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A partner protection package for HIV cure-related trials involving analytical treatment interruptions

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KD and AR conceptualised the Review, curated the data, and wrote the original draft. KD and AR drafted this Review and reviewed the sources, triangulating between insights from the partner protection workshop and results from the focused literature reviews, as well as their general backgrounds in public health and research ethics. The draft was circulated to all authors for review. TM, LF, LD, DP, TJV, WF, JT, GG, WBC, JAS, and MJP reviewed and edited the paper. The paper was finalised using an iterative process, until all comments had been addressed. All authors were actively involved in the partner protection workshop, as presenters or workshop organisers, with over half of co-authors representing perspectives from the community.

Declaration of interests

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Abstract

Analytical treatment interruptions (ATIs) have become a key methodological approach to evaluate the effects of experimental HIV cure-related research interventions. During ATIs, sex partners of trial participants might be at risk of acquiring HIV. This risk raises both ethical and feasibility concerns about ATI trials. We propose a partner protection package (P3) approach to address these concerns. A P3 approach would provide guidance to investigators, sponsors, and those who are designing and implementing context-specific partner protections in HIV cure-related trials involving ATIs. The approach would also help assure institutional review boards, trial participants, and communities that ATI trials with a P3 would provide appropriate partner protections. We offer a prototype P3 framework that delineates three basic considerations for protecting participants' sex partners during ATI trials: (1) ensuring the scientific and social value of the ATI and the trial, (2) reducing the likelihood of unintended HIV transmission, and (3) ensuring prompt management of any acquired HIV infection. We outline possible ways of implementing these basic considerations.

Introduction

Research on an HIV cure—which would eliminate or control HIV without the need for antiretroviral therapy (ART) for a sustained period—is a priority for people living with HIV,[1] HIV researchers, and research sponsors.[2] Five confirmed cases of individuals being cured of HIV during cancer treatment[3–5] and growing investments in scientific research are fuelling interest in finding cure strategies that would be applicable worldwide.[2,6]

A key methodological tool for testing HIV cure-related interventions is the analytical treatment interruption (ATI), which is a controlled and closely monitored pause of ART to evaluate the effects of potentially curative interventions.[7,8] In ATI trials, participants with HIV provide informed consent to interrupt ART and adhere to restrictions on their sex behaviour during the ATI to prevent onward HIV transmission. Yet participants' sex partners (henceforth partners) might still be at increased risk of acquiring HIV.[9] This risk is illustrated by two documented cases of HIV acquisition resulting from unprotected sexual activity with ATI trial participants who had interrupted suppressive therapy.[10,11]

The fact that ATI trials might expose participants' partners to research-related risks raises ethical concerns,[12,13] especially since investigators do not currently obtain the partners' consent to be part of ATI trials. The practice also raises feasibility concerns because long-term community support of ATI trials might be undermined in cases where the associated risks to partners are not carefully mitigated. In this Review, we propose a partner protection package (P3) approach for trials involving ATIs to address these concerns. A P3 approach summarises a bundle of measures that investigators and sponsors of ATI trials worldwide can use to reduce the risk of unintended ATI-related HIV transmission, address trial participants' desire for greater freedom of sexual expression, and help ensure that HIV cure-related trials can and will be done ethically. We explain why a P3 is needed, describe what the package might look like in practice, and identify possible future directions for a P3 in the evolving landscape of ATI clinical trials.[14,15] Our goal is to complement and expand upon existing consensus statements on how to rigorously and safely do ATI trials[7] by foregrounding ethical and community perspectives.

Analysis of available evidence

In developing our P3 proposal, we did ethical analysis informed by two sources. First, we reviewed notes from a virtual series of community-driven conversations facilitated by two authors (TM and LF) at the US National Institutes of Health (NIH) Division of AIDS (DAIDS) between November, 2020, and August, 2021. These conversations culminated in a DAIDS-sponsored virtual workshop, referred to as the partner protection workshop. The conversations and workshop included approximately 15 community members and 20 investigators, sponsors, socio-behavioural scientists, and bioethicists. These participants mainly drew on their experiences with ATI trials in the USA, notably trials led by the AIDS Clinical Trials Group and the Martin Delaney Collaboratories (funded by DAIDS and NIH). The discussions centered community voices around current challenges in ATI trials, including partner protection challenges.

Second, we did a focused literature reviews on partner protection approaches in ATI trials (table 1) and the ethics of risks to third parties or bystanders in health-related research (ie, people such as partners of ATI trial participants who do not participate in research studies, but whom the studies nevertheless place at risk; table 2).[58] We included a total of 49 journal articles, which were mostly written by authors based in the USA.

The case for partner protections in HIV cure-related trials involving ATIs

Despite intensified efforts, researchers have been unable to identify biomarkers signalling that HIV has been eliminated or HIV replication is tightly controlled.[59–61] Therefore, ATIs remain a key methodological tool for evaluating experimental HIV cure-related research interventions. Although early HIV cure-related trials involved short ATIs (lasting a few weeks) with restricted viraemia, extended ATIs (lasting a few months) with modest increases in HIV viral load (ie, >1000 copies/mL) are increasingly common.[7,62] ATIs are being extended both because data support their relative safety for participants, and because modest viraemia might be scientifically necessary to detect and promote post-intervention control (ie, sustained HIV control in the absence of ART).[7]

More than 20 HIV cure-related trials involving extended ATIs are now active or in the pipeline globally.[15,63] Extended ATIs pose major challenges in managing partner protections and increase the risk that participants might unintentionally transmit HIV to their partners. Some participants and partners have reported dissatisfaction with the required use of barrier protection or abstinence during ATI trials,[24] which might increase in length as ATIs extend from months to years. Additionally, in the era of undetectable=untransmittable, people living with HIV who maintain an undetectable viral load by taking ART as prescribed cannot sexually transmit HIV to others. Therefore, partners of ATI trial participants might assume that sex without protection carries no risk of acquiring HIV. For example, barrier-free HIV protection (eg, HIV suppression through ART) rather than condom-based protection has become the norm in many cultures.[17,23] ATI trial participants might also not be familiar or comfortable with disclosing their HIV status, asking about their partner's status, discussing the need for HIV prevention, or ascertaining whether partners are using pre-exposure prophylaxis (PrEP) with the goal of protecting their partners during an ATI.[9,21] Indeed, there are two documented cases of HIV transmission during an ATI, and in the ATI trial completed in 2022, several participants developed sexually transmitted infections (STIs) that resulted from unprotected sexual or drug-related activities.[64] These infections might have occurred after participants had been counselled about the trial's requirements for using barrier protection and other HIV prevention measures aimed at preventing unintended HIV transmission during ATI.

