THE FUTURE OF BIOMEDICAL HIV PREVENTION TRIALS: RESEARCHER VIEWPOINTS AND COMMUNITY SURVEY

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TAG
Treatment Action Group

The Future of Biomedical HIV Prevention Trials: Researcher Viewpoints and Community Survey

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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.

The primary aims of this report are:

- **To raise the profile of discussions that have been taking place regarding the ethical conduct of biomedical prevention trials in the era of pre-exposure prophylaxis (PrEP). Thus far, formal discussions on the future of biomedical prevention trials have largely taken place among researchers, statisticians, and government regulators in settings that are not broadly accessible to many community advocates.**
- **To describe results from a survey of diverse community members put together by TAG, the Black AIDS Institute (BAI), and the HIV Vaccine Trials Network (HVTN) that solicited feedback on new and existing areas of interest in biomedical prevention in order to further integrate advocate perspectives into a discussion that will ultimately affect research taking place in their communities.**

INTRODUCTION

Since HIV was first identified in the early 1980s, scientists, policy makers and the public have recognized the urgent need to develop approaches to safely prevent acquisition of the virus. Initial hopes that a preventive vaccine might be developed quickly were dashed by the realization that traditional approaches to immunization were not effective against HIV.[1] Over the years, researchers have tested a wide variety of possible biomedical interventions, including vaccines, microbicides (products applied locally at the site of potential HIV exposure), antibodies, and antiretroviral (anti-HIV) drugs.

In 2010, a study evaluating daily doses of the antiretroviral drug combination Truvada (tenofovir + emtricitabine) used as pre-exposure prophylaxis (PrEP) found that it significantly lowered the rate of HIV infection in men who have sex with men (MSM) and transgender women.[2] The trial—known as iPrEx—was the first to show that Truvada PrEP could successfully reduce the risk of acquiring HIV.

PREP, TREATMENT, AND THE PRICE OF SUCCESS

PrEP as the New Standard of Care

Importantly, Truvada PrEP was sufficiently successful at preventing HIV infection that the drug is now approved for this use in the United States and many other countries around the world (see the PrEPWatch website for the latest information on global approvals).[3] The accumulated evidence is now clear that when taken as directed, Truvada PrEP reduces the risk of sexually acquiring HIV by over 90%, with some modeling indicating upwards of 99% efficacy.[4] More recently a second antiretroviral drug combination, Descovy (tenofovir alafenamide + emtricitabine), has also been approved as PrEP in the United States, although only for cisgender men at risk for HIV infection.[5]

The development of PrEP as an effective biomedical prevention intervention against HIV is a success story, which has also complicated the effort to develop alternate approaches such as vaccines or longer-acting drugs or antibodies that might be less demanding on the user and possibly also safer in terms of potential side effects.

Testing whether a biomedical intervention can prevent HIV infection typically involves recruiting large numbers of volunteers who are at risk of exposure to the virus and then randomly assigning them to receive the intervention or a placebo (dummy version) of the intervention. The rates of HIV acquisition among trial participants in the different "arms" of the trial are then statistically evaluated to calculate whether the intervention significantly lessened risk. In some cases, a trial may compare a new intervention to an existing one (this was the case in the main trial of Descovy PrEP, which compared it to Truvada PrEP).

The effectiveness and increasing availability of PrEP have altered the landscape of biomedical prevention research dramatically.

Ethics demands that everyone in an efficacy trial is offered the best available standard of HIV prevention (referred to as the "standard of care" or "standard of prevention"). Up until the advent of PrEP, this normally meant provision of regular counseling and condoms. Concerns about how this issue was approached in some early PrEP efficacy studies led to the generation of World Health Organization (WHO) guidance documents[6] and subsequently good participatory practice guidelines delineating how researchers should ensure appropriate community input into the ethical design of biomedical prevention trials.[7]

The effectiveness and increasing availability of PrEP have altered the landscape of biomedical prevention research dramatically. For example, if all the participants in an efficacy trial of an experimental preventive HIV vaccine candidate regularly used PrEP, it would be highly unlikely that a sufficient number of HIV infections would occur for the researchers to be able to figure out statistically whether the vaccine had any effect. On the other hand, it would be unethical to ask people taking PrEP to stop in order to participate in an efficacy trial of an alternate approach.

A further complicating factor is that even where PrEP is approved, there can be profound disparities in access among different populations. In the United States, studies have found that Black and Hispanic men who have sex with men—who are at the greatest risk of acquiring HIV—are significantly less likely to be taking PrEP than white men who have sex with men.[8] Barriers to uptake can include cost, lack of insurance coverage, accessibility of clinics, stigma, medical mistrust, and racism.[9,10,11] A reduced likelihood of persisting with PrEP after starting has been reported for people of Black race, females, transgender women who have sex with men, people who inject drugs, those of younger age and residents of rural locations.[12,13]

The goal of ending the HIV epidemic is only likely to be achieved if an array of options can be made available, including vaccines.

One possible option for efficacy trials of new biomedical prevention interventions is to aim to recruit participants who are not using PrEP because they prefer not to. Studies in a variety of populations at risk for HIV infection have reported that PrEP acceptability is not universal (although in some cases lack of information, misconceptions, and other factors may contribute to a person's decision not to use it).[14,15] But the complex backdrop of disparities in access and uptake make it crucial to ensure that particular populations are not targeted for research in a way that might be exploitative of the challenges many face in using PrEP on a regular basis; recent discussions on this kind of recruitment strategy have emphasized the importance of ensuring that individuals are not on PrEP as part of an autonomous, "authentic choice" and not merely because of structural and financial barriers such as cost.

There is also a flip side to this equation: an ethical imperative to develop effective biomedical prevention interventions for people for whom PrEP is not appropriate. The goal of ending the HIV epidemic is only likely to be achieved if an array of options can be made available, including vaccines.[16]

The Impact of Treatment

Beyond PrEP use within trials, there is also the impact of HIV viral load suppression by antiretroviral therapy (ART) in preventing onward transmission. Maintenance of undetectable viral load has been proven to eliminate risk in all settings except the case of transmission via breastfeeding. In some populations and locales, a confluence of factors including earlier diagnosis, more rapid ART initiation, increased rates of ART use, and viral load suppression are contributing to declines in HIV incidence (the number of people being diagnosed with HIV over time).[17,18,19]

Much like the success of PrEP, the profound preventive effect of treatment has the potential to alter the landscape for biomedical prevention trials by reducing HIV incidence where trials are occurring. It's obviously good news that a trial participant (or any other member of the population) might have a reduced risk of being exposed to HIV, but it may add to the difficulty of proving that an experimental intervention is able to prevent acquisition of the virus.

These complex, evolving circumstances are spurring the consideration of novel, innovative trial designs for demonstrating that new HIV prevention strategies are effective.

PREP USE IN CURRENT TRIALS

As outlined in detail in a Treatment Action Group report issued in 2017,[20] there are three sets of guidelines regarding the appropriate standard of care for HIV prevention trials.[6,7,21] These existing documents are not entirely consistent, and none offers clarity on the provision of PrEP.[22]

In the absence of definitive guidance, the ethicist Jeremy Sugarman has argued that there is a "rebuttable presumption" for the inclusion of PrEP, meaning that researchers conducting a trial need to offer a compelling justification if they decide *not* to offer it to participants.[23]

There are several efficacy trials of biomedical prevention approaches that have been ongoing for some time, two including HIV vaccines, and they all allow participants to use oral PrEP if they choose, with access potentially facilitated through philanthropic funding for those in sub-Saharan Africa and via access programs from Gilead for those in North and South America without adequate insurance coverage.[24,25]

A FIRST ALTERNATIVE TRIAL DESIGN

The most recent HIV vaccine efficacy trial to launch is different.

Sponsored by Janssen Vaccines & Prevention B.V. and the HIV Vaccine Trials Network (HVTN) (which also provided the grant to support this report; see acknowledgements on page 2), the trial was initiated in mid-2019 and is named Mosaico. It is testing a "prime-boost" vaccine combination designed to induce immune responses capable of recognizing a wide variety of global HIV variants. The target populations are cisgender men and transgender people who have sex with cisgender men and/or transgender people, and the study is taking place in the United States, Argentina, Brazil, Italy, Mexico, Peru, Poland, and Spain. The aim is to enroll a total of 3,800 participants.

The approach to PrEP that the trial is taking was among those outlined by statistician David Glidden at an HVTN symposium on November 5, 2018 (titled "HIV Prevention Efficacy Trials of the Future"[26]), although Glidden described it in the context of studies of alternative PrEP approaches rather than vaccines.[27] People who are currently successfully using PrEP will be *excluded* from enrollment in the trial, the first time this has occurred. Instead the goal is to enroll those not desiring to be on PrEP out of "authentic choice" or because of medical contraindications.

