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Taking stock of the present and looking to the future: Envisioning challenges in the design of future HIV prevention efficacy trials

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Summary

Notwithstanding the recent success of antiretrovirals for HIV prevention, additional more effective or more acceptable biomedical interventions will ultimately be needed to end the HIV epidemic. Designing clinical trials to evaluate the efficacy of new products to reduce HIV infection risk is challenging due to the emergence of highly effective interventions to prevent HIV. However, implementation of these interventions is currently uneven, and the fact that multiple HIV prevention efficacy trials are underway evaluating new products means the field confronts uncertainty in the emerging standard of prevention. In this paper, we take stock of the current state of the HIV prevention field. We discuss the key challenges involved in designing future trials to evaluate the next generation of HIV prevention products. We highlight gaps in knowledge that

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HJ, DD, PG, EB, and MN conceived the study and participated in the writing of the paper.

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need to be filled in order to further the design research. We conclude that future trials are tenable, even in the context of existing and effective interventions, with careful statistical approaches and multi-disciplinary collaborative design discussions.

Keywords

HIV prevention; clinical trial design; HIV vaccine; pre-exposure prophylaxis; vaginal ring

Introduction

The HIV prevention landscape is evolving rapidly. Trials and subsequent observational studies have demonstrated the effectiveness of antiretroviral-based products for HIV prevention, including tenofovir-based oral pre-exposure prophylaxis, or PrEP (emtricitabine/tenofovir disoproxil fumarate, TDF-FTC). The results of several ongoing HIV prevention efficacy trials – including trials of oral and injectable antiretrovirals, passively infused monoclonal antibodies, and HIV vaccines – could have major implications for the design and conduct of the next generation of trials. Collaborative discussions involving experts in ethics, community, regulatory, clinical, laboratory and statistical science will be necessary for devising a clear path towards developing future prevention tools. This viewpoint presents an overview of the key statistical design questions and gaps in knowledge that will be faced as these discussions take place.

Current portfolio of effective biomedical HIV prevention tools

Many biomedical HIV prevention tools have been found to be effective in preventing HIV acquisition in adults, with evidence based primarily on randomized, placebo-controlled phase 2b or phase 3 efficacy trials. Table 1 summarizes the products, the evidence for their efficacy, and their implementation status in the Americas and southern Africa, where ongoing trials are primarily occurring. See also ^{1–3} for more comprehensive summaries. As is evident, the level of efficacy varies among the interventions. In many cases, implementation has been hindered by uptake and adherence challenges, as well as structural, economic, and other behavioral factors.

Overview of ongoing HIV prevention efficacy trials

Against the evolving backdrop of HIV prevention, several efficacy trials of new biomedical HIV prevention products are underway, all enrolling at-risk HIV-uninfected adults (Table 2). The trials all have broad eligibility criteria; participants are required to be sexually active and at risk of HIV acquisition, and local sites are given the freedom to determine how to recruit participants. Importantly, eligibility criteria for trials not evaluating PrEP agents do not place constraints on participants' usage of existing biomedical HIV prevention tools, such as oral PrEP. As for the trials evaluating PrEP, the two HPTN trials evaluating the relative efficacy of oral versus injectable PrEP require willingness to be randomized to oral or injectable PrEP and do not allow concomitant usage of oral PrEP, and the DISCOVER trial comparing two oral PrEP regimens requires that participants are willing to use oral PrEP. The HIV prevention packages provided to trial participants in all arms, as described in the study protocols, are highly similar across studies, and include risk-reduction counseling,

free condoms and lubricant, advocacy and referral for male circumcision, STI testing and treatment, and counseling and referral for PEP. Furthermore, for non-PrEP trials, education about oral PrEP is provided, and interested participants are either referred for oral PrEP or provided it by trial sites. A philanthropic fund has been set up to cover the cost of oral PrEP for trial participants during trial participation in settings in sub-Saharan Africa where it is not currently available in the public healthcare sector. The Gilead Global Access program provides access to oral PrEP for participants in the Americas not otherwise covered for oral PrEP.⁴

Two key differences emerge among the ongoing trials. First, while trials of candidate vaccines and the intravenously-infused broadly neutralizing antibody (bnAb) VRC01 are using placebo-controlled designs, the trials of oral or injectable PrEP regimens use oral TDF-FTC as the active control. Second, two PrEP trials in MSM- the DISCOVER trial and HPTN 083- are designed to evaluate whether the new PrEP agents are *non-inferior*, to oral TDF-FTC, i.e. do not have meaningfully lower efficacy, whereas all other designs are intended to evaluate *superiority* of the new product, i.e. whether the product yields lower incidence of HIV compared to either placebo or oral TDF-FTC. The choices of control arm and efficacy objective are critical decisions and will be discussed below.

