

# ETHICAL CONSIDERATIONS IN DETERMINING STANDARD OF PREVENTION PACKAGES FOR HIV PREVENTION TRIALS: EXAMINING PrEP

BRIDGET HAIRE, MORENIKE OLUWATOYIN FOLAYAN, CATHERINE HANKINS, JEREMY SUGARMAN, SHEENA MCCORMACK, GITA RAMJEE AND MITCHELL WARREN

## Keywords

antiretroviral therapy,  
 HIV/AIDS,  
 research ethics,  
 developing world bioethics,  
 guidelines,  
 international justice

## ABSTRACT

The successful demonstration that antiretroviral (ARV) drugs can be used in diverse ways to reduce HIV acquisition or transmission risks – either taken as pre-exposure prophylaxis (PrEP) by those who are uninfected or as early treatment for prevention (T4P) by those living with HIV – expands the armamentarium of existing HIV prevention tools. These findings have implications for the design of future HIV prevention research trials. With the advent of multiple effective HIV prevention tools, discussions about the ethics and the feasibility of future HIV prevention trial designs have intensified.

This article outlines arguments concerning the inclusion of newly established ARV-based HIV prevention interventions as standard of prevention in HIV prevention trials from multiple perspectives. Ultimately, there is a clear need to incorporate stakeholders in a robust discussion to determine the appropriate trial design for each study population.

## INTRODUCTION

Recent research has expanded the range of safe and effective HIV prevention modalities from the previously available behavioural and barrier methods to include voluntary medical male circumcision (VMMC)<sup>1</sup> and antiretroviral drugs (ARVs) used preventively.<sup>2</sup> ARVs have reduced HIV acquisition when delivered in both topical and systemic forms,<sup>3</sup> and two different strategies

have shown efficacy in particular populations: early treatment for prevention (T4P), which is treatment with ARVs for HIV-positive partners in HIV-serodiscordant couples (where one sexual partner has HIV and the other does not) before treatment eligibility; and pre-exposure prophylaxis (PrEP), using ARVs daily or peri-coitally to prevent HIV acquisition in HIV-negative people at high risk of HIV acquisition.<sup>4</sup> These salutary findings have implications for the design of future research trials, intensifying discussions about the ethical obligations to provide them and the

<sup>1</sup> B. Auvert et al. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2005; 2: e298; R. Bailey et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; 369: 643–656; R. Gray et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; 369: 657–666.

<sup>2</sup> S.S. Abdool Karim & Q. Abdool Karim. Antiretroviral Prophylaxis: a Defining Moment in HIV control. *Lancet* 2011; 378: e23–e25.

<sup>3</sup> Q. Abdool Karim et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in

Women. *Science* 2010; 329: 1168–1174; R.M. Grant et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *N Engl J Med* 2010; 363: 2587–2599; M.S. Cohen et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *N Engl J Med* 2011; 365: 493–505; J.M. Baeten et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *N Engl J Med* 2012; 367: 399–410; M.C. Thigpen et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *N Engl J Med* 2012; 367: 423–434.

<sup>4</sup> Grant et al. *op. cit.* note 3; Cohen et al. *op. cit.* note 3; Baeten et al. *op. cit.* note 3; Thigpen et al. *op. cit.* note 3.

Address for correspondence: Bridget Haire, Centre for Values, Ethics and the Law in Medicine, University of Sydney, Medical Foundation Building, Parramatta Road, Camperdown, Sydney, New South Wales 2050 Australia, Email: bridget.haire@sydney.edu.au.

The author has declared a conflict of interest which appears at the end of the article.

feasibility of fulfilling such obligations in resource poor settings. Specifically, it is critical to consider whether early T4P or PrEP should be added to the prevention package for participants in future HIV prevention trials. In this article, we focus primarily on questions related to PrEP.

In April 2012, a group of HIV prevention researchers, policy makers, bioethicists, and advocates participated in a panel discussion at the Microbicides 2012 conference in Sydney, Australia. They grappled with some of the considerations that need to inform decisions about the standard of prevention packages to use in HIV prevention trials in view of emerging evidence on novel HIV prevention modalities.<sup>5</sup> The organisers and some of the panelists, who co-authored this article, came from five different countries and four continents. This article aims to reflect that discussion and to extend it with new information, including the recent approval of combined daily oral tenofovir (TDF)/emtricitabine (FTC) as pre-exposure prophylaxis (PrEP) by the United States Food and Drug Administration (FDA),<sup>6</sup> and the recommendations from the US Centers for Disease Control and Prevention regarding the use of TDF/FTC for individuals at high risk of HIV acquisition.<sup>7</sup>

