of drug regulatory agencies in African states since the 1980s. That is, deregulated state regulatory agencies are increasingly creating a more "porous" path that expands this industry across borders and increases the traffic of clinical molecules for experimentation. This section details the short history of these developments, which sets the stage for the second hypothesis: the process of deregulation has created the means for new science-humanitarian networks to subsidize and conduct clinical research; these emergent formations shape new ethical debates, scientific rationales, and technological rationales. The latter hypothesis will be discussed in the next sub-section.

1.*Privatization and Legal Reorganization in the U.S*. The 1992 Prescription Drug User Fee Act (PDUFA) followed by the 1997 Food and Drug Administration Modernization Act (FDAMA, or PDUFA II) were legal measures that initiated FDA deregulation. PDUFA requires that the drug industry pay a user fee to the FDA, which totals nearly $1 billion since 1992 (Lawson, 2004). In exchange, the FDA must now fast-track all drugs submitted for marketed approval. That is, the review process has been shortened for every class of drugs, not just for those that were previously fast-tracked under the Orphan Drug Act, specifically designed for drugs to treat those diseases for which few or no therapeutics exist. Because the FDA was required to meet performance goals set by the pharmaceutical companies, the number of new drugs approved jumped to 80%, as compared to the pre-PDUFA period when 60% of new drugs were approved (Lawson, 2005).

After PDUFA and FDAMA were implemented, several major shifts in both drug development and FDA regulatory processes began to emerge. First, there was a huge increase in "me-too" drugs, or near copies of patented originals, flooding the FDA for approval. One of the main reasons why "me-too" drugs are proliferating is because they are developed by simple chemical modifications to existing marketed drugs, which, comparatively, require very little innovation and investment. This is combined with PDUFA and FDAMA's fast-tracking practices that more quickly approve a higher percentage of drugs. Together, the technological innovations of combinatorial chemistry that makes drug modification relatively inexpensive and FDA deregulation that can better guarantee approval makes "me-too" drugs more appealing and lucrative to the pharmaceutical industry.

Second, since PDUFA and FDAMA have been installed, more drugs have come off the market or have been black-boxed due to severe side effects than prior to its installation; and most of these drugs were known to have safety concerns even before they were approved. According to Wolfe and Sasich, workers at the FDA have described a "sweat shop" environment where regulators frequently approve drugs without thoroughly determining their potential side effects and health dangers (Willman, 2000). Wolfe reports that drug companies

will sometimes withhold their data and submit it to the FDA just before the deadline, making it very difficult to thoroughly review. Moreover, FDAMA, the replacement and extension law of PDUFA, eliminated the long-standing prohibition of manufacturers giving out information on unapproved uses of their drugs. Drug companies now have permission to circulate information on the use of drugs for diseases or clinical situations that the FDA never approved (Lawson 2005), easily expanding a drug's market.

Third, less and less FDA funds are being devoted to post-marketing surveys, monitoring prescription drug advertising, and manufacturing and import inspections (Sasich, 2000), all of which the FDA is required to do. Widely practiced in Europe, the post-marketing survey (also considered a fourth stage in a clinical trial) is especially important because it continues to monitor toxicity and side effects that may only be found in large numbers (such as one in ten thousand) and not detectable in a trial that utilizes less numbers of participants. The decline in post-marketing surveys does manage to keep a drug with severe side effects in circulation much longer.

2. *Privatization and Legal Reorganization in African states*. During the 1980s, the International Monetary Fund (IMF) implemented Structural Adjustment Programs (SAPs) that were meant to privatize the state while managing huge debts incurred by the severe decline of the international commodities markets of the 1970s. SAPs particularly targeted state structures, which were, at the time, deemed to be too economically wasteful to recover from problems generated by external debt. Implementing user fees throughout Africa meant that the role of the state in health care and drug manufacturing was severely rolled back and essential services ultimately collapsed (Turshen 1999; Samba 2004; Salako 1997). In Nigeria, the SAP was instituted in 1986 and by the early 1990s, two-thirds of the pharmaceutical industry went bankrupt due to currency devaluation and severe restrictions on imports needed to run the industry (Samba 2004). By the mid 1990s, fake and counterfeit drugs commanded nearly 80% of the pharmaceutical market for which a newly installed national drug regulatory agency could not adequately oversee because the SAP equally incapacitated it (Salako 1997). Preliminary research shows that such measures that rolled back state capacities leave workers untrained and especially unprepared for understanding new drug technologies; or the institutions themselves do not carry out adequate regulatory functions. At the local level, public research institutions are often accused of easily approving foreign clinical trials because they receive computers and other desperately needed equipment that the state otherwise does not provide.