Glidden has written that:

> *This design presents an ethical dilemma — it would create an apparent tension between enrolling participants and encouraging TDF/FTC [Truvada PrEP] use among people at risk for HIV. Even if participants make an informed decision to decline TDF/FTC, the investigators can appear complicit in providing a lower standard of prevention. Hence, such a trial calls for ethical safeguards to ensure that the choice not to use TDF/FTC is an informed one and requires that study staff regularly reengage participants on their desire not to use TDF/FTC. Participants should be able to change their minds and initiate TDF/FTC while continuing in the trial.*

People who are currently successfully using PrEP will be excluded from enrollment in the trial, the first time this has occurred.

Mosaico is following the recommendation Glidden makes here and is allowing participants to initiate PrEP and continue in the trial if they change their decision after enrollment. The possibility that a proportion of participants will start PrEP and thus be at a significantly decreased risk of HIV acquisition is accounted for in the trial's design, much as other ongoing efficacy trials of biomedical prevention interventions account for background PrEP use.

This type of approach to efficacy trials is also discussed in two articles published last year by HIV prevention researchers. Holly Janes and colleagues[26] wrote:

> *Challenging ethical issues have been raised around this approach, and the concept requires intensive stakeholder engagement to navigate the complex issues relating to ethics, regulation, community*

engagement, informed consent, and trial implementation. Ethical considerations would dictate that individuals not successfully using effective products would be identified only after being given comprehensive education on existing products and access to these products.

While the sponsors of Mosaico did seek broad stakeholder and community input, this has largely occurred out of public view, which represents a potentially significant shortcoming.

Addressing the ethical issues more specifically, Jeremy Sugarman, Connie L. Celum, Deborah Donnell, and Kenneth H. Mayer[28] highlight the challenges of ensuring that a potential participant genuinely considers PrEP to be unacceptable:

Given the trade-offs associated with use of a known effective means of prevention and use of another that is unproven, authenticity of expressions of unacceptability must be ensured. Historically, some participants have joined HIV prevention trials to obtain access to high-quality care and prevention services. Potential participants should decide about actual acceptability and usability of an appropriate proven prevention product under optimal circumstances, before deciding whether to participate in a clinical trial of an experimental product. . . .

Key aspects of any mechanism to ensure unacceptability will probably involve structured assessment of potential participants' knowledge and experience of various preventive methods and barriers to them. Furthermore, these methods should be developed with robust community engagement to ensure appropriateness and acceptability."

They also make the following recommendation:

Consideration should be given to engaging independent participant advocates during study recruitment and consent processes. Participants should also be reminded at enrollment and during the trial that their views on acceptability about existing prevention interventions might change and that they can begin an effective means of HIV prevention without withdrawing from the study.

As noted above, Mosaico has adopted the latter part but has not engaged independent participant advocates during study recruitment and consent processes.

Additional novel designs are in the works, such as the PrEPVacc study, which aims to compare different vaccine and PrEP regimens using statistical methodologies that calculate how many HIV infections a given regimen has averted.

The approach being taken by Mosaico represents but one of many ideas and proposals that are being discussed related to the conduct of efficacy trials in the era of more effective HIV prevention. Additional novel designs are in the works, such as the PrEPVacc study, which aims to compare different vaccine and PrEP regimens using statistical methodologies that calculate how many HIV infections a given regimen has averted.[29] There are also suggestions that it may be possible in some contexts to use alternate markers of HIV risk to evaluate the impact of interventions, such as the incidence of other sexually transmitted diseases.[30]

The U.S. Food and Drug Administration (FDA) has also expressed interest in the possibility of so-called "historical controls" where existing data from another cohort or outside surveillance may be used to estimate infections averted. However, each of these approaches carries various risks and benefits, and it will be crucial to educate community advocates and solicit their input on critical developments that could affect the reliability of data for interventions that are meant for use in their communities.

AVAC's recent launch of a Trial Design Academy and BAI's ongoing efforts through the Black Treatment Advocacy Network (BTAN) represent the kinds of community relationship building that should be funded in order to build up independent community mechanisms that can better inform ethical and reliable trial design efforts.

As one of the first alternative trial designs to be implemented, Mosaico is an important milestone and opportunity to solicit feedback from community members and advocates about how biomedical prevention research is evolving. The recent controversy over the lack of representation of cisgender women, transgender men, and communities of color in Gilead's application to the FDA for approval of Descovy as PrEP has also highlighted existing concerns about representation in research and access to new prevention tools.

SURVEY METHODOLOGY

TAG, BAI, and HVTN designed an online survey to solicit community perspectives on both existing and emerging biomedical prevention trial concerns to better inform the efforts of all stakeholders in the development of novel prevention products.

An online Google form survey, containing a total of 20 questions, was fielded from November 11, 2019, until January 6, 2020. An email announcement was shared with HIV-related listservs and organizational contacts of TAG, BAI and HVTN with encouragement to recipients to distribute further. The introduction to the survey explicitly stated that it was primarily aimed at individuals "who have some familiarity with HIV prevention research" but was open to all. A total of 89 responses were received. Responses were analyzed in sum and by self-reported demographic categories.

BACKGROUND ON RESPONDENTS

Responses were received from 14 countries: Australia, Barbados, Brazil, England, France, Germany, Guatemala, Italy, Kenya, Nigeria, Portugal, South Africa, Spain, and the United States (which accounted for the majority: 70).

Table 1: Respondent Demographics

Race/Ethnicity	%	Gender Identity	%	Sexual orientation	%	HIV status	%
White non-Hispanic	45%	Cisgender male	61.8%	Gay	59.5%	Positive	33.7%
Black/African American	23.5%	Cisgender female	20.2%	Straight	21.3%	Negative	64%
Hispanic/Latino/Latinx	11.2%	Nonbinary	3.4%	Bisexual	6.7%	Not answered	2.3%
Multiracial	3.4%	Transgender	1.1%	Other	5.6%		
Asian	1.1%	Two spirit	1.1%	Not answered	6.7%		
American Indian	1.1%	Other	6.7%				
Other	5.6%	Not answered	5.6%				
Not answered	10.1%						

The majority of respondents—67.4%—reported having had some involvement in community advocacy related to HIV prevention over the past two years. A wide range of examples were cited, including direct local education efforts among people at risk, participation in advisory bodies connected to research networks, and relationships with advocacy organizations such as AVAC, BTAN, and the European AIDS Treatment Group.

Community Advisory Board (CAB) Participation*	%
Clinical trials site or network community advisory board	35%
Other structured input body	22.5%
National CAB	19%
Local CAB for a nongovernmental organization	13.5%
Multinational CAB	12.3%
Pharmaceutical company CAB	4.5%

*Respondents could select more than one option

About a quarter of respondents (23.6%) had previously participated in a biomedical prevention trial. Asked whether they had taken part in any recent trainings, webinars, or discussions regarding the future of HIV prevention trial designs, a majority (66.3%) responded that they had.

Almost all (96.6%) of the people who completed the survey were based in countries where PrEP is approved. Of the remaining three, two were uncertain whether it was approved and only one was based in a country where it has yet to be approved (England).