## STANDARD OF CARE

In the setting of clinical trials, 'standard of care' is an umbrella term that describes the care provided to research participants. In HIV prevention trials the term has been used to describe at least four different, but related, considerations. First, it refers to the 'standard of prevention', which is the risk-reduction package provided to all participants in a trial.<sup>8</sup> This package comprises the measures used to help minimize the risk of HIV infection. Second, there is 'ancillary care', which is health care provided to trial participants for conditions that are not directly associated with the research question, such as

contraception and reproductive health care, cervical cancer screening, and treatment for unrelated illnesses that arise during trial participation.<sup>9</sup> Third, there is 'standard of care' regarding HIV treatment that will be provided to trial participants who seroconvert during the course of a trial. Fourth, 'standard of care' may refer to a proven effective intervention provided as the comparator arm in a trial to which the experimental intervention is compared.<sup>10</sup> This article focuses specifically on standard of prevention.

Both the standard of prevention in trials and the inclusion of a new HIV prevention modality as established practice in normative guidance and national health policies have profound impacts on design feasibility and the ability to interpret HIV prevention trials. In this paper we outline the tensions associated with determining the standard of prevention package for HIV prevention trials.

## CURRENT STANDARD OF PREVENTION PRACTICE

In HIV prevention trials, HIV prevention options currently offered to participants typically include provision of male condoms, female condoms on request, HIV testing and counselling, safer sex counselling, treatment of sexually transmitted infections (STIs), education and provision of or referral for VMMC, and access to sterile injecting equipment.<sup>11</sup> In addition, arrangements are often made to meet participants' requirements for health care not directly related to the trial, either through trial sites or through referral to local health services.

The evidence supporting the use of ARVs for prevention<sup>12</sup> raises the pivotal question about whether these new ARV-based prevention strategies (TDF/FTC PrEP and early T4P) should be included in the standard of prevention package for HIV prevention trials.

Focusing on the issue of PrEP, we begin with a review of relevant normative guidance on standards of prevention and care in HIV prevention trials in general. Next,

<sup>5</sup> Similar issues have been canvassed in Zaynab, Slack & Koen et al. HIV prevention responsibilities in HIV vaccine trials: Complexities facing South African researchers. *South African Medical Journal* 2010; 100: 45–48.

<sup>6</sup> Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm> [Accessed 18 Feb 2013].

<sup>7</sup> Centers for Disease Control. (CDC). 2012. CDC Issues Interim Guidance on Use of Medication to Prevent HIV Infection among Heterosexually Active Adults. (News release) August 9 2012. Atlanta, GA: CDC. Available at: <http://www.cdc.gov/nchhstp/newsroom/2012/PrEP-HeterosexualGuidance-PressRelease.html> [Accessed 18 Feb 2013].

<sup>8</sup> This term was coined in 2007 in the UNAIDS Ethical Considerations document in hopes of minimizing confusion caused the multiple meanings of 'standard of care'.

<sup>9</sup> H.S. Richardson. Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries. *Am J Public Health* 2007; 97: 1956–1961; L. Belsky & H.S. Richardson. Medical researchers' ancillary clinical care responsibilities. *BMJ* 2004; 328: 1494–1496.

<sup>10</sup> R. van der Graaf & J.J.M. van Delden. What is the Best Standard for the Standard of Care in Clinical Research? *The American Journal of Bioethics* 2009; 9: 35–43.

<sup>11</sup> L. Heise, K. Shapiro & K. West Slevin. *Mapping the Standards of Care at Microbicide Clinical Trial Sites*. Washington, DC: Global Campaign for Microbicides; 2008; B. Haire. 2013. Principal Investigator Questionnaire on HIV Prevention Trial Standards 2009–2012. (Unpublished) Sydney: University of Sydney.

<sup>12</sup> Abdool Karim et al. *op. cit.* note 3; Grant et al. *op. cit.* note 3; Cohen et al. *op. cit.* note 3; Baeten et al. *op. cit.* note 3; Thigpen et al. *op. cit.* note 3.

we consider scientific, regulatory, policy and community perspectives that may inform the question of whether PrEP ought to be included in the standard of prevention package. We then apply the guidelines based on such information.

## NORMATIVE FRAMEWORKS

There are two prominent sets of ethical guidelines that deal specifically with HIV prevention trials: the UNAIDS/WHO Ethical Considerations in HIV Biomedical Prevention Trials<sup>13</sup> and the HIV Prevention Trials Network (HPTN) Ethics Guidance for Research.<sup>14</sup> While both guidance documents intend to inform global HIV prevention research, they were derived by very different groups with unique primary missions; the UNAIDS guidance was developed by an international normative agency while the HPTN guidance was designed by a US-based global network engaged in HIV prevention research and is accordingly designed to address some specific needs of the network.<sup>15</sup> In some respects these documents are complementary, but they differ in the way that they outline the obligations regarding standards of prevention and care.<sup>16</sup>

Guidance point 13 of the UNAIDS/WHO document addresses standards of prevention, stipulating that there is an obligation to provide:

... access to all state of the art HIV risk reduction methods . . . 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.

