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Publisher: Routledge

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## The American Journal of Bioethics

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uajb20>

### How Good Is “Good Enough”? The Case for Varying Standards of Evidence According to Need for New Interventions in HIV Prevention

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Available online: 31 May 2012

To cite this article: Bridget Haire, John Kaldor & Christopher FC Jordens (2012): How Good Is “Good Enough”? The Case for Varying Standards of Evidence According to Need for New Interventions in HIV Prevention, *The American Journal of Bioethics*, 12:6, 21-30

To link to this article: <http://dx.doi.org/10.1080/15265161.2012.671887>

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Target Article

# How Good Is “Good Enough”? The Case for Varying Standards of Evidence According to Need for New Interventions in HIV Prevention

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In 2010, randomized controlled trials (RCTs) of two different biomedical strategies to prevent HIV infection had positive findings. However, despite ongoing very high levels of HIV infection in some countries and population groups, it has been made clear by regulatory authorities that the evidence remains insufficient to support either product being made available outside of research contexts in the developing world for at least two years. In addition, prevention trials in endemic areas will continue to test new interventions against placebo. But the judgments of evidentiary standards are never value-neutral. Using the recent trials and their contexts as case studies, we examine the basis for these decisions, which will potentially delay access to scientific innovation to the people who are most urgently in need of it.

**Keywords:** AIDS, biomedical research, human subjects research, regulatory issues, research ethics

During 2010, in the space of five months, two landmark studies, CAPRISA 004 and iPrEX, showed convincing, positive results using related but different biomedical strategies to prevent HIV (Abdool Karim et al. 2010; Grant et al. 2010). Both studies found that their interventions had partial efficacy, meaning that they reduced, but did not eliminate the occurrence of new HIV infection. Both tested strategies involving antiretroviral drugs used in HIV-negative people, but with different modes of administration—one a vaginally applied topical product, the other one orally administered. But neither product will be made available outside of the research in the developing world for at least two years. In addition, neither product will be used as “standard of prevention” in ongoing HIV prevention trials until confirmatory studies have been completed. In this article we examine the basis for these decisions, which will potentially delay access to scientific innovation to the people who are most urgently in need of it.

Reducing the incidence of HIV is both a public health priority and a moral imperative. Although World Health Organization (WHO) estimates of the extent of the international epidemic have declined slightly in recent years (UNAIDS 2010a), a number of southern African nations have estimated prevalence above 20% (UNAIDS 2010a)

and current infection rates in the range of 1–5% (UNAIDS 2010b). There are resurgent epidemics in men who have sex with men in the developed world (van Griensven et al. 2009), and despite the galvanizing of international will to provide universal access to antiretroviral drugs (ARV) over the last decade, the reality of treatment for all who need it remains a distant goal, particularly with the Global Financial Crisis having a potential impact upon key donors such as the President’s Emergency Fund for AIDS (PEPFAR). Preventing HIV acquisition, therefore, as well as treating those living with the virus, remains a critical public health goal in endemic areas.

New biomedical products of moderate efficacy have the potential to significantly slow the epidemic in these affected countries. Delay in introducing effective prevention strategies may result in hundreds of thousands of potentially avoidable infections.

In this context, it is reasonable to ask, how was the determination made that the two new trials do not provide sufficient evidence to support the products being made available outside research settings, or their use as standard of care controls (as opposed to inactive placebo) in control arms of new trials? The main sources of guidance available to make this judgement are specific ethical guidelines

The authors would like to thank Ian Kerridge, Andrew Vallely and two anonymous reviewers who made valuable comments on an earlier draft of this article.

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produced by UNAIDS/WHO (2007), the HIV Prevention Trials Network (Rennie et al. 2009), and UNAIDS/AVAC (2010), ethical analysis using the concept of equipoise, and regulatory requirements, in particular those of the U.S. Food and Drug Administration (FDA).

Application of FDA guidelines immediately raises the question as to whether the level of evidence being required for U.S. or other rich country settings is in the best interests of people at risk of HIV, and participants in new trials, in high-incidence developing countries.

### THE RECENT TRIALS

In July 2010 the groundbreaking results of the CAPRISA 004 were released to international acclaim, showing 39% efficacy of a vaginal microbicide using 1% tenofovir gel in a large scale IIB trial (Abdool Karim et al. 2010).<sup>1</sup>

In November 2010, the iPrEx results were published in the *New England Journal of Medicine*, showing a higher risk reduction than CAPRISA 004 (44%) using a combination of tenofovir and emtricitabine (TNF/FTC)<sup>2</sup> taken orally each day (Grant et al. 2010).