These considerations suggest a real and growing risk that participants in ATI trials might transmit HIV to their partners. Although ATI trials involve other specific ethical considerations,[65–70] the risk of a research-related HIV transmission to partners who do not participate in ATI trials—and hence do not consent to this risk—is an important but insufficiently addressed ethical concern. Measures to reduce the risk of HIV transmission in ATI trials can affect the rights and interests of both participants and their partners. For

example, requiring participants to include their partners in discussions with the research team could be seen as violating both the participants' and the partners' privacy rights.[26]

The growing risk of HIV transmission in ATI trials also raises concerns about these trials' feasibility. Specifically, potential participants might be reluctant to enrol in case their partners are placed at risk of acquiring HIV or the trials make demanding requirements in an effort to reduce this risk, such as extended use of abstinence or HIV prevention (eg, barrier protection or PrEP).[17,20,23,71,72] Likewise, HIV clinicians and public health experts might be hesitant to support ATI trials unless appropriate partner protections are in place.[21,73–76] Sponsors might be reluctant to support ATI trials if the risk of unintentional HIV transmission is not adequately managed. Even one additional transmission during an ATI could hamper HIV research generally. Finally, community and public support of ATI trials and HIV research might also decline if measures to protect participants' partners are not appropriately managed.

To address these concerns, a systematic and ethically justified approach to protecting partners of participants in ATI trials is needed. Such an approach would help to ensure that the research remains acceptable to communities of interest, and that its potential benefits, risks, and burdens remain fairly distributed.[40] This approach would also help sponsors, investigators, and participants to discharge their ethical obligation to take reasonable measures to protect third parties in research from undue harm.[49]

Proposed P3 framework

One way of developing a systematic and ethically justified approach to protecting sex partners of ATI trial participants is to systematise and buttress existing practices and recommendations in a comprehensive P3. A P3 would offer guidance to investigators, sponsors, and individuals who are designing and implementing trial-specific partner protections in HIV cure-related trials involving ATIs. The package would also help to assure institutional review boards (IRBs) who are responsible for protecting trial participants, third parties in research,[77] and communities that ATI trials using a P3 offer appropriate partner protections. Although a P3 would not eliminate the risk of HIV transmission during ATIs, it would help to assure stakeholders in ATI trials that the residual risk results from careful balancing of competing ethical and practical considerations, including permitting participants and their partners relative freedom of sexual expression. P3 would be analogous to—and have major overlap with—the established prevention package used in HIV prevention trials.[78–83]

To realise this proposal, the first step would be to develop a P3 framework that can guide the design and implementation of context-specific partner protections in specific ATI trials. Developing such a framework would involve identifying basic considerations for protecting the sex partners of participants in ATI trials, providing ethical justification for each basic consideration, summarising possible ways of implementing each basic consideration, using sound clinical and sociobehavioural evidence whenever possible, highlighting potential ethical limitations or tradeoffs with specific approaches to protecting partners, and providing explicit ethical justifications for excluding potential basic considerations or their possible implementation that have been discussed in the literature.

To establish a high-quality framework that benefits from broad stakeholder support, a P3 framework would need to be jointly developed by relevant stakeholders in ATI trials, including investigators, sponsors, bioethicists, social scientists, and community members, especially people living with HIV and their advocates, former ATI trial participants, and participants' partners. Robust data-driven stakeholder engagement practices[84] would need to be used to address unanswered questions. Similar to the established prevention package in HIV prevention trials,[78–83] the P3 framework would require periodical updates as scientific knowledge, methodologies, HIV prevention options and cure-related treatments, community attitudes, and ethical analysis evolve.

Sponsors and investigators could use the P3 framework to develop partner protection strategies that are tailored to the specific ATI trial, based on careful considerations of the given participant population, research setting, community input, available resources, local policies, and other relevant considerations.[83] The P3 framework could also be used to clearly communicate and justify the resulting trial-specific partner protections in research protocols, community engagement activities during the informed consent process, and in communications with enrolled participants.

A proposed prototype P3 framework

To illustrate our proposal, we offer a prototype P3 framework that outlines basic considerations for protecting participants' partners in ATI trials, as well as how these considerations might be implemented in practice (table 3). Our proposed framework is drawn from existing literature, although the empirical evidence on partner protections during ATIs remains relatively poor and remains largely coming from studies done in the USA. We hope that our prototype P3 framework can provide preliminary guidance for ATI trial sponsors and investigators until a comprehensive framework has been developed with broad stakeholder engagement.

Proposed basic considerations for protecting partners

Peluso and colleagues[9] were among the first to develop a risk mitigation package for partners of participants in extended ATI trials. This package included counselling checklists, HIV and ATI trial disclosure sheets that emphasised directed HIV testing, PrEP,[7,13,18,31,85] and post-exposure prophylaxis (PEP)[7,25] partner referrals and navigation assistance.[9] Here, we integrate this package[9] with recommendations from other authors, [7,13,21] current partner protection practices in the USA, and community recommendations made at the partner protection workshop.

