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Ethical and Efficacious Interventions: HIV Pre-Exposure Prophylaxis, Behavioral-Pharmaceutical Slippage and Biomarkers

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Introduction

On November 23, 2010 the iPrEx OLE clinical trial released its phase III (safety and effectiveness) findings. The randomized, multisite, placebo-controlled study tested the efficacy of Truvada (an antiretroviral pharmaceutical) as a pre-exposure prophylaxis (PrEP) for HIV. The trial investigators from Gladstone—a non-profit, clinical research management (CRM) company affiliated with UCSF and responsible for the management of the trial—recruited a total of 2,499 men who have sex with men (MSM), all self-reportedly at high risk for HIV-infection from eleven sites in six countries. Through the intervention Truvada-based PrEP was proven efficacious: the participants that received a combination oral tablet of tenofovir disoproxyl fumarate (TDF) and emtricitabine (FTC), sold under the brand name Truvada, experienced an average of 43.8% fewer HIV infections than those who received the placebo pill. Further, among those who ingested Truvada during at least 90% of the trial days, as verified serologically through biomarkers, the risk of infection was reduced by 72.8% in relation to the placebo. In December 2010 Time Magazine named iPrEx the top medical breakthrough of the year.

For nearly a decade prior, similar pharmaceutical PrEP trials had been conducted but none completed phase III—the phase in which safety and effectiveness are determined—and to date iPrEx is the only such trial to prove safe and effective upon completion of phase III. With such an understanding the leading question is: How is iPrEx different than its abandoned predecessors? The most relevant and recent trial to be abandoned was FEM-PrEP, which began in May 2009 and put forth the same intervention arm as iPrEx—the daily oral intake of Truvada (TDF/FTC). The trial included a cohort of 3,900 heterosexual women in Kenya, South Africa, Tanzania and Zimbabwe. It was abandoned April 18, 2011 when the Independent Data Monitoring Committee (IDMC) found no significant differences in HIV infection rates between the cohort of women receiving Truvada and the cohort receiving the placebo pill.

Ineffectiveness is only one cause for the termination of a trial as two additional terminated trials demonstrate. In July 2004 the PrEP trial conducted in Cambodia was terminated. This trial tested the effectiveness of an antiretroviral pharmaceutical known as Viread—comprised of tenofovir, like Truvada, but not emtricitabine—among a cohort of women who have high-risk commercial sex. The trial was abandoned not

because it was proven ineffective but because of ethical concerns among the trial participants and ACTUP-Paris, an organization with an important history in HIV activism and pharmaceutical development. The concerns participants and activists expressed included "alleged inadequate prevention counseling by the study investigators, a lack of pre- and post-test HIV counseling, and the nonprovision of medical services and insurance for those who seroconverted during the study or experienced adverse events related to the trial drug" (Singh and Mills 2005). Soon thereafter in February 2005 a HIV PrEP trial in Cameroon was terminated. In this case, as well, participant concern and public protests led by activist organizations contributed to the premature end of the trial. Activists claimed the investigators intentionally allowed participants to become infected and provided inadequate counseling, having only five counselors for four hundred participants (IGIN 2005). Discussing these failed trials Edward Singh and Jerome Mills suggest irresponsible reporting and activist demonstrations in the media played a significant role in the protest and subsequent abandonment of the trials. Singh and Mills also express concerns about the potential stigma such media attention may foster for tenofovir and future tenofovir PrEP trials.

Amidst a field characterized by controversy and shortcoming it is vital to understand what is different about the iPrEx trial and what may have influenced its success. The key discernable features include its geographical distribution, the constitution of its high-risk cohort and important methodological and ethical components in which matters of choice and adherence find new forms.

By recruiting 2,499 men who have sex with men (MSM) to participate, iPrEx became the first HIV PrEP trial to exclusively include a cohort of MSM. A study involving a cohort of MSM varies significantly from trials with cohorts of heterosexual women, primarily with respect to the differences in legacies of affect between the two groups. In *Impure Science* Steve Epstein illustrates aspects of this legacy with reference to ACTUP activism, a movement that called for and successfully influenced the development of desperately needed biomedical interventions. The success of ACTUP resonates in contemporary understandings of relationships between activism and biomedical developments for HIV treatment involving MSM, but as demonstrated by the cases of terminated trials involving commercial sex workers in Cambodia and heterosexual women who practice high-risk sex in parts of Africa, the influence of activist legacies may be particular to the high-risk group involved.