While the effects of both these products appear modest compared to some preventive measures, such as infant vaccines, they are substantial in the context of HIV prevention, where there had been no real technological advances, apart from male circumcision (which is rather old technology for a new purpose), in a quarter of a century.<sup>3</sup> Furthermore, the real benefit of these products may be substantially greater at the individual level, because the estimates found in the trials reflect the raw difference in HIV infection rates

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1. Microbicides are topical agents, in this case in the form of a gel containing the antiretroviral drug tenofovir, designed to prevent HIV acquisition when applied inside the vagina (products are also being developed for rectal use). In theory a microbicide product could empower women to protect themselves from HIV, as its use could be at a women's discretion and would not need to involve negotiation with a male sexual partner. In practice, development of products in this field has been beset with unexpected difficulties, with the first product ever subject to an efficacy trial being associated with increased risk of HIV acquisition, closely followed by several other products with negative (though not necessarily harmful) results (Padian et al. 2008).

2. The product consisted of tenofovir—the same active ingredient in the CAPRISA 004 product—together with a second antiretroviral drug, emtricitabine, taken orally. The combination is available as a single pill under the brand name Truvada, and is currently used in the treatment of people with HIV. The advantages of an oral product are again that it can be taken discreetly, but more importantly—like modern hormonal contraception—the act of protection is removed from the sexual context (“non coitally dependent,” in medical parlance). This makes it something that can be integrated into daily routine, arguably facilitating adherence.

3. Another biomedical strategy prevention strategy was found effective in May 2011. The study HPTN052 showed that early initiation of treatment in a person with HIV prevented HIV acquisition by that person's HIV uninfected sexual partner by 96%. Unlike PrEP and microbicide strategies, this approach works by reducing the infectivity of the index partner rather than directly blocking infection in the HIV negative partner.

between the two randomized groups in each study, without regard to the extent to which participants actually used the study products.

As pill taking and gel use are user-controlled activities that require ongoing adherence, both studies had strategies for testing adherence so that the efficacy of the product in high adherers could be compared to low adherers. In both trials, adherence was tested by measuring blood levels of the respective drugs. In each study, stepwise increases in efficacy were associated with evidence of adherence. In iPrEx, high adherers were 73% less likely to acquire HIV than the placebo group (Grant et al. 2010), and in CAPRISA 004 they were 54% less likely to acquire HIV (Abdool Karim et al. 2010). As adherence dropped, so too did efficacy in both studies. This strengthens the plausibility that reduction in HIV acquisition was due to the product, and suggests that the real efficacy of the products is very much higher than the estimate derived from the reported intent-to-treat analysis.

Adherence is critical to real world effectiveness of user-dependent methods. As Heise and colleagues (2011) point out:

With user-dependent methods like microbicides or condoms, focusing on the method's efficacy alone misses half the story. The protection that a prevention method confers is a function of both the inherent efficacy of the method and how consistently it is used. Indeed, given the particular transmission dynamics of HIV, consistency directly compensates for efficacy. In other words, using a low-efficacy method consistently for HIV protection can confer as much protection as using a high-efficacy method inconsistently.

Taking a pill, for example, or using a gel that increases rather than dampens sexual pleasure (Stadler and Saethre 2010) may prove to be more user-friendly than using a condom, which may increase the real-world effectiveness of PrEP and microbicides in HIV prevention.

### ETHICAL GUIDELINES ON STANDARDS OF PREVENTION AND PLACEBO

Three sets of guidelines provide specific advice on the standard of prevention issue in HIV prevention trials: UNAIDS/WHO in its “Ethical Considerations in Biomedical HIV Prevention Trials” of 2007, HIV Prevention Trials Network (HPTN) in its Ethics Guidance for Research (Rennie et al. 2009), and the UNAIDS/AVAC Good Participatory Practice Guidelines for HIV prevention trials (UNAIDS 2011).

The 2007 UNAIDS/WHO guidelines replace an earlier document that was specific to HIV-preventive vaccines, broadening the scope to the wider field of emerging HIV prevention technologies and encompassing social changes, such as the increased availability of antiretroviral therapy. It is in these guidelines, indeed, that the term “standard of prevention” was coined, to distinguish it from its sibling, “standard of care.”

Regarding the standard of prevention, Guidance Point 13 states:

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and *access to all state of the art HIV risk reduction methods* are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities. (Guidance point 13, Standard of Prevention, our italics)

The UNAIDS /WHO guidelines make a normative statement—that researchers must ensure that participants in HIV biomedical prevention trials have access to all state-of-the-art HIV risk reduction methods. They then go on to make a procedural instruction, which is that researchers should negotiate the incorporation of new prevention methods into existing trials with research stakeholders, including the community. Negotiation, the guidelines state, should take into consideration feasibility, expected impact, and the ability to isolate the impact of the biomedical HIV modality being tested.

