THE FORUM FOR COLLABORATIVE RESEARCH & AVAC

NEXT GEN HIV PREVENTION RESEARCH: CLINICAL TRIALS IN AN ERA OF HIGHLY EFFECTIVE STANDARDS OF CARE

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THE FORUM For Collaborative Research℠

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INTRODUCTION

The field of HIV prevention has markedly advanced since the introduction of oral pre-exposure prophylaxis (PrEP) 10 years ago. Multiple highly effective PrEP products are on the market and clinical trials for new PrEP modalities in the pipeline must evolve. A PrEP standard of care with highly efficacious products means that more traditional active-controlled trials would be infeasibly large, so a new approach is justified.

The Forum for Collaborative Research has been convening trial design, pharmaceutical, regulatory, and ethics experts to explore how to address that necessary evolution. One approach proposed is the use of a counterfactual trial design—where the performance of a candidate HIV prevention drug is compared to a calculated counterfactual HIV incidence. One method used to calculate the counterfactual HIV incidence is using the HIV recency assay. Members of the Forum's PrEP Project Steering Committee and Recency Assay Working Group reached consensus on the use of the assay in HIV prevention clinical trials. This satellite symposium serves to educate the scientific community and broader public on the justification for, design of, and current rollout of clinical trials using the recency assay for counterfactual HIV incidence estimation.

On July 25, 2023 the Forum partnered with AVAC to present this satellite session at IAS 2023 in Brisbane, Australia. This report provides a summary of that satellite session.

OVERVIEW OF DESIGNS OF RECENTLY COMPLETED HIV PREVENTION TRIALS

"The modern randomized controlled trial is a fairly recent innovation," says Dr. Sinead Delany-Moretlwe of Wits RHI who presented on clinical trial designs of recent HIV prevention trials. In 1948, the first randomized controlled trial (RCT) designs were published, but by the 1970s the US FDA required RCT data for approval of new drugs. An RCT relies on taking a sample population that is representative of the target population for the intervention, randomly assigning participants to an intervention option, following the groups over the same time taking the same measurements, and then assessing the different interventions against each other.

In certain, specific cases, such as when no other product is approved for the same indication, a placebo can be used as a comparator in an RCT. In the earliest PrEP trials, placebos were both ethically appropriate and methodologically useful for comparing the efficacy of PrEP because no antiretroviral-based HIV prevention modality was on the market at the time. The landmark Partners PrEP study randomly assigned participants to one of three study regimens - once daily TDF, combination TDF/FTC, or placebo. This study found that HIV incidence was 75% lower in the TDF/FTC group and 67% lower in the TDF group compared to the placebo group.[1] The Ring Study of the dapivirine vaginal ring for HIV prevention also showed moderate efficacy compared to a placebo.[2]

In 2015 the WHO recommended that PrEP containing TDF should be offered as a prevention choice for those with substantial risk of HIV. After the introduction of this guidance, the use of a placebo in HIV prevention trials was no longer appropriate: “The problem is,” says Delany-Moretlwe “at the time of that recommendation, there was variable implementation of TDF/FTC, and it wasn’t available widely in the places we would do those trials, but it did make the idea of placebo-controlled trials no longer justifiable.” Now that oral PrEP is available (if not widely so in all places), it would be unethical to conduct an HIV prevention trial without offering PrEP as a standard of care, as it is an approved and efficacious form of HIV chemoprophylaxis.

The biomedical HIV prevention field then entered the era of active-controlled trials. In an active-controlled trial design there is no placebo, and TDF/FTC-based PrEP options are the comparator group. In HPTN 083 and HPTN 084, the phase III trials of long-acting injectable cabotegravir for PrEP, oral TDF/FTC was used as the comparator.[3,4] Both HPTN 083 and HPTN 084 were stopped prematurely by the data safety monitoring boards because of evidence of substantial benefit in HIV prevention.