The geographical arrangement of iPrEx is relatively diffuse, with cohorts split among study sites in six countries—Brazil, Ecuador, Peru, South Africa, Thailand and the United States. Considering such diffusion, it is interesting that areas where controversial trials have been conducted in the past, such as Cameroon and Cambodia, are not included. Yet, the geographical distribution of trial sites seems suddenly less diverse when one realizes 1,200 of the 2,499 participants are from one country, Peru. This fact is intriguing because Peru is becoming increasingly popular as a site for United States based international clinical trials Unites States, largely due to the opportunities afforded by its less-developed regulatory landscape and the *pharmaceutical naïveté* of its populations (Petryna 2005). The United States is also a compelling site for this clini-

cal trial. The United States is a far less common site for trials, in large part due to the prominence of pharmaceutical use among its citizens and the more robust regulatory systems in place (Petryna 2005). However, the particular histories and public health structures of the two U.S. cities in which iPrEx is conducted afford rare opportunities for an international clinical trial to take root. Boston and San Francisco, the two cities included in the trial, are notably well fit for the trial as they each host particularly resilient HIV/AIDS care facilities. Because U.S.-based participants prove to be the most adherent to the pharmaceutical regimen in the trial, these many structural elements and the inclusion of such participants seem significant.

Using biomarkers to monitor adherence to the pharmaceutical regimen, iPrEx is methodologically unique among HIV PrEP trials. This practice allows for additional claims to be made about the efficacy of Truvada in the trial. Whereas many clinical trials, including the preceding HIV PrEP trials, may only claim the proven efficacy of the technology in question, the iPrEx trial was able to make further claims of efficacy based on the adherence data collected. Such data collection and monitoring allowed the investigators to show greater efficacy; an average of 72.8% reduction of HIV-infection risk among the participants who adhered most strictly to the protocol, as determined by the detected amounts of Truvada in their blood samples, which were collected monthly.

In this article I present the distinct qualities of iPrEx in conversation with ethical frameworks governing the conduct of clinical trials, highlighting the multiplicity of ethical constructions, influences of economic demands in scientific processes and the moral implications of biomedical participation evident in the trial. I also emphasize processes through which notions of choice, characteristic of neoliberal ideology, and particular methodologies for monitoring adherence allow for greater claims of efficacy to be made. At its very core this paper is an exemplar in the shifting terrain of modern biomedical practice and pharmaceutical development—it identifies processes that place a greater burden of responsibility on the individual patient, a biomedical participant imbued with neoliberal idealism.

Ethical Reformulations: Bioethics, Flexible Ethics & Ethicality

The ethics of clinical trials are determined according to multiple registers. A number of international statutes provide guidelines for ethical conduct, including the Nuremberg Code (1949), Declaration of Helsinki (1964–2000, 2008), The Belmont Report (1979), CIOMS/WHO International Guidelines (1993, 2002), and International Conference on Harmonization/Good Clinical Practice (ICH/GCP). Ethical frameworks established by clinical researchers also exist, such as one made of seven basic principles intended to answer the question: "What makes clinical research ethical?" constructed by Emanuel, Wendler, and Grady and adopted by the National Institutes of Health as part of an Ethical Principles in Clinical Research training tool. The seven principles include a valuable scientific question, valid scientific methodology, fair subject selection, favorable risk-benefit evaluation, independent review, informed consent and respect for enrolled subjects (Emanuel, Wendler, and Grady 2000). Clinical trials are conducted

and justified according to these ethical guidelines. The HIV PrEP trials must adhere to these guidelines, as well as additional ethical criteria developed alongside the legacy of ethical controversy associated with HIV treatment and prevention practices. With this legacy comes an expectation for HIV-related interventions to entail a community engagement component, as evidenced in the ACTUP Paris protest of the Cambodian trial and in the success of the iPrEx trial, deeply engaged with community activist organizations.