The normative statement in the 2007 UNAIDS/WHO guidelines encapsulates a universalist stance in its directive to supply participants in HIV prevention trial with “state-of-the-art” prevention interventions in the control arms of studies. The procedural point that follows, however, has the effect of opening up the standard for negotiation—a negotiation that is tipped in favor of research funders, particularly with respect to the provision regarding feasibility of subsequent trials, which is a determination that that can only be made by the research elite, and involves judgments of value as much as objective judgements.

So, in effect, the UNAIDS Guidelines propose a normative standard about how HIV prevention research is conducted<sup>4</sup>; however, in the commentary the interests of both science and society are mentioned as factors that might provide reason *not* to supply “state-of-the-art” HIV prevention technologies, even before getting into what “a proven intervention” means. Given that adding new partially effective prevention interventions into trials testing other as yet unproven interventions will necessarily complicate research and require larger sample sizes and exponentially more funding, the commentary undercuts the norm.

The HIV Prevention Trials Network (HPTN) Ethics Guidance for Research (Rennie et al. 2009) avoids the apparent contradictions in the UNAIDS/WHO by taking a pragmatic line, in which it parses the ethical aspect of standard of prevention into obligatory and aspirational elements. The full guidance point (9) states:

In partnership with key stakeholders, HPTN should establish a package of effective, comprehensive and locally sustainable prevention services to be offered to participants in each HPTN study.

4. This follows from the perspective that the interests of the research participant should take precedence over all other interests, in line with the Declaration of Helsinki (article 6) (World Medical Association 2004).

It then assigns “provision of prevention package” to the status of “ethical obligation” and “content of prevention package” to the status of “ethical aspiration.” Down-shifting the content of the package to “aspirational” is a minimalist approach. It obviously gives researchers much greater leeway in designing studies, and indicates a shift away from a strict obligation-based framework. These guidelines introduce the concept that a prevention package provided in a trial should be “locally sustainable,” which both points toward an intertwining of research ethics and public health intervention (as discussed in Macklin 2010), along with a whiff of relativism—that research participants are owed different duties according to where they live (Macklin 2004).

The other very specific set of guidelines is the UNAIDS/AVAC Good Participatory Practice Guidelines for HIV prevention trials. These guidelines also use the language of negotiation regarding the addition of newly validated HIV prevention technologies. Researchers are asked to “review” prevention packages, and to “negotiate” and “consult.” The standard for what constitutes a proven intervention is vague, and the language moves between “scientifically validated” and the stricter “approv[al] by relevant authorities.”

None of the three sets of guidelines discussed here offers a clear normative standard for the content of the prevention package in HIV prevention research. The UNAIDS/WHO 2007 guidelines come closest, with their statement that participants should be offered “state-of-the-art” prevention interventions.

#### GUIDANCE BASED ON THE REQUIREMENT OF “STATE-OF-THE-ART” PREVENTION FOR ALL TRIAL PARTICIPANTS

A central question posed by both the CAPRISA 004 and iPrEx results is whether tenofovir gel and oral TNF/FTC must, as a result of their success in reducing HIV infection rates, now be considered “state-of-the-art” HIV prevention, and thus included in the control arms of subsequent prevention trials. In March 2009 USAID, in anticipation of such quandaries, the Global Campaign for Microbicides (GCM), UNAIDS, and the Centers for Disease Control (CDC) met in Kampala, Uganda to discuss precisely how to determine when a prevention product can be deemed “state of the art.” They came up with a list of criteria that fall into four categories: the weight of evidence for a product and how this has been received by the broader scientific community; issues surrounding potential safety or cultural concerns; the feasibility of supplying the product; and the impact of adding the product to the enterprise of testing new HIV prevention modalities (McGrory et al. 2010).

Unlike male circumcision, the only other “new” prevention technology to emerge so far in HIV prevention, the use of vaginal or rectal microbicides and oral prophylaxis do not appear to present fundamental cultural issues for implementation, and both offer a form of protection that has hitherto been lacking in HIV prevention: a technology whose use is controlled by the receptive sexual partner. With

regard to issues of safety, there are considerable safety data available from earlier trials (e.g., Peterson 2007). Feasibility of supplying a new product is always challenging but, in the end, a matter of distribution logistics. Thus, the remaining issues are the weight of evidence and the impact of adding new technologies to the enterprise of HIV prevention research.

Large-scale efficacy trials of new prevention technologies for HIV are generally powered to detect reductions in infection rates down to about 30%, the lowest level at which it is considered that an intervention would have an advantageous public health impact, based on mathematical modeling studies (Stone 2010). The absolute size of the impact in any particular region, however, depends upon the dynamics of the HIV epidemic in the region, its scale, and the extent to which other prevention interventions are being used.

