THE FORUM FOR COLLABORATIVE RESEARCH

AIDS 2022 SATELLITE SESSION

Next Generation PrEP: From Science to Community Impact

Friday July 29, 2022
Montreal, Canada

1608 Rhode Island Avenue NW
Washington, DC 20036
www.forumresearch.org

THE FORUM
For Collaborative Research℠

Berkeley Public Health

CONTENTS

OPENING REMARKS

Introductory Remarks

Presenters:

- Veronica Miller, Forum for Collaborative Research
- Kenneth Mayer, Fenway Health
- Helen Rees, Wits Reproductive Health and HIV Institute

Advancements in HIV prevention science and expanding options for pre-exposure prophylaxis (PrEP), including oral PrEP, long-acting injectable cabotegravir (CAB-LA), and the dapivirine vaginal ring (DPV-VR), have created challenges for future PrEP trials. The availability of these effective products means that it is no longer ethical to conduct placebo-controlled PrEP trials; however, offering effective prevention options contributes to low numbers of HIV acquisition events in the active-control study groups of trials, requiring large numbers of participants to achieve adequate statistical power in HIV prevention studies.

The HIV Forum at the Forum for Collaborative Research aims at exploring the current science of and innovations in clinical trial designs for HIV prevention and how such innovations impact communities. The HIV Forum has focused on exploring alternative study designs, including using counterfactual estimates of HIV incidence in the absence of intervention, with recent infection testing algorithms (RITAs) as an option to generate such an estimate. Designing future HIV prevention clinical trials is a complex issue that must be engaged from scientific, statistical, ethical, and community engagement standpoints. PrEP remains a critical component to ending the HIV epidemic in sub-Saharan Africa and around the world. Thus, implications of a counterfactual study design for PrEP trials are essential to examine. This report summarizes the presentations and discussions of a satellite session hosted by the Forum at the 24th International AIDS Conference, Montreal, Canada, 29 July 2022.

SESSION I: SCIENCE

Reflections on Use of Counterfactual Approach in HIV Prevention Trial Design

Presenter: Deborah Donnell, Fred Hutch Cancer Research Center

Slides: Donnell IAS Counterfactuals

Highly effective PrEP products result in a decreasing number of HIV acquisition events in active-control arms, consequently requiring larger trials to statistically power and demonstrate non-inferiority of future investigational PrEP products. Conducting a randomized controlled trial (RCT) with incidence rates are below 1/100 person-years would be expensive, requiring large sample sizes, risk not gathering enough evidence of HIV acquisition events to prove effectiveness, and may require expanding enrollment to lower-risk populations. Thus, the counterfactual approach is an alternative method to estimate what the infection rate would have

been if there had been a placebo. The goal of the counterfactual study design is to estimate the effect of an experimental intervention relative to a placebo if the trial had a randomized placebo arm. The approach tries to imitate characteristics of the gold-standard placebo-controlled RCT design, such that within each group/arm there is an expected balance with respect to measured and unmeasured confounders and the follow-up time distribution in each site and background exposure risk is the same.

There is precedence in a non-inferiority trial for using external data as part of the success criteria for the experimental agent. The rationale for this claim is that the non-inferiority margin is based on prior placebo-controlled RCT results from an external trial, with the constancy assumption and effect preservation being accepted statistical principles:

- Constancy assumption:
    - The non-inferiority margin should account for bias or lack of reliability in the estimate of effect of standard
    - Prevention effect of standard compared to placebo is constant in prior and future trials where (1) the non-inferiority trial is not done under the same conditions as the prior trial and (2) the effect in the prior trial is subject to measurement uncertainty
- Effect preservation:
    - The non-inferiority margin should achieve preservation of a percentage of the effect of standard (e.g., 50%)
    - The experimental arm must not be unacceptably worse than the standard