In *Impure Science* Steve Epstein provides valuable insights into the development of such expectations by highlighting the role of community members and explaining his concept of *lay expertise*, a vital characteristic within the development of the AIDS activism movement and the subsequent development of effective pharmaceutical interventions. The lay expert is an "organic intellectual" that is able to "contest the mainstream experts on their own ground" (Epstein 1996). Epstein explains the ways AIDS activism in the United States promoted interactions between public and private forms of expertise and created new dynamics and standards of acceptance within scientific projects. The lay expert influenced the politicization of science. Pressured by the iconic ACTUP activism calling for desperately needed biomedical interventions, a significant infrastructure has developed to serve the needs of men who have sex with men in large U.S. cities, like San Francisco. Yet, in the case of the iPrEx trial, the significance of activism is not limited to San Francisco, or even the United States. In fact, there is a history of activism in Peru that influenced the creation of the trial, but that history too is controversial. Dr. Grant Colfax, Director of HIV Prevention for the San Francisco Department of Health, and Mark Cloutier, the outgoing Director of the San Francisco AIDS Foundation, have significantly different opinions about the Peruvian activist movement that influenced the development and success of iPrEx. Dr. Grant Colfax presents a comparison of the role of activism in iPrEx and the trial involving Cambodian commercial sex workers (interview with author, March 15, 2011):

> Kim Paige, who is an Epidemiologist here, was the primary investigator. Bob Grant (Principal Investigator of iPrEx) was her collaborator. They tried to implement a PrEP trial in Cambodia years ago now, working with commercial sex workers. They weren't able to get it through because of the commercial sex worker activist group. It's an interesting contrast about community activism and engagement being a positive and organic force on both sides. One led to the abortion of a trial, the other led to the success of a trial. It's an interesting tale of two trials.

Mark Cloutier is skeptical about the influence of activism and notes other interests (interview with author, March 7, 2011):

> Peru, there's a long history there. There's money—a lot of money, buckets of money—sent there through clinical trials. There are two very famous researchers and they're in competition with each other … (over) who's doing

> the best research and who has access to the population. There are certainly HIV activists down there that may be partners, but I wouldn't say they're leading the charge. It's the researchers.

Though their messages differ, viewed together these representations of the trial make apparent the influences of politics and capital as well as the global context in which clinical trials are conducted.

Adriana Petryna presents similar perspectives in her work while complicating ethical constructions concerned with globalizing clinical trials. In her published article, "Ethical Variability: Drug Development and Globalizing Clinical Trials," Petryna highlights the lack of ethical conduct in the administration of trials and the relevance of flexible ethics in the development of clinical trials around the world:

> New trials are being performed in geographical areas of political and economic instability and unprecedented health care crises and where subjects are readily accessible. Drug companies' apparent ease of accessibility to such areas raises questions about the unequal social contexts in which research is being performed and about how conditions of inequality are at present facilitating a global proliferation of pharmaceutical drugs trials (Petryna 2005).

Adriana Petryna explains trials are also being pushed to distant shores because the available pool of human subjects in the United States is shrinking—the relatively affluent U.S. population is using too many drugs (Gorman 2004). Treatment saturation is making Americans increasingly unusable from a drug-testing standpoint, as our pharmaceuticalized bodies produce too many drug-drug interactions, providing less and less capacity to show drug effectiveness and making test results less statistically valid. Indeed, whatever an American is ready to provide as a human subject, owing to a belief in scientific progress, altruism, or therapeutic need, will never be enough to satisfy the current level of demand for human subjects in commercial science (Petryna 2005). So, human-subjects trials are increasing in other countries, predominately less-developed counties, like Peru, where pharmaceutically naïve populations can be found.

It seems Adriana Petryna provides a provocative lens through which to view the iPrEx clinical trial, its many locations, aims and ethical constructions. It is certainly important to consider the future of HIV PrEP trials in this light, however the iPrEx trial is more complex than easy comparison can explain. Steve Epstein's notion of lay expertise and Adriana Petryna's pharmaceutical naïveté blend here to further ethical standards. Such an approach is evident in the trial's tireless efforts for community engagement and education. The construction of community forums and the reliance on community trust are responses to historical controversies over medicalization and serve as exemplars of the historical influence of activism and legacies of affect.

