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Control groups for HIV prevention efficacy trials: What does the future hold?

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Abstract

Purpose of review: Ending the HIV epidemic will require the development of additional effective immune-mediated and non-immune-mediated means of HIV prevention. Evaluating novel interventions requires large, controlled trials demonstrating efficacy. Recent advances in the field of HIV prevention necessitate new approaches to efficacy trial design.

Recent findings: Three classes of efficacy trial designs are possible: standard of prevention-controlled trials, active-controlled trials, and active-controlled trials augmented with external control data. Recent experience with these approaches provides lessons on considerations around and success of the designs. Additional experience and development is needed for the augmented active-controlled trial design.

Summary: Efficacy trials of new HIV prevention interventions are feasible but require careful consideration, given the complexity and dynamic state of the prevention field. While standard of prevention-controlled efficacy trials are reasonable approaches for HIV vaccine and monoclonal antibody efficacy trials, trials of new antiretroviral agents may require active-controlled designs.

Keywords

HIV prevention; randomized controlled trial; placebo; active control; efficacy trial

Introduction

Major advances in biomedical HIV prevention have occurred in the last two decades: research demonstrated that completely virally suppressed persons living with HIV cannot transmit HIV to their sexual partners,[1–3] ("U = U"),[4] and oral antiretrovirals (ARVs), when taken as pre-exposure prophylaxis (PrEP), are effective.[5–7] More recently, PrEP with long-

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acting injectable cabotegravir (CAB-LA) was found highly effective[8,9] and may circumvent some of the challenges associated with pill-taking adherence.

These advances bode well for reducing population HIV incidence,[10,11] but create challenges testing new interventions. Individual choice is critical in HIV prevention uptake,[12,13] thus a portfolio of prevention options is required. However, an effective HIV vaccine, which may be necessary for ending the HIV epidemic, remains elusive.[14–16]

A standard of prevention-controlled efficacy trial including a placebo arm has traditionally been required for regulatory approval of new HIV prevention modalities. Although there are settings and populations in which this design remains appropriate, there are other settings where alternative control groups are needed.

We overview three main study design options for future HIV prevention efficacy trials: 1) standard of prevention-controlled, 2) active-controlled, and 3) active-controlled augmented with external control data.

1. Standard of prevention-controlled trial design

In this study design, individuals without HIV are enrolled and have access to HIV prevention standard of care. To maintain blinding, participants are randomized to the experimental intervention or placebo on top of the standard of prevention, and HIV acquisition rates are compared between arms (Figure 1). Only individuals behaviorally vulnerable to HIV are recruited; those who are using or intend to use highly effective biomedical prevention may not be considered vulnerable to HIV. The Mosaico vaccine trial[17,18] (HPX3002/HVTN 706, ClinicalTrials.gov # NCT03964415) illustrates this design. Because it is unlikely that early generations of HIV vaccines will be as efficacious as PrEP, and because an active-controlled design would require witholding known effective prevention from the vaccine group, the Mosaico trial utilized a standard of prevention-controlled design. Potential participants were first counseled about and navigated to low/no-cost PrEP services. Those who declined PrEP were then screened for trial enrollment. Current use of oral PrEP or prior use of CAB-LA precluded enrollment in the trial. However, once enrolled, participants were counseled throughout follow-up about HIV prevention including PrEP and were linked to low/no-cost PrEP services or offered PrEP by the study site, if interested. Each site had a written PrEP plan delineating access for potential and enrolled participants which were reviewed and approved by local and centralized investigators and community. The standard of prevention-controlled design addressed the question critical to advancing an early-generation vaccine: Did the vaccine provide any efficacy? This is in contrast with the question addressed by an active-controlled design: Was the vaccine as effective as highly-effective ARV-based PrEP?

Mosaico successfully enrolled more than 3800 cisgender men who have sex with men and transgender (MSM/TG) persons across the Americas and Europe, randomized 1:1 to vaccine or placebo. After enrollment, fewer than 15% self-reported PrEP uptake. The study was closed early due to lack of efficacy in preventing HIV acquisition.[19]

There were several lessons learned from the Mosaico trial. Community engagement was critical for designing the trial, as it was community members who suggested that participants

be offered PrEP prior to enrollment. Ethicist input was also important: offering low/no-cost PrEP prior to screening ensured that participants' decision not to take PrEP was an "authenticity of expressions of undesirability."[20] Low PrEP uptake during follow-up despite having access suggests that PrEP was not of interest for this population.