### GUIDANCE BASED ON DRUG DEVELOPMENT STANDARDS

Most drug development occurs in the developed world in an environment of intense commercial and academic competition. The U.S. Food and Drug Administration handles high numbers of applications for the approval of new drugs, including applications for drugs that are very similar to drugs already on the market (“me too” drugs). In response, the FDA has developed stringent standards for evidence of efficacy (Hamburg 2010).

One of the key elements of these standards is the requirement that the efficacy of a product be proven in two separate trials each of which must have a  $p$  value of less than 0.05 (Stone 2010, 25).

A  $p$  value of 0.05 is the accepted threshold of statistical significance. A  $p$  value is a measure of statistical significance, and a  $p$  value of 0.05 means that there is a 1 in 20 probability that the results would have happened by chance if the factor being tested had in fact no effect—and the lower the number, the less likely that the result is due to chance. Kopelman (1986) points out that while this is “a reasonable and well-established convention, it is none the less a moral choice” (Kopelman 1986, 322).

Alan Stone, writing on behalf of WHO, adds that in theory a single trial that is statistically significant at the 0.001 level rather than two trials with  $p$  values of 0.05 would suffice (alongside other non-RCT evidence). Indeed, an earlier breakthrough in HIV prevention—the mother-to-child transmission trial, known as PACTG076, that established the use of antiretrovirals to dramatically reduce transmission from mother to infant—became standard of care on the basis of a single trial, the  $p$  value for which was 0.00006 (Connor et al. 1994).

Stone identifies the requirement for two trials one after the other as potentially posing “insurmountable practical and ethical difficulties, particularly if the first trial showed evidence of protection with a  $p$  value well below 0.05” (Stone 2010, 25).

The  $p$  value for the overall CAPRISA result was 0.017, with the 95% confidence interval of 6 to 60%, placing this trial squarely in that realm identified by Stone as posing “insurmountable . . . difficulties.” The rationale for requiring confirmatory studies is that the confidence intervals are wide, due in part to the fact that the trial was designed as a phase IIb study, which is essentially an underpowered efficacy study designed to give evidence that a product works, rather than an accurate estimate of its efficacy.

The iPrEx results are considerably stronger, with a  $p$  value of 0.005, and 95% confidence intervals of 32–74%. This means there is a 5 in 1000 probability that the result would have occurred by chance if the agent had no effect, and even the lowest end of the confidence interval is a level of efficacy that would, according to mathematical modeling, have significant public health benefits not only in endemic regions (Anderson and Garnett 1996; Vermund 1998).

On October 25, 2010, the U.S. Food and Drug Administration gave the go-ahead for fast-tracking its review of tenofovir 1% vaginal gel, the product used in CAPRISA 004 (CONRAD 2010). This allows the product sponsors to submit each section of their New Drug Application for “rolling review,” a process that is more time-efficient, as some aspects of the application can be completed and submitted for review as further data are being gathered. Without a “fast-track” approval, the New Drug Application could not be submitted until all sections were complete, and then the review would begin. The FDA stipulated the need for more data based on its preference for *two* well-controlled studies to verify the safety and efficacy of 1% tenofovir gel, so no final decision on licensure will be made until the results of another, confirmatory trial, which is due to end in 2013, are submitted (Global Campaign for Microbicides 2010).

In the case of oral tenofovir/FTC, although only one trial had been completed, the FDA requirement for two studies did not seem to be an impediment to the development of new prevention guidelines based on the findings of the trial. On January 28, 2011, the U.S. Centers for Disease Control (CDC) released “Interim Guidance: Pre-Exposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men” (CDC 2011) two months after the publication of the iPrEx results. This document provides a summary of the iPrEx results, with eligibility criteria and details of the medication regimen and recommended follow-up, written in a way that suggested that it was aimed at health care providers and research-literate members of at-risk populations.

The Interim Guidance follows an earlier CDC facts sheet, “Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States” (CDC 2010), which was released to coincide with the iPrEx publication. Despite the FDA’s stated preference for two positive trials before licensing (Stone 2009), the CDC seemed to draw a more definitive conclusion, stating that “The iPrEx trial findings offer a new tool to help combat HIV among MSM, one of the hardest hit populations in the U.S. and many areas of the world” (CDC 2010).

The iPrEx product is a combination of the antiretroviral drugs tenofovir and emtricitabine (TNF/FTC), sold as the combination pill Truvada. The TNF/FTC combination pill is already in use for the treatment of HIV, so it could potentially be prescribed for the indication of prevention rather than treatment—particularly with the interim guidelines in place (unlike tenofovir gel for vaginal administration, which is not yet manufactured in commercial quantities). For gay men and men who have sex with men<sup>5</sup> in the United States, access to this prevention technology is becoming a reality, although cost is currently a barrier.