Following this representation of bioethical frameworks, it needs to be noted that ethicality implies something different and is a point of departure for this paper. In Sharon Kaufman's recently published work, "Medicare, Ethics and Reflexive Longev-

ity," she articulates the difference between such bioethical guidelines and ethicality, and I use the term as she does, "to emphasize ethical rationality as constituted in and through political-economic structures, the organization of treatment practices and their effects on healthcare providers and consumers, and as located throughout the social fabric and enabled through the routines of clinical care" (Kaufman 2011). Explaining ethicality, Kaufman elaborates on the constructions of longevity-making, a process facilitated by Medicare policy and technological innovation that transforms end-stage diseases into chronic conditions and upholds the utilization of such a conglomeration as an ethical necessity.

The ethicality of PrEP has similar import. The conditions of HIV/AIDS treatment and prevention programs make for a characteristically different form of ethicality, but similar relationships between policy and biomedical innovation within the development and deployment of HIV PrEP programs hold the potential to influence definitions of ethical HIV-prevention measures. HIV PrEP moves the discussion of ethics from one pertaining to treatment to one concerned with prevention and in doing so, offers a valuable point of intervention for policy makers and healthcare providers to begin processes of amendment as prevention, as a mode of care, takes hold.

A brief outline of the mechanics of HIV PrEP ethicality begins as explanations regarding the ethics of PrEP trials point to Guideline 29 of the Helsinki Declaration, which indicates PrEP interventions should be tested against the best prophylactic interventions available (Singh and Mills 2005). Since PrEP trials themselves constitute a stage in the development of the first pharmaceutical prophylaxis for HIV, there is no established pharmaceutical standard of care. Safe-sex education and condoms are offered as the ethical alternative fit for accurate comparison. Interestingly, ethical disputes concerning PrEP do not emphasize the lack of pharmaceutical equivalence, but instead, take issue with counseling capacities, accepting the ethical guidelines as an operational definition of what is ethical. The parallel drawn between the ethicality Sharon Kaufman has identified and the form of ethicality expressed in iPrEx can be examined within this line of inquiry. Reliance on this ethical guideline reduces the realm of morality to an international code and an entity to be molded by the exigencies of economic configurations as well as the circumstances of time in relation to the development of well-vetted procedural codes.

The ethicality of HIV PrEP trials forms as innovative interventions pursue regulatory gaps, such as those created by the apparent lack of Guideline 29 of the Helsinki Declaration. By passing through these regulatory gaps, innovative interventions offer opportunities for new forms of vigilance among regulators, pharmaceutical companies and patients. As evidenced in activist demonstrations, pharmaceutical rollouts and the publication of further ethical mandates, all participating parties are implicated in morality-making processes, in the constitution of this ethicality. Yet, it seems the distribution of power is unbalanced in cases where ethics go unquestioned. The differences between issues that inspire ethical controversy and the issues that are accepted as ethically sound inspire this paper and what I believe to be an important form of vigilance. This very vigilance takes interest in evaluating iPrEx methodologies and their recep-

tion relative to those of methodologically similar placebo-controlled trials, such as those in Cambodia and Cameroon as well as the infamous Uganda-based trial that was terminated after a fierce debate concerning the ethics of using a placebo in a vaccine trial.

Informed by the experiences of terminated trials, in a May 2003 report the Global HIV Prevention Working Group, convened by the Bill & Melinda Gates and Kaiser Family foundations, concluded with a statement regarding the value of "combination prevention":

> A key finding from Uganda's experience is that no single factor or intervention can adequately explain the country's extraordinary progress in reversing its potentially catastrophic epidemic. Uganda's success underscores the effectiveness of a combination of proven approaches to HIV prevention: AIDS awareness campaigns, community mobilization, targeted behavior change programs—encouraging delayed initiation of sex, mutual monogamy, and condom use—voluntary counseling and testing, and treatment of STDs (Global HIV Prevention Working Group 2003).

