

HIV RESEARCH IN THE ERA OF PREP: THE IMPLICATIONS OF TDF/FTC FOR BIOMEDICAL PREVENTION TRIALS

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TAG

Treatment Action Group

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The authors of this report bear sole responsibility for the content.

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Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.

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INTRODUCTION

The development of biomedical interventions capable of preventing HIV infection—such as HIV vaccines, microbicides, and pre-exposure prophylaxis (PrEP)—is essential for reducing incidence and, ultimately, halting the pandemic. Testing the efficacy of experimental candidates involves the navigation of a complicated ethical tightrope: balancing the need to rigorously study emerging biomedical prevention strategies against the need to avoid exposing clinical trial participants to undue risk. The advent of PrEP with the highly effective antiretroviral drug combination tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, Truvada) introduces additional complexity, as decisions must now be made in regards to making TDF/FTC PrEP available to participants in clinical trials of other candidates.

The first section of this report reviews some of the published literature addressing this topic and the approaches to Truvada PrEP taken by recent biomedical prevention efficacy trials. The second section presents results from a small community survey conducted by Treatment Action Group (TAG) that solicited opinions on incorporating Truvada PrEP into biomedical prevention trials.

BIOETHICS LITERATURE REVIEW

The primary focus of the scientific literature addressing the use of Truvada PrEP in biomedical prevention trials is on ethical issues and implications for clinical trial designs, but there are also articles addressing whether the combination of PrEP and alternative interventions might have additive or synergistic effects that could enhance the magnitude and/or longevity of protection against HIV infection.

Currently, there are three sets of guidelines on providing HIV prevention services to participants in clinical trials of biomedical prevention interventions:

- Ethical considerations in biomedical HIV prevention trials – Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2007 [updated 2012].¹
- HIV Prevention Trials Network Ethics Guidance for Research - Rennie, S., Sugarman, J., and the HIV Prevention Trials Network (HPTN) Ethics Working Group, 2009.²
- Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials - UNAIDS/AIDS Vaccine Advocacy Coalition (AVAC), 2011.³

As highlighted in a commentary by Bridget Haire of the University of New South Wales' Kirby Institute and colleagues,⁴ there are notable differences between these three sets of guidelines. The UNAIDS/WHO document 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.”

The intent is clearly to recommend access to the best prevention options, but there is room for interpretation. At this juncture, Truvada PrEP is widely considered to be state of the art and scientifically validated, with the lack of efficacy observed in some trials involving women being largely attributed to inconsistent adherence in a meta-analysis incorporating data from all trials^{5,6} (although it has been

posited that differences in drug absorption in the rectal and vaginal tissues played a role^{7,8}). But Truvada PrEP is still only approved for HIV prevention in a small number of countries globally, and the guidelines therefore leave open the possibility of not providing access to trial participants in these locations.

The HPTN guidelines cite the relevance of local circumstances, stating that:

“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.”

The issue of the potential for ‘undue inducement’ is also raised:

“In addition, offering an extensive array of HIV prevention methods when these methods are not generally available in the community may also constitute undue inducement to participate and/or create strong inequities between study participants and non-participants.”

Both the HPTN guidelines and the UNAIDS/AVAC guidelines on good participatory practice emphasize the importance of consultations with key stakeholders, including community members.

Ultimately, however, as Haire and colleagues state:

“None of the three sets of guidelines...offers a clear normative standard for the content of the prevention package in HIV prevention research.”

In the absence of such a standard, recent published articles have expressed the view that the onus is now on researchers to justify not offering Truvada PrEP to participants in biomedical prevention trials.⁹ The ethicist Jeremy Sugarman, a co-author on the HPTN guidelines, refers to this as a ‘rebuttable presumption’ for including Truvada PrEP.¹⁰

Sugarman explains that there are two primary circumstances to consider: the use of Truvada PrEP instead of a placebo in the comparator arm of a trial, and offering access to Truvada PrEP to all participants in a trial as part of the background prevention package. A third scenario involves providing Truvada PrEP after ceasing administration of experimental long-acting PrEP agents to provide coverage as levels of the experimental agent slowly decline.

On the subject of comparator arms, the UNAIDS/WHO guidelines state:

“The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been scientifically validated in comparable populations or approved by relevant authorities.”

The phrase “no HIV prevention modality of the type being studied” clearly precludes the use of placebos in clinical trials of alternative forms of oral PrEP. These types of trials will require designs that assess whether the alternative form is either non-inferior or superior to Truvada PrEP, and this approach is being taken with the ongoing DISCOVER study sponsored by Gilead Sciences, which is evaluating Descovy, a new version of Truvada that contains tenofovir alafenamide (TAF) instead of tenofovir. The trial will assess whether Descovy is non-inferior to Truvada using a ‘double-dummy’ approach in which participants receive either Descovy plus placebo Truvada or Truvada plus placebo Descovy.

Although there might be room for interpretation regarding whether long-acting injectable PrEP candidates represent the same type of modality as oral PrEP, HPTN trials of a long-acting version of the integrase inhibitor cabotegravir (CAB-LA) are also using the double-dummy design (one arm of the trial will administer CAB-LA plus Truvada placebo, whereas the comparator arm comprises CAB-LA placebo plus Truvada). HPTN 083 is assessing whether CAB-LA is non-inferior to Truvada, whereas HPTN 084 will attempt to establish whether CAB-LA has superior efficacy. Both trials will provide up to 48 weeks of open-label Truvada PrEP after the CAB-LA dosing period ends.

Microbicides, vaccines, and passive immunization are generally considered to be different modalities to oral PrEP—although there are similarities between long-acting antiretrovirals and passive immunization with broadly neutralizing antibodies (bNAbs)—and placebo controls remain in use for efficacy trials of these approaches. The question in these circumstances is how Truvada PrEP should be incorporated into the background prevention package offered to participants.

The researchers conducting the HIV Vaccine Trials Network (HVTN) 505 trial, which compared a prime-boost regimen comprising DNA and adenovirus serotype 5 (Ad5) vaccines to placebo in men who have sex with men (MSM) and transgender individuals, were the first to face this issue.¹¹ Data from the iPrEx trial demonstrating Truvada PrEP efficacy in a similar population¹² emerged while HVTN 505 was ongoing, and the researchers responded by writing to all participants to inform them of the results and then conducting extensive consultations with the community and other stakeholders regarding how to accommodate the findings. An online survey of HVTN 505 participants was also undertaken.¹³

After an initial analysis found that it wouldn't be logistically feasible to amend the study design to evaluate the combined efficacy of the vaccines plus Truvada PrEP (largely as a result of the increase in sample size that would be required), three options were considered:

- Provision of information about Truvada PrEP to study participants but no further action.
- Provision of information about Truvada PrEP and referral of participants to sources of PrEP outside of the study.
- Provision of both information and Truvada PrEP to those participants who were interested as part of the study itself.