Our prototype P3 framework (table 3) includes three basic considerations for protecting participants' sex partners in ATI trials: ensure the scientific and social value of the ATI and the trial, reduce the likelihood of unintended HIV transmission or acquisition during ATI, and ensure prompt management of any acquired HIV infection. These three basic considerations reflect fundamental tenets in evaluating the risk and potential benefits of clinical research trials.[89] All recognised ethical frameworks for risk–benefit evaluations require that each research intervention in a trial (the ATI in this case) addresses a valuable research question (first basic consideration in our prototype P3 framework). When this

requirement is met, the frameworks then mandate that the risks of each intervention be minimised. Risk reduction can be done by minimising the likelihood of harms occurring (second basic consideration) or minimising the severity of any harms that do occur (third basic consideration).[89]

Our prototype P3 framework deliberately excludes two potential basic considerations for protecting partners discussed in literature. The first excluded consideration is obtaining the partners' consent to be exposed to ATI-related risks,[26] as sex partners are not active research participants.[9,21] Moreover, seeking their consent would effectively give partners the power to veto a potential ATI participant's decision to enrol in a trial, even when the potential participant strongly desires to contribute to HIV cure-related research. Partners' consent would also be difficult to obtain outside stable monogamous relationships and would be practically impossible to acquire in case of individuals who might have multiple sex partnerships.

The second potential basic consideration we excluded is financial compensation for pain, suffering, or loss of future wages for partners who acquire HIV during an ATI, given concerns about feasibility and cost. An important ATI trial sponsor in the USA, the NIH, is prohibited from providing financial compensation for research-related injuries for research participants, preventing compensation for participants' partners.[90]

Possible ways of implementing basic partner protections

Our prototype P3 framework outlines possible ways of implementing the three proposed basic considerations for protecting participants' partners, and highlights the potential ethical limitations and tradeoffs of the approach (table 3). To ensure the scientific and social value of ATI and the trial as a whole, sponsors, investigators, IRBs, and individuals implementing ATI trials should ensure that ATI trials use sound scientific methods to generate information that can be used to promote the health of people with experience of living with HIV in the future. For example, the trials should test a promising HIV cure-related intervention or combination of interventions; address research questions that are novel, innovative, and grounded in evidence; use a rigorous and feasible trial design and analysis plan; be done by high-quality research teams in adequately-resourced sites; and ensure that any successful interventions can be implemented downstream.[91] Sponsors, investigators, and individuals implementing ATI trials should also ensure that the given ATI (eg, short *vs* extended) is needed to answer the trial's research questions, meaning there is no feasible alternative for addressing these questions. Finally, sponsors and investigators should engage the community, including people living with HIV, when evaluating the importance of ATI and the trial (eg, through a community advisory board).

To reduce the likelihood of unintended HIV transmission during ATIs, sponsors and investigators should consider a range of possible measures. For example, they might carefully engage participants in ATI trials, enable and encourage participants to protect their partners, enable and encourage partners to protect themselves (when possible), monitor participants and trial results, select appropriate trial sites, practise good communication, and build trust among potential ATI trial participants and community members. Specifically, to enable and encourage participants to protect their partners both at the time of enrolment

and throughout the ATI trial, sponsors and investigators might provide information or counselling on HIV testing,[25] support HIV and ATI disclosure discussions, and facilitate access to HIV prevention methods (eg, barrier protection, PrEP,[7,9,13,17,18,21,31,85] and PEP[2,21]). Ideally, approaches in a range of formats[9,21] that are tailored to gender-diverse individuals[17,22] and local contexts should be used.[9] For example, for ATI trials involving young women with partners of unknown HIV status, HIV self-test kits might be offered to participants to empower them in discussions with their partners.[21] Communication with participants and their partners might also be enhanced by including or providing access to physicians and other members of the trial team who closely reflect the participants' sociodemographic characteristics.

Conversations at the partner protection workshop underscored the importance of facilitating partners' access to research information and communication with the trial team. This facilitation can include written information, in-person and telehealth visits,[21] provision of HIV testing, PrEP or PEP information and directed HIV testing, and PrEP and PEP referrals and navigation assistance.[7,21] Selecting trial sites that have relationships with community HIV physicians might help increase access to these services. Additionally, robust community ties can be important for protecting partners by promoting relevant and partner protection approaches. Community conversations, health promotion, and social marketing campaigns about ATI trials might raise awareness about HIV prevention needs for partners of ATI trial participants. Finally, to reduce the harm of HIV infections any partners might acquire during an ATI, trials should be done at sites with access to long-term, quality HIV-prevention tools and treatment, and established relationships with local health-care providers and services to ensure linkage to and retention in effective HIV prevention, treatment, and care.

Our prototype P3 framework also includes possible ways of reducing the likelihood of HIV transmission that might be controversial. For example, although STI monitoring of ATI participants is sometimes considered too intrusive, the partner protection workshop revealed support for limited monitoring of participants for STIs to protect their partners. Specifically, monitoring for incident STIs was seen as potentially acceptable in cases when it detects circumstances that might increase the likelihood of HIV transmission during ATIs; builds on measures that inform, empower, and motivate participants and their partners; is necessary to protect partners; uses the least intrusive, risky, and punitive means possible; and does not countervail other ethical considerations for clinical research.[92]

Similarly, we believe there is a poor relevance for protecting participants' partners by preferentially enrolling people who are judged to be at low risk of transmitting HIV.[26] This partner protection approach is controversial because predicting who is at high versus low risk of transmitting HIV can require investigators to ask intrusive questions, runs the risk of unfairly excluding potential participants due to possible investigator bias against non-monogamous sexual relationships, and might risk lowering recruitment numbers and diverse participants' representation. However, enrolment of some groups over others can be justified when it is supported by strong evidence. For example, investigators might consider preferentially enrolling prospective participants whose partners are on PrEP and hence are

protected from HIV acquisition,[7,9,13,17,18,21,31,85] or who state that they do not and will not engage in chemsex, which involves an increased risk of transmitting or acquiring HIV.[86–88]

Our prototype P3 framework deliberately excludes other possible ways of reducing the likelihood of HIV transmission. For example, the framework does not include limiting the use of placebo arms in ATI trials.[26] The track record of HIV cure-related interventions remains insufficient to support the prospect of direct clinical benefit for most experimental interventions, meaning that any perceived partner protection from these interventions is unfounded at this point. Similarly, the framework does not include physically isolating ATI participants; for example, in an inpatient unit. As other scholars highlight,[25] isolation would be unacceptably long, especially during extended ATIs, and risks exacerbating stigma and discrimination against people living with HIV. There are less restrictive ways of reducing the risk of transmission than isolation.