<sup>13</sup> Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). 2012 (English original 2007, additional guidance point added 2012). UNAIDS/07.28E/JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: [http://www.unaids.org/en/media/unaids/content/assets/documents/unaidspublication/2012/jc1399\\_ethical\\_considerations\\_en.pdf](http://www.unaids.org/en/media/unaids/content/assets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf) [Accessed 18 Feb 2013].

<sup>14</sup> S. Rennie, J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research. HIV Prevention Trials Network. Available at: <http://www.hptn.org/web%20documents/EWG/HPTNEthicsGuidanceV10Jun2009.pdf> [Accessed 18 Feb 2013].

<sup>15</sup> In addition, African countries including South Africa, Kenya and Uganda have developed their own guidelines for HIV prevention research. Thanks to an anonymous reviewer for highlighting these points.

<sup>16</sup> Disclosure: one of the authors of this article coordinated the 2007 and 2011 revisions of the UNAIDS/WHO guidance while two authors were members of the oversight committee producing the 2007 UNAIDS/WHO Guidelines. One of the authors was a primary author of the HPTN Guidelines.

This obligation is grounded in the ethical principle of beneficence. A key intention of the guideline is to prevent double standards between high- and low- or middle-income countries, and to be a tool in the progressive realisation of the right to health. Allowance is made for negotiation among stakeholders after new prevention modalities are validated or approved for use by relevant agencies, with respect to potential impact on feasibility and the ability to isolate the safety and efficacy of the biomedical HIV modality being tested.

The HPTN Ethics Guidance takes a somewhat different stance, distinguishing between an ethical obligation and an ethical aspiration. Using this framework, and also based in the ethical principle of beneficence, guidance point 9 on the standard of prevention identifies the provision of an 'effective' prevention package for trial participants as obligatory. The criteria offered for what constitutes an effective prevention package is one for which there is established evidence of efficacy, that is practically achievable in the trial setting, and that is reasonably accessible. The precise content of that package, however, is defined as an 'ethical aspiration'. The commentary states that in certain settings proven risk reduction methods such as male circumcision may be culturally inappropriate and others such as needle exchange may be illegal. It goes on to argue that providing an array of state-of-the-art risk reduction methods that are not available outside the trial could constitute undue inducement to participate. The HPTN document also provides guidance on other aspects of research, including specifying processes of community engagement, capacity building, and partnerships.

The HPTN document is structured to address issues that arise sequentially from before the trial starts to its conclusion and it identifies stakeholders responsible for implementing guidance points. In addition, it specifies a conception of justice in its underpinning principles, namely 'social justice', which is defined as 'the ethical concerns related to treating people equally, avoiding exploitation, and trying to reduce health disparities'.<sup>17</sup> Implicitly, this conception focuses on equality between people inside the trial and people outside the trial in a local community, in contrast to concerns about reducing global health disparities between people in high-income countries and those in low- and middle-income countries.<sup>18</sup> This approach to the standard of prevention reflects the HPTN document's genesis as a document produced for and by a research network. In designating actions as obligatory or aspirational, the document

<sup>17</sup> S. Rennie, J. Sugarman and the HPTN Ethics Group, *op. cit.* note 9, p. 14.

<sup>18</sup> When conducting a study, a principal investigator can address within-country disparities through cooperation and referral networks with local health services, but international disparities may be impossible to address due to major funding and infrastructure deficits.

intends to help clarify the extent to which particular guidelines must be met by those responsible for it.<sup>19</sup>

While the UNAIDS guidelines recommend the adoption of all state-of-the-art risk reduction methods, the HPTN document takes a less categorical stance. The rationale for the latter is to guard against people within a trial having access to a higher standard of prevention than is available to local communities, which might be unfeasible to integrate into local health systems.<sup>20</sup> This approach effectively shifts the discourse about double standards, understood elsewhere to mean disparities between high-income countries and low- and middle-income countries, to one that centres on the local community.<sup>21</sup> The UNAIDS recommendation, on the other hand, supports access to a standard of prevention than the local community may only aspire to, which can be justified on the basis that participants bear a greater risk than other community members by exposure to an unlicensed product.