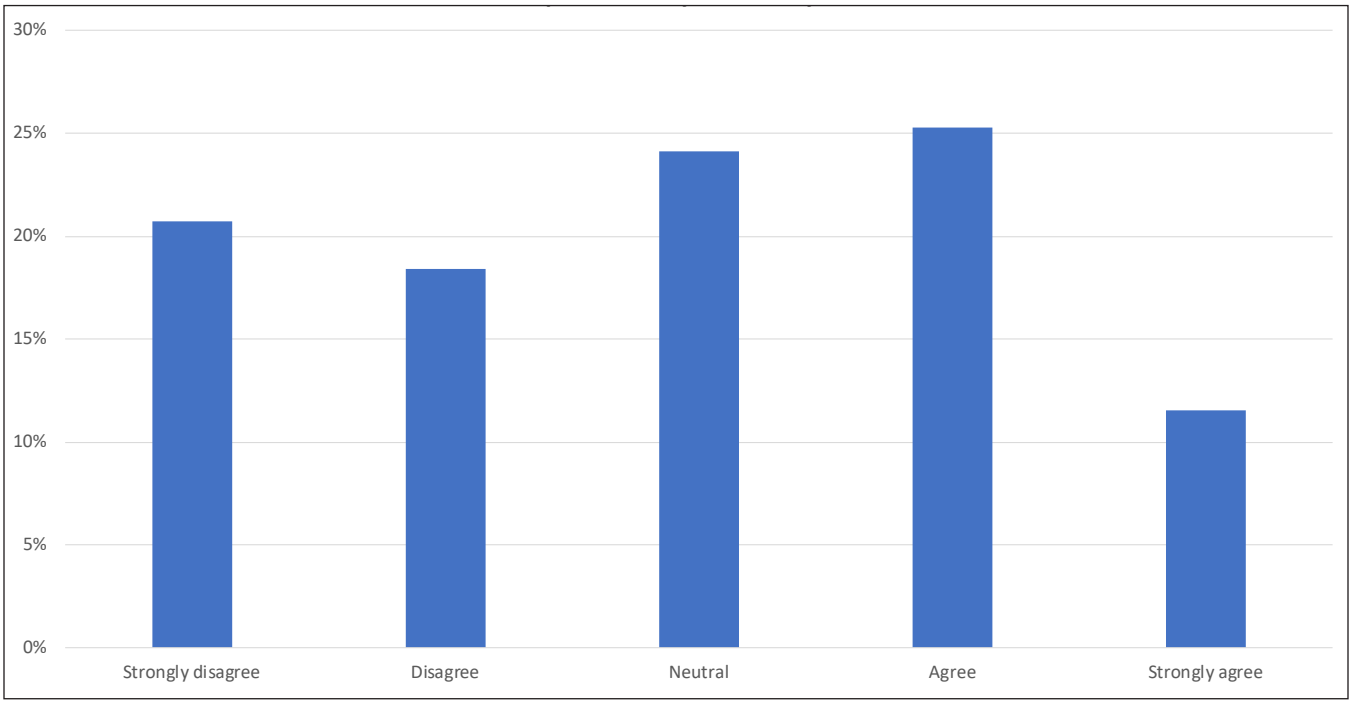
QUESTIONS ON BIOMEDICAL HIV PREVENTION RESEARCH

Perception of Sufficiency of Existing Tools to End the Epidemic

The survey asked participants how strongly they agreed with the following statement: "All the tools needed to end HIV as an epidemic in my community now exist." As with several other survey questions, a scale of 1-5 was used (1=strongly disagree to 5=strongly agree).

Overall, 20.7% strongly disagreed with this statement, while only 11.5% strongly agreed. In total, 36.8% of participants agreed or strongly agreed with the statement, while 39.1% disagreed or strongly disagreed (while 24.1% selected "3," the middle option between agreement and disagreement).

Figure 1: Perception of sufficiency of existing tools to end the epidemic



Among participants identifying as male, 64.3% either agreed or strongly agreed, compared with only 16.7% of female participants. A more substantial proportion of Black participants strongly agreed compared with those identifying as white non-Hispanic or Hispanic (21.7% vs. 5.9% and 0%). This was consistent with more skepticism about this proposition generally among white non-Hispanic respondents, with only 23.5% agreeing versus close to half of all nonwhite respondents.

Figure 1b: Agreement that we have all tools needed to end the epidemic by gender

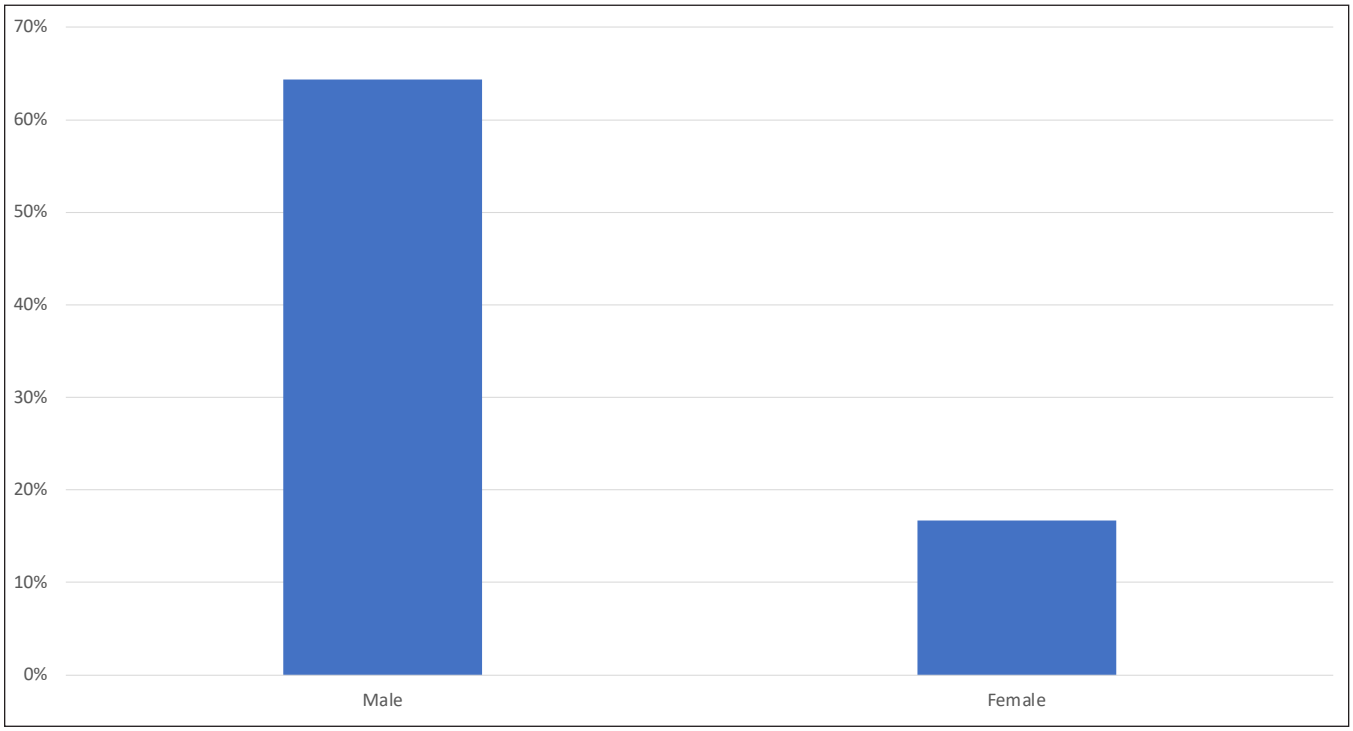
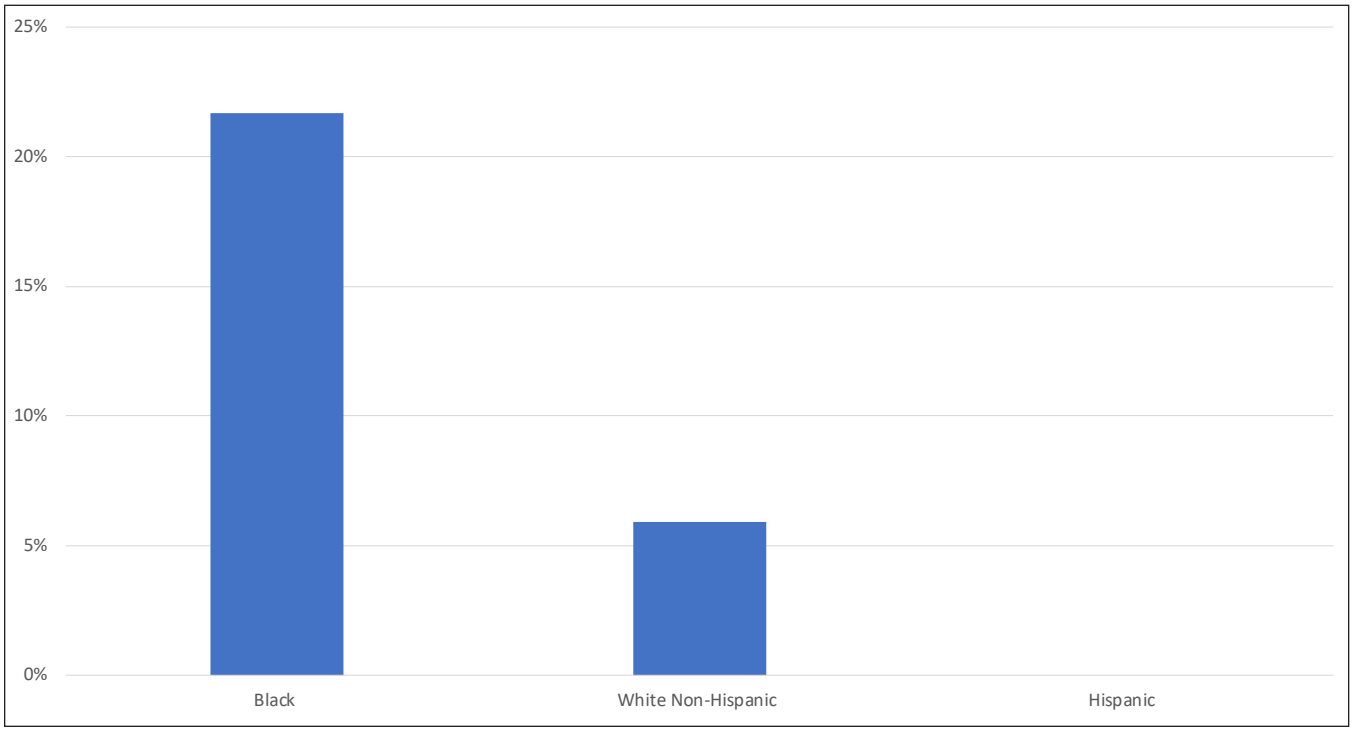


Figure 1c: Agreement that we have all the tools need to end the epidemic by race



Asked how confident they were that members of their community will be strongly represented in biomedical HIV prevention research design, implementation, analysis, and scale-up (also on a scale of 1 to 5), slightly more participants were not confident (42.7%) than were confident (37%), with 20.2% at the midpoint.

