

## Innovative Clinical Trial Designs to Accelerate Increase in PrEP Choices: A High-Level Report

On July 18, 2021, The Forum for Collaborative Research convened a satellite session at IAS 2021, the annual conference of the International AIDS Society. The Forum for Collaborative Research (the Forum) is a public/private partnership that addresses cutting-edge science and policy issues through stakeholder engagement and cross-sector dialogue and collaboration. The Forum addresses specific hurdles in drug development for human immunodeficiency virus (HIV), hepatitis B (HBV), transplantation associated virus infections (TAVI), primary sclerosing cholangitis (PSC), non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), and genetically based rare diseases.

The purpose of the session was to convene a diverse group of stakeholders to discuss upcoming and ongoing pre-exposure prophylaxis (PrEP) trials, specifically those involving an innovative design based on the counterfactual placebo incidence estimate.

This new design uses estimates of HIV incidence among people not randomized within a PrEP study as an external control to measure possible protection from HIV infection and, therefore, PrEP efficacy. The use of HIV incidence estimates while not new in other settings such as surveillance and program evaluation, does have certain implications in the context of PrEP product development and regulatory review that require robust discussion between scientists and statisticians, the pharmaceutical industry, regulators, and community representatives. The Forum's satellite session served as a public forum for one of these conversations.

### The Challenges

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There is a need for more PrEP products to meet the needs of all people who could benefit from PrEP. However, designing trials to test PrEP products is challenging, as there are currently two highly efficacious oral PrEP products to use as an active comparator. The nature of the HIV epidemic is changing, as well. With lower HIV incidence in many places and highly effective oral PrEP, there are important questions about how to design trials to demonstrate efficacy and safety of new PrEP products while also satisfying regulatory requirements for their approval, said Dr. Veronica Miller, Director of the Forum.

### The Future of PrEP: Trial Designs to Meet the Need

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Recent PrEP studies have used active controls, meaning that patients in the study are randomized either to the new candidate PrEP agent or receive a known effective PrEP agent. However, this design works best for situations where the investigational agent is clearly superior or non-inferior to the standard-of-care, according to Dr. David Glidden, a professor of biostatistics at UCSF. In new PrEP trials, both the investigational agent and

standard-of-care product could be highly efficacious in preventing HIV infection but not be able to show clear superiority or inferiority of the new investigational PrEP compared to that active control.

This problem opens the door to a new way of measuring efficacy. One such way is to measure the “background” incidence of HIV and use it as a comparator. There are several ways to get this estimate, generally using some sort of auxiliary data source to calculate the background incidence of HIV.

One method is using a recency assay. Recency assays have been used for some time in HIV population-level surveillance, using cross-sectional recency testing to infer HIV incidence. When people are screened to enter a PrEP trial, they could also be screened for having been recently infected. The number of screened recent infections can give an estimate of HIV incidence within the test’s recency period.

This type of recency testing does come with some important practical considerations, though. They require calculation methods to account for variations in the assays used. According to Dr. Glidden, it may also become difficult in screening to ensure that the population tested “recently” infected is representative of the overall study population.<sup>1</sup>

What can we learn from the use of recency testing for HIV surveillance? The Tracking with Recency Assays to Control Epidemic (TRACE) study, funded by PEPFAR through the CDC, monitors real-time recent infections identified in clinical care settings. Over 30 PEPFAR supported countries have or will establish recency testing locations.

According to Dr. Jessica Justman of ICAP at Columbia University, the CDC has used recency data along with back calculation methods to get HIV incidence estimates in areas where recency testing has been done. TRACE has also used this data along with weighting methods to extrapolate incidence for those who weren’t tested. Dr. Justman emphasized that recency testing is not approved for individual use. The majority of locations do not return recency results to individuals and are strictly using the test as a part of their surveillance systems.

Recency assay holds a lot of promise in the field of HIV surveillance, but how can it be effectively used to inform new trial design?