Given two highly effective HIV prevention products (oral TDF/FTC, and injectable cabotegravir), HIV incidence in clinical trials is very low. The incidence across both groups in HPTN 083/084 was ~1%. “You have such low incidence because you have agents that are able to prevent HIV; you then are required to have much bigger sample sizes,” says Delany-Moretlwe, which now causes us to consider new approaches to determine efficacy of HIV prevention agents.

THE COUNTERFACTUAL APPROACH: TOOLS AND DATA SOURCES AVAILABLE FOR PREVENTION TRIALS

In active-controlled trials “we’re seeing incidence rates well below 1 per 100, more like 1 per 1000 scenario which makes it very difficult for us to design non-inferiority trials,” says Dr. Deborah Donnell, professor of biostatistics at Fred Hutchinson Cancer Center, who presented on counterfactual approaches in HIV prevention trials. Calculations show sample size with a highly active control, like cabotegravir, could balloon up to 40,000-80,000 participants.

This sample size issue causes concerns for investing in more active-controlled trials. Trials with large sample sizes will likely be prohibitively expensive, but also, according to Donnell, “another epidemiological problem is that when you have sample sizes that large, even though we did them for COVID [vaccines], in the context of HIV we would almost inevitably expand into populations that are not at such high risk of HIV, so I really think it becomes counterproductive.” These concerns force us to consider alternative options to a traditional active-controlled design and have led us to the use of a counterfactual trial approach.

The goal of the counterfactual approach is to estimate the absolute efficacy of the product as if there was a placebo arm. In a counterfactual trial, study participants are still randomized to either the active control or the experimental product, but the study includes a planned estimation(s) of the HIV infection rate without any biomedical prevention agents.

Generally, when moving from placebo-controlled to active-controlled trials, the performance of the active control against placebo in a prior trial is used to determine the non-inferiority margin when comparing a new product against that active control. This comparison relies on the constancy assumption—the effectiveness of the active control remains constant when applied in a new setting.

A similar assumption is employed when using a counterfactual placebo estimate. In addition to using the active control for one of the randomized arms in the trial, the effectiveness of the new agent is compared to a calculated counterfactual placebo incidence rate that shows what HIV incidence *would have been* if there were a placebo arm in the trial.

Several approaches have been proposed to calculate the counterfactual placebo incidence estimate. Estimates can come from external concurrent trials or registrational cohorts. The HIV recency assay could also be used to assess HIV incidence in the study population.[5] Adherence data and biomarkers of exposure may be used to triangulate HIV incidence. All of these are not without their caution. However, with these approaches, the estimation of counterfactual HIV incidence does not have the protection of randomization. Efficacy estimates are also intrinsically less statistically reliable, so replication of results across multiple trials remains important, and estimations can be influenced by ecological trends in HIV incidence. Having a strong absolute efficacy of new products compared to the estimate will be key, as smaller margins could lead to early termination of trials. “Valid counterfactual placebo estimates do offer us feasible trials yielding, we hope, scientifically valid results, without the continued use of placebos,” says Donnell.

INSIGHT STUDY INITIAL RESULTS

Dr. Irene Mukui from the University of Washington presented initial results from the INSIGHT cohort study, which employed the recency assay to estimate HIV incidence. A recency assay determines whether an HIV positive sample is considered a “recently” acquired infection. In conjunction with viral load, a recency testing algorithm is used to classify infections based on recency, and the number of recent infections in a population can be used to estimate the HIV incidence.

INSIGHT was initially designed as a phase III study to determine the efficacy of long-acting islatravir for HIV prevention among cisgender women. However, the study was halted by the FDA due to safety concerns. INSIGHT then pivoted to become a non-intervention, prospective, open-label cohort of cisgender women ages 16-30 on daily TDF-based PrEP. During recruitment, individuals were not screened for HIV status, so that those who were HIV positive would not be screened out of the study and therefore not contribute to the incidence calculation.