However, as PrEP use becomes more widespread and options expand, more people may desire PrEP, and the strategy of enrolling people not desiring PrEP, who are willing to be randomized to an experimental intervention or placebo, may become more challenging. If this strategy is pursued in future trials, we must ensure that authentic choice determines enrollment. Otherwise, we run the risk of enrolling vulnerable populations who do not have adequate knowledge of or access to PrEP. Multiple studies showed the populations without adequate knowledge of or access to PrEP are more likely to include people of color in the U.S., and younger people and women globally.[21,22] Authentic choice may also become more challenging to achieve the more similar the participant experiences are across existing PrEP options and the experimental intervention under study. With these caveats, this trial design remains an important and ethical option, particularly when assessing the efficacy of novel non-ARV agents, where an active-controlled trial would create the ethical dilemma that persons receiving the active product (e.g., an experimental HIV vaccine of unknown efficacy) would not have access to ARV-based PrEP.

2. Active-controlled

In an active-controlled trial design, individuals without HIV are enrolled and randomized to the experimental intervention or an active control (Figure 1). Blinding is maintained with use of a placebo or 'dummy' for each arm, i.e., participants receive the experimental intervention plus a placebo version of the active control, or the active control plus a placebo version of the experimental intervention. The success of the experimental intervention is evaluated by comparing HIV incidence between the two arms. Pre-specified success criteria may entail establishing superiority or non-inferiority of the experimental intervention relative to the active control. Superiority of the intervention means that the HIV incidence under the experimental intervention is lower than that under the active control, non-inferiority means that the HIV incidence is 'not meaningfully higher' under the experimental intervention vs. active control.

HPTN 083[8] and HPTN 084[9] (ClinicalTrials.gov #NCT02720094 and NCT03164564, respectively) evaluating CAB-LA for HIV prevention serve as useful illustrations: HPTN 083 was a randomized double blind, double dummy, non-inferiority trial, while HPTN 084 was similar but with a superiority objective. HPTN 083 enrolled more than 4500 cisgender MSM and transgender women (TGW) and HPTN 084 enrolled more than 3200 cisgender women. In both trials, CAB-LA was compared to oral tenofovir disoproxil fumarate plus emtricitabine (TDF-FTC) (i.e., active control). The active-controlled design compared a highly effective ARV PrEP agent (TDF-FTC) with a new ARV PrEP agent (CAB-LA). The HPTN 083 protocol cites the UNAIDS/WHO on Ethical Considerations in Biomedical HIV Prevention Trials (Guidance Point 15): "The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality *of the type being studied* that has been shown to be effective in

comparable populations." TDF-FTC PrEP was proven effective in cisgender MSM and cis- and transgender women at the time these two trials were planned.

Investigators from both trials incorporated feedback from community groups and ethicists early in study design. HPTN 083 was designed as a non-inferiority trial because there was substantial evidence from multiple trials that TDF-FTC was highly effective in MSM/TGW. Non-inferiority trials require a reliable estimate of active control efficacy because efficacy of the experimental intervention is established through comparison with the active control. Supporting the assumed efficacy of TDF-FTC, it was important to select populations similar to those enrolled in previous placebo-controlled TDF-FTC trials that demonstrated efficacy.[5,23] HPTN 084 was designed as a superiority trial because trials of TDF-FTC in women had both positive[24] and negative[25,26] results.

The high efficacy of CAB-LA has implications for future active-controlled PrEP trials. For example, will the most appropriate comparator be CAB-LA, or will it be acceptable to use TDF-FTC? It will be difficult to demonstrate superiority over CAB-LA, as clinic administration minimizes the adherence challenges that appear to influence oral PrEP efficacy.[27–30] Its high cost has restricted CAB-LA adoption as standard of care,[31,32] thus providing it as part of a clinical trial raises questions around post-study access. Daily oral PrEP was the comparator in both PURPOSE-1[33] and PURPOSE-2[34] studies (ClinicalTrials.gov #NCT04994509 and NCT04925752, respectively) of semi-annual lenacapavir compared with oral PrEP, and the prematurely terminated Merck studies (MK- 8591–022[35] and MK-8591–024[36]) of oral monthly islatravir (ClinicalTrials.gov #NCT04644029 and NCT04652700, respectively). However, all of these studies were launched prior to U.S. Food & Drug Administration approval of CAB-LA for PrEP. Community, ethical, and regulatory engagement will be required in selecting the appropriate comparator for future PrEP trials. A key limitation of the active-controlled design is that it can only address *relative* efficacy of the experimental intervention.