Excitement About New Technologies

From a menu of the different types of novel biomedical prevention technologies in development, participants were asked which they considered most exciting. The two most frequently selected were HIV vaccines (28%) and multipurpose prevention technologies—such as those that aim to prevent multiple different infections or combine birth control with an HIV prevention strategy (24.7%).

Confidence in Representation in Biomedical HIV Prevention Research

Asked how confident they were that members of their community will be strongly represented in biomedical HIV prevention research design, implementation, analysis, and scale-up (also on a scale of 1 to 5), slightly more participants were not confident (42.7%) than were confident (37%), with 20.2% at the midpoint.

White non-Hispanic participants felt more confident compared with all other race groups combined (50% vs. 25.6%). A similar picture emerged for participants who identified as gay (45% vs 27.9% of other respondents). Nearly half of male participants were confident or very confident about their community being represented, while only 22.3% of female participants and no transgender/gender-nonconforming (TGNC) participants felt this way. While only five respondents identified as TGNC, it is notable that four of them said they were extremely *not* confident that their community would be represented.

Figure 2: Confidence in representation in biomedical HIV prevention research by race

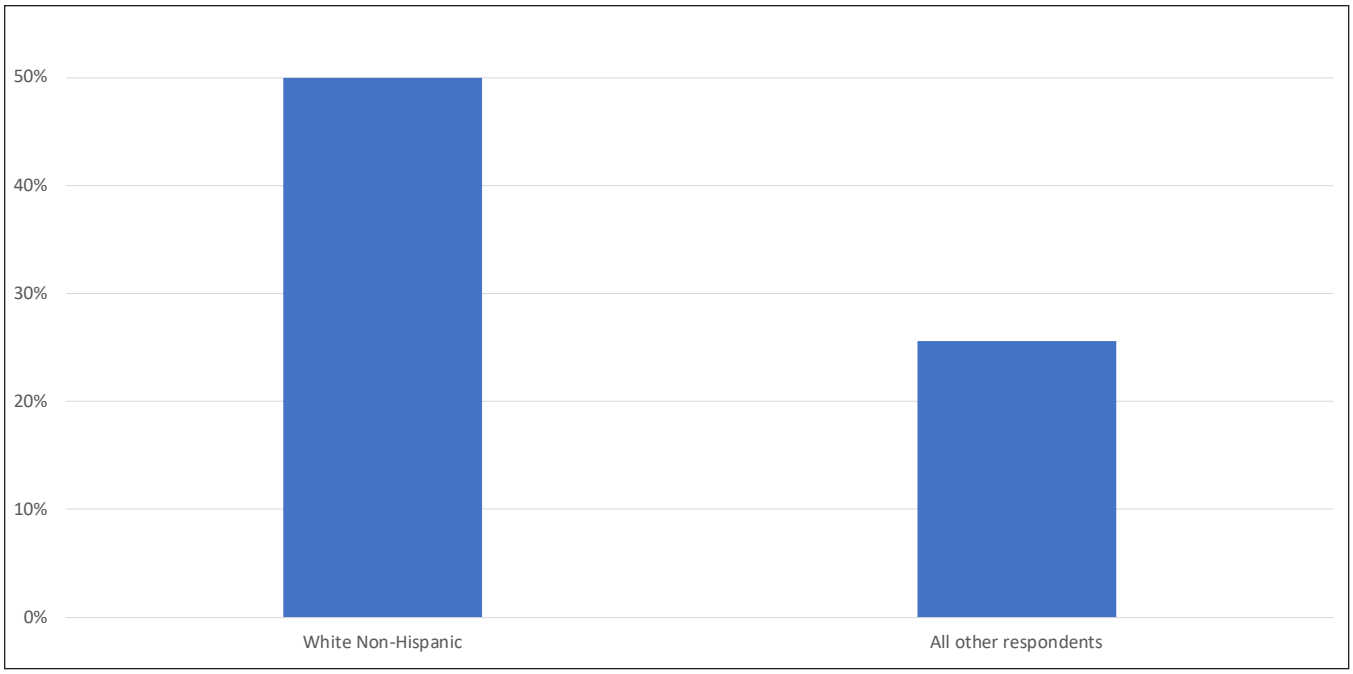
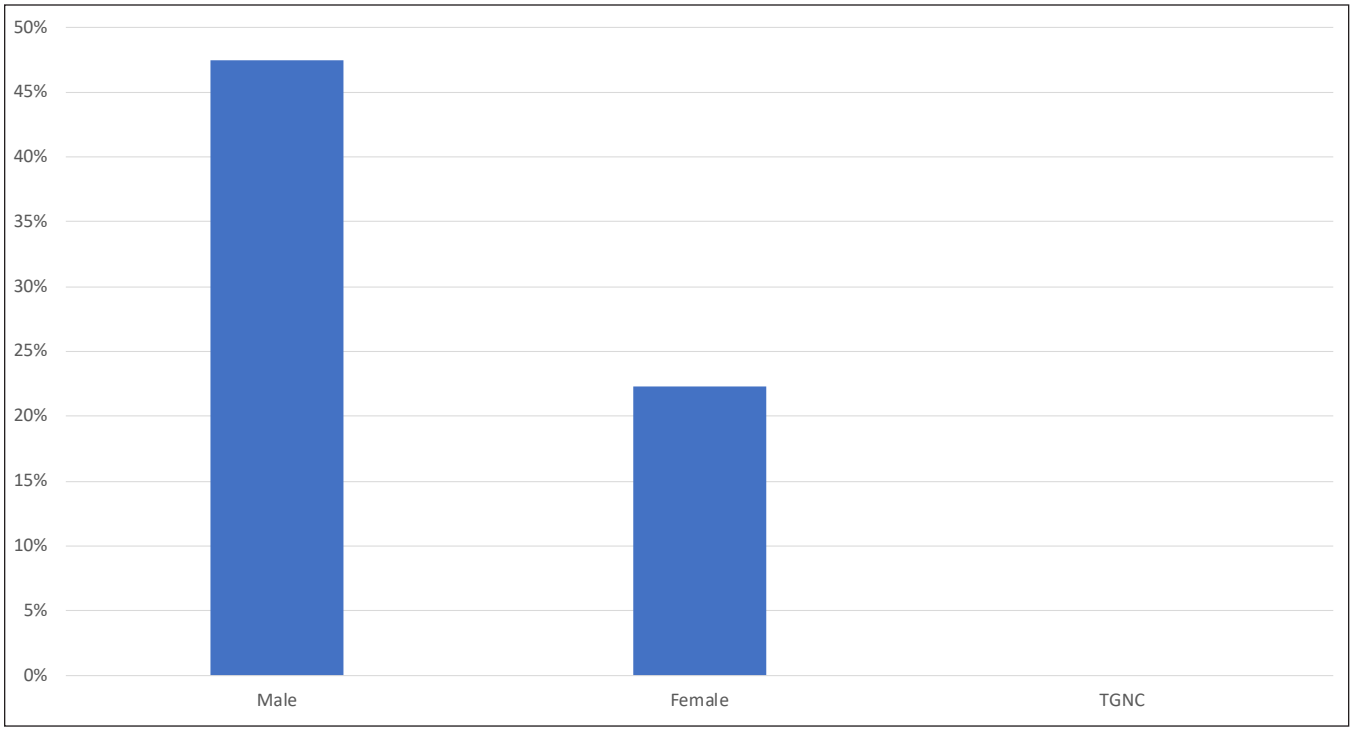


Figure 2b: Confidence in representation in biomedical HIV prevention research by gender



Likelihood of Community Participation in a Biomedical Prevention Trial

On the topic of trial participation, we asked how likely participants thought it was that members of their community would enroll in a biomedical prevention trial. Overall, more believed it was likely or very likely (45.5%) than unlikely (25%), but a substantial proportion were unsure (29.5%).

Among white non-Hispanic participants, 61.8% responded that their community was "likely" or "very likely" to enroll versus 41% of Black participants and versus about one-third of all other respondents considered together. Older people expressed greater confidence than younger, with 48.9% of those aged 40 to 59 and two-thirds of those over 59 years old selecting "likely" or "very likely" versus only 26.1% of participants aged 24–39.