Despite the apparent conclusion by the CDC that the TNF/FTC combination pill is ready to be offered to MSM for HIV prevention purposes, it continues to be tested against a placebo comparator in four out of five studies (AVAC 2010).<sup>6</sup> The rationale to continue to test the combination against placebo in the other trials is outlined by the U.S. community advocacy organization AVAC (AIDS Vaccine Advocacy Coalition):

These [iPrEx] data can't be extrapolated to people at risk of HIV via heterosexual sex or injection drug use. Differences in biology of the vagina and rectum, and between HIV risk in sexual versus injection exposure make it essential that ongoing placebo-controlled trials looking at PrEP in these contexts must continue. (AVAC 2010)

There will inevitably be an element of judgment involved in deciding whether evidence in one setting (protection against rectal HIV exposure in men) can be translated into another (vaginal exposure in women). The question that needs to be addressed is whether there is any latitude for allowing different standards of evidence to come into play, depending on the urgency and magnitude of the public health problem being addressed.<sup>7</sup>

It is entirely reasonable to ask this question, given that drug regulation is reactive and its systems change. A potted history of the FDA shows that until 1962, drugs only had to show safety, not efficacy, before licensing. Later, in response to thalidomide, regulators became so risk-averse that women of childbearing age were banned from participating in early-stage clinical trials altogether. As Edgar and Rothman (1990) note, the post-thalidomide FDA adopted an adversarial rigor not only in the level of safety data required, but also in its aversion to the Type 1 error—a statistical blip that produces a false positive result in a clinical trial, when the result was due to chance. This perspective, which led to the requirement that efficacy be proven to a

very high degree of stringency, was then changed by the persuasion of AIDS activists, who asserted that access to emerging therapies—use of “any and all” therapies—was justified in a deadly epidemic, even if the approval system let through some drugs that were not truly effective (Edgar and Rothman 1990).

This approach bore fruit. In 1987, pressure from AIDS advocates resulted in the FDA changing its rules so that investigational drugs could be sold for serious or life-threatening diseases, well before they had been proved to be effective against the more demanding standards that had been previously in place (Edgar and Rothman 1990, 123). A year later, the FDA adopted a new regulation that involved the agency in the planning of research to assure a more efficient pathway through the regulatory system.

The caution surrounding the new HIV prevention technologies is in stark contrast to arguments advanced by AIDS activists in the late 1980s.

The issues raised by new HIV prevention technologies are in some respects different from those of HIV treatment in the earlier years, in that there is already an effective prevention technology—the condom—and effective treatment has been established so that infection is not a death sentence. Treatment, however, is expensive and inconvenient, has side effects, and may not be sustained in all contexts. Condoms require the willingness of the insertive partner to use one, and to use one correctly, in every instance in which exposure is possible. In southern Africa in particular there is an urgent need to break the cycle of infection through enabling receptive sex partners to control their own protection; thus, microbicides and TNF/FTC offer a new avenue of risk reduction and a chance to curtail the epidemic. It is also clear that for many people, the threat of infection remains as acute and irreducible as the threat of death was to people living with HIV in decades past.

Turning to the impact of adding new technologies, some participants in the Kampala Standard of Prevention consultation argued for a particularly stringent standard of accepted efficacy before a new prevention strategy would be classed as state of the art and therefore required to be offered to all trial participants. They suggested that a strategy needed endorsement by normative agencies and approval by national regulatory authorities and even inclusion in national prevention policies where the trial is taking place (McGrory et al. 2010, 34). Each of these steps would involve at the very least several months, and more often several years, from the time of results being released to the point of licensure and inclusion in national strategic plans. These discussions indicate a perspective that seeks to delay the introduction of new prevention technologies for as long as can be justified, on the utilitarian premise that facilitating research into new prevention technologies through the retention as long as possible of minimal preventive interventions in control participants will enable the development of maximally effective products, ultimately preventing more infections (and saving more lives) than earlier introduction that complicates research design.

5. We use the term “gay men and men who have sex with men” in recognition that homosexually active men have distinct and different identities, and that gay identity ought not to be subsumed under a behaviorist term.

6. The fifth study is a direct “follow-on” study for iPrEx participants, which offers open-label access to the drug for all, and provides less intensive counseling in order to get a more “real-world” result (AVAC 2010).

7. Recall that from 1977 to 1993, women were not allowed in early-stage FDA trials due to perceived risk, and data were routinely extrapolated from men (Merkatz and Junod 1994).