The consultative process led to the adoption of the third approach: educational information about Truvada PrEP was developed for participants, who were also given the option of being referred to providers willing to prescribe the drug. The researchers secured a donation of Truvada from Gilead Sciences and the HVTN contracted a mail-order pharmacy for participants who needed the drug distributed directly to them.

The size of HVTN 505 was expanded from an originally planned target of 1,350 participants to 2,200 for two reasons: to evaluate vaccine efficacy in preventing HIV acquisition following the results of the RV144 trial in Thailand¹⁴ (the original design focused on the endpoint of post-infection viral load setpoint), and to accommodate PrEP utilization during up to 20% of the period participants were at risk (this could reflect 20% of participants using PrEP consistently or a greater proportion of participants using PrEP, but not necessarily for the entire study period).

Uptake turned out to be very limited, however, with only 13 individuals (1%) in each arm reporting Truvada PrEP use.¹⁵

Three ongoing efficacy trials provide examples of how provision of Truvada PrEP is currently being handled. All of the protocols have been through multiple levels of review, including by regulatory agencies, institutional review boards, and community advisory boards (CABs).

The HPTN and HVTN are collaboratively conducting two efficacy trials of passive immunization with the bNAb VRC01.¹⁶

- HVTN 704/ HPTN 085, enrolling 2,700 MSM and transgender individuals who have sex with men at sites in Brazil, Peru, and the United States.
- HVTN 703/HPTN 081, enrolling 1,500 women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.

In the 085 trial, Truvada PrEP is being offered free of charge to all participants; those based in the United States who choose to receive it are referred to a program that integrates provision of the drug into their primary health care. Participants in Peru and Brazil, where Truvada is not yet licensed for PrEP, will be referred to demonstration projects.¹⁷

A different approach is being taken in 081. Information on Truvada PrEP is being made available, along with referrals to access programs where possible, but the drug itself is not being provided. The study protocol explains that this is based on differing recommendations for PrEP use in women and the lack of local regulatory approvals. However, the protocol text acknowledges HIV prevention standards are continually evolving and states: “arrangements for provision of PrEP in this trial will take into account current evidence regarding PrEP efficacy in the populations to be enrolled in this trial, community consultation, guidance from international/regional/national/local and other regulatory authorities, and advice from persons/groups with bioethics and human subjects protection expertise.”¹⁸

HVTN 702 is an ongoing HIV vaccine efficacy trial in South Africa, and, although the protocol is not publicly available, the study co-chair Linda-Gail Bekker has stated that participants are being referred to Truvada PrEP pilot projects or the private sector, where the drug is available for R263 per month. A recent news report from Bhekisisa, the health journalism center of the Mail & Guardian newspaper, suggests that this has led to some controversy, with Tian Johnson from the African Alliance for HIV Prevention arguing that unequal access to Truvada PrEP among participants is unfair and compromises study participants’ rights.¹⁹ But Johnson also acknowledges that there is a responsibility on the part of the government to make Truvada PrEP available through the public sector and states: “While being guided by national policies on PrEP ... trials would do well to engage advocates to explore opportunities to accelerate the national PrEP agenda.”

These examples highlight the fact that uncertainties remain regarding the appropriate strategies for addressing Truvada PrEP in biomedical HIV prevention trials, and emphasize the importance of rapidly improving the global accessibility of the intervention.

PrEP in Combination

In addition to the ethical issues surrounding Truvada PrEP, there is some evidence to suggest that the combination of the drug with vaccines may have additive or even synergistic effects in enhancing or extending the duration of protection against HIV.^{20,21} This evidence primarily derives from studies in the SIV/maaque model,^{22,23} but it has been reported that some participants in the PrEx study developed T cell responses to HIV that were associated with reduced infection risk^{24,25}; this has not been a universal finding, however, and an analysis of participants in the Partners PrEP efficacy trial did not find evidence for such an association.^{26,27}

Several possible mechanisms for synergy between PrEP and HIV vaccines have been proposed in a paper by Holly Janes and colleagues:²⁸

- Receipt of PrEP during the period when a vaccine is being administered (which typically lasts 3–12 months) could provide protection while vaccine-induced immune responses are developing.
- Vaccines transiently activate CD4 T cells, potentially rendering them highly susceptible to HIV infection, and PrEP could shield these vulnerable cells if exposure to HIV occurs during this time.
- A partially effective vaccine might help to provide protection in PrEP users if there are periods of low drug levels (as a result of lower adherence or at the tail end of a dose of a long-acting agent).
- PrEP drug levels at the site of HIV exposure might allow abortive infection, during which HIV antigens are generated that could potentially boost vaccine-induced immune responses.²⁹
- A combination of PrEP and a vaccine could increase the threshold for viral escape by requiring mutations at both the site targeted by the PrEP drug and the sites targeted by vaccine-induced immune responses

The authors of the paper also outline some possible approaches to studying combinations, which typically would require increases in sample size compared with assessments of a single agent. The upside, they argue, is that: “although future efficacy trials will be more complex in their design, study implementation, and evaluation of endpoints, they may become more relevant and applicable to diverse populations and better suited to the ultimate goal of reducing HIV incidence at a population level.” In the ongoing HVTN 702 vaccine trial, levels of Truvada PrEP will be assessed using dried blood spots to explore questions related to how the products interact.

QUESTIONNAIRE METHODOLOGY

To gauge community attitudes regarding PrEP provision in biomedical prevention clinical trials, TAG developed and disseminated a questionnaire to be completed by community advocates engaged in HIV prevention research. The questionnaire was drafted by TAG staff and finalized with feedback provided by five biomedical prevention advocacy partners.