Finally, to reduce the harm of HIV acquisition during an ATI, our prototype P3 framework suggests that trials should be done at sites with access to long-term, quality HIV prevention tools and treatment in the community, and established relationships with local health-care providers and services to ensure linkage and access to and retention in effective HIV prevention and care programmes. Any partner diagnosed with HIV should be referred to HIV treatment services without delay, regardless of whether the HIV infection is known to be related to the ATI or not.[25]

We envision that our prototype framework can guide sponsors, investigators, and other individuals implementing ATI trials in developing partner protection plans that are tailored to the given trial context, and reflecting carefully about the potential ethical tradeoffs between protecting participants' partners, and other scientific and ethical considerations (table 3). We also hope that careful consideration of these tradeoffs will allow sponsors, investigators, and others to identify ways of avoiding or mitigating these potential ethical tradeoffs in protecting partners. For example, if investigators diagnose a new STI in a participant on an ATI trial, they can face the ethical tradeoff between protecting the participants' partners (because STIs increase the likelihood of HIV transmission and might signal unprotected sex practices[21]) and ensuring the trial's scientific and social value (because restarting the participant on ART to protect partners entails terminating the ATI and losing valuable scientific data). To avoid this tradeoff, investigators might consider offering or referring the individual to an STI treatment, additional HIV prevention counselling, and psychosocial support as needed. However, restarting ART can be justified if these measures are not successful. Investigators might also consider revisiting the trial's counselling materials to avoid similar situations in the future.

Possible future directions

Our prototype P3 framework is intended to jump start the development of a comprehensive P3 framework. Ideally, a comprehensive P3 framework would expand on several emerging issues in ATI trials.[7,93]

One issue is what extended ATIs (eg, months to years long) imply for partner protections. Although the experience with extended ATIs is currently poor, these trials are becoming

increasingly frequent and require further research. A comprehensive P3 framework would ideally provide guidance on when it is safe for trial participants to resume sex without HIV prevention (eg, barrier protection, or PrEP) after an extended ATI. This recommendation should include guidance on extended ATIs in which an experimental HIV cure-related intervention appeared to keep participants' HIV suppressed without ART.[85] A comprehensive P3 framework should also clarify how effective PrEP is in protecting participants' partners during extended ATIs, including whether it is possible to relax other partner protection measures (eg, barrier methods) if partners regularly take PrEP.

A second issue concerns how partner protections might need to be adapted as ATI trials expand to new populations and settings. To date, most ATI trials have enrolled gay men from the USA,[14,94–96] and the authors' own experience as well as the existing literature—and hence our prototype P3 framework—are largely restricted to this context. However, cisgender and transgender women, sexual and gender minorities, and racially and ethnically diverse groups are increasingly being engaged in ATI trials,[17,22,23] and some of these groups are more likely to be at risk of gender-based or intimate partner violence.[9,22] Likewise, HIV cure-related trials involving ATIs are increasingly being done in Europe (eg, France, Spain, the UK),[15] and Africa (eg, South Africa).[97,98] A comprehensive P3 framework would ideally offer guidance on how to adapt partner protections to diverse trial populations and settings. The basic considerations for protecting partners and the ways of implementing these considerations set out by our prototype P3 framework will probably apply across populations and settings. However, the specific tools to protect partners in a given trial site need to be context-specific. For example, materials to counsel participants on how to disclose HIV status and ATI trial participation and negotiate protections with their partners (eg, barrier protection methods) need to be tailored to the extent of HIV stigma and intimate partner violence in the community. Similarly, the materials to inform participants' partners about HIV prevention methods need to reflect current use of these methods (eg, PrEP) in the community. Information about local laws regarding criminalisation,[15] which could place participants or their partners at risk of legal prosecution, will also be context-specific.

A third issue is how a comprehensive P3 framework might address the risk of unintended HIV transmission beyond sexual contact, for example in participants who might inject drugs. Counselling on HIV prevention, ATI disclosure scripts and other tools to reduce the likelihood of non-sexual HIV transmission would need to be tailored to these contexts.

Finally, efforts should be made to evaluate our prototype P3 framework and the results of its use to develop a comprehensive framework. For example, investigators' participation in ATI trials could be made contingent upon the availability of a robust partner protection plan, and such plans could be analysed to identify any missing approaches or tools in our prototype framework. To evaluate the prototype P3 framework, it would also be helpful to gather information about potential ATI-related HIV transmission events. For example, investigators might collect information from ATI trial participants on any incident HIV diagnosis for their partners by use of a standard case report form. To determine whether HIV transmission occurred within or outside the relationship, HIV genotyping for both the trial participant and the partner would be necessary with the consent of both parties. However, this practice might not be possible because partners are not enrolled in the trial.

Ultimately, we hope a comprehensive P3 framework could help inform future guidance on partner protections in ATI trials. For example, the field of HIV prevention research has established guidance on the standard of prevention in HIV prevention trials.