One problem with this approach, on its own terms, is that it offsets infections prevented by earlier introduction of new technologies against infections prevented later using putative “better” prevention technologies. This is a gamble, as there is no assurance that prevention technologies will increase in efficacy at a rate that justifies delay. It disturbs the deontological underpinnings of contemporary research ethics and posits a utilitarian approach—and one where the calculus rests upon the gamble that research is successful. This moral framework would be unlikely to gain support in industrialised countries, raising the question of why it would be considered in developing nations.

Setting the evidentiary bar high facilitates ongoing placebo-controlled trials, which make research cheaper and more efficient. Faster research *may* result in finding more effective product more quickly. However, there is no guarantee of this.

### CLINICAL EQUIPOISE

The philosophical concept of equipoise provides another way to consider whether it remains acceptable to conduct placebo-controlled trials when studies such as CAPRISA and iPrEx have established the efficacy of specific prevention products. Equipoise posits that randomized controlled trials (RCTs) are morally justified where there is genuine uncertainty as to whether one therapy is superior to another (the received context is therapeutic rather than preventative). It is drawn from “the principle of therapeutic beneficence and non-maleficence that apply in the traditional relationship between physician and patient” (Jansen 2005). Initially it was understood that the uncertainty needed to exist in the mind of the individual doctor (Fried 1974), but in 1987 a groundbreaking article by Freedman developed the concept that the “genuine uncertainty” should be within the medical community, which he dubbed “clinical equipoise.” Clinical equipoise—defined as an honest, professional disagreement among expert clinicians—is frequently cited as normative standard of what remains a most contested concept (Ashcroft 1999).<sup>8</sup>

The validity of any form of equipoise in clinical trials has been challenged by Miller and Brody (2003; 2007), who argue that research is fundamentally different from medical treatment, as its goals are the production of generalisable knowledge, not the best interests of the patient/participant. They propose that non-exploitation of participants should be the norm that regulates research, not equipoise. However what they propose in its stead is a minimal sketch of an anti-exploitation norm which, taken to its logical conclusion, would require that research participants be either altruistic actors, or handsomely compensated, neither of which is reasonable or likely in HIV prevention research in the

developing world (London and Zollman 2010; Schüklenk 2010).

So according to the Freedman model, neither CAPRISA 004 nor iPrEx disturbs clinical equipoise, given that the medical and research community—which is made up of individuals who are directly invested in the ongoing project of HIV prevention research—has decided that it does not.

It is clear, however, that Freedman did not anticipate a study with a *p* value of 0.017—let alone one of 0.005—being deemed unconvincing, as he defines a successful clinical trial as one that disturbs equipoise.

In contrast to Freedman, Halpern (2006) offers a definition of equipoise that provides a seemingly objective standard:

that equipoise exists if well-designed studies have yet to answer the question as to which of the two interventions are to be preferred for a particular population of patients.

Halpern’s definition is a neat, evidence-based solution that appears to displace the consensus focus of Freedman’s clinical equipoise. When applying it to the CAPRISA 004 and iPrEx results, however, it is clear that interpretation still has a role. For example, did CAPRISA 004 answer “the question,” or was it underpowered?

It is very difficult to argue that iPrEx does not disturb equipoise, given that the level of evidence is deemed high enough for the CDC to issue interim guidelines for use (CDC 2011). The justification for ongoing placebo-controlled trials in this instance is that the trial population was limited to gay men and men who have sex with men. Adhering literally to Halpern’s “particular population” specification in this instance means limiting potential access not only by gender but by sexual orientation, despite the facts that women are also exposed to HIV through receptive anal intercourse, and both heterosexually active and homosexually active men may be exposed through insertive sex. Indeed, if TNF/FTC provides a level of protection for a man exposed to HIV through unprotected anal sex, it is biologically plausible that it must also protect a man exposed through insertive vaginal sex. This raises issues of whether the limitations are politically, let alone scientifically, valid. Can results from a trial in men be extrapolated to people more generally (consider that in the post-thalidomide era of the 1970s and 1980s, this was the standard practice)? Has iPrEx proven preexposure prophylaxis, or must the results be replicated a range of populations with a myriad of different exposures? Is it really reasonable to claim that the iPrEx results don’t disturb equipoise for men and women exposed to HIV through other routes?

The apparent clarity of Halpern’s equipoise quickly leads back into the same, value-laden territory.