Study design questions faced in planning future efficacy trials of new or modified HIV prevention products

How should an efficacy trial of a new HIV prevention product be designed?

The approach to future trial design will depend on the results of the trials currently underway (see appendix pp. 6–9), as well as considerations around the availability of proven interventions. Major design questions are listed in Panel 1. Here, we refine the questions for specific scenarios, provide guidance on how the questions might be tackled, and highlight gaps in knowledge that need addressing to facilitate answering the questions.

A fundamental design question is the population to be enrolled in the trial. Efficacy trials are typically conducted in high risk populations, for both ethical and scientific reasons. But a new question will increasingly be at the forefront of trial design: Are participants successfully using an effective HIV prevention product, such as oral PrEP, eligible for participation? While formally restricting eligibility based on successful use of effective products has not yet been done in the HIV prevention field, our view is that recruiting participants with a demonstrated unmet need for prevention could be justified. Challenging ethical issues have been raised around this approach,^{10,11} and the concept requires intensive stakeholder engagement to navigate the complex ethical, regulatory, community engagement, informed consent, and trial implementation issues (see Box 2). Importantly, ethical considerations would dictate that individuals not successfully using effective products would be identified only after comprehensive education around existing products and access to these products had both been provided. As well, access to existing prevention would remain available to all participants throughout the trial. A design could accommodate post-enrollment uptake of established prevention products in the same way that current

vaccine and monoclonal Ab trials accommodate use of PrEP in the “background”—with assumptions about underlying HIV incidence that anticipate some level of on-trial use.

The standard of prevention that is provided to all trial participants has a major impact on trial design assumptions. Determining the standard is a challenging task that involves multiple stakeholders, and considering relevant national and international guidelines and product availability. For future trials, this choice may be especially challenging when an existing product has been shown to be highly effective, with durable protection, high uptake and high adherence in the population. Adding this product to the HIV prevention package may reduce HIV incidence to a level so low, even in a population considered to be at high risk, that resources would not support a trial of sufficient size. How should a vaccine- which arguably would be the most effective tool for ending the HIV pandemic- be evaluated in this context? On the other hand, if an existing product is effective but not well-accepted or not feasible in the population of interest, is it reasonable that a better-accepted or more feasible intervention be evaluated without adding this product to the prevention package? Guidelines around the standard of prevention in HIV prevention trials have been put forth by UNAIDS¹² and the HPTN Ethics Working Group.¹³ While many ethicists have reflected on these guidelines and highlighted differences between them, no clear consensus has been reached, reflecting underlying tensions between obligations to study participants and the necessity to conduct research to discover more effective and user-friendly HIV prevention tools.^{10,11,14–18} Some have called for the development of processes around determining the standard of prevention,^{14,16} recognizing the difficulties of achieving sufficient stakeholder education and input into this decision for individual trials in development.^{10,16,19} One point of consensus that has emerged is that ongoing and future trials are ethically compelled to include the provision of oral PrEP in the standard prevention package, unless justified by trial investigators on ethical and scientific grounds.^{10,18,20,21} The process by which oral PrEP was added to standard prevention packages of ongoing trials, which involved stakeholder engagement and the procurement of resources to ensure access to oral PrEP, is a useful case study of how ongoing trials have adapted to the changing standard of care.²¹ Future considerations around the composition of the standard of prevention package must acknowledge the potential for the standard to change over the course of a trial, e.g. due to the results of efficacy trials of other products. As well, the standard may vary across geographic regions and at-risk populations, which raises the possibility that the standard provided to participants may differ across sites enrolling to the same trial. Determining the standard of prevention is especially complicated after a product is proven effective and licensed but commercial manufacturing is not yet fully scaled, as the current evidence base and clinical practice must be considered and the near-future situation must be anticipated.