Matters of Choice, Adherence and Behavioral-Pharmaceutical Slippage

Revisiting prevention approaches from past projects, such as those in Uganda, illuminates the epistemic transition being made in HIV PrEP trials more generally and iPrEx specifically, in which distinctions between behavioral and pharmaceutical interventions are in flux, and what is effective is being reconsidered. The words of one iPrEx Principal Investigator demonstrate this transition:

> Prevention has had a rough ride. It's clear that as prevalence has increased every year and seemingly, incidence right behind it, we haven't made much headway on prevention. The emphasis has been primarily on behavior change and condom usage and the statistics speak for themselves. We are not winning the war. In a word, we need biomedical technologies to really start turning off the incidence tap. Otherwise, I think [we are] really in a lot of trouble in terms of how we treat our way out of this epidemic. (Bernal and Barra 2009)

Such reliance on treatment for prevention is not unique to the trial, but indicative of a trend in HIV-prevention programs. In San Francisco and Boston, the U.S. cities where iPrEx has been conducted, the trial intervention resonates with "treatment as prevention" programs put forth by public health departments. These programs approach HIV prevention from a different angle, emphasizing treatment for HIV-positive individuals, but maintain the same ideal as PrEP interventions: high pharmaceutical adherence rates. The efforts are motivated by the knowledge that greater adherence to the pharmaceutical regimen generally reduces the HIV viral load and in turn, the likeli-

hood a HIV-positive individual will transmit the virus.

To monitor adherence within the iPrEx trial, biomarkers for the active pharmaceutical were employed. The use of biomarkers allows for the acknowledgement of behavior to be bypassed as the experiences of participants are cloaked in rates of adherence. Importantly, this process also allows for claims of greater efficacy in the trial and introduces a significant neoliberal expectation—the expectation of adherence—fostered in the report of the intervention's effectiveness among the most adherent members of the cohort. In an efficacious framing, the participant who chooses to adhere to the regimen will be successful. Justification of such an intervention, once controversial but rendered logical and ethical, proceeds in this way. Appeals for FDA approval that boast 72.8% efficacy among those who are at least 90% adherent may very well find greater success than reports of 44% efficacy among a cohort that has consumed the pharmaceutical half as often as instructed. Monitoring participants on an individual level with biomarkers also allows for adherence to be analyzed on multiple levels, within which geographic and cultural correlations have been found. According to the iPrEx Director of Community Relations (interview with author, March 31, 2011):

> Only fifty percent of the Andean participants have detectable levels of the drug in their blood, which means fifty percent do not take the drug. Meanwhile, U.S. participants have the highest concentration of the drug in their blood—around ninety-three percent.

In explanations of the disparities found, the Director of Community Relations points to a variety of cultural differences, including age, experience with biomedicine, knowledge of HIV and activism. Differences in age—notably, older U.S. participants and younger Andean participants—are explained alongside histories of HIV-related activism among gay communities, broadly defined and with reference to 'surviving the epidemic' and ACTUP demonstrations in the United States. Motivations to participate are also explained, based on the premise that U.S. participants join the trial because they want to help while Andean participants need to help themselves, as the money 'makes a difference in Peru.' In a state where prejudice seems as troublesome as inequality, especially among 'vulnerable populations'—female sex workers, MSM, transgendered women—access to care is noted as all-important, and the trial provides access, however temporary.

Though one might find justifiable reason for concern within the disparate conditions of the trial and its results, the element of choice complicates the lessons learned from such disparities. The iPrEx Director of Community Relations states (interview with author, March 31, 2011):

> The good thing about seeing this lack in the adherence is that they were making a choice. They were making a choice and taking it. What we were emphasizing was the use of condoms, reduction of the number of sex partners and the practice of safe sex because we don't know if Truvada works, and we

> don't know if you're taking a placebo.
>
> We're telling the participants every month that they shouldn't trust the study medication. So, they have to continue other prevention strategies. They're making the choice of taking it or not. They really didn't know.