Initial results presented at IAS 2023 were limited to only the INSIGHT cohort's South African sites. Of the 2,365 people screened, the median age was 24 and two-thirds (68%) reported unemployment. 284 (12%) of those screened had previously used PrEP for HIV prevention and 733 (31%) had a curable STI. 109/2365 (4.6%) screened HIV positive at entry. Eighteen (17%) of those 109 (17%) had prior knowledge of their HIV status. Among the 18 with prior knowledge of their status, 8 (44%) reported knowing for 2 years or less. Though 30 recency assay tests were still pending, of the 79 HIV positive samples tested, 5 were found to be recent infections (see below).

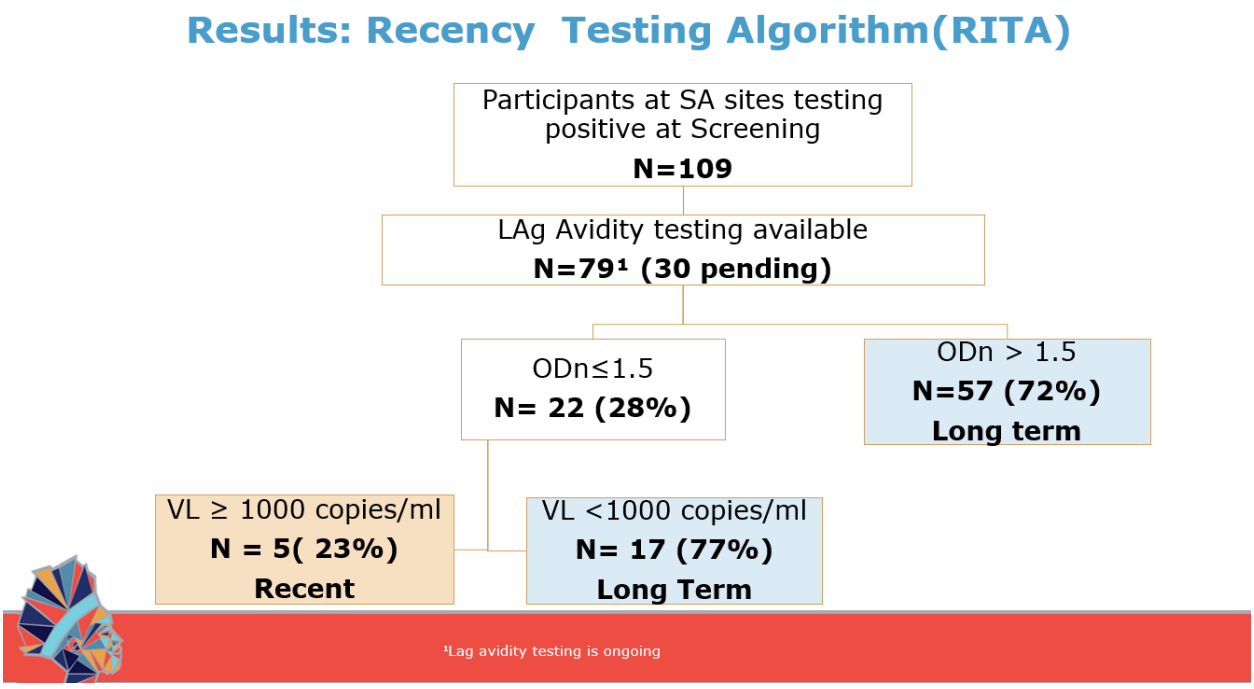

Figure 1: Recency Testing Algorithm (RITA) Preliminary Results from INSIGHT Study Cohort (Mukui, IAS 2023)

While it is still too soon to determine the incidence rate based on the recency assay (as there are still outstanding samples to be tested with the recency assay), the INSIGHT cohort will continue to use the recency assay as a method to determine counterfactual HIV incidence.

HIV RECENCY ASSAY: LESSONS LEARNED AND CHALLENGES PRESENTED

"If we are to get to the goal of 10 million people on PrEP, we need more PrEP options so people have more choices, and we can bring more people into PrEP care. This requires innovation in the science…as well as in health equity. It's never about the drugs alone," says DrMoupali Das, HIV Prevention Clinical Development Lead at Gilead Sciences. Das is also leading Gilead's phase 3 clinical trials of lenacapavir, a new long-acting injectable PrEP.