Although both documents recommend engagement of stakeholders in establishing the standard of prevention packages for trials, the UNAIDS/WHO document states that the final package should be ‘based on consultation among all research stakeholders including the community’. It also states that the consultative process needs to take into consideration scientific validation<sup>22</sup> of the tools to be included in the package and whether relevant authorities have approved the use of such tools for HIV prevention.<sup>23</sup>

In addition to these two sets of guidelines, there is a set of consensus points developed by a group of HIV prevention researchers and bioethicists in 2009 at a ‘Standard of Prevention’ consultation in Uganda.<sup>24</sup> These consensus points are consistent with the UNAIDS/WHO guidelines stating that a new intervention is considered ‘state of the art’ when it is approved by a relevant regulatory authority or included in normative guidelines. However, they also encouraged trials already underway (for example, on-going PrEP trials) to continue, in order to get maximum information about preventive modalities in different populations. Further, consensus was not reached

on the potential role of research to ‘drive or “ratchet up” the standard of care available in many settings’.<sup>25</sup>

## SCIENTIFIC CONSIDERATIONS

To determine whether PrEP should be integrated into the standard of prevention, it is necessary to review the relevant scientific information. The cascade of positive trial results using ARV for HIV prevention began in July 2010 with CAPRISA 004. This trial looked at the efficacy of 1% tenofovir gel formulated as a topical PrEP agent (a microbicide) for intra-vaginal application before and after sex. Tenofovir gel reduced the risk of HIV infection in study participants by 39% when compared to those using placebo, with a strong correlation between detectable drug and observed efficacy, thereby providing the first indication of the importance of adherence for protection.<sup>26</sup> These results await a confirmatory trial, as CAPRISA 004 was a test-of-concept trial, not designed to provide sufficient evidence to support licensure. As discussed later in this paper, a subsequent trial known as VOICE that tested daily use of tenofovir gel did not confirm the results.<sup>27</sup> So whether licensure is forthcoming will depend on the results of a further trial of pericoital gel use, known as FACTS 001, that commenced in October 2011.

Four months after the results of CAPRISA 004 were made known, results from the iPrEx study were published, showing that daily oral PrEP, a combination of tenofovir/emtricitabine (TDF/FTC) in tablet form, reduced HIV acquisition by 44% in a population of men who have sex with men (MSM) and transgender women who have sex with men at high risk of acquiring HIV. Again, efficacy increased with improved adherence to the study product.<sup>28</sup> Further evidence showing the efficacy of TDF/FTC as PrEP came in 2011 from two trials among heterosexual people in Africa. The Partners PrEP study showed a 75% reduction in HIV incidence in HIV serodiscordant couples

<sup>19</sup> S. Rennie & J. Sugarman. Developing Ethics Guidance for HIV Prevention Research: the HIV Prevention Trials Network Approach. *J Med Ethics* 2010; 36: 810–815.

<sup>20</sup> Ibid.

<sup>21</sup> S. Rennie, J. Sugarman and the HPTN Ethics Group. *op. cit.* note 9.

<sup>22</sup> For a critique of scientific validation, see B. Haire, J. Kaldor & C.F.C. Jordens. 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* 2012; 12: 21–30.

<sup>23</sup> The flexibilities of the UNAIDS/WHO guidance can be seen, for example, in the decision by the Phambili vaccine trial in Johannesburg to offer voluntary medical male circumcision (VMMC) without a national policy being in place in South Africa.

<sup>24</sup> S. Philpott, L. Heise & E. McGrory, et al. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 2011; 37: 244–248.

<sup>25</sup> K. Shapiro & S.R. Benatar. HIV prevention research and global inequality: steps towards improved standards of care. *Journal of Medical Ethics* 2005; 31: 39–47.

<sup>26</sup> Abdoool Karim et al. *op. cit.* note 3.

<sup>27</sup> Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women. September 28, 2011. Pittsburgh, PA: MTN. Available at: <http://www.mtnstopshiv.org/node/3619> [Accessed 18 Feb 2013].

Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. Nov 25, 2011. Pittsburgh, PA: MTN Available at: <http://www.mtnstopshiv.org/node/3909> [Accessed 18 Feb 2013].

The TDF/FTC arm in the VOICE trial is continuing, and results are expected in early 2013.

<sup>28</sup> Grant et al. *op. cit.* note 3; P.L. Anderson et al. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine* 2012; 4.

using combined TDF/FTC, with its tenofovir-only arm showing a 67% reduction.<sup>29</sup> The TDF2 study, conducted among heterosexual men and women in Botswana, showed a 62% reduction in HIV acquisition using TDF/FTC.<sup>30</sup>