c. Key Themes in the Science and Technology Studies Literature

1. Drugs and new experimental industries. This research project is very much informed by both medical anthropology and STS concerns with drug circulation and consumption especially in the post-colony (such as Whyte et. al. 2003; Masquelier 2001; Lakoff 2006; Regis 2002; Petryna et. al. 2006) – work that was influenced by earlier writings on the anthropology of pharmaceuticals (van der Geest 1996; Nichter and Vuckovic 1997; Ferguson 1983; Del Vecchio Good 1995). But following the Women for Unity in Cambodia (James 2004) and Sunder Rajan (2005), who both observed a disproportionate relationship between third world experimentation (and subjects) and first world drug markets (and consumers), this study contributes to a growing body of STS literature on *experimental production* that: analyzes experiment as a speculative exercise (Rheinberger 1997; Sunder Rajan 2005); mediates relationships between the pharmaceutical industry, the laboratory, and the clinic (Oudstroom 1993); examines scientific and journalistic texts as locations in which to analyze the testing of technologies (Oudstroom 1999); examines the emergence of the contract research organization that facilitates and industrializes clinical trials (Petryna 2005; Fisher 2006);

generates relationships between national and international standards, and studies of practice, co-production, and identity (Reardon 2004; Lakoff 2006; Petryna et al. 2006; Sismondo 2004; Greenslit 2006); analyzes the social construction of clinical trials (Epstein 1995; 1996; Petryna et al. 2006); manages drug and health information (Healy 2002; Dumit and Greenslit 2006); and demonstrates how value, normality and risk are built into clinical trial paradigms, which produce an unlimited maximization of drug prescriptions and market expansions (Dumit 2005; Dumit and Greenslit 2006) as well as the invention of new pathologies (Fishman 2004).

This study will expand on this body of STS work by making several new interventions. Following especially Dumit's (2005) work that poses questions about clinical research and the generation of new markets and forms of value, this project seeks to analyze the proliferation and dynamics of a clinical trial industry that in the context of AIDS, and differential economic, technological, and institutional capacities, operates in profoundly different ways than in the U.S. or Europe. While some work (Petryna 2005) has identified that the industry's tremendous growth is due to patent application and new drug pipeline explosions, the question remains as to how and why we are seeing such explosions in the first place. Moreover, situating the locus of trial dynamics in African countries (where state regulatory agencies are weak and social marketing firms, foundations, and development agencies increasingly facilitate trials) provides a brand new perspective on the business of clinical trials in transnational formation. While contract research organizations serve the experimental end of the pharmaceutical industry (Petryna 2005; Fisher 2006) outside of Africa, the social marketing firm and development industry play a similar role. That is, these agencies serve as the predominant force in subsidizing and conducting (HIV related and other infectious disease) clinical trial research. In other words, new kinds of markets, business structures, and new forms of accumulation are facilitated by clinical research in this part of the world; and the pharmaceutical industry, which is in the business of operating within its usual market schemes, plays the least significant role, usually as a "partner" in these endeavors, and at times, it has no role at all.

2. Emergent ethical paradigms. Critiques of bioethics paradigms have emerged in both the medical anthropology and STS literature that directly address human subjects research and/or existing bioethics paradigms that guide ethical decision-making in medicine and experimentation. Kleinman (1999) points to the disjuncture between the actual realities of people's world and bioethics, while Das (1999) analyzes bioethics and accountability. Bosk (1999, 2005); Bosk and de Vries (2004); and de Vries (2004) have analyzed the procedural cultures of institutional review boards while Marshall and Koenig (2004) critique structural conditions that produce problems with risk and standardizing ethics. Cohen (1999) firmly situates ethics in the realm of political economy and international policy, and argues for the short-comings of simple doctor-patient interactions as a framework to analyze ethical practices. Other work in the ethics of medical technologies and biotechnology focuses on how such technologies come to shape practice and organizational strategies (Dumit 2000; Franklin 1995; Lock 2001; Rapp 1999) as well as how ethics is incorporated into the design of the randomized trial (Marks 1997). In her employment of "ethical variability," Petryna (2005) has provided an excellent foundation for which to understand the debates on clinical trial ethics for which she highlights the role of "crisis" in considering ethical practices. Following Petryna as well as Fischer's notion of "ethical plateaus" (2003), which details novel ethical conundrums that rise out of the application of new technologies and legal frameworks, this study explores new ethical paradigms not previously anticipated by especially PrEP research. These ethical frameworks are located within African states and are not driven solely by