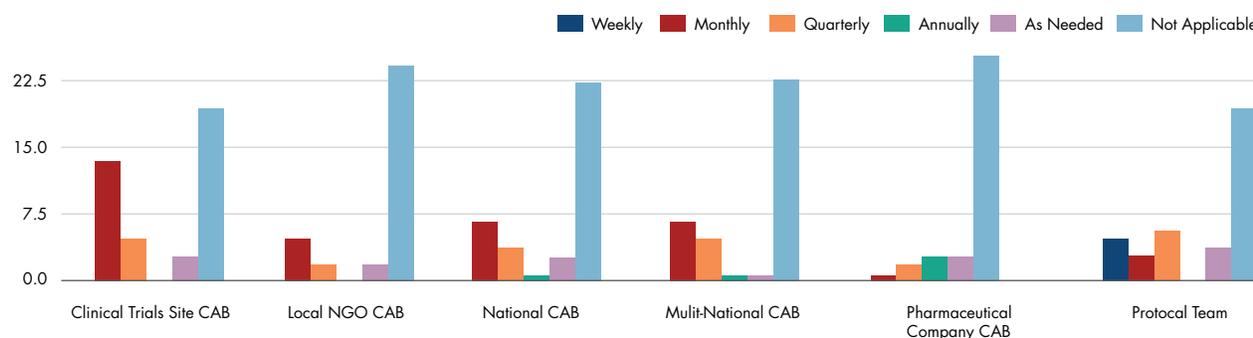
The online questionnaire was launched by TAG on March 7 and closed March 20, 2017. It was heavily promoted via HIV prevention and advocacy list-servs and social media.

QUESTIONNAIRE RESULTS

A total of 49 responses from individuals in 11 countries were received: United States, 63.8%; South Africa, 8.5%; Brazil and Canada, 4.3% each; and France, Kenya, Serbia, Thailand, Uganda, United Kingdom, and Zimbabwe, 2.1% each. Eighty-seven percent of questionnaire respondents reported that TDF/FTC is approved in their countries as PrEP; 60.9% reported that most people who want PrEP in their communities are able to access it without difficulties (via clinicians, access programs, or demonstration projects).

Approximately 92 percent of respondents reported having been involved in HIV prevention research advocacy work over the past two years. Nearly all respondents reported that they participated in at least one CAB or similarly structured input body to provide community input into HIV prevention research (see Figure 1).

Figure 1. Participation in CABs or similarly structured bodies to provide community input into HIV prevention research (percentage of respondents)



Respondents reporting involvement in a clinical trial site CAB, local non-government organization (NGO) CAB, national CAB, multi-national CAB, pharmaceutical company CAB, and/or clinical trial protocol team, including the frequency of involvement: weekly, monthly, quarterly, annually, or as needed.

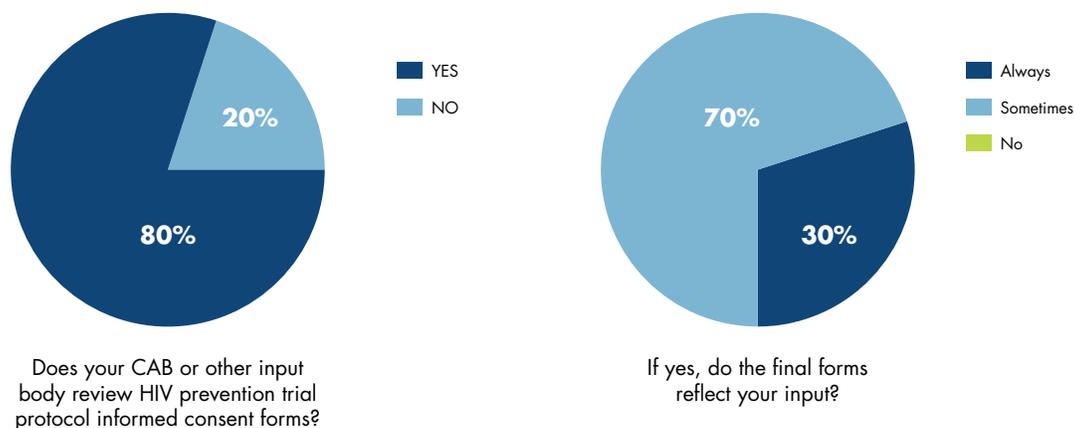
CAB Input Outcomes

The majority of respondents reported being meaningfully engaged in biomedical HIV prevention clinical trial design and implementation processes through CABs and other input bodies. Sixty percent of respondents reported providing input during early stages of clinical trial development, such as when protocols were being drafted; 72 percent reported providing input during late stages of clinical trial development, such as when protocols had been drafted, but were being reviewed; 60 percent reported input if a study's recruitment was slow or retention was a problem; 60 percent reported providing input before or immediately after closure of a study; and only 24 percent reported providing input while data were being analyzed or prepared for peer review.

Roughly three-quarters of respondents (73.9%) reported that final protocols sometimes reflected their input as community members. Twenty-one percent reported that final protocols always reflected their input; 4.3% reported that their input was never reflected in final protocols.

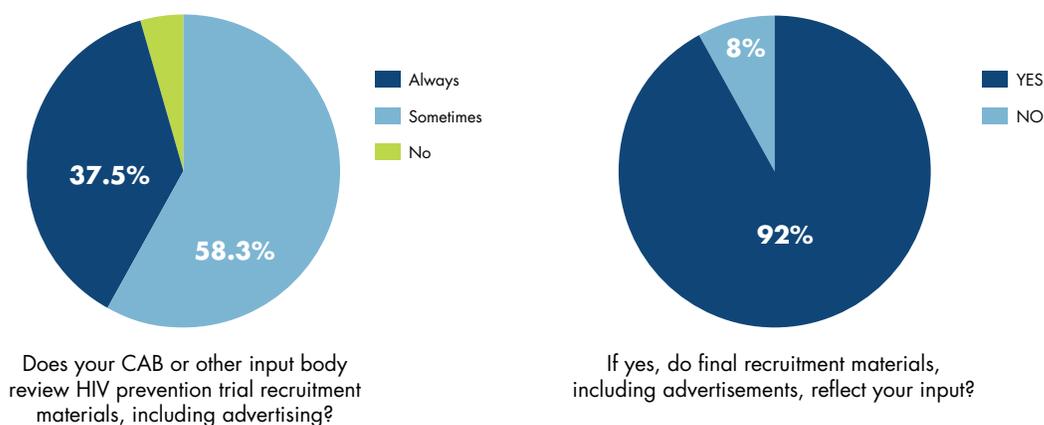
Input into protocol informed consent forms—ensuring that clinical trial participants are provided with clear and accurate information regarding a study's requirements and risks before agreeing to enroll—has always been considered to be essential to research advocates representing participant interests. Eighty percent of respondents reported belonging to CABs that facilitate the review HIV prevention clinical trial protocol informed consent forms, 70% of whom reported that the final informed consent forms reflected their input (see Figure 2).