Even with a comprehensive P3 framework in place, efforts should continue to develop methodological alternatives for evaluating HIV cure-related experimental interventions, such as biomarkers of viral rebound, which could reduce the need for ATIs in cure-related trials. There is also a need to develop new technologies to help participants protect their partners, such as reliable and convenient home-based viral load testing to reduce the risk of unintended HIV transmission during ATIs.[99–101] Similarly, efforts to make effective HIV prevention methods (eg, barrier protection and PrEP) universally available should continue to protect the partners of ATI trial participants and populations at risk of acquiring HIV. Finally, sponsors, investigators, IRBs, and communities should recognise that ATI trials involve specific ethical considerations other than those included in the P3 framework.[35]

Recognising that our P3 proposal can only be one part in facilitating HIV cure-related research, we hope that it will spark momentum to develop a comprehensive P3 framework that offers systematic and ethically justified guidance for protecting the partners of participants in HIV cure-related ATI trials for diverse communities. A comprehensive P3 framework has the potential to reduce the risk of unintended HIV transmission in ATI trials, while also balancing the concerns about sexual restrictions expressed by participants and their partners. Therefore, a comprehensive P3 could make a key contribution to the successful and ethical conduct of HIV cure-related trials and, ultimately, the development of effective HIV cure strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

- Analytical treatment interruptions (ATIs) are used to evaluate the effects of experimental HIV cure-related interventions. During ATIs, sex partners of trial participants might be at risk of acquiring HIV.
- This Review proposes a partner protection package (P3) to address concerns around onward HIV transmission during trials involving ATIs.
- Our P3 proposal is informed by a series of community-driven conversations and two focused literature reviews.
- The prototype P3 delineates three basic considerations for protecting participants' sex partners during ATI trials: (1) ensuring the scientific and social value of the ATI and the trial, (2) reducing the likelihood of unintended HIV transmission, and (3) ensuring prompt management of any acquired HIV infection.
- The prototype P3 also outlines possible ways of implementing the three basic considerations and highlights ethical limitations or tradeoffs with specific approaches.
- A comprehensive P3 framework could help make a crucial contribution to the successful and ethical conduct of HIV cure-related trials involving ATIs, and ultimately, the development of effective HIV cure strategies.

Search strategy and selection criteria

References for this Review were identified through searches of Embase and Scopus for articles published from database inception until Oct 31, 2022. To identify journal articles or letters on partner protection approaches in ATI trials, we combined search terms related to “HIV cure research”, “analytical treatment interruption”, “partner protection”, and “risk mitigation”. To identify journal articles on the ethics of risk to third parties in health-related research, we combined search terms related to “ethics”, “bystander risk”, “third party risk”, and “clinical research”. Additional journal articles were identified through searches of the authors’ personal files. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only journal articles published in English were included. Please see the appendix (p 1) for more details.

Table 1:

Focused literature review on partner protection approaches in ATI

	Location of corresponding author	Article type (study design)	Key findings or conclusions
Bromwich and Millum (2017)[16]	USA	Ethical analysis	Analyses common concerns about informed consent in HIV cure-related trials involving ATIs and recommends that the informed consent process should give prospective participants a fair opportunity to understand the information relevant to making a good decision about study enrolment. To the extent possible, the informed consent process should help prospective participants to make good decisions (eg, by requiring that they pass a comprehension test before enrolling and addressing misunderstandings one by one)
Campbell et al (2022)[17]	USA	Sociobehavioural research (qualitative interviews)	Summarises perceptions on ATIs and partner protection measures from ten HIV serodifferent couples in the USA who are diverse in terms of race, ethnicity, sex, and gender; underscores the relational aspects of ATI trials, and the need to engage partners without HIV
Dawson (2019)[13]	USA	Commentary	Examines relational ethics approach to managing risks to participants' partners in ATI trials; outlines four layers of responsibility: researchers' obligations to ATI participants, researchers' obligations to partners, participants' responsibilities to partners, and partners' obligations to practice safe sex
Dee et al (2019)[18]	USA	Correspondence	Expresses community concerns regarding reporting of cases of unintended HIV transmission by Lelièvre and Hocqueloux (2019);[10] argues that PrEP remains an important tool to prevent unintended HIV transmission during ATI trials (despite absence of universal availability of PrEP), together with counselling, and use of barrier protection; advises that PrEP access might reduce legal liability risks for ATI trial participants and research sites
De Scheerder et al (2021)[19]	Belgium	Sociobehavioural research (nested qualitative interviews)	Summarises experiences of 11 participants involved in HIV cure reservoir trial involving an ATI; reports that participation in the ATI phase can become burdensome due to the risk of HIV transmission caused by viral rebound
Dubé et al (2018)[20]	USA	Sociobehavioural research (qualitative interviews)	Summarises perspectives of 36 informants from three stakeholder groups (12 peope with HIV, 11 clinician-researchers, and 13 policy makers and bioethicists) on ATIs; provides general considerations for effective and ethical implementation of ATIs inclusive of robust partner protection measures and counselling of study participants during ATIs
Dubé et al (2021)[21]	USA	Sociobehavioural research (qualitative interviews)	Summarises ethical and practical considerations for risk mitigation to sex partners during ATIs derived from 21 in-depth interviews with five types of informants (bioethicists, community members, biomedical HIV cure researchers, sociobehavioural scientists, and epidemiologists), and HIV care providers; reviews possible measures to protect both ATI participants and their sex partners
Dubé et al (2021)[22]	USA	Sociobehavioural research (qualitative interviews)	Summarises considerations for increasing racial, ethnic, gender, and sexual diversity in ATI trials as this relates to partner protection measures derived from 21 in-depth interviews with five types of informants (bioethicists, community members, biomedical HIV cure researchers, sociobehavioural scientists, and epidemiologists), and HIV care providers; highlights needs to pay attention to and recognise the importance of gender and power dynamics in ATI trials
Dubé et al (2022)[23]	USA	Sociobehavioural research (qualitative interviews)	Summarises perceptions on ATIs and partner protection measures from ten racial, ethnic, sex, and gender diverse minority HIV serodifferent couples in the USA; discusses how partners with and without HIV would want to keep each other protected during ATIs, and underscores relationship dynamics in decisions to participate in HIV cure-related research
Dubé et al (2022)[24]	USA	Sociobehavioural research (nested surveys)	Summarises experiences of ACTG 5345 participants undergoing a short-term ATI in the USA. In this study, about half of participants who completed the post-ATI questionnaire reported sex during the ATI. One participant reported that their partner did not like the partner protection measures
Eyal and Deeks (2019)[12]	USA	Editorial	Introduces the special *Journal of Infectious Diseases* (2019) supplement on partner protections in ATI trials
Eyal and Magalhaes (2019)[25]	USA	Commentary	Evaluates ethical acceptability of isolating ATI trial participants and concludes that isolation is unwarranted, although the ethics are complex