scientists, but more so by community advocates or AIDS activists. This situation differs significantly from Epstein's (1995; 1996) findings where the development of lay expertise and AIDS activism in the U.S. created the groundwork for new clinical trial standards where people living with HIV made increasing demands to be more urgently involved in antiretroviral clinical research—demands that led to the necessary revisal of trial protocols. Preliminary research thus far shows that while AIDS advocates in African states are very welcoming and even advocating new prevention technology research, they approach it with far more caution and scrutiny than did their U.S. activist counterparts in the 1990s. This study seeks to ethnographically analyze these different agendas, concerns, and ideas as they are firmly situated in disproportionate political and economic frameworks across borders and technological divides.

3. PRIOR WORK AND RELATED STUDIES

Dr. Kristin Peterson is a cultural anthropologist whose work focuses on science, medicine and technology studies. Her research over the last seven years has centered on the relationship between policy-making and pharmaceutical circulation. Her PhD dissertation, *HIV/AIDS and Democracy in Nigeria: Policies, Rights and Therapeutic Economies*, was based on ethnographic interviews with scientists, policy makers and AIDS activists. It examined pharmaceutical governance as shaped by global trade, intellectual property law, and AIDS activism; and also analyzed how the transition from military to civilian rule shapes expectations of treatment and creates new institutional structures that produce (or not) pharmaceutical availability. Drawing upon the dissertation, the book manuscript has been solicited by Duke University Press and will be submitted for review by the end of 2007. A number of articles either published or under review reports on research covering issues such as bioprospecting, NGOs, and ethics (Peterson 2001); questions of science, AIDS cure claims, and local clinical trials (Peterson, *Medical Anthropology Quarterly*, under review); and treatment policies as an outcome of structural adjustment programs that have contributed to the rise of fake and counterfeit drugs as well as new patient, doctor and pharmacist practices (Peterson, Duke University Press, under review). An article on Nigeria's national clinical trial debates that address lay and scientist's notions of ethics (Peterson and Folayan) is also currently in preparation. All of these studies rely on in-depth ethnographic interviews and archival data as primary material.

4. RESEARCH METHODOLOGY AND PLAN OF WORK

The study is methodologically organized around interviews and focus groups with key actors, archival and document gathering, and ethnographic data collected by participant observation at conferences on clinical trial ethics and multilateral funding consortiums. To save time and cut down on costs, Cambodia has not been selected as a research site. The study will only focus on African states, research and activism.

a) Methodological Approaches and data analysis:

1. Review of Primary Literature and Development of Interview Questions

The success of ethnographic interviews depends on asking questions that elicit detailed yet nuanced responses, which can be triangulated with other data. To achieve this, considerable time will be spent developing a set of questions that can be used in both focus groups and ethnographic interviews. While a key feature of ethnographic interviews is their open-endedness, well-constructed questions that concretely index the literature can contribute significantly to a good interview. To develop such questions, January - April 2008 will be spent

reading the relevant scientific, medical, and bioethics literature; development literature; media; advocacy group (promoting prevention technology) websites throughout the world, but particularly in Africa; social marketing and development agency websites and reports; and conference proceedings on PrEP and other HIV prevention technologies such as microbicides and HIV vaccines.

The literature will be examined using a grounded theory approach that seeks to identify vocabulary, themes, uncertainties and examples that are of particular concern to a community of practitioners, in this case scientists, scientific agencies, regulatory workers, AIDS activists, PrEP advocacy groups, former trial subjects, and development agencies and social marketing firms who are funding and conducting PrEP trials. Particular attention will be given to the stated research goals, ethical concerns, and proposals for future drug distribution as an outcome of successful trials. The literature review will also be used to map changing funding patterns as well as trends in "strategic international agency partnerships" in order to better understand the role and impact of these new institutional mechanisms and financial support.