3. Active-controlled augmented by external control

To overcome the key limitation of the active-controlled design, the trial may be augmented by external control data to evaluate absolute prevention efficacy.[37] Several types of external control data have been put forward, which we discuss in turn.

a) Historical placebo arm—Historical placebo arm HIV incidence from clinical trials conducted in the same geographic area as the active-controlled trial, may serve as external control. We illustrate this approach using data from the antibody mediated prevention (AMP) trials (HVTN 703/HPTN 081 and HVTN 704/HPTN 085;[38] ClinicalTrials.gov #NCT02568215 and NCT02716675, respectively). Specifically, we compare the placebo arm incidence in the AMP trial among women in sub-Saharan Africa [(SSA) HVTN 703/HPTN 081] with a 'counterfactual placebo' HIV incidence estimate based on blinded placebo arm data from historical HIV prevention trials conducted among women in SSA in the preceding 10 years (Figure 2).[14,39–42] We also compare the placebo arm incidence among MSM/TG persons in the U.S., Peru, Brazil, and Switzerland (HVTN 704/HPTN 805) with a counterfactual placebo HIV incidence estimate based on blinded placebo arm data

from historical HIV prevention trials conducted among MSM in the preceding 10 years (Figure 3).[5,15,23,43,44] This analysis illustrates how a historical external control would have performed, had it been used (see Supplemental Materials).

Placebo-group HIV incidence estimates for women in SSA have been relatively stable in recent years. The counterfactual placebo HIV incidence is 4.0% (95% CI: 3.7%, 4.3%) (Figure 2 and Table 1), higher than the observed placebo-group HIV incidence in HVTN 703/HPTN 081 of 3.1% (95% CI: 2.0%, 4.4%).

Historical HIV incidence estimates from studies enrolling MSM have been more variable (Figure 3). The counterfactual placebo HIV incidence is 3.1% (95% CI: 2.6%, 3.5%), similar to the observed placebo-group HIV incidence in HVTN 704/HPTN 085 of 2.9% (95% CI: 2.1%, 4.0%) (Table 1).

The limitations of historical placebo arm data as external control are numerous[45] including the possibility of lack of available historical data for some regions that may be included in a future trial. Another is the numerous demographic, behavioral, epidemiologic, and socio-cultural factors that influence HIV incidence, only a small fraction of which are measured in HIV prevention trials. Furthermore, there is considerable heterogeneity in whether and how HIV behavioral vulnerability is measured, making adjustment for these factors difficult. A third major limitation is potential bias due to calendar time trends in HIV incidence, associated with an improving standard of HIV prevention, increased penetration of HIV treatment, and other epidemiologic and societal factors that influence transmission.

b. Incidence of non-HIV sexually transmitted infections (STIs)—Another approach leverages the historical correlation between incidence of HIV and other STIs to estimate counterfactual placebo HIV incidence.[46–48] The historical studies must have been conducted in contexts without HIV or STI biomedical interventions that would change their correlation, e.g., without HIV PrEP or doxycycline postexposure prophylaxis (PEP) to prevent bacterial STIs. There are three other strong assumptions underlying the method:[48] 1. There is a common correlation between HIV incidence and STI incidence across the historical studies and the active-controlled trial; 2. The common correlation can be estimated with historical data; and 3. At least one intervention in the active-controlled trial does not influence acquisition of the STI. This approach is described using data from HVTN 704/HPTN 085 in Supplemental Materials.