Figure 2. Informed consent (percentage of respondents)



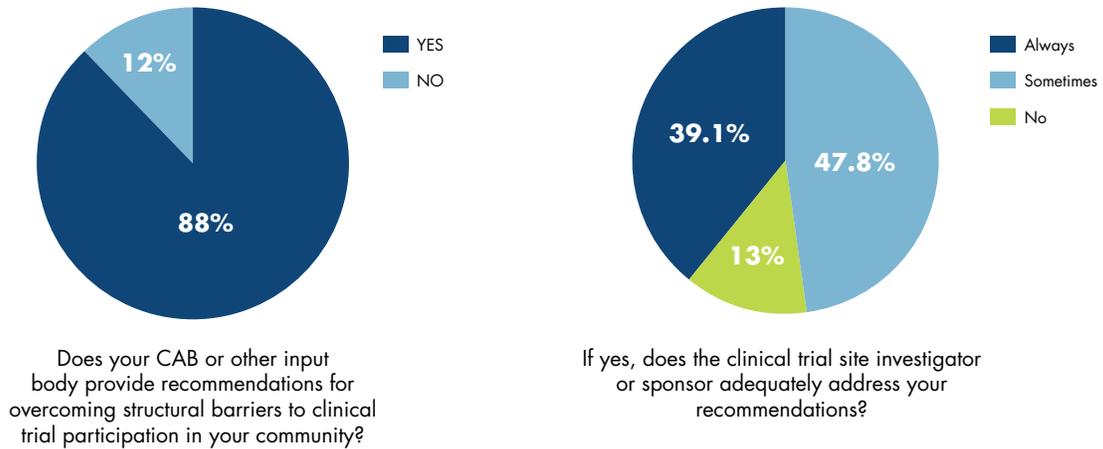
Community input into HIV prevention recruitment materials and advertising, as part of broader communication plans for clinical trials, is also necessary to ensure awareness of participation opportunities and that correct and balanced information is being disseminated to stakeholders. Ninety-two percent of questionnaire respondents reporting engagement in CABs that review HIV prevention trial recruitment materials, including advertising (see Figure 3).

Figure 3. Recruitment materials (percentage of respondents)



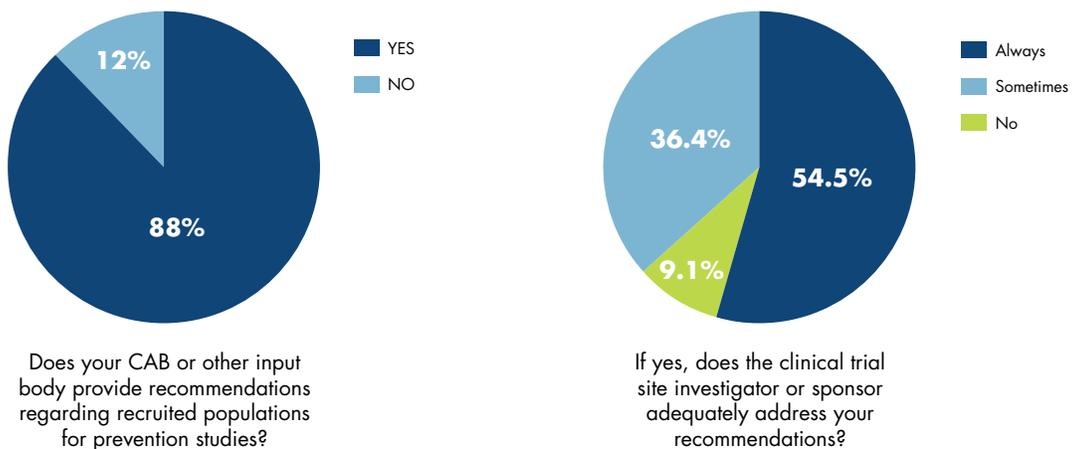
Structural barriers to clinical trial enrollment and retention include lack of child support, transportation, translation services, and stipends. Ensuring clinical trial participant access to support services that are necessary to maximize recruitment, enrollment, and retention goals remains a priority of research advocates. Eighty-eight percent of questionnaire respondents reported engagement in CABs that provide recommendations for overcoming structural barriers to clinical trials (see Figure 4).

Figure 4. Overcoming structural barriers (percentage of respondents)



Another primary objective of biomedical research advocacy is the enrollment of participants that represent affected communities. In the case of HIV prevention research, this must include those that are most disproportionately affected by HIV infection rates: women and young MSM of color, transgender women, sex workers, and people who inject drugs. Eighty-eight percent of questionnaire respondents reported involvement in CABs that provided recommendations regarding the recruitment in key populations and subpopulations (see Figure 5).

Figure 5. Recruiting participants from key populations (percentage of respondents)



The halting of two PrEP efficacy clinical trials planned in Cambodia and Cameroon, in response to concerns raised by local, national, and international activists, prompted AVAC and UNAIDS to develop *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (GPP) in 2007, with an updated edition being released in 2011. Although the PrEP trials had been designed in accordance with international guidance on ethics and clinical research, the criticism of the studies underscored a disconnect between some community stakeholders and research teams. The GPP guidelines sought to address how best for research teams to engage meaningfully with community advocates and civil society to help ensure the ethical development and implementation of HIV prevention trials.

Eighty-four percent of questionnaire participants reported being aware of the GPP guidelines; 69.6% reported that their CABs follow these guidelines, whereas 8.7% noted that their CABs did not follow these guidelines, and 21.7% didn't know whether their CABs were adherent to the GPP guidelines.

Truvada PrEP as a Standard of HIV Prevention

Guidelines recommend that the state-of-the-art package of prevention services—risk reduction counseling, condoms and lube, and circumcision are historical examples of package components—known as the 'standard of prevention' be provided to all HIV prevention clinical trial participants. Eighty-six percent of questionnaire respondents agreed that TDF/FTC should also be considered a standard of HIV prevention that should be provided to participants in clinical trials.

As explained by one respondent, however, the provision of TDF/FTC in biomedical HIV prevention clinical trials is dependent on a number of factors, including what 'provision' actually entails and the scientific objectives of the study:

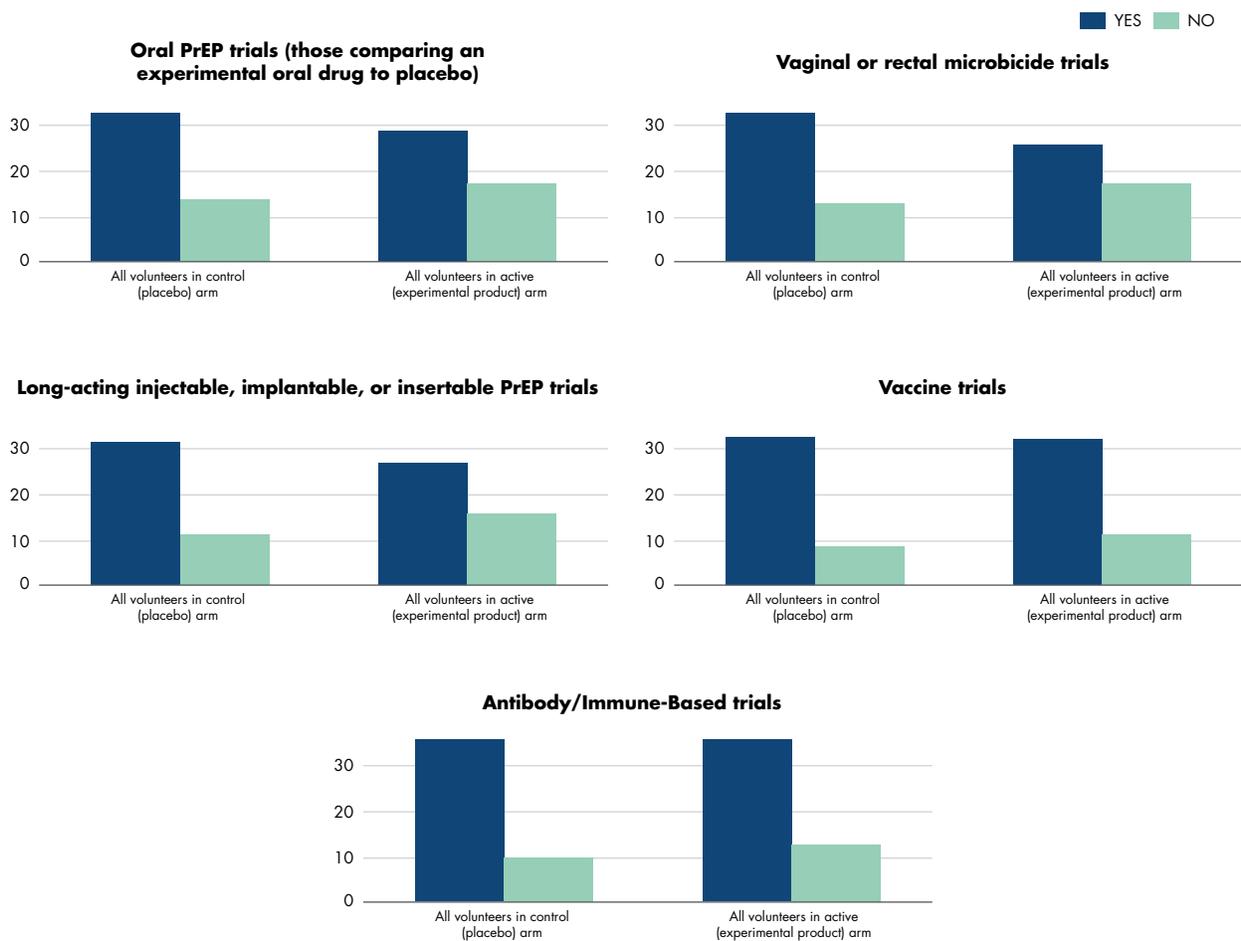
This is not a yes/no answer. While on the one hand I agree PrEP should be part of risk-reduction packages, this needs to be nuanced. There is a big difference between providing, facilitating access, or allowing participants who are on PrEP to continue using it. In each of these scenarios, for each population under study, in each part of the country (where access varies greatly), there needs to be a weighing of the practical and ethical considerations of choosing one of these options. The other element to consider is whether offering an increasingly varied and effective suite of risk-reduction packages makes it nearly impossible to test new interventions (for lack of incident infections—which unfortunately remains the only measure we have to test efficacy, in the absence of correlates of protection). Is it ethical NOT to develop new tools for those who find currently available tools unacceptable, impractical or inappropriate for their circumstances?

Respondents were also asked for which study participants should Truvada PrEP be offered as part of the standard of prevention in their home country (see Figure 6). Responses were comparable across all five of the clinical trial scenarios listed, with approximately 75 percent of respondents recommending TDF/FTC in control (placebo) arms of all biomedical prevention trials. Fewer respondents recommending TDF/FTC in control arms recommended TDF/FTC in active (experimental product) arms in trials of oral PrEP; vagina or rectal microbicides; and long-acting injectable, implantable, or insertable products, whereas there was a trend toward great acceptance of TDF/FTC being offered to volunteers in the active arms of preventive vaccine and antibody and immune-based therapy trials.

As one respondent noted, however:

PrEP should be “standard of prevention” everywhere except where there is a medical reason against this (where for example another ARV-based intervention was being tested, and where doubling up would increase risk of harm). The way [this] is framed is too simplistic to answer properly, as whether those of the active arm should get Truvada depends on the other study drug.

Figure 6. For which study participants should TDF/FTC PrEP be offered as part of the standard of prevention in your country (number of respondents)?



Another lingering issue is how to actually incorporate PrEP into background standard-of-prevention options in clinical trials. In the HVTN 702 trial in South Africa, for example, study participants receive referrals to local programs where they may obtain TDF/FTC, as opposed to active provision of PrEP as a component of prevention services. This is similar to the approach being employed in the VRC01 study HVTN 703/HPTN 081. It has been argued that TDF/FTC should be offered through these trials themselves.⁹

Questionnaire responses regarding the extent to which biomedical prevention trial sponsors must provide PrEP varied. Forty-eight percent said that sponsors should provide free, onsite TDF/FTC PrEP services (free medication and required lab tests, medical consultations, and adherence counseling); 27.9% said that sponsors should provide referral to outside clinics, programs, or demonstration projects for both PrEP medication and services); 23.9% said that clinical trial sponsors should provide free TDF/FTC, but provide referrals to outside clinics, programs, or demonstration projects for related PrEP services; 2.1% said sponsors should provide education about PrEP, but nothing further.

Open-ended responses were no less varied and, in many cases, indicated that decisions regarding how best to facilitate access to TDF/FTC in clinical trials will depend on the trial itself, including its design and where it is being conducted:

Truvada PrEP should be offered in all prevention trials, but if patient decides to take Truvada PrEP, they shouldn't be counted in either trial arm (active versus placebo), but monitored in a third, Truvada PrEP arm instead.

1) In order to get usable data in the context of PrEP as standard of prevention, trials are going to need to collect samples that allow for objective evaluation of use. Given that these data will be collected for benefit of trial, the participants should benefit from lab infrastructure, etc. 2) Standard of prevention is the provision of the best available standard. Provision means just that. You don't tell people how to use condoms and then suggest they go pick them up elsewhere. PrEP is not solely the medication. Therefore the whole package needs to be provided.

This depends on where the trial is being conducted AND how the trial is designed—for the previous questions about Truvada provision, I did not select answers for some as it depends on how the trial is designed (and the question framework implies the trials are placebo controlled, which may not be the case for alternate PrEP).