A set of questions and examples to stimulate open-ended discussion in ethnographic interviews will be produced through the literature review. These interviews will solicit 1) perspectives and experience on this failed trial; 2) expertise on clinical trials in terms of general approaches, ethics, and new shifts in human subjects research; 3) perspectives on legal and policy reforms and related challenges posed to drug regulatory authorities; and 4) the role and impact of new science-humanitarian consortiums subsidizing and administering PrEP clinical trials. The orientation of primary questions is outlined below.

2. Ethnographic Interviews and Focus Groups

Approximately 80 ethnographic interviews with all actors involved from the pre-clinical stages to the aftermath of the human subjects trial (including scientists, scientific agencies, regulatory workers, AIDS activists, PrEP advocacy groups, former trial subjects, and development agencies and social marketing firms who are funding and conducting PrEP trials) will be conducted for this project, requiring two hours on average. All interviews will be fully transcribed. For those interviews conducted in West Africa and Malawi, a Nigerian transcription service will be used for cost and ease. All other interviews conducted in the US and Europe will be transcribed by a research assistant. Special translation and transcription arrangements will be made for those interviews conducted in French (Cameroon and France). The transcripts will be returned to the interviewee for editing and final approval. The approved transcripts will then be uploaded into ATLAS-ti, a qualitative data-analysis software package. ATLAS-ti, based on Juliet Corbin and Anselm Strauss' conception of grounded theory, can be used for electronically coding data, creating theoretical memos, tracing connections, and developing theory.

Interviews will be conducted face-to-face whenever possible, as the travel budget allows. The selection of research sites for this project reflects the attempt to cluster interviews to the degree possible and to minimize international travel. Two research consultants, one located in Lagos, Nigeria and the other located in Lilongwe, Malawi, will help to conduct interviews in order to cut down on travel costs. When otherwise unavoidable, interviews with key researchers will be conducted via telephone. The interviews will be transcribed and circulated back to the interviewee for final approval.

Focus groups will only be conducted in Nigeria where the PI has already established contacts with former clinical trial subjects who have yet to be formerly interviewed. These discussions will address motivations for, and experiences of, being enrolled in a clinical trial and will be triangulated against individual interview data. The objective of these focus groups

is to establish patterns of ethical practices from the 1990s onward as well as identify whether such patterns can be linked to larger structural issues.

Interviews will be conducted at several research sites. The research sites in the U.S. that conducted and generated both pre-clinical data and funded and/or carried out tenofovir PrEP trials include: Center for Disease Control, National Institutes of Health, Family Health International, The Gates Foundation, Gilead Sciences, California Regional Primate Research Center at the University of California, Davis and the University of Washington. These latter three carried out pre-clinical data in animal models. It should be noted that with the exception of the Cambodian site where the NIH jointly conducted a PrEP trial with FHI, all shut down sites included those conducted by FHI. The research project intends to nevertheless interview those researchers located at the CDC and the NIH as their expertise in prevention trials is invaluable and they continue to carry out tenofovir PrEP clinical research.

The research sites outside of the U.S. include those who hosted the trials, community advocate groups who contested trial ethics and designs, and organizations who facilitated trial dialogues: University College Hospital at the University of Ibadan; Nigerian Microbicides and Vaccine Advocacy Group Nigeria; University of Ghana; African Microbicides Advocacy Group, Reseau sur l'Ethique, le droit, et le VIH/SIDA (REDS); University College Hosptial, Lilongwe, Malawi; SIDACTION; ACT UP Paris; UNAIDS; International AIDS Society; and all in-country regulatory agencies. The PI has made initial contact with nearly all of the workers at these sites and has very good access to carry out this research project.

3. Participant Observation

Participant observation will be carried out at conferences on PrEP work and human subject trials. Attendance at these meetings will provide access to a broad network of international and U.S. scientists, donors, PIs, AIDS activists and community advocates of prevention technologies. The conferences will provide a broader scientific and ethical context of PrEP and other prevention technologies that situate the tenofovir trials more thoroughly. The two main conferences to be attended are the 2008 International AIDS Conference in Mexico City and the 2009 International Conference on AIDS in Africa (venue yet to be announced). At both these conferences scientists report on the latest prevention technology findings with advocates presenting on their own work.

b. Research Questions and Analytic Goals

The interview questions provided here are limited examples of the kinds of questions that will be asked during an interview, all of which have received Michigan State University Institutional Review Board approval. The interview questions will be refined and fleshed out during the literature review component of the study.