	Location of corresponding author	Article type (study design)	Key findings or conclusions
Eyal (2019) *[26]	USA	Commentary	Provides a low-hanging fruit approach to addressing the risk of HIV transmission in ATI trials and evaluates different risk mitigation strategies at different stages of study conduct: recruitment (eg, exclusion criteria, informed consent, and payment), trial operations (eg, education, ART restart, isolation, and placebo), protective care for partners (eg, designing partners as study participants), and measures to reduce harm from infection (eg, treatment support and conflict of interest)
Eyal (2019)[27]	USA	Commentary	Clarifies one barrier to greater partner protection—the false belief that increased protections would make sponsors or research institutions liable in the case of HIV transmission
Folayan et al (2019) †[28]	Nigeria	Correspondence	Argues that current evidence for partner protections supports undetectable=untransmissible when the partner with HIV is undetectable, and PrEP should not be withheld from sex partners of ATI trial participants during ATIs; point out that ATI trials offer an opportunity to collect evidence about PrEP efficacy in the context of viral rebounds
Johnson and Folayan (2019) †[29]	South Africa	Correspondence	Expressed concerns on reporting of HIV transmission events as part of a therapeutic HIV vaccine trial, namely the tone of reporting, amount of personal details included about people involved, and value judgement about the participant being an HIV activist
Julg et al (2019)[7]	USA	Consensus statement	Summarises consensus from 41 experts on the conduct of ATI trials and highlights offering PrEP and HIV testing referral information as ways to reduce the risk of HIV transmission to sex partners
Lau et al (2022)[30]	Australia	Mathematical modelling	Estimates the risk of HIV transmission during ATIs depending on ATI duration, ART restart criteria, and type of sex acts
Lelièvre and Hocqueloux (2019) *[10]	USA	Case report	Summarises the first case report of HIV-1 transmission to a sex partner during ATI, in HIV serodifferent heterosexual couples after oral sex in a therapeutic HIV vaccine clinical trial done in France; recommends reinforcing the risk of secondary HIV transmission during ATI trials in conversations with participants and proposes prescribing PrEP to partners
Lelièvre (2019)[31]	USA	Commentary	Argues for PrEP provision to sex partners of ATI trial participants, but raises possible complications (eg, PrEP efficacy only evaluated in combination with other HIV prevention tools, effect might differ between population groups, absence of data on PrEP efficacy against viral rebounds in ATI trials, HIV acquisition can occur among PrEP users, safety concerns with use of PrEP, policy considerations, and privacy concerns with secondary partners); concludes that PrEP for partners should be complemented by a wide range of partner protection measures
Margolis and Deeks (2019)[32]	USA	Commentary (debate)	Presents two opposing views on the use of ATIs: Margolis argues for the need to capitalise on sensitive assays to reduce the risk of unintended HIV transmissions, while Deeks argues that ATIs remain unavoidable in HIV cure-related studies, and risks to partners or non-participants can be managed through informed consent and careful monitoring
Peluso et al (2020)[9]	USA	Commentary	Outlines a practical approach to risk mitigation during ATI studies done at the University of California, San Francisco, including: treatment interruption study risk mitigation script, pre-ATI risk mitigation counselling checklist, ongoing ATI risk mitigation counselling checklist, ATI study disclosure sheet, and partner-directed PrEP education and navigation materials
Ugarte et al (2020)[11]	Spain	Case report	Summarises the second case report of HIV-1 transmission to a sex partner during ATI, in HIV serodifferent couples of men who have sex with men in a therapeutic HIV vaccine clinical trial done in Spain; recommends prescribing PrEP to sex partners without HIV during ATI and recognising that PrEP implementation remains restricted in some countries
van Paassen et al (2022)[33]	Netherlands	Sociobehavioural research (qualitative interviews)	Summarises results from 20 in-depth interviews with people who initiated ART during acute HIV infection in the Netherlands, and reports that viral rebound and increased infectiousness during ATI are major concerns; of the study sample, more than half of participants would consider undergoing a brief ATI, but only one would consider an extended ATI

ATI=analytical treatment interruption. PrEP=pre-exposure prophylaxis.

*Journal articles or letters added from the authors' personal databases or identified by the focused literature review on the ethics of third-party risks in health-related research (table 2).

†Journal articles or letters identified by an anonymous peer reviewer.

Table 2:

Focused literature review on the ethics of third-party risks in health-related research