Confidence in Prioritization of Communication Around Safety in Trials

There was little evidence of mistrust of researchers, with the vast majority of participants (95.5%) expressing confidence that any safety issues in trials are properly communicated and explained during the informed consent process. Asked for an opinion on how members of their community view the prioritization of safety in trials by researchers, a majority (55.7%) felt there was confidence in the researchers to act in good faith, with relatively few (14.8%) suggesting a lack of trust on this issue.

There was little evidence of mistrust of researchers, with the vast majority of participants (95.5%) expressing confidence that any safety issues in trials are properly communicated and explained during the informed consent process.

Figure 3: Likelihood of community participation in a biomedical prevention trial by race

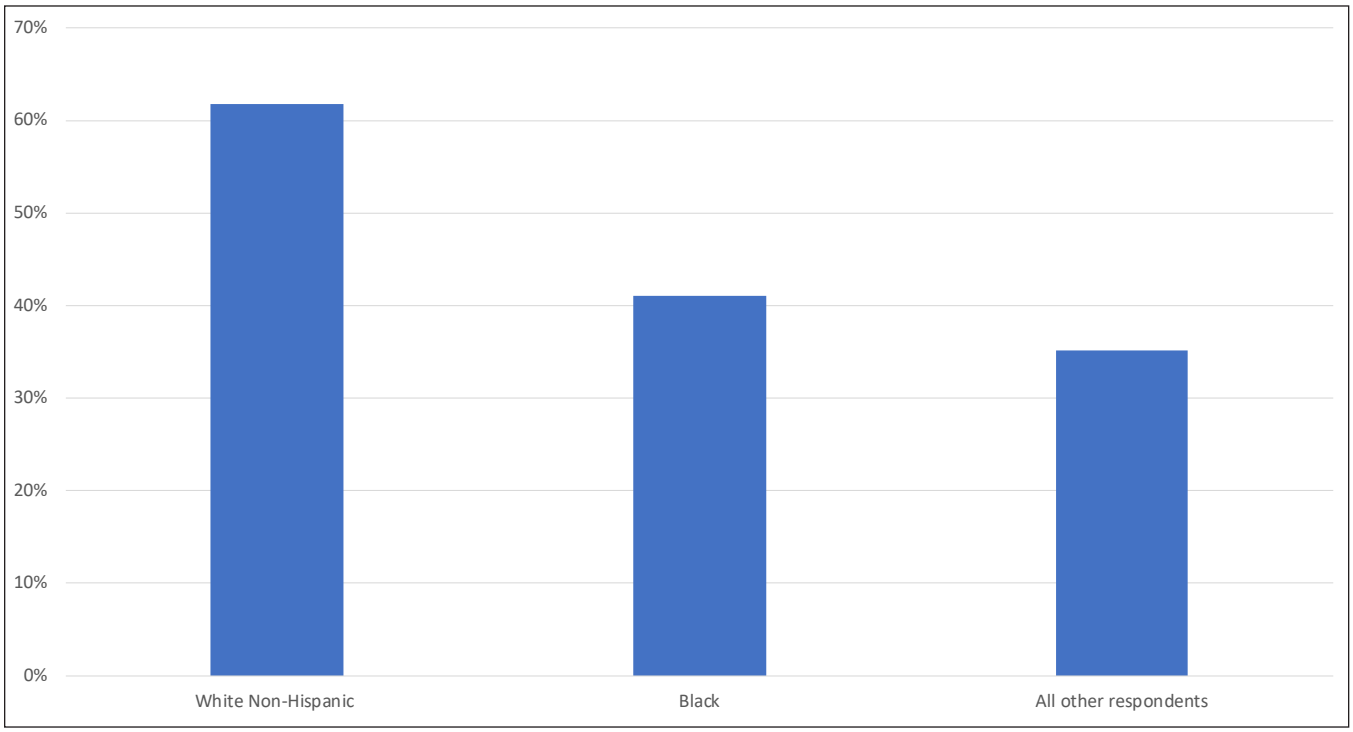
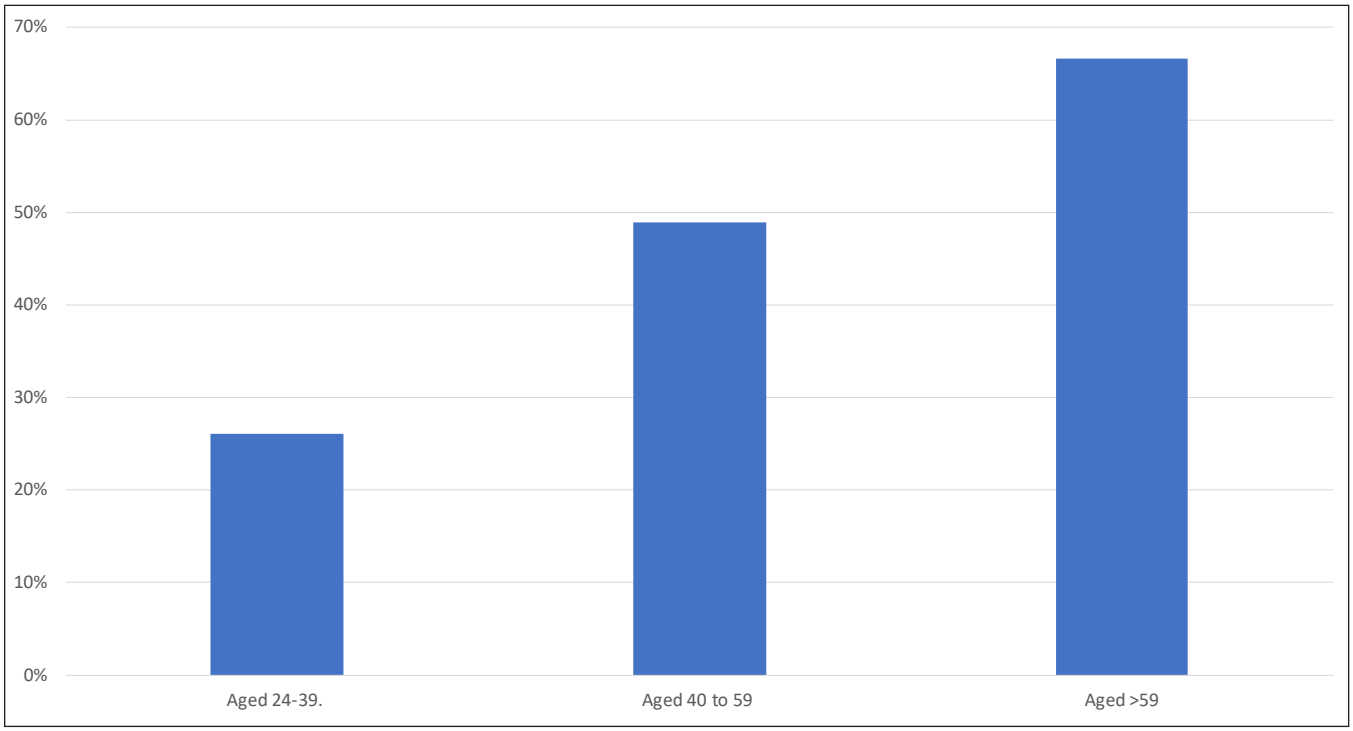


Figure 3b: Likelihood of community participation in a biomedical prevention trial by age



Barriers to Participating in Research

An open-ended question on the top barriers to taking part in biomedical HIV prevention research in their community prompted a range of responses, with several themes emerging.

Twenty-six percent of respondents mentioned issues such as lack of awareness, information, and research literacy. Distrust of the research/medical community and government came up frequently (22.5%), with references to examples of historical mistreatment such as the Tuskegee syphilis study.[31] Eight people (9%) cited the related issue of racism and lack of representation of communities of color among research staff, doctors, and trial leadership.

Additional populations cited as underrepresented and not engaged were women, sex workers, people who use drugs, and transgender people. One respondent wrote: "there typically are not even ways to identify trans and especially non-binary people in biomedical research; we are almost always miscategorized. Clearly the research is not designed by us, for us, or even with us in mind, let alone meaningfully involved."

Six respondents (6.7%) highlighted the stigma still associated with HIV and being perceived as at risk for the infection.

In terms of practical considerations, 14.6% of respondents cited time as a key obstacle, with one emphasizing, "it is critical that research sites are funded adequately to support evening and weekend hours." Additional logistical issues included transportation and provision of childcare.

Additional populations cited as underrepresented and not engaged were women, sex workers, people who use drugs, and transgender people.