The choice of control arm is another longstanding design issue, with controversy in the HIV prevention field dating back more than 20 years to the design of mother-to-child transmission studies. Specifically, some argued at the time that the use of placebo control was unethical given the established efficacy of oral and intravenous azidothymidine (AZT) to the mother during labor and delivery; placebo was selected as comparator given that the oral and intravenous AZT regimen was not feasible to implement in the local population.^{22,23} Much has been written since about the choice of appropriate comparator, e.g.^{24,25} and general medical ethical guidance documents^{26,27} as well as HIV-specific guidance from

UNAIDS¹² address the issue, although there continues to be lack of consensus within the HIV prevention field around criteria for the choice of placebo vs. active control.^{10,11,13–15} Some ethical guidance hinges on an imprecise concept of “similarity” of the experimental intervention relative to a proven intervention^{10,18} If a new intervention is “similar” or in the same prevention “class” as a proven intervention, it is generally agreed that ethics would mandate comparing the new intervention to the existing intervention, i.e. to use an active control. If a new intervention is in a different class, but is highly likely to be effective based on preliminary research, some have argued it may still be compelling to use the existing intervention as the control, e.g. to examine if the new intervention has advantages in terms of safety or adherence while reducing HIV incidence to a similar or lower level. However, there is considerable disagreement around the optimal approach for a new intervention in an as-yet-unproven class. Here, in our view, the most compelling objective is likely to continue to be establishing efficacy relative to a placebo, as use of a placebo optimizes interpretation of trial results. Moreover, in this situation it is difficult to imagine that there would be equipoise in randomizing participants to an active control, and if the interventions are sufficiently different for the participant it may be difficult to recruit individuals willing to be randomized to one of the two. We emphasize that use of a placebo does not imply that existing prevention modalities are not provided to participants; rather the placebo would be given *in addition* to the standard of prevention package that is provided to all participants. This is the approach currently employed in ongoing vaccine and monoclonal antibody efficacy trials. We suggest that to make further progress on establishing general guidance as to the choice of control arm for HIV prevention trials, the field needs consensus around what attributes of an intervention are relevant when determining similarity or class membership (see Box 2). For example, is it the mechanism of action that is relevant, or in addition is the mode and frequency of administration, the side effects and tolerability, and the cost and infrastructure needed to deliver the intervention pertinent?

If an active control is used, another question is whether the trial is blinded (requiring double dummy products) or the trial is open-label. Effective blinding minimizes the possibility that participants have different behavior – and exposure to HIV – across arms, and thus allows the biological efficacy of the new product to be estimated as closely as is possible in a clinical study. In contrast, in an open-label study, both the biological effect, as well as behavioral effects of intervention such as non-adherence or risk compensation are incorporated, and thus product *effectiveness* is estimated.²⁸ In our view, blinding is generally preferred for trials of products that have not yet been efficacy-tested, with effectiveness research a natural next step. Alternatively, a useful design would include both blinded and unblinded control arms, to be able to evaluate both efficacy and effectiveness in the same population.

Multiple experimental intervention arms may be warranted. For example, if there are different variations on an intervention (e.g. multiple dosing strategies, modes of delivery, or adherence packages for optimizing use), including parallel intervention arms – i.e. where participants are randomized to Intervention 1 or 2 or a shared placebo – would allow efficacy to be assessed head-to-head. On the other hand, if two candidate interventions are known to have different mechanisms of action, a resource-efficient design to consider is a *factorial design*, in which participants are randomized to double Placebo, Intervention 1 (plus Placebo

2), Intervention 2 (plus Placebo 1) or the combination of Interventions 1 and 2. A factorial design will generally require a smaller sample size than a 4-arm parallel design (with arms Intervention 1, Intervention 2, Placebo 1, and Placebo 2), or separate trials of the two interventions (Intervention 1 vs. Placebo 1 in one trial, and Intervention 2 vs. Placebo 2 in a second trial). It also has the merit that potential synergies (or antagonism) between interventions can receive preliminary evaluation.²⁹ A potential barrier to factorial trial design is the necessity for collaboration among product developers and other stakeholders, across classes of products; this is a challenge that deserves attention by the field (Box 2).