Lenacapavir is a potent capsid inhibitor that can be administered twice annually and is already approved for HIV treatment for those with multi-drug resistant virus that have failed other regimens. Gilead's PURPOSE program is a comprehensive program that encompasses two pivotal phase 3 trials. The PURPOSE 1 trial investigates lenacapavir as well as oral F/TAF, separately, for PrEP in young women and adolescent girls in South Africa and Uganda, and PURPOSE 2 is investigating lenacapavir for PrEP in gay cisgender men, transgender men, transgender women, and nonbinary people.

The counterfactual design in the PURPOSE trials is bolstered by the use of the Pearl Index in contraceptives research. The Pearl Index is used to determine the efficacy of contraceptives by comparing the birth rate among those on an investigational contraceptive to a known birth rate in the same population of those who are *not* on any birth control. "This can be applied to HIV," Das says, "if we know the HIV incidence in a specific population, then we can provide an investigative PrEP drug, observe the HIV incidence, and if there's a meaningful decline...then we can conclude the new drug for HIV prevention is working. The beauty of this design is that allows the evaluation of *inherent* efficacy rather than *comparative* efficacy." But this requires a knowledge of the background HIV incidence to show that inherent efficacy.

One such way is using recent infection testing algorithms (RITAs). Das reminds us, "We have been using [recency assays] for a long time in epidemiology and public health." But how do we apply these public health tools to the context of a clinical trial? The Forum for Collaborative Research brought together diverse stakeholders and published a consensus paper on the use of RITAs in clinical trials for HIV prevention (linked here). This method involves administering a recency assay at screening for trial enrollment and calculates the background HIV incidence rate in the population based on the number of recent infections found during the screening process.

This approach was tested in the SIENA study to understand HIV incidence in two hyper endemic areas in Uganda, as well as in the ECHO-RITA trial to understand the performance of the recency assay. Both showed incidence estimates that were reasonable and justified pursuing the counterfactual approach using the recency assay in the PURPOSE trials, which are designed to use a counterfactual comparison as an endpoint.

COMMUNITY THOUGHTS ON THE COUNTERFACTUAL APPROACH

"We are in this discussion for good reason because we find ourselves in a period where the choice of products is not only growing but we have these interventions that are effective for HIV prevention. These, again, only qualify as effective when they are available and accessible to the communities that need them," says Ntando Yola, Community Engagement Lead at the Desmond Tutu Health Foundation.

Community advocates, Yola says, have become quite familiar with the placebo-controlled design and its many iterations, including the double-blind, double dummy approach used in HPTN 083/084. This is a testament to how much time and effort it takes to consult with and engage with communities. Through HPTN 083/084 engagement, advocates saw a new design approach and were able to communicate the trial design to their communities because community engagement started long before the trial. When done well, they provide more confidence among the community in the trial and can strengthen clinical trial designs by including input from the people that will participate.

Gilead's PURPOSE 1 study has been an important example of engaging community stakeholders and advocates on the counterfactual trial design. As early as 2019, Gilead engaged with community advocates in Uganda and South Africa on the trial design. This has led to the establishment of a sustainable method of advisory through the Global Community Accountability Group. This sustained engagement precipitated the inclusion of pregnant and lactating people in the PURPOSE 1 study.

Moving forward, AVAC has created a trial design academy to convene communities and research experts to confront technical challenges and advance HIV research agendas. The Forum continues to include community voices on its steering committee when discussing consensus on the use of the recency assay in clinical trials. Yola highlights that it is important to invest in *platforms* that equip and empower communities and advocates.

Yola says this "highlights the important concept that if we are engaging in ongoing processes, this helps communities to hear these concepts, digest the concepts, interpret and translate and debate the concepts over and over and over again." There is no overemphasizing the return on investing in community engagement for these next generation HIV prevention trials. These investments build confidence in the research and creates a sustaining pattern of continued trust in the research, which attracts trial participants, who in turn become more informed and are more confident in contributing input to future trial designs.