These principles are relevant for generating a statistical framework of a counterfactual hypothesis based on measurement of placebo, active, and experimental data in future PrEP trial designs. Future trials will be designed such that they are randomized with both experimental and active-control arm(s), ensuring internal validity for a direct causal comparison of HIV incidence rates between active-control and experimental arms. The addition of the counterfactual estimate, measured in the context of prior/current RCT data, can help address the issue that only a limited number of HIV acquisition events are expected and can allow for estimating a placebo-controlled efficacy of the intervention. This method requires a high-quality measurement of incidence and cohort characteristics. Future trials that attempt to use the counterfactual approach to establish sufficient evidence should consider 3 statistical principles:

- Active-control group satisfies constancy
- Experimental and active-control groups have “similar” infection rates
- Experimental and active-control groups have lower infection rates than “placebo”

Multiple approaches are under investigation for generating a counterfactual placebo estimate, which includes the following:

- Bridging from contemporary “placebo” data
    - Registrational Cohort/Post-trial access data – same participants

    - Placebo data from external trials – different participants
- Cross-sectional incidence assessed during screening for enrollment in "untreated" participants
- Bridging active-control efficacy using adherence-efficacy relationship of active-control
- Assessing placebo risk using reliable predictors of HIV exposure risk

These methods for estimating the counterfactual placebo have utility and were presented at CROI 2022 by Deborah Donnell in: "Counterfactual Estimation of CAB-LA Efficacy Against Placebo Using External Trials"[1]. This is just one study that utilized the counterfactual placebo estimate and demonstrates utility of this novel statistical approach. Further exploration of strengths and challenges of using the counterfactual placebo in PrEP trials, using counterfactual placebo estimation as part of study site selection, follow.

Use of the Recent Infection Testing Algorithm to Estimate Background HIV Incidence in Micro-Epidemic Areas Within Uganda

Presenter: Flavia Matovu Kiweewa, Makerere University-Johns Hopkins Research Collaboration

Slides: **Kiweewa AIDS**

The use of a counterfactual placebo estimation method that estimated cross-sectional HIV incidence during screening for enrollment in "untreated" participants, was demonstrated in the PURPOSE 1 study in Uganda. A RITA was used to characterize the baseline HIV incidence in two regions of Uganda to aid in study site selection for the PURPOSE 1 study, a phase 3 trial evaluating the safety and efficacy of long-acting lenacapavir for PrEP, compared to oral PrEP with tenofovir alafenamide fumarate (TAF) and emtricitabine (FTC) among adolescent girls and young women in South Africa and Uganda.

The primary endpoint in PURPOSE 1 compared HIV incidence in the two study groups to background HIV incidence. A high background HIV incidence (>3.5/100 person-years [PY]) is required for a feasible sample size. Four sites were identified as potential study locations:

- Kalangala and Masaka – these two sites had known recent HIV incidence estimates
- Mityana/Mubende and Hoima – these two sites did not have known HIV incidence but had socioeconomic and behavioral characteristics suggesting increasing HIV incidence. This included known areas of commercial sex work, such as Bars, nightclubs, lodges, gold mines, factories, farmlands, islands, and landing sites.

[1] Donnell, Conference on Retroviruses and Opportunistic Infection (CROI) 2022, OA #86. https://www.natap.org/2022/CROI/croi_133.htm

Thus, a RITA was utilized at the Mityana/Mubende and Hoima sites to characterize background HIV incidence for study site selection.

The following HIV diagnostics were used as part of the RITA:

- HIV diagnosis and confirmation via Alere Determine™ HIV-1/2 (Abbott, Abbott Park, Illinois, USA) and OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test (OraSure Technologies, Bethlehem, Pennsylvania, USA)
- Positive cases were further assessed with Sedia® HIV-1 Limiting Antigen Avidity EIA (Sedia Biosciences Corporation, Beaverton, Oregon, USA)

Participant characteristics, including information on the young women and adolescent girls' sexual history and socioeconomic background, were collected:

- Median time living in the community was 1.2 years, demonstrating the transient nature of the participants
- Over 90% had 2 or more sexual partners in the past 3 months, demonstrating the high-risk profile of the participants
- Most study participants reported never (32%) or rarely (34%) using condoms in the past 3 months
- Most study participants (91%) reported that their partner provided financial or material support