	Location of corresponding author	Article type (study design)	Key findings or conclusions
Botkin (2001) *[34]	USA	Regulatory analysis	Argues that it is possible to protect the rights and welfare of third parties in survey and pedigree research (eg, family members) without hindering those projects with extensive consent requirements; applies the conditions for waiving informed consent from research participants set out in the USA research regulations to third parties and concludes that obtaining information about family members and social contacts for research purposes generally meets these conditions
Eyal et al (2018)[35]	USA	Commentary	Advances a procedural approach for protections owed to study non-participants (eg, fetuses, sex partners, household, and community members); proposes using a questionnaire on non-participant risks as part of grant applications and establishing guidelines for acceptable risks based on information gained from these questionnaires; these guidelines can be as simple as a checklist
Eyal et al (2019)[27]	USA	Informal literature review and guideline review	Informally reviews key research ethics guidelines and regulations, academic scholarship, and research studies and finds differences in how they consider risk to third parties in medical research; suggests that deeper investigation of the ethics of protecting research bystanders is needed
Eyal (2020) *[36]	USA	Ethical analysis	Argues that positions on the appropriate protection of third parties in research can inform positions about the appropriate protection of study participants; specifically, insofar as upper limits to risks to third parties are implausible, so are upper risk limits to participants
Fernandez Lynch (2020) *[37]	USA	Ethical analysis	Argues that non-consenting research participants and non-consenting third parties, when exposed to similar research- related risk, are entitled to the same protection; however, instead of the minimal risk threshold set out in regulations for research involving non-consenting participants, the reasonable risk threshold from tort law should be applied to both non-consenting participants and third parties
Frowe (2020)[38]	Sweden	Ethical analysis	Argues that recently proposed threshold accounts of permissible risk imposition on third parties (eg, near zero risks, risks no greater than in ordinary life) are implausible. Proposes instead that we should use a ratio account, weighing the potential risks to third parties against the potential benefits of the trials, when third party consent is not always required; suggests that higher risks might be imposed on third parties if they benefit from the research; identifiable third parties should sometimes be given the opportunity to refuse exposure to research-related risks
Hanser (2020)[39]	USA	Ethical analysis	Argues that third parties can have rights to not be endangered by research activities that are strong enough to require obtaining their informed consent; the strength of these rights depends on the likelihood and magnitude of harm to third parties, and how the harm is related to the research activity
Hausman (2007)[40]	USA	Ethical analysis	Examines whether IRBs should have the responsibility of protecting third parties from research risks—either process- related or outcome-related; argues that IRBs are not the appropriate bodies to protect third parties because: third-party protection is a matter of public policy, not of regulation, IRBs need to be concerned only with human participants per mandate, there might be conflict between protecting participants versus third-parties, and different criteria should govern protection of participants versus third parties
Herington and Tanona (2020)[41]	USA	Ethical analysis	Argues that research ethics is inadequate to govern risks to third parties, that third-party risks must be treated as political and institutional problems, and that third-party risks are problems of justice that must be solved with a political philosophy of science
Holder (1982) *[42]	USA	Case study	Examines ethical and legal considerations for risks to sex partners in contraceptive research and the risk of unwanted pregnancy; advances that participants should be asked to discuss the study with their partners but obtaining the partners' consent or permission is not required
Kendler (2001)[43]	USA	Case study	Argues that the risks to third parties from obtaining family history information in biomedical research can be minimised by safeguards to confidentiality and data integrity and rarely warrant obtaining third party consent, even in research on purportedly sensitive disorders (eg, psychiatric disorders and drug use)

	Location of corresponding author	Article type (study design)	Key findings or conclusions
Kimmelman (2005) *[44]	Canada	Ethical analysis	Argues that traditional research ethics is inadequate for addressing risks to third parties by reviewing various cases and established ethical principles; calls for a sustained inquiry on the ethics of third-party risk in biomedical research
Kimmelman (2007)[45]	Canada	Guideline review	Reviews how ethics codes have approached risks to third parties and argues that existing guidance is not comprehensive; states that third parties deserve protections, and outlines possible considerations for their provision (eg, risk, whether bystanders can be identified in advance, whether bystanders are individuals or plural, and whether bystanders are historically disadvantaged)
Kimmelman (2020)[46]	Canada	Ethical analysis	Reiterates why third parties who are exposed to research-related risks are entitled to protections; argues that IRBs are in the best position to signal to researchers and sponsors that third parties should be protected in research
Lounsbury et al (2007)[47]	USA	Guideline review	Argues that data collection and management strategies can reduce risks to third parties (eg, family members, friends, co-workers) in psychosocial and health-behavioural research, such that their consent to these risks is not required
Murphy and Weijer (2022)[48]	Canada	Ethical analysis	Rejects the standard view that third parties are owed protections because they are similar to research participants, or because the ethical principles governing research should be extended to them; argues instead that third parties in publicly funded research are owed protections as citizens of liberal states to whom the state owes duties of justice
Resnik and Sharp (2006) *[49]	USA	Ethical analysis	Examines ethical and regulatory aspects of third-party risks and argues that researchers and IRBs have an ethical obligation to minimise those risks, including taking reasonable measures to protect directly affected third parties from undue harm; reviews possible duties owed to third parties based on degree of risk:[50] no risk—inform participants about risks to third parties, minimal risk—take reasonable measures to protect third parties, such as informing them or obtaining their informed consent, more than minimal risk, and serious risks—do not do the research or redesign it to reduce risks to third parties
Reverby (2020) *[50]	USA	Historical analysis	Distinguishes between third parties who are victims of research practices (eg, sexual partners, children, and families) and those who are bystanders (eg, affected populations); suggests that victims are owed compensation, while bystanders are owed reparations
Robertson (2021)[51]	USA	Ethical analysis	Reviews the ethics of research that tests interventions, which, if proven safe and effective, risk disadvantaging third parties; argues from the perspectives of the harm principle, status quo bias, and bias against interventional research versus programme intervention that research involving such third-party risks is ethically acceptable
Shah et al (2018)[52]	USA	Commentary	Addresses risks to bystanders in the context of human challenge trials related to Zika research; proposes that sponsors establish comprehensive ethics review committees to review studies involving major third-party risks, especially when the studies' social value is uncertain; these committees would serve in part as signals to the public about the sponsors' commitment to ethical research
Sorensen (2001)[53]	Denmark	Ethical analysis	Explains that research involving personal information on health and demographic factors, which can pose risks to third parties, is acceptable to do without informed consent because the research has no interest in the individual data, only in statistical distribution and associations
Vong (2019)[54]	USA	Commentary	Argues that the ethical duty to avoid harm makes it more important, all other things being equal, to avoid harms rather than avoid reduction of benefits. Applied to the context of research that involves risks to third parties, trials that pose risks by potentially reducing third parties' health benefits should be preferred to trials that pose risks by potentially harming third parties' health
Vong and Levinson (2020)[55]	USA	Ethical analysis	Risks to third parties that result from risk displacement (eg, a study intervention that reduces the risk of unprotected sex among adolescent participants, but by assuming constant willingness to engage in such sex in the host community, adolescent third parties are thereby exposed to increased risk) might be ethically problematic when the inequitability concentrates risk in a subset of a population. Also, studies are ethically problematic when they pose additional risks to already vulnerable or disadvantaged populations, or when they create undue influence in people's decisions about whether or not to participate in research
Walen (2020)[56]	USA	Ethical analysis	Argues that, unlike research participants, third parties are not directly involved in research. Because it is necessary to obtain a person's informed consent when they are research participants and put at risk, obtaining consent from third parties exposed to similar risks is typically unnecessary
Wikler (2020)[57]	USA	Ethical analysis	Argues against tasking IRBs with the ethical review of third-party risks, given that there is no history of serious abuses of third parties and the scope of such an ethical review would be difficult to limit, especially when distant and potentially long-term third-party risks are concerned

IRBs=institutional review boards.