STAKEHOLDER DISCUSSION

"Is the recency assay the new gold standard for counterfactual trials?" asks Dr. Kenneth Mayer, Medical Research Director at the Fenway Institute and moderator of the session. In response, Donnell highlights that while the recency assay and RITAs are the primary efficacy comparator in upcoming trials, given the novelty of this approach, many would like to have a plan to "triangulate" the recency assay incidence estimates with other existing data. Das concurs, saying that while the recency assay is the primary comparator for the PURPOSE trials, they will be triangulating with other data sources, such as rectal gonorrhea incidence rates, oral PrEP adherence data, and other incidence estimations from outside the trial data. Dr. Veronica Miller, Director of the Forum for Collaborative Research says the US FDA in their conversations have said they want more than one data source for the efficacy determination.

"What are some of the combination of data in different settings that you think would be useful?" asks Miller. Das acknowledges that there is a tension when it comes to the optimal trial design. For the PURPOSE trial they implemented a requirement to not have an HIV test in the prior 3 months, which can be challenging in populations where regular testing is common. As PURPOSE 2 started, many current PrEP users (as high as 30-40%) enrolled in the study. This led the investigators to revise the protocols to exclude people who were currently on PrEP, which is a markedly different design and is in tension with the overall goal of increasing PrEP uptake worldwide.

Delany-Moretlwe thinks that more data will be key to moving more towards the counterfactual approach and convincing the broader scientific community that it is a feasible way to run HIV prevention clinical trials. She highlights that the INSIGHT study cohort and the PURPOSE trials will be good first steps to show that the recency assay approach works. Once more trials are underway, if new products continue to be highly efficacious, then it will allow for comparison of things like product attributes or delivery method in much the same way that highly efficacious contraceptive products are compared.

Dr. Jerome Singh, professor of Clinical Public Health at the University of Toronto and Honorary Research Fellow at the Howard College School of Law, University of KwaZulu-Natal, and co-chair of the HPTN Ethics Working Group, highlights that attention still needs to be paid to the recency assay. A vexing ethical concern is the question of returning recency results to individuals. Should individuals screened with the recency assay be required to participate in partner notification? Should they be required to identify other people in their sexual networks? While PEPFAR does not disclose results from the recency assay, Mukui concurs the ethical question of returning results ought to be debated. The PURPOSE studies are not disclosing recency assay results to anyone, as per the label of the assay they are using.

Mukui and Donnell also highlight a potential issue that the recency assay was developed prior to the adoption of treatment as prevention, and we do not yet know the effect that quickly starting ARVs for a recent infection may have on the performance of the assay. Donnell suggests more data might help address this unique challenge.

CONCLUSION

Conversations on the counterfactual trial design must continue as more results become available from the INSIGHT study and the PURPOSE studies. Lessons learned from these prevention trials can help inform future studies of broadly neutralizing antibodies (bNAbs) and vaccines as standards of care continue to evolve. And most importantly, continuing to engage communities on the design is crucial. "As the complexity grows—of the trial designs, of the statistical analyses, of the regulatory pathway—it raises the bar of the engagement," says AVAC's Director, Mitchell Warren. "What strikes me is that we're all grappling with what it all means…it's hard for all of you in the research, design, and implementation world, but it's even harder when you think about the bar that got raised for research literacy and engagement."

On the other hand, “The whole community is participating in the research…communities can be completely involved in a trial, even if they’re not randomized into it,” adds The Forum’s Dr. Miller. This is just one of several exciting opportunities the future of these trials holds, she says, “This also gives us an opportunity to think about HIV prevention efforts at the program level and how …the clinical research paradigm and the program paradigm can begin to speak with each other.”

As the counterfactual approach continues, the Forum remains dedicated to monitoring the outcomes of trials and real-world performance of the recency assay. Future convenings will cover the use of the recency assay in these trials and implications for regulatory approvals of drugs studied using the counterfactual approach. Lessons learned can then be applied to other fields, including clinical trials for bNAbs and vaccines. The counterfactual approach in HIV prevention is still in its infancy, though it has now opened the doors to even more innovation.

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