### IMPACT ON FUTURE HIV RESEARCH

Our key point about CAPRISA 004 and iPrEx is that different decisions could reasonably be made both regarding licensure and roll-out of the products in some endemic areas, and in the composition of “standard of prevention” in

8. Of note, Freedman would take a dim view of the purposeful underpowering of IIb studies: “the results of a successful clinical trial should be convincing enough to resolve the dispute among clinicians” (1987, 144).

subsequent trials. For example, the South African regulators could have decided that, given that country's high HIV incidence in women, licensure of tenofovir gel was justified (presumably with some follow-on open-label studies to gather more data). If the 39% efficacy rate of CAPRISA 004 translated into real-world effectiveness, this could have prevented 100,000 new infections per year. While it could be argued that any modeling should be based on the lower end of the confidence interval, 6%, the higher level of efficacy shown in the more adherent trial participants is suggestive of higher, rather than lower, efficacy.

As we have explained in our discussion of the ethical guidelines, licensure of tenofovir gel in any country would have the follow-on consequence of requiring that tenofovir gel would need to be added into various other prevention studies as part of the "standard prevention package."

### STANDARD OF PREVENTION AND STANDARD OF CARE—NEW TERMS, OLD DEBATE

In many respects, the issues raised in HIV prevention trial design as new technologies emerge are not new. "Standard of prevention" is a new term for one aspect of the "standard of care" debate that erupted in the 1990s. Briefly, "standard of care" came to international attention in 1997 when placebo-controlled trials of strategies for preventing mother-to-child HIV transmission in the developing world were criticized (Angell 1997; Lurie and Wolfe 1997). Criticisms were made on the grounds that a partially effective intervention had been established by the PACTG076, and using a placebo rather than an active control was inconsistent with international ethical guidance on this issue and arguably exposed women and their fetuses to avoidable harm (e.g., Lurie and Wolfe 1997). Proponents of the trials responded that when research was designed to be responsive to the health needs of a particular setting use of a placebo was justified if that was the operational standard available in that setting (e.g., Varmus and Satcher 1997). As Macklin (2001) notes, the issue was never resolved, and there are reasonable, well-informed people on both sides of the argument.

At the heart of the issue is a conflict between the obligation of a researcher to have a physician-like duty-of-care to research participants, and the need for research interventions that are applicable to health problems in the circumstances of the developing world.

This is salient to HIV prevention research, as introducing a newly validated intervention (tenofovir gel, TNF/FTC, or both) as "standard of prevention" would require larger sample sizes and exponentially more funding and infrastructure for ongoing and planned trials. If the first successful technology is only modestly effective, its introduction as the new standard of prevention may effectively inhibit the search for optimal much more effective, affordable and sustainable HIV prevention technology. On the other hand, the populations enrolled in HIV prevention trials are among those at highest risk of acquiring HIV and it is not reasonable to withhold newly validated pre-

vention technologies. The questions common to both the debate from the 1990s and the current issues in HIV prevention research are: Are people exploited if they are exposed to suboptimal treatment for the benefit of others? Should research participants have access to interventions that are significantly better than what is generally available in their countries? Are suboptimal arms in research studies ethical if the research is intended to answer a significant question in global health?

### DISCUSSION

The argument that research participants should be supplied with state-of-the-art prevention comes from a deontological—duty-based—perspective, grounded in the duty that a doctor has to act in the medical best interests of patients. This philosophical perspective deems clinical research to be akin to clinical practice, and underpins documents such as the Declaration of Helsinki. Denying a research participant access to best-practice treatment or prevention for the purposes of a research study would be exploiting that person for the putative future benefit of others (in Kantian terms, treating the person as "mere means"). This is a universalist perspective, which posits the duties owed to a person by merit of his or her personhood as being the same as those owed to any other person, unless there are morally relevant differences. As Macklin (1999, 51) notes, universal principles "require interpretation in the light of relevant empirical facts and contexts before they can be applied."

The converse view is that participants in HIV prevention research studies generally reduce their risk of HIV acquisition and gain access to better medical services through their participation in trials (e.g., in a tenofovir trial self-reported condom use rose from 52% to 95%; Peterson 2007). Adding in newly validated prevention technologies would necessitate increased sample sizes and complicate getting a clear answer to the research question, according to this view. This perspective privileges the enterprise of HIV prevention research over the protection of individual trial participants, using the rationale that participants are already better off than the general local community. A problem with this perspective is that it takes a minimalist view of justice, apparently accepting the HIV incidence in southern Africa, for example, as an appropriate normative standard, rather than a raging injustice.

Current ethical guidance in HIV prevention trials places disproportionate emphasis on negotiation, which, given the substantial inequities between the negotiating parties, is likely to result in outcomes that suit the interests of research enterprise over the interests research participant. The rise of "proceduralism" in ethics, where processes of negotiation are privileged over setting normative standards, has been likened to "research at the auction block" (London and Zollman 2010). The problem with auctions is that they enshrine the values of the market, not standards of fairness (Schüklenk 2010).