Amidst these positive results are those of two ARV-based HIV prevention trials that did not demonstrate a benefit of daily oral TDF/FTC and tenofovir as PrEP: the FEM-PRP,<sup>31</sup> and VOICE<sup>32</sup> trials, respectively. In FEM-PRP, the failure of oral TDF/FTC was linked to poor adherence, indicated by only 31% of women in the active trial arm having detectable drug in their blood.<sup>33</sup> The VOICE study also did not demonstrate a protective effect for the daily use of tenofovir gel or tenofovir-only oral PrEP and both these arms were stopped for futility.<sup>34</sup> Thus, two products that had positive results in other trials, tenofovir gel in CAPRISA 004 and oral tenofovir PrEP in Partners PrEP, were unable to be confirmed in VOICE. Speculation about these conflicting results includes discussion of the different dosing schedule for gel use (VOICE used a daily rather than a peri-coital dosing schedule), and possible adherence issues with the tablet. Although differences in the populations studied, sexual behaviours, genital mucosal integrity, and other co-factors for acquisition may have played a role, low levels of actual gel or tablet use, resulting in inadequate genital tract drug concentrations, seems to be the explanation for these divergent trial results.<sup>35</sup>

The VOICE trial included an arm studying daily oral TDF/FTC which was also found ineffective.

## REGULATORY CONSIDERATIONS

Regulatory authorities that stipulate the level and strength of evidence required for licensure can have a

<sup>29</sup> Baeten et al. *op. cit.* note 3.

<sup>30</sup> Thigpen et al. *op. cit.* note 3.

<sup>31</sup> L. Van Damme et al. Preexposure Prophylaxis for HIV Infection among African Women. *New Engl J Med* 2012; 367: 411–422.

<sup>32</sup> Microbicides Trial Network. *op. cit.* note 24.

<sup>33</sup> Van Damme et al. *op. cit.* note 22.

<sup>34</sup> Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women. September 28, 2011. Pittsburgh, PA: MTN. Available at: <http://www.mtnstopshiv.org/node/3619> [Accessed 18 Feb 2013].

Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. Nov 25, 2011. Pittsburgh, PA: MTN Available at: <http://www.mtnstopshiv.org/node/3909> [Accessed 18 Feb 2013].

The TDF/FTC arm in the VOICE trial is continuing, and results are expected in early 2013.

<sup>35</sup> A. van der Straten, L. Van Damme, J.E. Haberer & D.R. Bangsberg. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS*. 2012 Apr 24; 26(7): F13–F19. The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review. C.A. Hankins & M.R. Dybul. *Curr Opin HIV AIDS*. 2013 Jan; 8(1): 50–58.

considerable impact on trial design. The recent FDA approval of, and CDC guidance for, the use of daily oral TDF/FTC PrEP highlight the importance of considering it when determining the standard of prevention for trials that include sites in the USA and/or are funded by the US government. This will be especially complex for multi-country HIV prevention trials where other nations have not yet approved PrEP, since they may raise concerns about interpretability and double standards. Of interest, the FDA had requested that its Antiviral Advisory Committee that considered the TDF/FTC application discuss the implications of approval of TDF/FTC for PrEP for future placebo-controlled trials. Unfortunately, the Advisory Committee did not have time to undertake such discussions.<sup>36</sup>

## POLICY CONSIDERATIONS

While the scientific and regulatory questions and issues are complex, considerations about national policy can make decision-making about standard of prevention packages in research even tougher, particularly due to the time lapse between scientific validation of an intervention and it being adopted as policy. One case in point is the Phambili HIV vaccine study that took place in South Africa and enrolled until September, 2007.<sup>37</sup> The trial included VMMC in the standard of prevention package offered to male study participants, preceding by three years the launch of a national VMMC programme in South Africa in April 2010.<sup>38</sup> The decision to include VMMC in the trial was made on the basis of the scientific validation of VMMC for HIV prevention.<sup>39</sup> By the time the Phambili trial started, the WHO/UNAIDS had made a recommendation to adopt VMMC in high incidence

<sup>36</sup> See FDA. 2012 Meeting Materials Antiviral Advisory Committee. May 11 2012 meeting of the Antiviral Drug Advisory Committee Questions to the committee available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM305774.pdf> [Accessed 18 Feb 2013]; Transcript of meeting available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM311519.pdf> [Accessed 18 Feb 2013]; All meeting materials available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm295937.htm> [Accessed 18 Feb 2013].

<sup>37</sup> G. Gray, S. Buchbinder & A. Duerr. Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. *Curr Opin HIV AIDS*. 2010 Sep; 5(5): 357–361.

<sup>38</sup> Treatment Action Campaign (TAC). TAC Briefing on Adult and Adolescent Voluntary Medical Male Circumcision (VMMC). Capetown, South Africa:TAC. Available at: <http://www.tac.org.za/community/node/3190> [Accessed 18 Feb 2013].

<sup>39</sup> Auvert et al., *op. cit.* note 1. Bailey et al. *op. cit.* note 1. Gray et al. *op. cit.* note 1.

countries such as South Africa.<sup>40</sup> Had the investigators waited for the national programme, Phambili participants would not have had access to a proven effective intervention. This example shows that it is possible, where scientific validity is unequivocal, for trial protocols to adopt interventions as standard of prevention ahead of national guidelines.