It is very difficult to elect one option without context. It depends on what is available locally, in which population this is being tested, etc. There can be no blanket motherhood statement on whether/how PrEP should be offered/provided in trials.

To me the 'correct' answer will be site specific—ethically the aim is to make PrEP reasonably available without unreasonable barriers (and ideally the presence of a trial should make PrEP access to those outside the trial easier too). Items 2, 3, or 4 could be appropriate, depending on advice from locals and the structure of available services.

Have the services all together help to ensure the retention of the participants.

PrEP is not widely available to the general public due to lack of affordability. And due to its high efficacy, it will be very difficult for comparison to other prevention options. If Truvada is offered at all, it should be as a comparator arm of the study, but not for the control or experimental arms.

If PrEP is available to anyone in the trial, it should be available to everyone (unless, of course, PrEP is the product under investigation in the trial). I think we need to start doing run-in trials that enroll people who have already indicated that they do not want and will not use PrEP, even if provided. This seems to me to be the only ethical way of doing affordable trials while not violating the ethical imperative to safeguard the health of trial participants to the greatest extent possible.

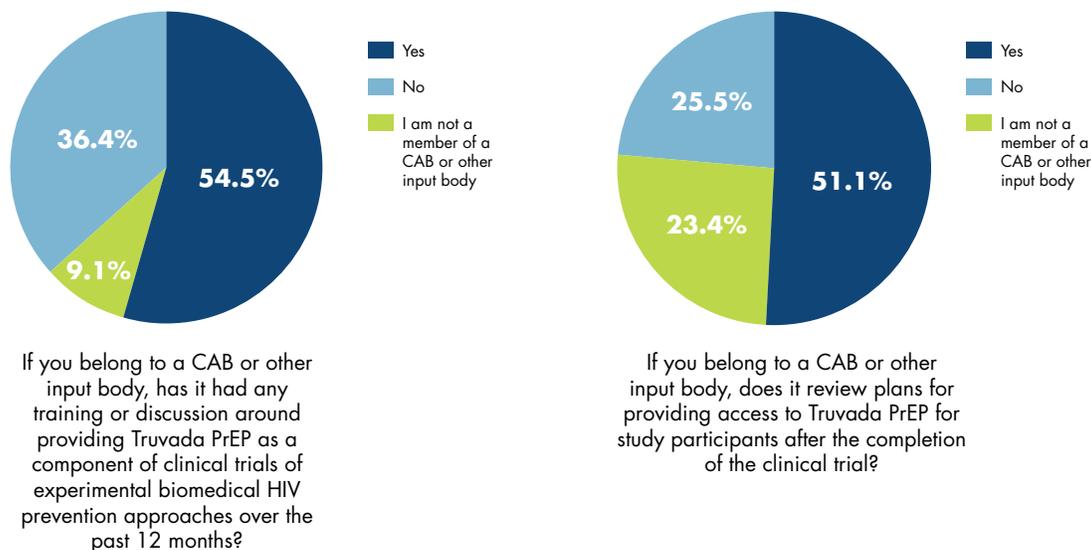
People in Serbia that are in need for Truvada are very ill, and usually these are people who are socially vulnerable, so they need free medication and lab tests....

Who should receive Truvada during a clinical trial is VERY dependent on the research questions and the intervention being offered. It is an ethical responsibility to disclose to participants that they have other options. This is required to be part of the informed consent. I'm not sure why the clinical site would be ethically obligated to provide Truvada.

There are people who can avoid acquiring HIV by taking Truvada. Everything should be done to connect these people with Truvada. It is the ethical responsibility of the research enterprise to connect these people to Truvada. Some people will be able to access Truvada for free with nothing but a referral, but others will not. Therefore, to cut across structural barriers that prevent SOME from accessing PrEP, the trial sponsors should provide it for everyone onsite. It would be unethical to stop at a referral because this would mean some people who need PrEP to stay HIV-negative would get it and some would not. I don't think we can expect research sites to have all the staff and equipment onsite to provide all Truvada services, but at least the medication can be provided onsite and services can be included too—just off-site.

Respondents were also asked about CAB activities pertaining to the provision of TDF/FTC PrEP as a component of biomedical prevention clinical trials over the past 12 months (see Figure 7). Approximately 60 percent of respondents reported CAB trainings or discussions pertaining to Truvada PrEP as a component of biomedical prevention trials, with slightly more than half also being provided with the opportunity to review plans for Truvada PrEP provision to study participants following completion of a planned trial.

Figure 7. TDF/FTC provision training, discussions, and planning in CABs (percentage of respondents)



CONCLUSION: KEY ETHICAL CONSIDERATIONS FOR PREP PROVISION

A limitation of our survey was that, in an effort to reduce survey length, we did not collect quantitative data on PrEP provision in more nuanced trial scenarios. Qualitative commentary from respondents frequently emphasized that there is no one-size-fits-all approach, and outlined some key ethical tensions that are not easily resolved and should be considered on a case-by-case basis by researchers, community members, and other key stakeholders. Again, as stated by Sugarman, there are two primary circumstances to consider: the use of TDF/FTC PrEP instead of a placebo in the comparator arm of a trial, or offering access to TDF/FTC PrEP to all participants in a trial as part of the background prevention package. When offered as part of the background package, the further consideration is whether to be more active or passive in provision of TDF/FTC and accompanying services.

Modality and Medications Being Tested

How TDF/FTC PrEP is provided depends on what biomedical prevention modalities and medications are being tested. According to UNAIDS/WHO, "The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been scientifically validated in comparable populations or approved by relevant authorities." Novel oral PrEP regimens must be shown to be non-inferior in comparison to TDF/FTC; however, vaccines, microbicides, long-acting injectables, bNAbs, etc., could conceivably be tested against placebo with TDF/FTC education and referrals offered only as part of the background prevention package. Still, some modalities have tremendous similarities to oral PrEP, and some efficacy trials such as those looking at CAB-LA have opted to use double-dummy placebo models to avoid thorny ethical issues around PrEP provision. In contrast, efficacy trials of VRC01 have not employed the double-dummy design,

despite bNABs being, in many respects, long-acting antiretrovirals. This highlights a need for broader consultation regarding what may constitute a “HIV prevention modality of the type being studied.”

Another issue to be considered before allowing PrEP use in a trial is that PrEP may have additive or even synergistic effects when combined with the experimental agent, as outlined by Holly Janes and colleagues. Similarly, any medication being studied for which TDF/FTC is contraindicated would obviously preclude PrEP use in a trial.