All historical and ongoing HIV prevention trials have used HIV acquisition as the primary endpoint. There is currently no validated *surrogate endpoint*, or replacement endpoint, confirmed to satisfy the Prentice definition³⁰ in any population. The USA FDA and other regulatory authorities do have accelerated approval mechanisms, whereby an intervention is approved based on a phase 2 study using a surrogate endpoint that is deemed “reasonably likely” to predict the effect of the intervention on the clinical endpoint in the target population.³¹ Accelerated approval still requires that adequate and well-controlled studies designed to verify clinical benefit, e.g. a randomized observational phase 4 trial, are underway at the time of approval, or conducted post-licensure, to confirm the anticipated level of efficacy.³² For any of the ongoing HIV prevention efficacy trials, if the experimental product is found to be efficacious, a key secondary objective will be to evaluate biomarkers as potential surrogate endpoints for HIV acquisition. In particular, immune response biomarkers will be evaluated in vaccine and monoclonal antibody trials, and measures of adherence will be evaluated in PrEP trials. See³³ and³⁴ for technical discussions of the evidence that may be used to evaluate potential surrogates. The results of these analyses will be critical for determining whether an accelerated approval process could be used for a future product. We presume in what follows that HIV acquisition will continue to be the primary endpoint for future trials, given the current lack of a validated or “reasonably likely” surrogate.

Trial design requires specifying a primary efficacy objective. Under a classical frequentist framework, this means selecting a null hypothesis that is to be tested using the trial data. The null hypothesis codifies the bar that is set regarding the efficacy of the new intervention relative to control. A key question is whether the trial is designed to test the null hypothesis that the intervention and control arms have the same HIV incidence, i.e. the null is 0% efficacy relative to control. A 0% null has been used in historical and ongoing placebo-controlled “test of concept” trials³⁵ and is also being used in the HPTN 084 trial evaluating whether injectable PrEP is superior to oral PrEP (the active control) in African women (Table 2). However, as more effective products are developed, a higher bar for efficacy may be needed to warrant further development of a new intervention. On the other hand, the safety, acceptability, and practicality of an intervention may influence the choice of null hypothesis; mathematical modeling of intervention impact^{36–38} suggests it may be reasonable to set a lower bar for interventions that require fewer resources for delivery, or that are more likely to be taken up and adhered to. A lower bar may also be set to anticipate imperfect adherence to the intervention in the trial population; experience with oral PrEP has suggested that adherence can be higher outside the context of placebo-controlled efficacy trials.^{39–41}

For a trial where the goal is to compare a new intervention to an existing intervention (an active control trial), the efficacy objective may be to demonstrate non-inferiority or superiority. Assessing noninferiority – that the new intervention is not meaningfully worse than the active control – is reasonable if the new intervention is believed to have somewhat similar efficacy but to have other advantages, e.g. in safety or acceptability. However, to demonstrate non-inferiority, a reliable estimate of the efficacy of the existing intervention in the population of interest is required, based on historical placebo-controlled trials. This has been a barrier to using a non-inferiority objective in some HIV prevention contexts, e.g. in the HPTN 084 trial of injectable vs. oral PrEP in African women. Because oral PrEP has not been found to be reliably effective in this population- historical estimates of efficacy are highly variable⁴² - the HPTN 084 trial is designed to demonstrate that injectable PrEP is more effective than oral PrEP, i.e. it uses a superiority objective. A related difficulty with the non-inferiority objective for HIV prevention is the uncertainty in efficacy for user-dependent interventions such as oral PrEP, where efficacy varies dramatically with level of adherence. Traditional statistical methods for defining the non-inferiority objective accommodate some uncertainty in the level of active control efficacy,⁴³ but given the exceedingly wide range of efficacy estimates for current user-dependent products, the development of more flexible statistical methods for non-inferiority design is warranted (see Box 2).

Another choice regarding efficacy objective is the primary analysis population. Most historical and ongoing HIV prevention efficacy trials have focused on the modified intention to treat (MITT) population, defined as participants enrolling HIV negative and retrospectively verified to have been HIV-uninfected at enrollment, to optimize interpretability and maintain integrity of the randomization. However, secondary analyses in *per-protocol subgroups*, e.g. participants receiving all vaccinations or using product as-directed, have been conducted. In the case of oral PrEP, adherence has been measured biologically in a subset of trial participants, and analyses of drug efficacy “when taken” have been conducted and have influenced the field.^{44,45} This raises a key question for future products that are also adherence-dependent, and for which reliable adherence measures are available: Are there settings where the primary analysis of efficacy should be causal inference-based analyses of efficacy in adherers? More generally, what role do adherence analyses, and immunological and virological correlates analyses in trials of vaccines and monoclonal antibodies, play in the choice of the next efficacy trial designs? In our view, per-protocol analyses should continue to be relegated to secondary analysis, given the untestable assumptions that are required to ensure their validity,⁴⁶ but trials should be designed to permit the estimation. In particular, specimens need to be collected to ascertain the intermediate outcomes- adherence or immune response. As well, any factors that potentially associate with the intermediate outcome and with HIV infection, i.e. potential confounders, need to be measured.