## COMMUNITY CONSIDERATIONS

While researchers and research networks differ with regard to the level and timing of community consultation, to date many critical decisions made by researchers and sponsors designing clinical trials have been made well before the studies commence. At the time of grant writing, for example, researchers may have identified a 'high-incidence population' but not the specific communities with which the research will take place. This makes undertaking preparatory work in communities within tight timeframes very difficult. Therefore guidelines that require consultation with research stakeholders and communities to help define standard of prevention packages can entail practical challenges.<sup>41</sup> While there are recognised efforts by multiple HIV prevention trial networks to engage community representatives in dialogue about the design and implementation of these trials,<sup>42</sup> extensive grassroots consultations prior to conclusion about the content of the standard of prevention packages for research may not, and indeed cannot, always occur.<sup>43</sup>

While some researchers make exceptional efforts to achieve meaningful community engagement in all aspects of clinical trial design and implementation, grassroots consultation in developing countries has its special challenges due the complexity of randomized clinical trials and limited understanding of the concepts in the community at large. This is further compounded by low levels of

literacy in many resource poor countries<sup>44</sup> resulting in limited participation and contribution of communities towards meaningful discussions around evolving standards of care for participants in clinical trials.

Timing is also critical: where researchers consult with the community after trials have been designed or after ethics approval of research protocols, community dialogue may be limited to simply ensuring successful community entry and entreating community support and subsequent ongoing input for project implementation.<sup>45</sup>

UNAIDS and AVAC developed the Good Participatory Practice guidelines document (GPP) that details expected engagement processes with communities throughout the lifecycle of a trial and describes how to establish mechanisms that give communities opportunities for input in the research. Such inputs include discussing the standard of prevention packages.<sup>46</sup> The use of the GPP principles is expanding<sup>47</sup> and multiple efforts at promoting their wider use are being undertaken by HIV prevention research networks.

Even where research has mechanisms to facilitate dialogue with community representatives, having communities negotiate the standard of prevention packages remains difficult given a myriad of issues that constrain this practice, including the structural inequalities that exist between researchers and community members – and indeed between high- and low-and-middle-income countries.<sup>48</sup> In view of these limitations, standard prevention packages should be provided in line with clearly defined guidelines as a responsibility of researchers to the research participant.<sup>49</sup> The utilisation of GPP as a practice guide in the design and implementation of HIV prevention research is expected to better systematise community engagement and promote greater ownership of research by communities.

The inclusion of PrEP in prevention packages provided to study participants could build critical service delivery capacity in the absence of country policies. As a consequence, this might facilitate the development of supportive policies and appropriate responses to the results of

<sup>40</sup> World Health Organization/UNAIDS. 2007. New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications. Montreux, Switzerland. Available at: [http://libdoc.who.int/publications/2007/9789241595988\\_eng.pdf](http://libdoc.who.int/publications/2007/9789241595988_eng.pdf) [Accessed 18 Feb 2013].

<sup>41</sup> New HIV Vaccine and Microbicides Advocacy Society (NHVMAS). 2012. Research Community Request For Better Process Of Community Engagement, Informed Consent And Standard Of Care In HIV Research In Nigeria. Lagos, Nigeria: NHVMAS. Available at: <http://nhvm-as.org/website/eventcontent.php?eventid=%20141> [Accessed 18 Feb 2013].

<sup>42</sup> For an example of effective community consultation, see A. Valley et al. The Benefits of Participatory Methodologies to Develop Effective Community Dialogue in the Context of a Microbicide Trial Feasibility Study in Mwanza, Tanzania. *BMC Public Health* 2007; 7: 133.

<sup>43</sup> M.O. Ukpong. Perspectives on Community Engagement in Standard of Prevention Package Negotiation for Clinical Trials. Presentation at the M2012 Symposium. Microbicide 2012, Sydney, Australia, USA. 15–19 April 2012.

<sup>44</sup> Low literacy does not mean that people lack the capacity to understand research concepts, but it can pose communication challenges that require commitment to overcome. See P. Ndebele, D. Wassenaar, E. Munalula & F. Masiye. Improving understanding of clinical trial procedures among low literacy populations: an intervention within a microbicide trial in Malawi. *BMC Medical Ethics* 2012; 13: 29.

<sup>45</sup> Ibid.

<sup>46</sup> UNAIDS/AVAC. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, 2nd ed. Geneva, Switzerland: UNAIDS/AVAC. Available at: [http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/manual/2010/Guidelines\\_Biomedical\\_HIV\\_Prevention\\_2010\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/manual/2010/Guidelines_Biomedical_HIV_Prevention_2010_en.pdf). [Accessed 18 Feb 2013].

<sup>47</sup> Ibid 35, 37.

<sup>48</sup> Ukpong. *op. cit.* note 33.