The STI approach has major limitations. Few, if any, future studies are expected to measure HIV and STI incidence in the absence of PrEP and effective bacterial STI prevention;[49] the set of historical data with which to estimate the HIV vs. STI correlation may be fixed. Additionally, individual-level factors associated with the correlation between HIV and STI outcomes differ among historical studies and adjusting for these factors is necessary for accurate inference.

c. Additional approaches—Several other external control data sources are being developed. HIV recency assays have long been used to estimate HIV incidence in a population given a cross-sectional sample; they can identify individuals infected in the

recent past.[50–54] HIV prevention trials routinely test individuals at trial screening, and recency testing could be applied to estimate past HIV incidence in the screened population. For this to work, recruitment must target individuals not recently tested for HIV, yet willing to enroll in an HIV prevention trial; finding such populations may be difficult in areas with high HIV testing and PrEP uptake. Also, individuals screened for a trial may differ from individuals enrolled, and these differences will induce bias if they are associated with HIV. These challenges notwithstanding, two ongoing trials are utilizing the recency assay approach: the PURPOSE-1 and PURPOSE-2 trials compare HIV incidence in the lenacapavir arm with HIV incidence in the screened population estimated using HIV recency assays.[33,34]

Another approach is to leverage a biomarker that predicts the efficacy of the active control to infer efficacy of the experimental intervention relative to a counterfactual placebo. For trials utilizing oral PrEP as the active control, plasma ARV drug levels may be used as the biomarker given historical evidence oral PrEP efficacy is strongly associated with plasma drug level.[55,56] This approach has been used to estimate efficacy of oral emtricitabine and tenofovir alafenamide (TAF-FTC) based on the active-controlled DISCOVER trial (ClinicalTrials.gov #NCT02842086).[6,57] The approach requires multiple historical placebo-controlled trials of an intervention to establish that a biomarker predicts efficacy, with standardized specimen collection and biomarker assays. Identifying a biomarker that predicts efficacy of the active control is challenging for interventions such as vaccines that may have multiple mechanisms of action. An important simple and special case occurs, however, if active control efficacy is believed to be constant, based on similar efficacy estimates across diverse historical settings. In this case, the assumed active control efficacy may be used to infer efficacy of the experimental intervention, without use of a biomarker.

A final approach is to use a ‘baseline control,’ whereby HIV incidence in a run-in period, or registrational cohort, is the external control. Participants remaining without HIV at the end of the run-in period and satisfying other trial eligibility criteria are eligible for enrollment. This approach is being used to evaluate efficacy of TAF-FTC and FTC-TDF in the ongoing PrEPVacc trial[58] (ClinicalTrials.gov # NCT04066881). Its application requires that individuals behaviorally vulnerable to HIV be followed without effective prevention intervention prior to trial enrollment. Accounting for differences between individuals enrolling in the run-in period vs. the trial is important. The approach is also sensitive to bias due to secular trends in HIV incidence.

Study designs and analytical approaches combining multiple sources of external controls, for increasing precision and robustness, are compelling and require investigation.

Conclusion

Success in HIV prevention poses challenges in designing clinical trials evaluating new preventive interventions. While traditional randomized, standard of prevention-controlled trials with a placebo arm are appropriate and feasible to evaluate novel non-ARV HIV prevention methods, such as vaccines, careful conduct is critical to ensure that standard of care is a consequence of authentic individual choice. Active-controlled designs are

now the norm for evaluating new PrEP agents, with oral PrEP as the active control. With excellent efficacy of injectable PrEP, the appropriate active control is an open question and demonstrating superiority or non-inferiority to injectable PrEP is a challenge. Active-controlled designs augmented with external control data hold promise for evaluating absolute efficacy of the intervention, yet further methodological development and experience with these approaches is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- There are 3 main classes of designs of future HIV prevention efficacy trials: standard of prevention designs, active-controlled designs, and active-controlled designs augmented with external controls.
- The potential and ideal design depends on the class of experimental intervention, the target population, the criterion for success of the intervention.
- Considerations around study design are dynamic, and influenced by scientific evidence and availability, regulatory status, ethical considerations, community input, and acceptability and uptake of other preventive interventions.