Confidence in Post-Trial Access

The survey asked how confident respondents were that they and/or members of their community would be able to access these new prevention strategies if the studies were successful and the interventions were licensed and approved. Half of all participants were confident or very confident. There were some notable demographic differences: 63.7% of gay participants felt confident or very confident, compared with 35.7% of respondents who did not identify as gay. A clear majority (62.7%) of participants identifying as male were similarly confident, versus 23.6% of female participants. Only one out of five total TGNC respondents felt confident they would have access.

Figure 4: Confidence in post-trial access by sexuality

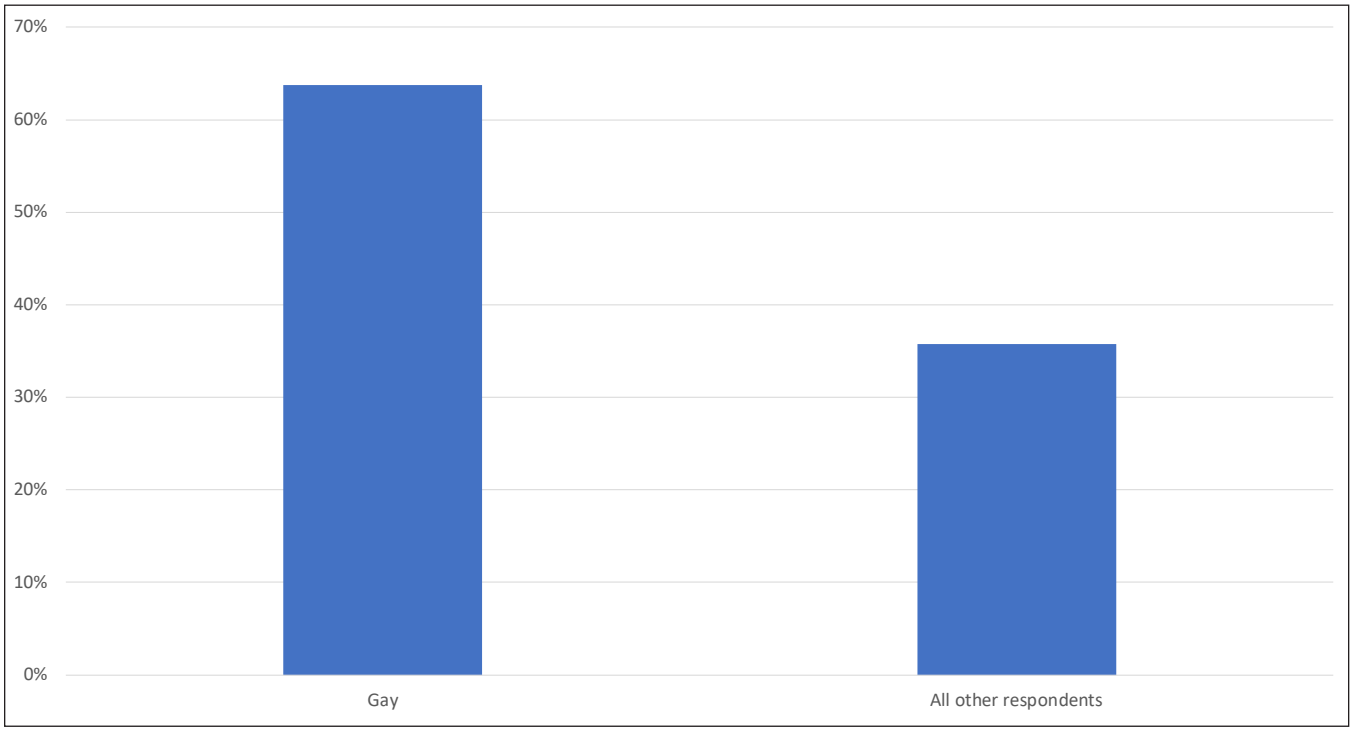
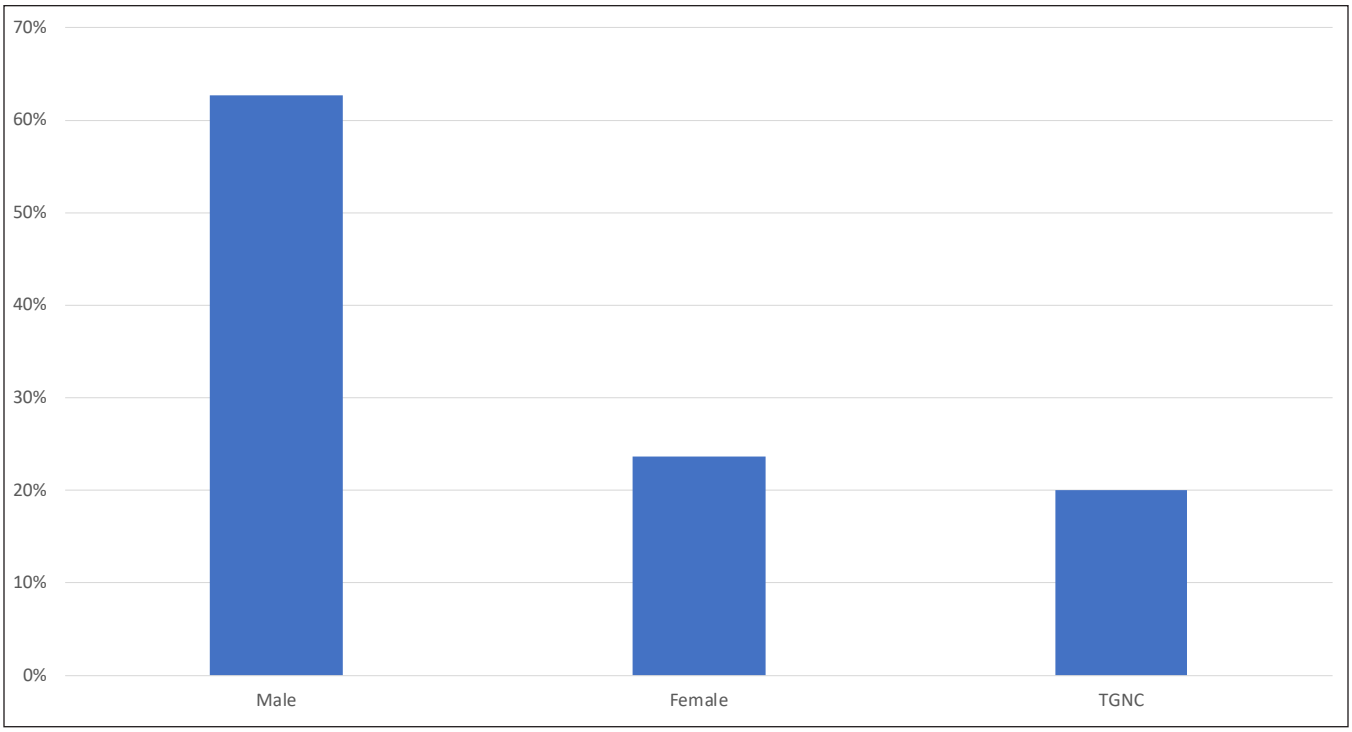


Figure 4b: Confidence in post-trial access by gender



PREP PROVISION

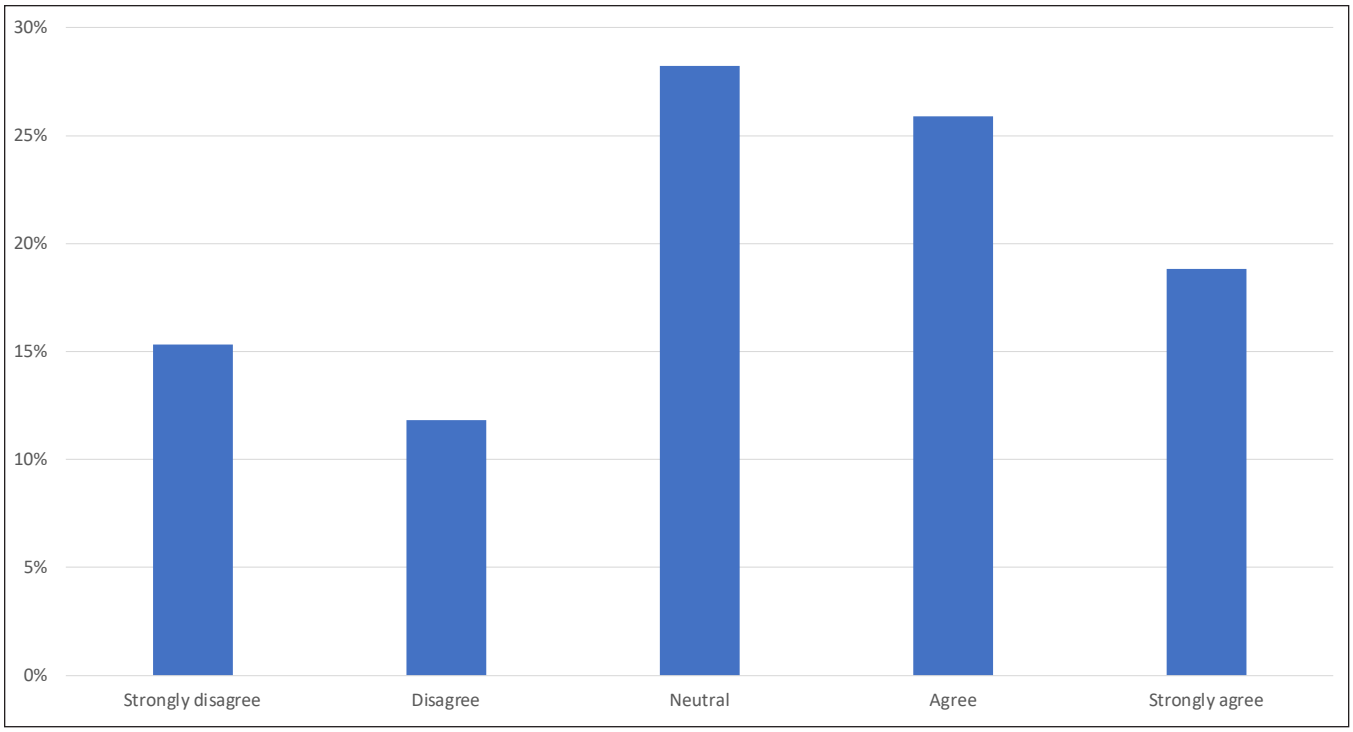
Shifting to the issue of PrEP provision in biomedical prevention trials, the survey asked participants whether they felt researchers have an obligation to help enrollees access PrEP if they could not do so because of structural, economic, or social barriers. For most the answer appeared clear, with 84.1% responding "yes."