Ethical Obligation to Develop New Prevention Technologies

Although survey results tended to favor erring on the side of actively providing PrEP, including free provision of TDF/FTC, it was favored comparatively less for participants in experimental arms. Commentary from respondents often reflected that, as a result of the high efficacy of TDF/FTC PrEP, it would become impossibly complex to develop new technologies if there were broad uptake of PrEP in the experimental arm of a trial. In terms of offering PrEP as part of the background prevention package for control or experimental arms, those who favored more passive education and referral tended to highlight similar concerns about the practicalities for research if TDF/FTC PrEP is always provided for free as part of the trial.

Approval Status of TDF/FTC as PrEP in Trial Location/Other Significant Barriers to Local Access

UNAIDS/WHO and HPTN guidelines both leave room for interpretation about the ethical obligations of offering PrEP in trial sites in which TDF/FTC has not been approved as PrEP. Questionnaire commentary varied, with many respondents adamantly advocating for trial sites to do everything to eliminate barriers to PrEP by providing TDF/FTC and accompanying services, particularly in situations in which TDF/FTC has not been approved or in which significant barriers to successful access outside of the trial exist. Others argue that trial sites have no ethical obligation to facilitate access and that doing so could pose some sort of undue inducement to participate in the trial. Outside of PrEP provision, some respondents emphasized that researchers should be doing their part to ensure broader PrEP access in the communities in which they conduct research.

Novel Recruitment of Individuals who Decline PrEP and/or are Intolerant

Some respondents suggested that individuals who decline PrEP and/or are unable to take TDF/FTC for medical reasons, such as nephrotoxicity, could be recruited for biomedical prevention trials; however, it is possible that this approach would carry the risk of introducing selection bias.

RECOMMENDATIONS FOR ALL BIOMEDICAL PREVENTION TRIALS

1. Participants in all biomedical prevention trials should be provided with education and referrals for oral TDF/FTC PrEP and accompanying services as part of a standard prevention package. Trials should routinely provide data on the number of participants who have been successfully linked to PrEP as a way of monitoring impartial education and referrals to PrEP.
2. Novel oral PrEP regimens must be shown to be non-inferior to oral TDF/FTC and never compared with placebo.

3. Given the high efficacy and large evidence base for TDF/FTC PrEP, it should be the standard that researchers opting for only passive referrals to PrEP or placing restrictions on PrEP use among trial participants must make the case for why they cannot or will not provide or allow PrEP in their trial
4. Local community and key stakeholder input on PrEP provision is essential. CABs should be trained and consulted on PrEP provision in biomedical trials.
5. GPP guidelines should be the standard by which trials operate, and GPP guidelines should be integrated into UNAIDS/WHO and HPTN guidelines. Guidelines must be updated to reflect evolving community perspectives on PrEP provision in clinical trials.

Given the complex practical and ethical implications of providing PrEP as part of biomedical prevention trials, it is perhaps not surprising that existing guidelines do not entirely agree on overarching standards. Responses to the questionnaire that we developed also reflected this complexity, indicating the need to balance the ethical responsibility of providing state-of-the-art HIV prevention tools for participants and the ethical responsibility of developing new biomedical tools for prevention. This is particularly challenging when we do not have correlates of protection to facilitate trial design.

A few overarching recommendations emerged from both the literature review and the questionnaire for all biomedical prevention trials. First, all trial participants should receive comprehensive education on PrEP and referrals to PrEP services if they are interested. In terms of more active provision of TDF/FTC to participants, feedback and guidelines are more nuanced; however, in all trial scenarios presented in the questionnaire there was a strong preference for PrEP to be provided if at all possible. Forty-eight percent of respondents believed that sponsors should provide free, onsite TDF/FTC PrEP services, whereas 27.9% of respondents only wanted referrals for medication and services and 23.9% of respondents wanted free medication provided and referrals to outside medical services. The clear preference for active provision of PrEP supports a second recommendation made by ethicist Jerry Sugarman: given the high efficacy and large evidence-base for TDF/FTC PrEP, researchers should always be required to make the case for why they will not provide PrEP or allow its use in a trial, placing the burden of proof on restricting access rather than the reverse.

All guidelines and feedback showed a strong preference for significant community and key stakeholder input on PrEP provision at all levels of study development and implementation. All three sets of guidelines available on the topic clearly state community input as a core value, with GPP going much more in-depth on what that involvement should entail. In TAG's survey, most respondents had experience providing input as part of a CAB in the early and late stages of trial development, as well as implementation; however, important gaps remain. Only 24% of respondents reported being involved while data were being analyzed or prepared for peer review, meaning that community interpretations of findings may be lacking from the analysis, including perspectives on PrEP referrals and uptake among participants. Only 69.6% of respondents were able to confidently state that their CABs followed GPP guidelines, possibly demonstrating a need for UNAIDS/WHO and HPTN to provide better guidance and incorporate GPP into their own guidelines. When it comes to community involvement on PrEP provision specifically, there is even more room for growth. Only 60% of respondents indicated that they had any training or discussion around PrEP provision as part of their CAB, and only 51% of respondents reviewed plans for Truvada access as part of their CAB.