<sup>49</sup> P.B. Miller & C. Weijer. Fiduciary Obligation in Clinical Research. *J Law Med Ethics* 2006; 34: 424–440.

PrEP demonstration projects. Assuming that trial feasibility is not undermined by trials becoming too expensive to conduct or difficult to interpret, it can be argued that the immediate potential benefit of reduced HIV infection risk for study participants is a legitimate derivable benefit from the trial for the community, even if this cannot be sustained beyond the research.<sup>50</sup>

## APPLYING THE GUIDELINES

Given that the USA FDA has approved the use of daily oral TDF/FTC as PrEP, at first glance the UNAIDS/WHO ethical guidance would appear to favour its inclusion in the HIV prevention package for future HIV prevention trials. However, the UNAIDS/WHO guidelines indicate that approval must be by relevant authorities.<sup>51</sup> Of course, many national regulatory authorities may hesitate to approve PrEP without WHO recommendations. In this regard, WHO has published guidance on the use of PrEP in demonstration projects for HIV-serodiscordant couples and men and transgender women who have sex with men at high risk of HIV.<sup>52</sup> Such demonstration projects are intended to gather further information about adherence, HIV testing protocols, drug resistance and other factors considered key to the development of general guidance for implementing PrEP.<sup>53</sup>

If TDF/FTC PrEP were to be deemed to be part of the standard of prevention package for HIV prevention trials, by definition it would need to be offered to all participants.<sup>54</sup> Given its anticipated effects, this would necessitate larger sample sizes to achieve the same number of HIV seroconversion endpoints. HIV prevention trials that included a TDF/FTC standard of prevention would therefore be both more expensive and take longer to reach a conclusion. An example of this design could be an HIV vaccine efficacy trial in the US. While the primary comparison would be between the efficacy of the experimental vaccine and the placebo vaccine, all the participants in both groups could be offered daily oral

TDF/FTC as part of the risk reduction package. The sample size would be at least twice as large as it would have been, had PrEP not been available.<sup>55</sup> There are additional considerations for an HIV vaccine efficacy trial conducted in resource limited settings. Here, the use of TDF/FTC as part of the standard of prevention package could create differences between trial participants and their communities, particularly where public access to this drug as part of treatment of HIV is not universal, let alone for PrEP. This would be considered by many to be problematic from a social justice perspective, but further empirical research is required to understand how standards of prevention affect health care availability and social dynamics.

The ethical obligation to provide state-of-the-art prevention packages during HIV prevention trials therefore needs to reconcile the tension between a moral obligation to ensure optimal protection of and benefits for study participants, and the imperative to find effective user-friendly HIV prevention technologies.

## MOVING FORWARD

Despite considerable progress in developing safe and effective means to prevent HIV infection, there remains a need to develop and test approaches in different populations. In doing this work, a balance needs to be struck between prioritising the protection of trial participants and facilitating ongoing research into new HIV prevention technologies that might prove safer, more acceptable, less expensive, more effective, and more feasible in low-and middle-income countries. Not all new options will be better in all respects (and some might fail), but the goal is to have a set of options to cover different contingencies. How to facilitate this through research remains controversial, and is a subject of ongoing debate and discussion. These debates and discussions emphasize the difficulty of reaching a consensus on the appropriate standard of prevention package for HIV prevention trials for different study populations in different countries.

There is a broad consensus that for all HIV prevention trials, all study participants should receive a standard HIV prevention package including male and female condoms, STI treatment, and behaviour change communication, as well as education and referral for VMMC in the instance of heterosexual men who are at particular

<sup>50</sup> M. Ukpong, *op. cit.* note 33.

<sup>51</sup> At the time of writing, this issue was under review with regard to the French trial PrEP Ipergay. Ipergay tests episodic PrEP against a placebo comparator in men who have sex with men (MSM), and is being reviewed to determine whether this is ethically appropriate, given the evidence for PrEP efficacy and the FDA approval. <http://www.ipergay.fr>.

<sup>52</sup> World Health Organisation. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects. July, 2012. Geneva, Switzerland: WHO. Available at: [http://www.who.int/hiv/pub/guidance\\_prep/en/index.html](http://www.who.int/hiv/pub/guidance_prep/en/index.html) [Accessed 18 Feb 2013].

<sup>53</sup> *Ibid.*

<sup>54</sup> Discussion of alternative trial designs, such as those in which daily oral TDF/FTC PrEP is used as an active comparator, is beyond the scope of this article.