The survey described the specific approach being taken to PrEP in the Mosaico trial (without naming the trial) and asked whether participants had questions—or could think of questions that might be raised in their community—and whether they needed more information.

Participants were roughly split overall on needing more information; 46.6% replied that they did, and 53.4% said they did not. A slight majority of gay participants (63%) felt they did not need more information, while most participants of other sexual orientations (52.6%–66.7%) needed more information. Most males (59%) considered themselves sufficiently informed, compared with 41% of female participants.

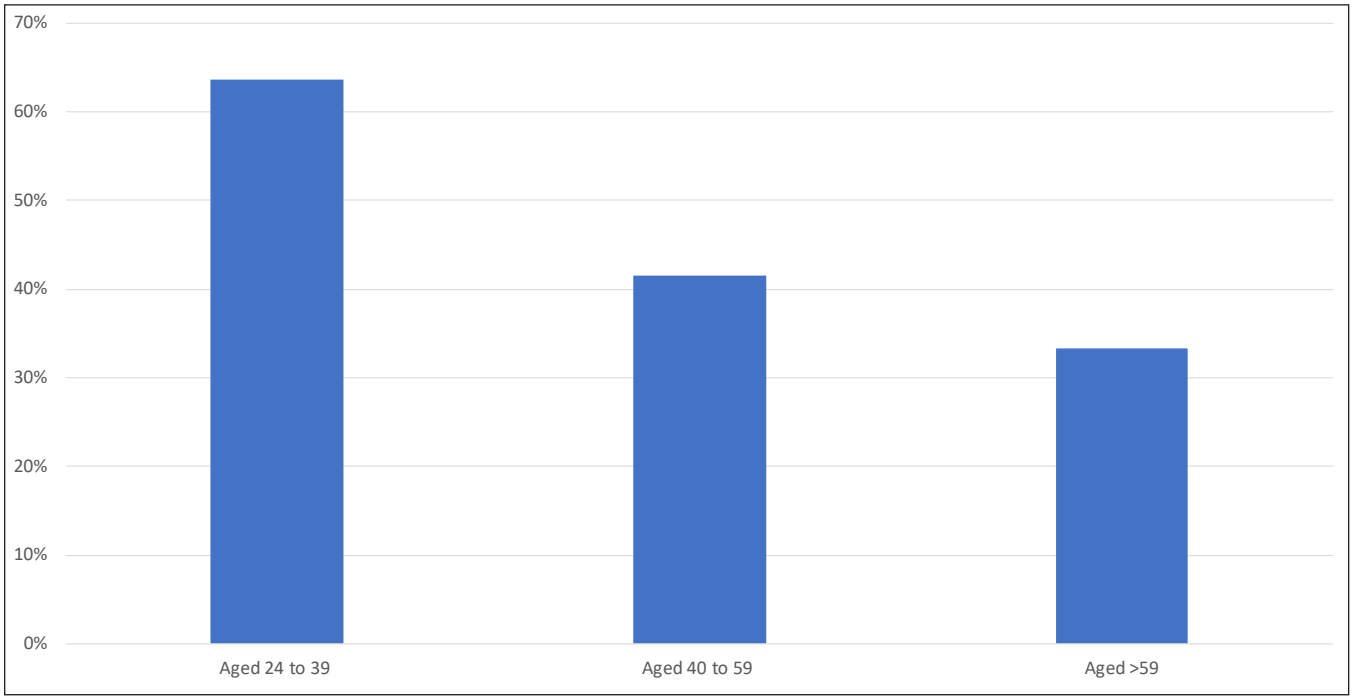
The survey also asked people to express the extent to which they agreed or disagreed with the approach on a scale of 1 to 5, if they believed they had enough information to form an opinion. A total of 44.7% participants agreed or strongly agreed with the approach, versus 27.1% who disagreed or strongly disagreed. Participants selected "3" on the scale most frequently (28.2%).

Figure 5: Agreement with enrolling people not on PrEP by choice



There was some demographic variance: Participants aged 24 to 39 were more likely to agree (63.7% agreeing or strongly agreeing) than those aged 40 to 59 (41.5%) and those older than 59 (33.3%). The answers should be interpreted cautiously, as written feedback described considerable uncertainty, and the idea appeared new to many people. See accompanying text box [page 15].

Figure 5b: Agreement with enrolling people not on PrEP by choice by age



A number of people raised potential concerns about the trial design that echo those that ethicists and researchers have described:

- "I would be more convinced of this approach if a small pilot study was conducted with qualitative data to explore ethical concerns and feedback from participants."
- "How is their knowledge of PrEP measured?"
- "Needs to be communicated very clearly, don't want the appearance of folks being dissuaded from PrEP."
- "It's confusing. Seems likely that some people would feel that 'if one is good, two is better.'"
- "People need to be allowed to take PrEP and counseled on its availability, if it is available and standard of care where they live. It should also be provided free of charge to those on prevention trials (either in conjunction with vaccine or as a comparator with PrEP options). This will increase the sample size requirements but is the only ethical thing to do since we know PrEP is available and works."
- "This could be an approach for people for whom PrEP is not recommended."
- "I question if they are not willing to take PrEP once a day, would they be willing to actually fully participate in a clinical trial? Also, I think if there were ways to include those who are taking PrEP daily in clinical trials and isolating the effects of the new treatment to gauge efficacy, this would be best."
- "This will dramatically reduce the number of eligible people to participate, I do not think this is the best way to go about doing this."
- "How much would people be implicitly pushed into it, and/or influenced by economic/access challenges?"
- "Ability to assess someone's agency for accessing and adhering to PrEP? Need to take these into account within the context of possible trial participation."
- "I think a vaccine is probably still really far off, PrEP is here and works, and instead of trying to find people who are 'high risk' and refuse PrEP and studying whether a vaccine being tested works on them, it would be way better to use more effective counseling techniques to convince those people to start and persist in using PrEP."
- "Individuals enrolled in a vaccine trial, without PrEP, may assume they're at lower risk and covered by the potential vaccine."
- "Screening people in this way might be awkward and complicated."
- "I disagree with this approach. Firstly, all study participants should not receive treatment that is less than the current standard of care—and for prevention, this includes oral PrEP. It is up to the researchers to design research that allows for PrEP use."
- "There could be an ethical conflict if in competitive recruitment processes, recruiters don't put enough efforts explaining how effective PrEP is and how infrequent side effects are."

COMMUNITY INPUT

Participants rated how important they believe it is for community members to have meaningful input into decisions on a range of issues related to the development of and access to biomedical HIV prevention strategies. Responses were extremely consistent, with more than 85% selecting "important" or "very important" for each aspect, with the sole exception being the technical topic of statistical methods and modeling:

- Protocol development and trial design for efficacy trials (93.2%)
- Statistical methods/modeling for efficacy trials (64.4%)
- Participant recruitment and retention (93.2%)
- Interpreting trial results/findings (86.5%)
- Communication of study results and results dissemination strategies (95.4%)
- Implementation research (studying the optimal way to deliver an intervention after it's approved) (93.2%)
- Plans to provide trial participants with access to a new prevention strategy after the clinical trial ends (98.8%)
- Pricing (86.2%)
- Providing and scaling up access to new prevention strategies that are proven to work in trials (93.1%)

From an array of possible community engagement strategies, participants were asked to select the three that they feel are most effective. The proportion of participants who selected a given strategy is in parentheses.