Choice imports notions of patient freedom and serves here as an ethical caveat to the concern that may otherwise be fostered in a trial with so much at stake. When pharmaceutical adherence, seroconversion and medical access define one's experience, the alleged choice that is being referenced can hardly be thought of as choice at all. Choice, as a mode of conduct within prevention efforts, is an undeniably neoliberal offering. To be a successful participant within this biomedical structure one must bear individual risks and responsibilities, and become an adaptable subject (Foucault 1978, 1990). Community-wide efforts for prevention rely on compliance and the acceptance of potential risks to physical, psychological and social health. However, with an acutely biomedical representation of adherence and choice, further concerning elements of the participants' experiences may be overlooked, such as the perceptions of toxicity that were far more common among the Andean cohorts, comprised of pharmaceutically naïve populations. The iPrEx Directory of Community Relations also offers an explanation of the way toxicity and risk appear in the trial (interview with author, March 31, 2011):

> Among other things, we do monitor adverse events. We also monitor social harms in the trial. One of our major concerns was a high report of suicidal ideation and suicidal attempts during the blinded phase of the study. We were really concerned to know if the study medication was affecting these situations. So, these participants were immediately identified and we started monitoring depression and trying to establish a scale. If we had an extreme case of depression, we would refer them to a psychiatrist and the study would assume the cost of that. Of course, at the clinic there are counselors, but we did refer them to specialized care.
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> We had several cases where study participants took all of the study medication to … They took all of the study medication to commit suicide.
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> They assume they are taking the active medication and not the placebo because if you are taking a bunch of the placebos, you get … (a sugar high). We took those cases and realized there was no difference between the active arm and the placebo arm.

In this example, it is apparent that the risk of consuming a pharmaceutical used for HIV prevention weighs heavy on the minds of the Andean participants. Also apparent in this example is the attention given to such cases by clinical trial investigators.

Such response differs significantly from and has perhaps been inspired by the counseling services that were deemed inadequate in previous trials.

Recognizing the challenges, the primary investigator for the trial, Dr. Robert Grant, takes an interesting tack. During a forum with various community members, trial participants and other investigators, Grant exclaims, "Let's celebrate every pill. Let's celebrate every pill people are willing to take!" (Bernal and Barra 2009) These events and their responses demonstrate the ways scientific and medical practices adapt over time, the sometimes concerning realities of medical participation, and exactly how flexible ethics can be.

Conclusion

As we look toward the future and analyze what treatment-oriented prevention efforts may look like, the implications suggest many potential forms. Currently, there are three ongoing HIV PrEP clinical trials in phases IIb and III: the Bangkok Tenofovir Study (CDC 4370), Partners PrEP and VOICE (MTN 003). The CDC-sponsored Bangkok Tenofovir Study has completed enrollment of 2,400 injecting drug users (IDU) and expects results in 2012. The Partners PrEP study is funded by the Bill and Melinda Gates Foundation, involves a cohort of 4,700 serodiscordant heterosexual couples and its anticipated date of completion is in 2013. The National Institutes of Health (NIH) and the Microbicide Trials Network (MTN) sponsor the VOICE trial, are also expected to be completed in 2013. In addition to the intervention of daily oral TDF or daily oral TDF/FTC as incorporated in other ongoing or recently completed trials, VOICE incorporates 1% Tenofovir gel applied daily and topically, combining elements of iPrEx and CAPRISA, the only two successfully completed phase III trials.

If Truvada becomes the new clinical standard for prevention and pharmaceutical methods for prevention are placed in insurance policies, trials for new pre-exposure prophylaxes will continue to emerge and likely, with increasing frequency. The impact of such trials is not known, but the common path of trials and their proliferation is known. It is likely future trials will continue the quest for ethical accountability as they are exported in the search for more human subjects because U.S. regulatory demands require the recruitment of more participants to prove the long-term safety of products. In addition, competition among companies to bring drugs to market intensifies this recruitment (Petryna 2005). Influenced by the need to be statistically significant, testing the efficacy of other pre-exposure prophylaxes after the new clinical standard is adopted will require larger cohorts. The search for human subjects will be pushed to distant shores while community engagement and choice will remain the modus operandi, the foreground of neoliberal intervention and the basis of an ethics—basic elements in the construction of HIV PrEP ethicality. Ultimately, as PrEP is proven safe and effective, an important question is introduced: Is PrEP the ethical intervention?

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