RITA results:

- Hoima had a lower estimated HIV incidence rate (3.11 per 100 PY [95% confidence interval: 0.84, 11.5]) as compared to that of Mityana/Mubende (23.2 [13.1, 41.2] per 100 PY)
    - Hoima: Of the 372 total participants, 47 were diagnosed with HIV. 7 of those were classified as recent infections
    - Mityana/Mubende: Of the 371 total participants, 144 were diagnosed with HIV. 30 of those were classified as recent infections
- There were no associations between individual-level characteristics and recent HIV infection, suggesting that the difference in HIV incidence between the two sites is attributable to the socio-structural differences between the two regions

The higher background HIV incidence among adolescent girls and young women in Mityana/Mubende indicated that this population was appropriate for HIV prevention studies, and that this region was confirmed as a study site for PURPOSE 1. Further, this demonstrated recent infection testing has utility for HIV prevention trials, in this instance for study site selection.

Using Recent Infection Testing Algorithms in Background HIV Incidence Estimation

Presenter: Eduard Grebe, Vitalant Research Institute

Slides: Grebe Using RITAs for bHIV Estimation

The use of RITAs in PrEP trials to establish counterfactual background HIV incidence rates in lieu of a placebo arm is a novel use without established best practices and several issues need to be considered to avoid bias in cross-sectional HIV incidence estimations with RITAs. The technical and methodological issues related to use of RITAs principally impact two statistical aspects of results:

- Accuracy of incidence estimates – related to potential biases
- Precision of incidence estimates – represented by the width of confidence intervals

Changing epidemiological realities, including earlier diagnosis and ART initiation, present challenges for the use of RITAs. These issues are pronounced in key population studies, regional or subnational studies, and PrEP clinical trials. Two key parameters of the recency assay can result in bias of HIV incidence estimates:

- Mean duration of recent infection (MDRI) – the average duration of the 'recent' state after HIV infection, while infected for less than specified time cutoff (T)
- False-recent rate (FRR) – the proportion of individuals infected for longer than T who nevertheless appear recently infected

These two parameters are sensitive to the epidemiological context, and therefore, they differ from population to population. The MDRI and FRR are not inherently biological properties, but future PrEP clinical trials that use RITAs should seek an algorithm with a maximally long MDRI and a minimal FRR for optimal accuracy. In addition to these two parameters, a perennial problem is avoiding selection bias in PrEP clinical trials that utilize the novel RITA method for recruitment of study participants. Selection bias can generally be avoided in a study that uses random sampling framework, like one used in a population-level survey. Any routine use of recency assays at the clinical level, or in smaller studies such as key-population studies, may introduce selection bias due to the non-random nature of recruitment.

An emerging problem in the use of RITAs is that increasingly early HIV diagnosis and treatment initiation impacts the MDRI. The MDRI will decrease in populations where individuals who recently acquired HIV initiate ART treatment early on in diagnosis, leading to viral suppression and causing the RITA to classify them as a long-term infection. This results in a biased MDRI and is particularly pronounced in populations with frequent testing. In one instance, early diagnosis/treatment led to a 60% reduction in MDRI, introducing significant bias in incidence estimates.

An unbiased estimate of the MDRI, the effective MDRI, can be acquired by incorporating a survival function representing 'survival' in the undiagnosed/untreated state of disease, helping address the issue of early diagnosis and ART treatment. This novel methodology for obtaining effective MDRI is facilitated by a user-friendly tool for MDRI estimation, found **here.** This statistical platform allows users to input key parameters as part of the RITA, including time cutoff T, the recency assay used, viral load threshold, and adjustment for early diagnosis/treatment, among others. Of note, there are fields to adjust for HIV subtype distribution, which is an important aspect of MDRI estimation. The dynamics of immune markers can depend on HIV subtype, meaning that the mix of subtypes in the population of interest should be considered. These components are integral parts in obtaining the effective MDRI and creating a less biased estimate of the recency test in RITAs.