Trial designers must also determine over what time frame efficacy should be evaluated. If efficacy varies over time, e.g. due to time-varying adherence or waning immunity, the level of efficacy will depend fundamentally on the time frame. For this reason, vaccine efficacy is typically evaluated over a fixed time period. PrEP efficacy has typically been measured with variable-length follow-up. Comparing the efficacy of different products is best done over a common time frame.

Novel measures of the efficacy of new interventions deserve investigation (see Box 2). The traditional measure of efficacy is 1 minus the relative risk of HIV acquisition in intervention vs. control arms. However, in some future trials, HIV incidence may be exceptionally low, and this poses statistical challenges for estimating relative risks. The problem is that the precision with which a relative risk is estimated depends primarily on the number of HIV infection endpoints. Measuring efficacy instead on an absolute risk scale could be advantageous, since precision would be influenced by the number of person-years at risk, and therefore smaller sample sizes may be needed to ensure adequate power and precision.^{47,48} This and other attributes of the statistical performance of alternative efficacy measures deserve further exploration by statisticians (see Box 2).

How should a modified version of a product be evaluated?

If an experimental product is found to confer statistically significant efficacy vs. placebo, but insufficient efficacy to clearly motivate pursuing licensure or implementation, a modified version of the product may be developed and would require evaluation. For example, a new vaginal ring might be formulated with a different anti-HIV drug. A vaccine might be formulated with a different adjuvant to increase the durability of the immune response, or using a different strain of HIV. Other product modifications may be designed to optimize adherence, extend the duration of protection afforded by the product, or combine contraception and HIV prevention.

Generally, an efficacy trial of the new product with HIV infection endpoints would be required, although the aforementioned guidelines on trials utilizing surrogate endpoints would arguably apply. Moreover, the considerations above regarding the population enrolled, standard HIV prevention package, control and intervention arms, and efficacy objective would apply. Of particular importance in this context is whether the appropriate control arm is the existing product or a placebo.

Summary and Conclusions

The portfolio of effective biomedical tools for preventing HIV acquisition in adults is increasing rapidly, and now includes male and female condoms; medical male circumcision; testing and treatment of STIs; provision of ARVs to infected persons (as TasP), to high-risk uninfected persons (as PrEP), and following inadvertent exposure (as PEP); and potentially the vaginal ring in the near future. Yet, major challenges are being faced in implementation and optimization of use. Seven ongoing HIV prevention efficacy trials are evaluating additional products- two vaccines, a bnAb regimen, an oral PrEP agent, and an injectable PrEP agent- with efficacy results expected between 2020 and 2022.

The changing landscape of HIV prevention, and the results of the ongoing trials, including the secondary analyses correlating HIV incidence with adherence and immunological and virological markers, will have a major impact on the design of future trials of novel or modified products. Anticipating the study design questions that the field will face in coming years is challenging, and creative design approaches are needed for the next generation of HIV prevention trials. With rigorous statistical approaches and intensive communication

efforts across science, advocate, trial participant, industry partner and sponsor communities, we conclude that future trials of new HIV prevention products are feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1:**Major Design Considerations for Future HIV Prevention Efficacy Trials**

- **Trial population:** Should the trial be conducted in the highest-risk populations even when the product may reduce HIV in other populations?
- **Standard of prevention:** What HIV prevention package is provided to all trial participants? Is it the set of currently-available HIV prevention tools, including oral PrEP, or does it include additional products, e.g. those currently in efficacy trials?
- **Control arm:** Is a placebo (over and above the standard of prevention) the comparator, or is an existing product the comparator, i.e. an “active control” is used? Is the trial blinded or open-label?
- **Intervention arm(s):** Is there more than 1 intervention arm? Are the interventions studied individually or in combination?
- **Primary endpoint:** HIV acquisition, or a surrogate endpoint?
- **Efficacy objective:** Is the traditional relative risk efficacy measure used- or an alternative measure? What is the efficacy under the null hypothesis? If an active control is used, is the objective to demonstrate that the new product is superior, or merely non-inferior, to the active control?