## Testing the New Strategy

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Two clinical development programs are testing this new approach – using recency testing together with other methods to calculate the counterfactual placebo estimate. We can learn a lot as these two programs unfold regarding evaluating PrEP product efficacy. The session included a presentation from the two pharmaceutical companies

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<sup>1</sup> For additional information on the use of the recency assay to estimate HIV incidence see Parkin et al (2021) presented at IAS (page 226). [https://www.ias2021.org/wp-content/uploads/2021/07/IAS2021\\_Abstracts\\_web.pdf](https://www.ias2021.org/wp-content/uploads/2021/07/IAS2021_Abstracts_web.pdf)

undertaking studies using the counterfactual approach in PrEP studies, followed by two multi-stakeholder panel discussions.

Gilead Sciences is investigating lenacapavir, a capsid inhibitor, for PrEP. A novel approach was needed to investigate its efficacy. An active control design would have posed a special challenge of greatly increasing the sample size and complexity of the study. The new clinical trial design principle is based on the Pearl Index for contraceptives and deliberation in HIV Forum working groups on translating and applying such an approach in HIV prevention. Using the Pearl Index, a candidate contraceptive can be tested by comparing the incidence of pregnancy of the women on the contraceptive to a known counterfactual pregnancy incidence among women that are not on contraceptives. A similar methodology has now been integrated into PrEP efficacy studies.

Dr. Moupali Das, who works on the PURPOSE trials at Gilead, shared several important considerations when using a counterfactual approach to determine efficacy. Since several assays and algorithms have been used to estimate the counterfactual, the test properties need to be well characterized and adjusted. Furthermore, the characteristics of the trial participants need to be matched to those of the people used to derive the counterfactual HIV estimates. Finally, trial sites with robust and high background HIV incidence estimates should be chosen to compare the efficacy of the investigational agent. The primary endpoints for both PURPOSE studies is a comparison of HIV incidence of those on lenacapavir to the estimated counterfactual HIV incidence.

Merck & Co. is testing islatravir for PrEP in two planned/ongoing studies—IMPOWER 022 and IMPOWER 024. IMPOWER 022 tests islatravir for prevention of HIV in cisgender women at high risk for HIV infection, with the primary endpoint comparing HIV incidence among those on islatravir to those randomized to the active control, Truvada. “This is really more a traditional superiority trial,” said Dr. Mike Robertson of Merck & Co. However, in the IMPOWER 024 trial, studying islatravir in men who have sex with men and transgender women, the primary endpoint will be a comparison to the counterfactual estimate.

Since this is a new approach for showing efficacy with candidate PrEP products, special attention must be paid by regulatory authorities who are reviewing them. A main consideration for FDA reviewers will be seeing consistency among the counterfactual estimate and other known HIV incidence measures, as well as ensuring that HIV incidence in the study was sufficiently high during the study period, shared Dr. Stephanie Troy who is a reviewer with the FDA Division of Antivirals.

Similarly, Tohlang Sehloho of the South African Health Products Regulatory Authority (SAHPRA) emphasized that study sponsors will need to be careful to ensure that selection bias and confounding are minimized, especially when determining the counterfactual estimate such that they do not interfere with the perceived effect size of the intervention.

These studies are not done in a vacuum, though. Ntando Yola from the Desmond Tutu Health Foundation highlighted that the field of PrEP research must continue to bring communities directly into the development of the clinical research programs early. This ensures that the research can become more sustainable, and that community engagement isn't pinned to a specific trial, but rather supported at a community-level for all the research that is happening in those places.

## Challenges and Opportunities in Trial Implementation

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In the third portion of the satellite session a panel of community advocates, epidemiologists, and social scientists discussed their views on the new trial approach. Panelists were asked to look ahead at the trials that are being implemented with the counterfactual approach and comment on possible considerations those trials might need to take as they move forward.

In one sense, we are in “difficult times, because we’ve got good products,” said Rachel Baggaley, the Unit Head for Testing, Prevention and Populations, Global HIV, Hepatitis and STI programs at the WHO in Geneva, who also served as co-moderator of this session. This means that future trials for PrEP products will need other measures for comparison to highly efficacious existing PrEP. Finding harmony among various international regulatory authorities will be quite important as these trials continue. Baggaley mentions that one area of concern is that people testing positive at enrollment for the trial, including those testing recently infected, might not have the same characteristics as the study’s target population. This could cause problems for the counterfactual estimates and highlights the need for triangulating the counterfactual estimate with other data sources.