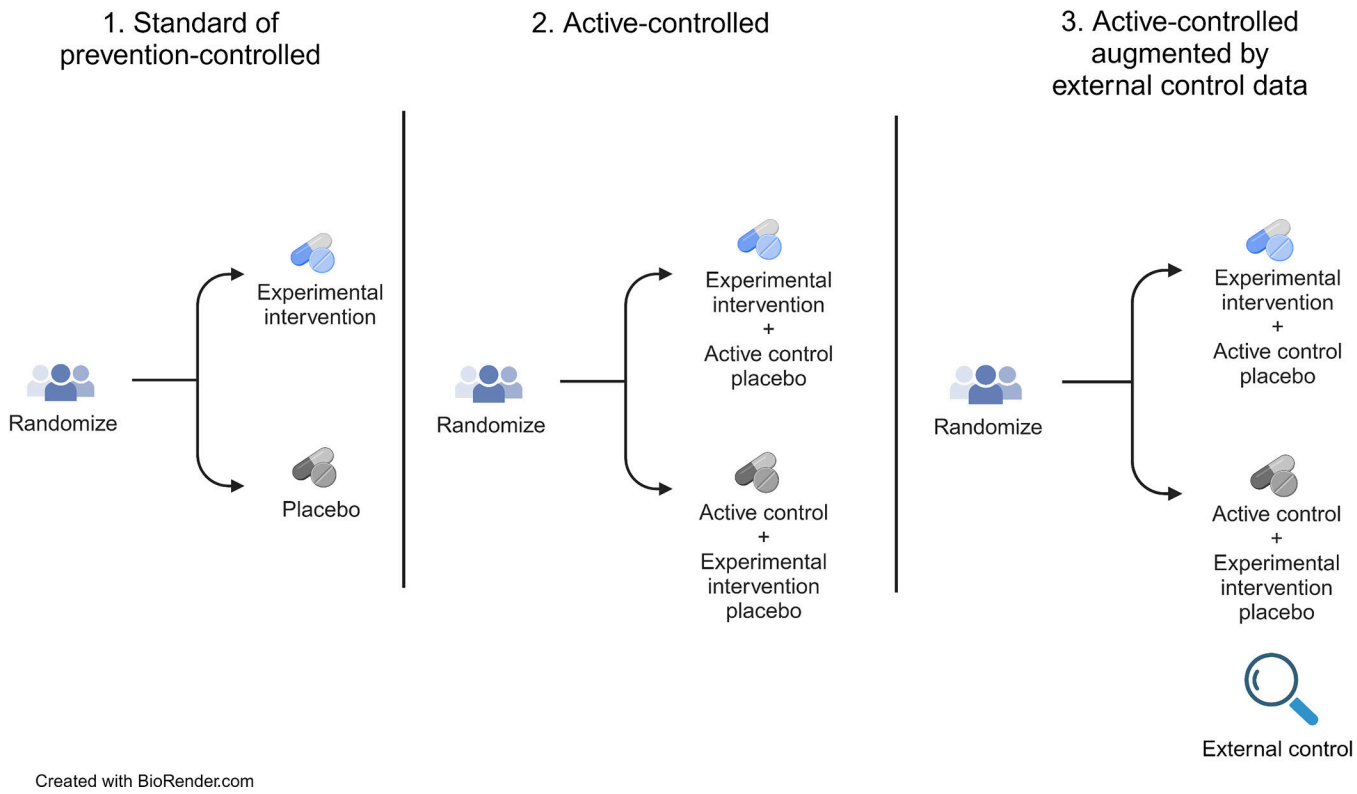

Figure 1.
Main study design options for future HIV prevention efficacy trials

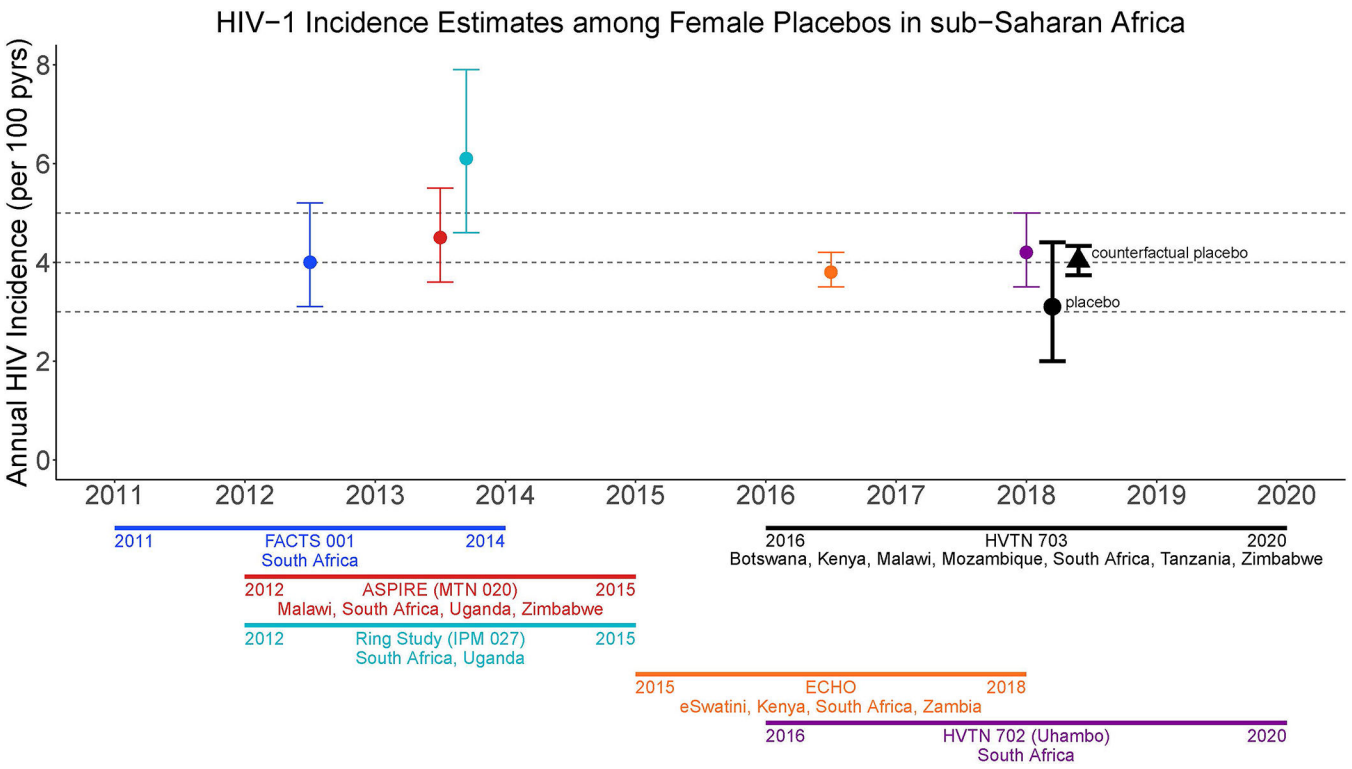

Figure 2.

Historical placebo-arm HIV incidence for HIV prevention efficacy trials in women in SSA, 2011 to 2020 spanning eSwatini, Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe, and a counterfactual placebo HIV incidence estimate based on the historical incidence data. The placebo-arm HIV incidence for HVTN 703/HPTN 081 (2016–2020; Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe) is shown for comparison.

FACTS 001 (ClinicalTrials.gov #NCT01386294)

ASPIRE (ClinicalTrials.gov #NCT01617096)

HVTN 703 (ClinicalTrials.gov #NCT02568215)

Ring Study (IPM 027) (ClinicalTrials.gov #NCT01539226

ECHO (ClinicalTrials.gov #NCT02550067)

HVTN 702 (ClinicalTrials.gov #NCT02968849)