Box 2:**Key Knowledge Gaps and Opportunities for Research Aimed at Optimizing Future Trial Designs**

What characteristics of an HIV prevention intervention are relevant when defining intervention classes?

What are viable statistical methods and necessary data to collect to infer counterfactual placebo incidence, for trials without placebo arms?

How to navigate ethical, community, regulatory considerations around conducting trials in those not successfully using existing products to prevent HIV?

How to enhance collaboration among HIV prevention stakeholders to permit future trials comparing preventive interventions in different classes, e.g. factorial designs, to maximize resource-efficiency?

Improved statistical methods are needed to set appropriate non-inferiority margins for settings where efficacy of the existing intervention is variable and difficult to predict in advance of a noninferiority trial.

Do alternative measures of prevention efficacy, e.g. based on absolute risk of HIV, have merit in terms of statistical performance, interpretability, and generalizability?

Table 1.

Biomedical HIV prevention tools found to be effective* at preventing HIV acquisition in adults.

Intervention	Evidence of efficacy based on phase 2b or phase 3 efficacy trial(s), except where noted	Implementation status
Approved interventions, currently in use		
Male condoms	70–95%, depending on use consistency	Actively promoted in most countries, but protection often compromised by inconsistent or incorrect use
Female condoms	Safety, acceptability, functional performance assessed, but no efficacy trials estimating efficacy against HIV	Limited uptake due to e.g. cost, mechanical difficulties, male partner reluctance, lack of availability
Medical male circumcision	3 efficacy trials showing 48–61% efficacy over 18–24 months; fourth trial was stopped early for low power	Recommended as public health measure by US CDC; WHO and UNAIDS recommended urgent roll-out. Rates are not on-target to meet UNAIDS goals for VMMC between 2016 and 2020
Treatment as prevention (TasP)	96% efficacy over median 20 month followup in serodiscordant partners confirmed by subsequent observational studies. Several trials of Universal Test and Treat combination prevention have recently concluded, with mixed results regarding HIV incidence. The Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) (HPTN 071) trial has completed follow-up, but results have not been made public.	WHO recommended “test and treat” strategy; UNAIDS has set “90–90–90” target for 2020, of which one component is having 90% of HIV-infected people globally in treatment with fully suppressed viral load. Considerable economic, infrastructure- related, social, behavioral, and ethical challenges to implementing these recommendations. According to UNAIDS, at the end of 2016, 70% of people with HIV were aware of their status, 53% of whom had access to ARV treatment globally.
Tenofovir-based oral ARVs as preexposure prophylaxis (PrEP)	44–79%, over 0.7 to 1.6 years follow-up in MSM, injection drug users, and serodiscordant couples; efficacy increases with the level of adherence. Variable efficacy among individual at-risk women; no efficacy in two trials, due to inadequate adherence and potentially other behavioral, biological, and virological factors	WHO recommends tenofovir-based oral PrEP be considered for any population at “substantial risk” of HIV (3 or more infections/100 person-years). Licensed in the US and South Africa, and included in the HIV prevention guidelines of 26 countries, with 10 having national access programmes, but significant variability within countries regarding PrEP access and uptake. In many parts of the world, including southern Africa, oral PrEP is only available to participants in clinical trials and implementation or demonstration projects.
Post-exposure prophylaxis (PEP)	Observational studies suggest PEP is effective (Ethical considerations preclude an RCT)	Recommended in international guidelines for over 15 years; recent guidelines cover both occupational and non-occupational exposure. Limited uptake, including in the context of occupational exposure, partly due to insufficient awareness.
Testing and treatment of other STIs	8 of 9 efficacy trials of STI treatment for prevention of HIV showed no effect (mean follow-up range: 1.2 to 3.8 years). Nevertheless, observational studies consistently show strong associations between sexually-transmitted infections (STIs) and HIV infection risk	Given the clinical benefits of STI treatment, and the multiple possible interpretations of the negative trial results, STI testing and treatment are still recommended in HIV control programs where there is a high STI burden
Interventions efficacy tested, with regulatory approval pending		
Dapivirine vaginal ring	27% and 31% efficacy over 1.6 and 2 yrs follow-up, respectively, based on 2 large efficacy trials among women in southern and eastern Africa. Higher adherence is associated with lower HIV risk.	Undergoing review by the EMA. Two open-label extension trials to further examine safety and acceptability and trials evaluating safety and adherence in adolescents and pregnant and lactating women are underway.
Interventions found to be effective, but not being pursued for approval or implementation		
Topical 1% vaginal tenofovir gel	39% efficacy over mean 18-month follow-up in South African women but no risk reduction in two other efficacy trials in African women. Women found it challenging to use the gel consistently.	No subsequent work currently planned