1. For scientists generating simian data on tenofovir as PrEP:

Primary questions will be oriented toward seeking: 1) the factors that influence and initiated emergent HIV prevention technology research; 2) the interpretation of simian data and how it gets translated into categorizing tenofovir (or other clinical molecules) as a model candidate for HIV human PrEP trials especially when inconclusive data on the efficacy of tenofovir and microbicides exist; 3) if the criteria for molecular candidates for human HIV trials have changed over time in the context of the AIDS crisis; 4) how "favorable results" get defined and standardized in AIDS PrEP research; 5) the perceived role of AIDS activism in guiding HIV PrEP clinical research; and 6) the perceived role in funding in guiding HIV PrEP research.

2. For regulatory workers in African states:

Primary questions will be oriented toward seeking a thorough understanding of: 1) the role, structure, and constraints of the agency; 2) the application process for foreign clinical trials, approval criteria, number of clinical trial applications over ten years, and approval rates; 3) the agency's relationship to national and local institutional review boards as well as the ministry of health in terms of approval and oversight processes; 4) the approval and monitoring processes for tenofovir and reasons for initiating trial shut down (in Malawi and Cameroon); 5) perceived ideas on the effectiveness of regulatory oversight; 6) relationship with FDA in the U.S., and 5) informed opinions as to why the trial shut down.

3. For regulatory workers in the U.S:

Primary questions will be oriented toward seeking a thorough understanding of: 1) procedural changes since the institution of PDUFA and FDAMA; 2) the application process for overseas clinical trials, approval criteria, number of clinical trial applications over ten years, and approval rates; 3) the agency's (changing?) relationship to African states institutional review boards, regulatory agencies, and ministries of health, and their perceived functioning in terms of approval and oversight processes; 4) perceived ideas as to why applications for foreign clinical trials are on the rise; and 5) the impact this has on the approval process.

4. For FHI, Gates, and the primary sites of investigation in African countries:

Primary questions will be oriented toward seeking an understanding of: 1) what sparked an initial interest in funding/working on an HIV PrEP technology—what potentials did the science show?; 2) the perceived reasons why the tenofovir PrEP trials became so contentious; 3) perceived ideas of numerous community and media responses relating to ethics, trials designs, and scientific rationales and what accounts for the difference in these ideas between the "community" and researchers?; 5) perceived ideas of the outcome of consultative meetings sponsored by UNAIDS and IAS; 6) institutional reactions to the tenofovir PrEP trial controversy; 7) the relationship between funding and research; and 8) marketing potential in Africa.

5. For AIDS activists and prevention technology advocates in France, Cameroon, Ghana, Nigeria, and Malawi

Primary questions will be oriented toward seeking an understanding of: 1) initial reasons for and interest in becoming involved in "community" concerns over clinical trials; 2) the primary concerns over the tenofovir trials and whether those same concerns exist across prevention technology research; 3) perceived ideas relating to ethics, trials designs, and scientific rationales and what accounts for the difference in these ideas between the "community" and researchers; 4) perceived ideas of media responses to the trial; 5) perceived role of the "community" in PrEP clinical research; 6) perceived ideas of the outcome of consultative meetings sponsored by UNAIDS and IAS; 7) the relationship between funding and research; and 8) marketing potential in Africa.

6. For former human subjects enrolled in HIV related clinical trials

Primary questions will be oriented toward seeking an understanding of: 1) his or her mode of recruitment and motivation to participate in a clinical trial; 2) his or her experience with informed consent procedures; 3) his or her comprehension of the trial; 4) procedures required of him/her in order to be enrolled in the trial; 5) how care of subjects was being handled throughout the trial; 6) experiences with health and/or post-trial monitoring.

c) Schedule of Research

The proposed study will take three years, beginning in January 2008 and ending in December 2010. The schedule of work will be as follows:

1. January 2008-December 2008

- Collect and analyze articles, grants, and journals focused on the tenofovir PrEP trials and other PrEP research, and refine an existing set of a preliminary questions for ethnographic interviews (January-April 2008).
- Conduct first six interviews in May 2008 in Nigeria: (two each) regulatory workers, AIDS activists and primary investigators of tenofovir at University College Hospital at the University of Ibadan in order to conduct an initial evaluation of the interview questions (May 2008).
- Transcribe and analyze first six interviews, and return to interviewees for editing and approval. Refine interview questions, develop organizational structure for data analysis (May 2008).
- Conduct on-site interviews in Nigeria to include regulatory workers, AIDS advocates, scientific researchers (June 2008)
- Interviews will be transcribed shortly after they are conducted, so that they can be returned to the interviewee for editing in a timely manner (July 2008).
- Construct and refine codes for analysis of interviews using Atlas-ti software (July 2008).
- Refine and revise interview questions based on summer experience and review of recent journal articles and SNF grants (July and August 2008).
- Conduct on-site interviews with Paris AIDS activists and UNAIDS officials who facilitated international dialogues on tenofovir trials (Sept 2008)
- Present preliminary findings at annual meetings of the Societies for the Social Studies of Science in Rotterdam, Netherlands
- Conduct on-site interviews in Lilongwe, Malawi with regulatory workers, AIDS advocates, national ethics board, and primary research investigators (Oct-November 2008, 4 weeks total)
- Continue analysis of transcript data and draw out comparisons and themes as laid out in the research questions that orients this study. (December 2008)

<u>2. January 2009-December 2009</u>

- Continue analysis of existing transcript data and initiate focus group discussions and analysis in Nigeria (January-March 2009)
- Conduct interviews with AIDS activists, regulatory officials, media, and primary research investigators in Cameroon (April 2009)
- Continue data analysis in Nigeria (May 2009)
- Conduct interviews with AIDS activists, regulatory officials, media, and primary research investigators in Ghana (June 2009)
- Initiate interviews in the US (July-August 2009)
- Prepare findings to present at the International Conference on AIDS in Africa, Society for the Social Studies of Science, and the American Anthropological meetings (fall 2009)
- Continue data analysis at both MSU and Nigeria (fall 2009)

<u>3. January 2010-December 2010</u>

- Conclude interviews in the US (January-March 2010)
- Conclude data analysis (April-June 2010)
- Conclude follow up research and shut down research sites in Lililongwe and Lagos (July 2010)
- Initiate articles and book manuscript (August 2010)
- Complete two articles and book draft (December 2010)

d) Research Ethics

The human subjects for this study will be research scientists, development agency and social marketing firm officials who fund the trials, AIDS activists, HIV prevention technology advocates, former trial subjects, primary clinical trial investigators, ethics and internal review boards, and regulatory agency officials located in the U.S., France, Nigeria, Cameroon, Ghana, and Malawi. With the exception of former trial subjects, initial contact will be made by phone or email, and the aims and scope of the study will be explained. Former trial subjects will be recruited for interviews through local NGOs where they are members of support groups. A representative from the NGO, and not the PI, will provide information supplied by the PI on the study to the potential interviewee. If these former trial subjects agree to be interviewed by the PI in either a group or individual format, then their names will be known only to the PI. If a potential interviewee does not agree to be interviewed, then the PI will not know his/her identity. All interviewees will be told that their participation in the interview component of the study is fully voluntary. A copy of the informed consent will be provided ahead of the interview and s/he will receive a copy; a detailed explanation of the informed consent will be explained immediately prior to the interview. This consent form will give interviewees the opportunity to remain anonymous, or to designate other conditions for use of the interview material. The consent form will also indicate that interviewees will have the opportunity to review and edit the transcripts of their interviews before direct quotes are excerpted. All engagement with interviewees will follow the code of ethics of the American Anthropological Association. Michigan State University has granted IRB approval for the project.

5. DISSEMINATION

Research results will first be presented at the annual meetings of the Societies for the Social Studies of Science, the American Anthropological Association, and the African Studies Association. This will provide opportunities to get feedback from other social scientists as the research progresses. Results will also be published in journals such as *Science, Technology and Human Values*, *Social Studies of Medicine*, and as a book. The book and journal articles resulting from this study will be of interest to a wide cross-section of researchers in the social studies of science because the study has been designed to draw out key themes in this interdisciplinary field. Results will also be disseminated at future International Conference on AIDS in Africa and the International AIDS Conference. A policy report will be produced and disseminated to all of those who volunteered and contributed to the research process; it will also be disseminated to institutions and organizations that are actively planning PrEP and other prevention technology research as well as working actively on overseas community preparedness in clinical trial research (these include leading research institutions and international development agencies). The policy report will take a "lessons learned" approach and will make concrete suggestions for future interactions between research scientists and community advocates.

6. RESULTS OF PRIOR NSF SUPPORT

The PI has not received NSF funding during the past five years.