Dr. Connie Celum, a professor at the University of Washington who has extensive experience as a clinical trialist, is hopeful of the opportunities for getting accurate estimates of HIV incidence in low PrEP-uptake regions. Specifically, she thinks triangulating the counterfactual estimate from surveillance data collected at outpatient clinics for young women and girls as well as in HIV vaccine trials like HVTN 702, HVTN 705, and the ECHO contraception trial will be useful. These sources should be able to give a “placebo” arm incidence estimate.

Recency assay testing to estimate HIV incidence is important in many ways, says Ayesha Kharsany, a senior scientist and epidemiologist at the Centre for the AIDS Programme of Research in South Africa (CAPRISA). Her work has involved comparing recency assay estimates to more traditionally calculated cohort estimates of HIV incidence. Recency assay-based methods can be implemented quickly and offer a benefit of speed for evaluation of interventions over traditional methods. However, in the context of a PrEP trial she cautions that a recency assay based estimate needs to be generated “closest to the time that they are likely to be applied.” As the recency-based HIV incidence estimate is a function of several of the test’s parameters, Kharsany emphasized that it’s important to understand how those test parameters could be affected by the scale-up of universal test and treat programs.

When asked about considerations for community confidence in the studies, Grace Kumwenda, an HIV prevention advocate and Chief-of-Party of a key population HIV/AIDS programme in Malawi said, “for me, personally, with the new design, the new approach, stakeholder engagement will become even more critical because there are some serious questions that this is raising for us as communities,” Some of those questions that participants and communities involved in the studies might have include: how will efficacy be measured in this context? How will recency results be communicated to participants, especially in countries where their results are disclosed to them? How will data from previous studies be handled in terms of informed consent for the participants of those previous studies? “As we get into this exciting phase of this new approach, what we’re asking for is: let’s get a little bit more structured. Let’s have an education plan for communities so that we move together on this path,” said Kumwenda.

In addition to community involvement, remembering social and behavioral drivers behind efficacy will be important to interpreting the studies’ results. HIV, in many ways, is a socially constructed disease, said Dr. Kate MacQueen of FHI360. Previous studies on oral PrEP showed differing efficacy in different trial populations, which has major implications for drug access after the studies conclude. Therefore, it’s important to understand that if there are differences in efficacy whether those are caused by the way results were measured, or possibly underlying biases that are socially driven.

These questions require that the studies that will be underway not be siloed into different lanes of disparate scientific knowledge but rather become a systematic base of knowledge from across various disciplines. MacQueen cautioned that it is important to keep an open mind in this kind of research. It is possible that what we don’t know could be driving observed incidence outcomes.

## Conclusions

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In an era with two highly efficacious oral PrEP drugs, testing new ones that might improve adherence proves to be a difficult task. Using a placebo would be unethical but using an active control could require a large sample size to show superiority or inferiority. Using a counterfactual HIV incidence estimate to determine candidate PrEP efficacy appears to be a promising innovation in the field.

Dr. Debra Birnkrant, head of the FDA’s Division of Antivirals in the Center for Drug Evaluation and Research stated in the session that the FDA supports the approach taken in the trials for both islatravir and lenacapavir using counterfactual estimates. However, the FDA, along with many of the other speakers at this session, recognize some challenges that come with this approach. These challenges include using multiple methods to determine counterfactual HIV incidence (beyond just recency assay testing), and the novelty of testing efficacy using an external control in PrEP studies.

Because of this novel and innovative approach, further collaboration among stakeholders will be critical to understanding the details of using counterfactual approaches in these trials. This session served to take conversations about the counterfactual design that started at The Forum to a global audience. Now, as the trials begin, further collaboration

is warranted to ensure the successful exchange of knowledge regarding the counterfactual design's performance in various regional and viral subtype contexts, as well as facilitating discussions around the responsible use of data collected from the studies.