REFERENCES

1. UNAIDS/WHO. Ethical considerations in biomedical HIV prevention trials. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2007 [updated 2012]. Available from: http://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pdf
2. Rennie, S., J. Sugarman, and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research. HIV Prevention Trials Network. Available from: https://www.hptn.org/sites/default/files/2016-05/HPTNEthicsGuidanceV10Jun2009_0.pdf
3. UNAIDS/AVAC. Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials. 2nd ed. Geneva, Switzerland: UNAIDS/AVAC. June 2011. Available from: http://www.avac.org/sites/default/files/resource-files/Good%20Participatory%20Practice%20guidelines_June_2011.pdf
4. Haire B, Kaldor J, Jordens CF. How good is "good enough"? The case for varying standards of evidence according to need for new interventions in HIV prevention. *Am J Bioeth.* 2012;12(6):21-30. doi: 10.1080/15265161.2012.671887.
5. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS.* 2016 Jul 31;30(12):1973-1983. doi: 10.1097/QAD.0000000000001145. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4949005/>
6. Flash CA, Dale SK, Krakower DS. Pre-exposure prophylaxis for HIV prevention in women: current perspectives. *Int J Womens Health.* 2017 May 31;9:391-401. doi: 10.2147/IJWH.S113675. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5459979/>
7. Karim SS, Kashuba AD, Werner L, Karim QA. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *Lancet.* 2011 Jul 16;378(9787):279-281. doi: 10.1016/S0140-6736(11)60878-7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652579/>
8. Wahl A, Ho PT, Denton PW, et al. Predicting HIV Pre-exposure Prophylaxis Efficacy for Women using a Preclinical Pharmacokinetic-Pharmacodynamic In Vivo Model. *Sci Rep.* 2017 Feb 1;7:41098. doi: 10.1038/srep41098.
9. Cowan EA, Macklin R. Is preexposure prophylaxis ready for prime time use in HIV prevention research? *AIDS.* 2014 Jan 28;28(3):293-295. doi: 10.1097/QAD.000000000000055. http://journals.lww.com/aidsonline/Fulltext/2014/01280/Is_preexposure_prophylaxis_ready_for_prime_time.1.aspx
10. Sugarman J. Ethical considerations regarding oral preexposure prophylaxis in HIV prevention trials. *Curr Opin HIV AIDS.* 2016 Jan;11(1):109-115. doi: 10.1097/COH.0000000000000214. http://journals.lww.com/co-hivandaids/Fulltext/2016/01000/Ethical_considerations_regarding_oral_preexposure.17.aspx
11. Dawson L, Garner S, Anude C, et al. Testing the waters: Ethical considerations for including PrEP in a phase IIb HIV vaccine efficacy trial. *Clin Trials.* 2015 Aug;12(4):394-402. doi: 10.1177/1740774515579165. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4506251/>
12. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* 2010 Dec 30;363(27):2587-2599. doi: 10.1056/NEJMoa1011205. Epub 2010 Nov 23. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/>
13. Fuchs JD, Sobieszczyk ME, Madenwald T, et al. Intentions to use preexposure prophylaxis among current phase 2B preventive HIV-1 vaccine efficacy trial participants. *J Acquir Immune Defic Syndr.* 2013 Jul 1;63(3):259-262. doi: 10.1097/QAI.0b013e318296df94. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714219/>
14. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med.* 2009 Dec 3;361(23):2209-2220. doi: 10.1056/NEJMoa0908492. <http://www.nejm.org/doi/full/10.1056/NEJMoa0908492>
15. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med.* 2013 Nov 28;369(22):2083-2092. doi: 10.1056/NEJMoa1310566. Epub 2013 Oct 7. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4030634/>
16. Zhou T, Georgiev I, Wu X, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science.* 2010 Aug 13;329(5993):811-817. doi: 10.1126/science.1192819. Epub 2010 Jul 8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2981354/>
17. HIV Vaccine Trials Network/HIV Prevention Trials Network. HVTN 704/HPTN 085: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men. Available from: <https://www.hptn.org/sites/default/files/2016-05/HVTN%20704%20HPTN%20085%20Protocol%20Version%201.compressed.pdf>
18. HIV Vaccine Trials Network/HIV Prevention Trials Network. HVTN 703/HPTN 081: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection. Available from: https://www.hptn.org/sites/default/files/2016-05/HVTN703_HPTN081_v1.0_FINAL.compressed.pdf
19. Msomi N. Should everyone be getting the HIV prevention pill as part of this new study? *Bhekisisa.* 2017 June 22. Available from: <http://bhekisisa.org/article/2017-06-22-00-hiv-vaccine-trial-why-not-everyone-is-getting-the-hiv-prevention-pill>
20. Excler JL, Rida W, Priddy F, et al. AIDS vaccines and preexposure prophylaxis: is synergy possible? *AIDS Res Hum Retroviruses.* 2011 Jun;27(6):669-680. doi: 10.1089/AID.2010.0206. Review. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101085/>
21. McNicholl JM. Combining biomedical preventions for HIV: Vaccines with pre-exposure prophylaxis, microbicides or other HIV preventions. *Hum Vaccin Immunother.* 2016 Sep 28:0. [Epub ahead of print] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215580/>

22. Le Grand R, Dereuddre-Bosquet N, Dispinseri S, et al. Superior Efficacy of a Human Immunodeficiency Virus Vaccine Combined with Antiretroviral Prevention in Simian-Human Immunodeficiency Virus-Challenged Nonhuman Primates. *J Virol*. 2016 May 12;90(11):5315-5328. doi: 10.1128/JVI.00230-16. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934744/>
23. Ross TM, Pereira LE, Luckay A, et al. A polyvalent Clade B virus-like particle HIV vaccine combined with partially protective oral preexposure prophylaxis prevents simian-human immunodeficiency virus infection in macaques and primes for virus-amplified immunity. *AIDS Res Hum Retroviruses*. 2014 Nov;30(11):1072-1081. doi: 10.1089/AID.2014.0030. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4208560/>
24. Kuebler PJ, Mehrotra ML, McConnell JJ, et al. Cellular immune correlates analysis of an HIV-1 preexposure prophylaxis trial. *Proc Natl Acad Sci U S A*. 2015 Jul 7;112(27):8379-8384. doi: 10.1073/pnas.1501443112. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4500209/>
25. Kuebler PJ, Shaw BI, Leadabrand KS, et al. Brief Report: HIV-1 gp120 T-Cell Responses Correspond to Infection Outcomes in the Global iPrEx Chemoprophylaxis Trial. *J Acquir Immune Defic Syndr*. 2016 Jun 1;72(2):184-188. doi: 10.1097/QAI.0000000000000923. http://journals.lww.com/jaids/Fulltext/2016/06010/Brief_Report__HIV_1_gp120_T_Cell_Responses.9.aspx
26. Pattacini L, Murnane PM, Baeten JM, et al. Antiretroviral Pre-Exposure Prophylaxis Does Not Enhance Immune Responses to HIV in Exposed but Uninfected Persons. *J Infect Dis*. 2015 Jun 15;211(12):1943-1952. doi: 10.1093/infdis/jiu815. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4836720/>
27. Pattacini L, Baeten JM, Thomas KK, et al. Regulatory T-Cell Activity But Not Conventional HIV-Specific T-Cell Responses Are Associated With Protection From HIV-1 Infection. *J Acquir Immune Defic Syndr*. 2016 Jun 1;72(2):119-128. doi: 10.1097/QAI.0000000000000919. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4866890/>
28. Janes H, Gilbert P, Buchbinder S, Kublin J, Sobieszczyk ME, Hammer SM. In pursuit of an HIV vaccine: designing efficacy trials in the context of partially effective nonvaccine prevention modalities. *AIDS Res Hum Retroviruses*. 2013 Nov;29(11):1513-1523. doi: 10.1089/AID.2012.0385. Epub 2013 Jun 25. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3809388/>
29. Kersh EN, Adams DR, Youngpairoj AS, et al. T cell chemo-vaccination effects after repeated mucosal SHIV exposures and oral pre-exposure prophylaxis. *PLoS One*. 2011 Apr 26;6(4):e19295. doi: 10.1371/journal.pone.0019295. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3082568/>