An important contextual issue to address here is that the issue at stake is standards of prevention, rather than treatment for an illness, and whether this makes a difference to the putative obligations to participants. Two fallacious points are frequently made regarding participants in HIV prevention research—the first is that if people “engage in risky behavior” (e.g., Bloom 1998; Slack et al. 2005) that puts them at risk of HIV acquisition, this cannot be said to create an obligation for researchers. The second is that the counseling/condom provision in HIV prevention trials discharges any obligation to participants, who are receiving a higher standard of behavioural prevention than is available in their locales.

The problem with the first point is that it assumes a disproportionate level of personal responsibility for what is essentially a structural risk—a woman in Kwa Zulu Natal in South Africa, for example, faces a 25% lifetime risk of HIV acquisition, while an Australian woman’s risk is less than one-thousandth of that. Discourses of personal responsibility make no sense in the face of such odds, without even needing to go into issues of forced sex and sex as an economic imperative.

Second, to claim that provision of condoms and counseling discharges any responsibility to supply newly validated technologies again positions the level of HIV risk and access to risk reduction in a trial community as an appropriate normative standard, and the baseline incidence of HIV as something that maybe fairly exploited for the goals of a research project.

## CONCLUSION

Both the iPrEX and CAPRISA 004 resist black-and-white determinations as to whether or not they should be implemented either programmatically or as standard of prevention. The problem with iPrEX is that the trial was limited by both gender and sexual behavior. The problem with CAPRISA 004 is that the lower end of the confidence interval for tenofovir gel—6% efficacy—would not constitute a useful or cost-effective intervention. But waiting for the results of trials that will not be completed for several years can be viewed as an inadequate response to these very promising data, given the urgency of need in southern Africa for new risk reduction interventions, and in particular those that are controlled by women.

As our discussion of the iPrEX and CAPRISA004 trials shows, evidentiary requirements and regulatory regimes are not objective standards, but involve moral decisions. Whether it is more important to eliminate any possibility of a Type 1 error, or to facilitate access to modestly effective, but imperfect, new technologies, is a question of values.

The competing interests are particularly difficult to navigate. On the one hand, the enterprise of HIV biomedical prevention research—which holds out the hope of cheap, effective, user-friendly products—may be threatened if the new technologies become “standard of prevention.” Proving a new intervention against the background of these partially effective technologies would require an exponential increase in sample sizes and budgets, threatening feasibility.

People at high risk of HIV who enter prevention trials generally reduce their risk as a result of their participation (e.g., Peterson 2007), and arguably, this discharges the obligation to protect participants. On the other hand is there is the (contested) tenet from the Declaration of Helsinki that the researcher’s *primary obligation* is the reduce risk for research participants, ahead of considerations of future beneficiaries of research. This is the basis upon which “standard of prevention” packages are supplied—to prevent the vulnerability of high-risk populations being exploited for the future benefit of others, and to position the well-being of the research participant at the center of the research endeavour.

The guidelines do not solve the dilemma, because while UNAIDS stipulates use of “state-of-the-art” interventions in the control arm of HIV prevention trials, the definition of this term is vague until the point where regulatory approval is granted, which delays any obligation to provide a new technology potentially for years. The guidelines other than UNAIDS are weaker still, with prevention packages being undefined, and negotiation and consultation being emphasized over normative standards.

Moving on from the guidelines, then, the philosophy-of-medicine concept of equipoise and its application needs attention. The question then becomes, is there sufficient uncertainty regarding the results of CAPRISA 004 or iPrEX to continue with placebo-controlled trials? We have argued that there is no easy answer to this, as received models of equipoise are inadequate umpires. The strength of the evidence from the RCTs must ultimately be evaluated, and this again requires value judgments.

Thus far, the judgments have been made favor of the continuation of trials using placebo controls rather than adding one or both of the new technologies into the “standard of prevention.” This sits uncomfortably with the fact that the CDC is releasing interim guidance documents on TNF/FTC for US gay men and men who have sex with men (CDC 2011).

The decision to continue using placebo controls while waiting for the results of confirmatory studies of CAPRISA 004 and iPrEX means that the high-incidence populations required for efficient testing of other new prevention technologies have been maintained for other, subsequent trials. This is a significant moral choice that weighs the potential benefit of delay over the benefits of immediate rollout in endemic areas. The populations likely to gain from these decisions may be those at lower risk of HIV who already have good access to condoms, for whom only a very highly effective product would be advantageous. It may mean that we are more likely to find a highly effective HIV prevention technology faster (though that is a gamble). It certainly means that in the immediate future, infections that could have been prevented by early uptake of new technologies will not be. ■

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