<sup>55</sup> The HIV Vaccine Trials Network (HVTN) 505 Study currently taking place in the US is not yet providing oral TDF/FTC for PrEP to participants, but is offering information about it and monitoring drug levels. See *HVTN 505: Expansion in Response to an Evolving Field*. Seattle, WA: HVTN Available at: <http://hvtnews.wordpress.com/2011/09/13/hvtn-505-expansion-in-response-to-an-evolving-field/> [Accessed 18 Feb 2013].

risk of HIV exposure.<sup>56</sup> However, currently there is no consensus regarding whether PrEP should be part of the standard of prevention package in HIV prevention trials and whether it should be used as a comparator arm. Decisions by national authorities are not the only factors to be considered in making this determination, but there is a lack of a clear decision-making framework at the international level to clarify whether PrEP should be included. While there are some conflicting trial results, the FDA approval of TDF/FTC for the purposes of PrEP fulfils the 'scientific validation' requirement of the UNAIDS/WHO Guidelines. However, stakeholder agreement is needed, and the stakeholders – including regulatory bodies, trial communities, research sponsors and HIV prevention researchers – have different interests, perspectives, and levels of influence on the issue.

Reducing and eliminating HIV acquisition is a global health priority. The goals of HIV prevention research must be to find the most effective and efficient ways of using existing tools, including ARV-based prevention, and to establish the effectiveness of new tools. Randomised controlled trials are an important part of this.

In addition, there is a need for further empirical research on standard of prevention practices and beliefs that might inform decision making about whether or how to include newly validated technologies. Research into what has been offered at various trial sites to date, how this was justified (including how various guidelines were used), and what were the perceived consequences of this in terms of both short- and long-term health benefits for trial participants and their communities would be most valuable to inform ongoing discussions. A pivotal question is whether higher standards of care for trial participants eventually 'ratchet up' standards in their communities, or whether such standards promote inequity.

Determining the appropriate trial design and prevention package for a particular study in a specific HIV risk population requires careful consideration, taking account of national and international guidelines, ARV programme coverage, and the perspectives of researchers, ethics committees, trial sponsors, regulators, communities, and other HIV prevention trial stakeholders. There is currently no documented evidence on consultative decision-making processes for defining the standard of prevention packages for HIV prevention research. The field needs to develop processes that engage all stakeholders in realistic and practical decision-making in a time-sensitive manner, without undue prioritisation of

financial considerations above the interests of trial participants.

#### Conflicts of Interest

Sheena McCormack is Chief Investigator on a UK PrEP pilot study in men who have sex with men.

Gita Ramjee is co-chair of the South African FACTS 001 tenofovir gel trial.

#### Acknowledgements

The contents and options expressed in this manuscript are solely the responsibility of the authors. Jeremy Sugarman's work on this project was supported in part by the National Institute of Allergy and Infectious Disease, National Institute of Drug Abuse, and the National Institute of Mental Health under Cooperative Agreement # UMI AI068619 to the HIV Prevention Trials Network.

#### Biographies

**Bridget Haire** is the Vice President of the Australian Federation of AIDS Organisations (AFAO), and was the Community Chair of the Microbicides 2012 conference. She is completing a PhD at the Centre for Values, Ethics and the Law in Medicine, University of Sydney.

**Morenike Oluwatoyin Folayan** is an Associate Professor with the Obafemi Awolowo University, Ile-Ife, Nigeria.

**Catherine Hankins** led the revision processes for the 2007 and 2012 UNAIDS/WHO Ethical Considerations in biomedical HIV prevention trials. She is Deputy Director, Science at the Amsterdam Institute for Global Health & Development and an Honorary Professor in the Faculty of Epidemiology & Population Health at the London School of Hygiene and Tropical Medicine.

**Jeremy Sugarman MD, MPH, MA** is the Harvey M. Meyerhoff Professor of Bioethics and Medicine at the Berman Institute of Bioethics at the Johns Hopkins University. He is an internationally recognized leader in the field of biomedical ethics with particular expertise in the application of empirical methods and evidence-based standards for the evaluation and analysis of bioethical issues. Dr Sugarman is currently chair of the Ethics Working Group of the HIV Prevention Trials Network.

**Sheena McCormack** is a Clinical Epidemiologist who has been coordinating HIV prevention trials since 1994 and became a Professor of Clinical Epidemiology at Imperial College in 2012. A consultant in HIV/GU Medicine since 1991, Sheena has been working at the Chelsea & Westminster Hospital Dean Street clinic in Soho since 1996.

**Gita Ramjee, PhD** is the Director of the HIV prevention Research Unit, of the South African Medical Research Council in Durban. Dr. Ramjee is internationally renowned for her work on HIV prevention, and was recently recognized by her peers with a lifetime achievement award.

**Mitchell Warren** is the Executive Director of AVAC, an international non-governmental organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of AIDS vaccines, male circumcision, microbicides, PrEP and other emerging HIV prevention options as part of a comprehensive response to the pandemic.

<sup>56</sup> B. Haire. *op. cit.* note 1.