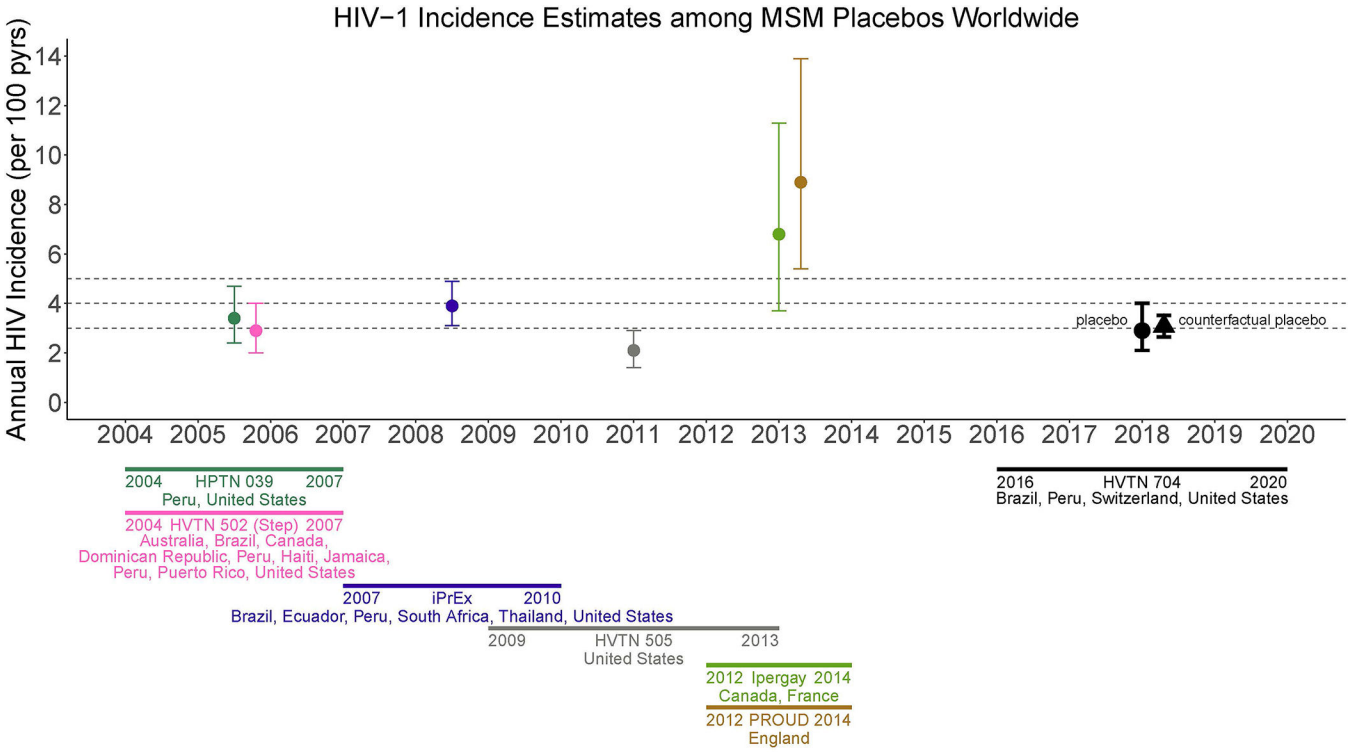

Figure 3.

Historical placebo-arm HIV incidence for HIV prevention efficacy trials in men who have sex with men (MSM), 2004 to 2014 spanning Australia, Brazil, Canada, Dominican Republic, Ecuador, England, France, Haiti, Jamaica, Peru, Puerto Rico, South Africa, Thailand, United States, and a counterfactual placebo HIV incidence estimate based on the historical incidence data. The placebo-arm HIV incidence for HVTN 704/HPTN 085 (2016–2020; United States, Peru, Switzerland, Brazil) is shown for comparison.

HPTN 039 (ClinicalTrials.gov #NCT00076232)

HVTN 502 (ClinicalTrials.gov #NCT00865566)

HVTN 704 (ClinicalTrials.gov #NCT02716675)iPrEx (ClinicalTrials.gov #NCT00458393)

Ipergay (ClinicalTrials.gov #NCT01473472)

PROUD (ClinicalTrials.gov #NCT02065986)

Table 1.

Comparison of observed and counterfactual placebo-group HIV incidence rates in the AMP studies, HVTN 703/HPTN 081 and HVTN 704/HPTN 085.

Trial	Subset	Observed placebo HIV incidence (95% CI)	Placebo HIV incidence accounting for PrEP (95% CI)	Historical data-based counterfactual placebo HIV incidence (95% CI)	RGC-based counterfactual placebo HIV incidence (95% CI)
HVTN 703/ HPTN 081	Overall	3.1% (2.0%, 4.4%)	3.1% (2.0%, 4.2%)	4.0% (3.7%, 4.3%)	--
	South Africa	3.2% (1.8%, 5.1%)	3.3% (1.8%, 5.1%)	4.6% (4.2%, 4.9%)	--
HVTN 704/ HPTN 085	Overall	2.9% (2.1%, 4.0%)	3.9% (2.6%, 5.5%)	3.1% (2.6%, 3.5%)	4.5% (3.5%, 5.8%)
	United Stated	1.2% (0.5%, 2.3%)	2.2% (0.7%, 4.2%)	2.3% (1.7%, 2.9%)	4.4% (3.5%, 5.7%)
	Peru	5.2% (3.4%, 7.6%)	5.4% (3.4%, 7.7%)	3.0% (2.3%, 3.7%)	4.6% (3.5%, 6.0%)

PrEP=pre-exposure prophylaxis

RGC=rectal gonorrhea

AMP= antibody mediated prevention

HVTN 703/HPTN 081 (ClinicalTrials.gov #NCT02568215)

HVTN 704/HPTN 085 (ClinicalTrials.gov #NCT02716675)