Intervention	Evidence of efficacy based on phase 2b or phase 3 efficacy trial(s), except where noted	Implementation status
ALVAC-HIV + AIDSVAX subtype B/E gp120/alum vaccine regimen	Estimated 44% efficacy at 18 months, and 30% efficacy at three years post-last vaccination in a community-based trial in Thailand. Immune correlates and sieve analyses provided evidence of potential mechanisms for protection.	Vaccine regimen has been modified for the subtype C epidemic in southern Africa, and to generate more durable immune responses, and is being evaluated in an ongoing efficacy trial (HVTN 702).

*
For references, please see the suggested reading list (appendix pp. 2–5).

Table 2.

Ongoing HIV prevention efficacy trials: Key design features. HR = hazard ratio.

Trial	Concept	Population	Efficacy Hypothesis [±]	Final Analysis Time
HVTN 702 (Phase 2b/3) ALVAC + subtype C gp120/MF59 vaccine vs. placebo (Injections Months 0, 1, 3, 6, 12, and 18) ⁵	Similar to RV144 vaccine; modified for subtype C epidemic, MF59 adjuvant, Month 12, 18 boosts added	5,400 men and women in South Africa	50% vaccine efficacy over 2 yrs., rejecting the null of 25% efficacy	2021
HVTN 705 (Phase 2b) Ad26.Mos4.HIV + subtype C gp140/alum vaccine vs. placebo (Injections Months 0, 3, 6, 12) ⁵	Mosaic prime designed to have global coverage of HIV strains	2,600 southern African women	50% vaccine efficacy over 2 yrs., rejecting the null of 0% efficacy	2020
HVTN 703/HPTN 081 and HVTN 704/HPTN 085 (AMP Studies; Phase 2b) IV infusion of VRC01 bnAb (10 mg/kg VRC01 or 30 mg/kg) 8-weekly for 10 infusions, vs. placebo ⁶	Proof of concept that broadly neutralizing antibodies protect from HIV	2,700 MSM and TGW in the Americas and Europe, 1,900 women in southern Africa	60% efficacy (dose-pooled) over 80 weeks, rejecting the null of 0% efficacy	2020
DISCOVER (Phase 3) Oral T/DAF vs oral TDF-FTC ⁷	T/DAF formulation may have improved safety compared to oral TDF-FTC	5,400 MSM and TGW in the USA, Canada, and Western Europe	T/DAF is non-inferior to TDF-FTC *	2020
HPTN 083 (Phase 2b/3) Injectable PrEP (cabotegravir) vs. oral PrEP (TDF-FTC) ⁸	Injectable PrEP may have adherence advantages relative to oral PrEP; level of oral PrEP efficacy well-established for MSM	4,500 HIV-uninfected MSM in the Americas, Asia, and South Africa	Injectable PrEP is non-inferior to oral PrEP (HR = 0.75 over approx. 2.4 yrs.), rejecting null of HR = 1.23	2022
HPTN 084 (Phase 3) Injectable PrEP (cabotegravir) vs. oral PrEP (TDF-FTC) ⁹	Injectable PrEP may have adherence advantages relative to oral PrEP; level of oral PrEP efficacy not well-established for women	3,200 HIV-uninfected women in sub-Saharan Africa	Injectable PrEP is superior to oral PrEP (HR = 0.54 over approx. 2.6 yrs.), rejecting null of HR = 1.0	2022

[±]In statistical terms, the alternative hypothesis used to design the trial

* Further details of the DISCOVER trial are not known