As with the MDRI, FRR estimates are context-dependent and especially sensitive to epidemiological contexts given most primary immune markers of recent infection are highly sensitive to ART. Thus, long-infected individuals can appear to look recently infected on recency assays. This necessitates the inclusion of a viral load threshold and/or ART detection in a RITA. Appropriate MDRI and FRR estimates are crucial for accurate cross-sectional incidence estimation. This is both in population-level surveys and in PrEP clinical trials where background HIV incidence serves as the counterfactual. Optimization of RITAs (maximizing MDRI and minimizing FRR) is critical to ensure ideal accuracy and precision of incidence estimates. Further, this contributes to proper maximization of power and feasible sample size requirements in prevention studies.

SESSION II: COMMUNITY IMPACT

Maximizing the Use of Data for Community Impact – Recorded Commentary

Presenter: Grace Kumwenda, Pakachere IHDC

Benefit to the community in the face of innovative HIV prevention trial designs must be ensured above all else. There are more HIV prevention options today compared to 10 years ago and as the landscape progresses, ethical conduct in HIV prevention clinical trials remains paramount. In the face of evolving HIV prevention trial designs, such as those that use the counterfactual placebo, communication and informed consent—including a detailed conversation on risks and benefits of study participation—remain critical components to facilitating ethical research and to ensuring respect, autonomy, and dignity for study participants.

Continued community involvement in research—not at the end but at the beginning—, is a must as trial protocols are developed. Community involvement in trial design becomes even more important as the field moves forward with novel trial designs, such as those using the counterfactual placebo. Studies that use external controls as a counterfactual placebo have different implications for communities when compared to a traditional trial that enrolls study

participants in a placebo-arm trial. The novel methods raise the question: what does community engagement look like with these new methods? With more complex trials being carried out, the need for improved communication strategies that allow engagement with gatekeepers, community advisory boards, and the media, are necessary. Further, the local media should be trained to educate, communicate with, and inform community members about ongoing trials. Such strategic involvement and training of local media can facilitate beneficial community engagement as HIV prevention trials are carried out.

Guidance for best practices in clinical trials needs adaption to better reflect novel HIV prevention trial designs. As the field moves toward utilizing community-level data, having input from the community is empowering. Additionally, ensuring community understanding of their data use and how their data informs trial outcomes is essential to ethical, beneficial research.

Maximizing the Use of Data for Community Impact – Panel Discussion

Panelists:

- Ntando Yola, Desmond Tutu Health Foundation
- Joan Nabawanuka, Makerere University-Johns Hopkins Research Collaboration
- Jeremy Sugarman, Johns Hopkins University

As HIV prevention trial designs evolve and progress, the templates used for engaging with communities must move along with these advancements. Explaining how HIV prevention trials work—from placebo-controlled designs, to double-dummy/double-blind designs, to the novel counterfactual designs—remains a critical component of informed consent with communities in the research process. Another important aspect is working with the staff that interfaces with study participants, including community outreach teams who carry out the informed consent process and are tasked with appropriate messaging. It is crucial in this evolving landscape to craft appropriate messaging for community outreach, for informed consent, and in managing expectations of study participants. In the context of next-generation trials and expanding options for PrEP, strengthening and maintaining relationships with communities remains at the foundation of the field.

Communities often lack information with respect to research, and communicating novel trial designs, particularly to study participants that may be illiterate, is increasingly complex. To address this, explaining trial design terminology—such as ‘placebo,’ ‘double-blind,’ and other terms— should be in protocols to ensure community understanding.

As the toolbox of HIV prevention options expands, trial designs for future agents need to be ethically and scientifically sound. Given the uncertainties of novel methods, transparency remains a hallmark requirement for future research. Novel counterfactual estimates are importing tools used for surveillance in the clinical and research space. Caution must be used when jumping between these spheres. Crosstalk between these domains is critical to ensure ethical research that has social value, and benefits the welfare of individuals and the broader community.