- Working with local AIDS service organizations or other community-based organizations (54%)
- Social media (47.2%)
- Community advisory boards (CABs) or similar advisory groups (46%)
- Working with existing HIV prevention advocacy groups (45%)
- Community events/town hall meetings (33.7%)
- Focus groups (30.3%)
- Informal meetings with local advocates (30.3%)
- Local media (27%)
- Hearing from opinion leaders (family, religious leaders, etc.) (26%)
- Websites for the trial (22.5%)
- Online education events such as webinars (17%)

RESEARCHERS AS ACTIVISTS

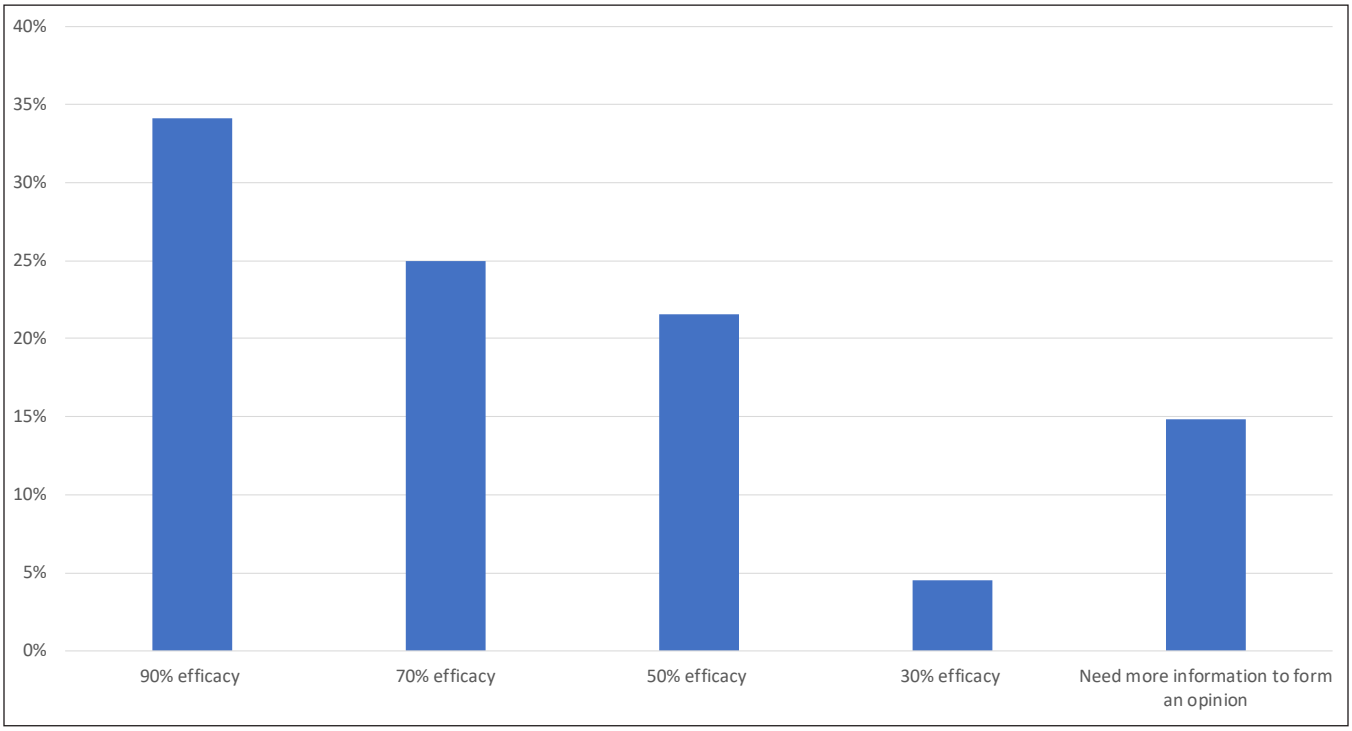
The survey asked how involved researchers should be in advocacy around access to and pricing of new biomedical prevention interventions. A clear majority (79%) agreed or strongly agreed that they have an important role to play.

ACCEPTABLE EFFICACY

The last survey question raised the issue of partial efficacy, noting that biomedical prevention interventions may be developed that are not completely protective but rather reduce the risk of HIV acquisition by a certain amount (e.g., 60%). Participants were asked if there is a minimum threshold of efficacy that would be needed in order to justify making a new HIV prevention intervention available in their community, with options of 90%, 70%, 50%, or 30% efficacy.

Overall, the highest level of 90% efficacy was most frequently selected (34.1%), followed by 70% efficacy (25%) and 50% efficacy (21.6%). Very few participants (4.5%) believed 30% efficacy would be sufficient. Gay participants tended to have a higher threshold of acceptable efficacy from a new intervention, with 43.5% saying that 90% efficacy should be the minimum, compared with 23.8% of other respondents.

Figure 6: Acceptable efficacy for making an intervention available



CONCLUSION

There remains an urgent need for novel, effective biomedical prevention interventions, but the challenges associated with proving efficacy in trials are only likely to increase. Important discussions are occurring regarding solving these challenges, but the recent launch of a first alternative efficacy trial design with little public debate indicates that there is much work to be done to involve a broad range of communities in the dialogue about future trial designs. The results of our survey offer a preliminary indication of views on the topic at this moment in time and emphasize the need for more consultation and education.

RECOMMENDATIONS

- The community advocate networks and advisory bodies that address HIV prevention research need to be further supported and leveraged to educate members about the possible novel trial designs that are under discussion.
- Broader community input needs to be sought on the optimal approaches for evaluating how potential trial participants are making judgments regarding the acceptability of PrEP.
- The development of biomedical prevention trials featuring new designs that seek to reduce the potential impact of PrEP use on evaluating efficacy requires robust and broad community consultations from the earliest stages. Furthermore, information on those consultations must be made available publicly so that it is accessible to people considering participating in the trial after it is launched. In the case of trials with

industry sponsors, this may require advance planning to ensure that community members who participate in discussions are released from any confidentiality agreements.

- Educational efforts should be targeted toward communities where the trials are taking place before the trial launches, and not only afterward. Informational resources such as trial websites should be available online before the trial launches.
- Community-based organizations for—and run by—members of communities most at risk of HIV acquisition must be supported and involved in efforts to both educate and provide feedback on new approaches to testing biomedical prevention interventions.
- Biomedical prevention efficacy trials using novel designs are teachable moments—opportunities to publicize and bolster broad public discussion and education about how the field is progressing and adapting to new challenges. This has not occurred optimally around the launch of Mosaico and discussions should take place to ensure that these opportunities are not missed in the future.
- Post-trial access plans for interventions that prove sufficiently efficacious should be clearly prespecified by trial sponsors.

GLOSSARY

Efficacy/Efficacious and Effectiveness
Efficacy and efficacious refer to how well an intervention works in the controlled context of a clinical trial. Effectiveness refers to how well an intervention works in the real world, outside of a clinical trial.

Efficacy trials
Clinical trials designed to test how well a particular intervention works. For biomedical prevention approaches, efficacy trials enroll people at risk for HIV acquisition and are typically large, enrolling several thousand people. The aim is to measure whether the new intervention reduces the risk of acquiring HIV. Ethics requires that all participants be offered the best available HIV prevention strategies and counseling. The most common efficacy trial design involves randomly assigning participants to receive a new approach or a dummy version (placebo), but some studies could compare to an existing intervention rather than a placebo.

HIV incidence
HIV incidence is a measurement of how many people are diagnosed with HIV infection during a given period of time.

Pre-exposure prophylaxis (PrEP)
The use of antiretroviral drugs or other interventions to prevent acquisition of HIV infection. Truvada (a combination of tenofovir and emtricitabine) was the first drug to be approved by the U.S. Food and Drug Administration (FDA) for use as oral PrEP. A second combination drug, Descovy (tenofovir alafenamide and emtricitabine), has also been approved by the FDA for cisgender men and transgender women but has not yet been approved for use in cisgender women or transgender men. Research is also underway to find other methods of giving PrEP, such as injections or implants under the skin, as well as additional drugs that can be used for PrEP.

U=U (Undetectable=Untransmittable)
A public health campaign to educate people about the evidence that having an undetectable HIV viral load means that you cannot transmit HIV to a sexual partner (perinatal transmission via breastfeeding is still possible). This campaign supports efforts for people to know their HIV status and to seek medical care, because using antiretroviral treatment medications is good for their health and protects their partner(s). Also referred to as Treatment as Prevention.

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