* Journal articles or letters added from the authors' personal databases or identified by the focused literature review on partner protection approaches in ATI trials (table 1).

Table 3:

A prototype P3 framework for HIV cure-related studies involving ATIs

	Potential ethical limitations and tradeoffs
Ensure scientific and social value of an ATI and the trial[32,85]—conduct ATI trials only when an ATI is the best method for addressing valuable research questions and can be used appropriately	
Ensure scientific and social value	
Ensure the trial uses sound scientific methods to generate information that can be used to promote the health of future people with HIV (eg, tests a promising HIV cure-related intervention or combination of interventions; research questions that are novel, innovative, and grounded in prior evidence; the trial design and analysis plan are rigorous and feasible; implementation of successful interventions is feasible)	No major ethical limitations or tradeoffs
Ensure the given ATI (eg, short vs extended ATI) is needed to address the research questions	No major ethical limitations or tradeoffs
Engage community members including people with HIV (eg, through community advisory boards) to evaluate the scientific and social value of using the given ATI and testing the given HIV cure-related intervention[9]	No major ethical limitations or tradeoffs
Select appropriate trial sites	
Ensure adequate site capacity for the safe and successful conduct of ATI trials (including regular and robust community relationships) or robust plans for developing this capacity	No major ethical limitations or tradeoffs
Engage community members, including people with HIV, in site selection (eg, through community advisory boards)	No major ethical limitations or tradeoffs
Manage conflicts of interest	
Carefully identify and manage any potential conflicts of interest between research sponsors and investigators[26]	No major ethical limitations or tradeoffs
Reduce likelihood of unintended HIV transmission during ATI—conduct ATI trials only when HIV transmission risks are adequately mitigated	
Carefully engage participants in ATI trials	
Use evidence-based enrolment methods to mitigate HIV transmission risk (eg, preferentially enrol prospective participants whose partners are on PrEP,[7,9,13,17,18,21,31,85] or who state they do not and will not engage in chemsex[86–88] or unprotected insertive anal intercourse)	Risk of reducing scientific and social value (eg, recruitment challenges) or reducing diverse representation (eg, less diverse enrolment due to questions about specific and potentially stigmatized sexual practices)
Counsel on HIV risk reduction and enrol participants who are willing to protect their partners as much as possible, employing methods such as ATI disclosure, HIV prevention (eg, barrier protection, PrEP[7,9,13,17,18,21,31,85]), or abstinence as appropriate	Risk of placing participants who disclose HIV or ATI trial participation at risk of physical or social harm (eg, gender-based or intimate partner violence)[9,22]
Enrol participants who are fully informed[9,26] about and fully appreciate the implications of undergoing an ATI	No significant ethical limitations or tradeoffs
Screen for STIs, discuss positive STI tests with participants, and carefully consider allowing participants with multiple STIs to continue in the trial	Risk of imposing unjustified burdens, risks, or restrictions for participants; risk of reducing scientific or social value (eg, recruitment challenges), or reducing diverse representation (eg, less diverse enrolment due to STI screening)
Enable and encourage participants to protect their partners	
Provide information or counselling on HIV testing,[21] HIV prevention (eg, barrier protection, PrEP,[7,9,13,17,18,21,31,85] and PEP[7,21]) with use of evidence-based materials and approaches in a range of formats (eg, fact sheets, presentations, videos, and text messaging) that are tailored to diverse individuals (eg, with respect to gender, sex, age, sexual orientation, education level, etc) and specific locations[9]	No major ethical limitations or tradeoffs

	Potential ethical limitations and tradeoffs
Provide or refer to HIV prevention options (eg, no cost barrier protection, PrEP referral for partners)	No major ethical limitations or tradeoffs
Encourage participants to inform their partners and provide counselling[7,9,21] on HIV and ATI trial participation disclosure,[7,9,21] provide sample disclosure scripts,[9] offer disclosure role playing sessions as needed	No major ethical limitations or tradeoffs
Encourage participants to include their partners in trial visits (eg, optional site visits and discussions with the trial team)[9,21]	No major ethical limitations or tradeoffs
Provide mental health support or counselling referrals as needed[18,21]	No major ethical limitations or tradeoffs
Offer peer support[17] (eg, former ATI trial participants)	No major ethical limitations or tradeoffs
Encourage partners to communicate with the trial team[9,17] (eg, provide written information tailored to partners, invite partners to accompany participants during trial visits in person or via telehealth)[21]	Risk of violating partners' privacy,[7] given the need to contact them
Offer information or counselling on HIV prevention (eg, barrier protection, PrEP,[7,9,13,17,18,21,31,85] and PEP[7,21]) with use of evidence-based and partner-specific materials and approaches in a range of formats, including fact sheets, presentations, videos, and text messaging[25]	Risk of violating partners' privacy,[7] given the need to contact them
Provide HIV testing, PrEP,[7,13,18,31,85] and PEP[7,21] referrals and navigation assistance[9] (eg, refer partners to full range of PrEP options)	Risk of violating partners' privacy,[7] given the need to contact them
Facilitate access to mental health support[18,21,53] or counselling as needed	Risk of violating partners' privacy,[7] given the need to contact them
Engage the local community in discussions about trial involving ATIs[9]	Risk of violating partners' privacy,[7] given the need to contact them
Promote broader community engagement about ATI trials and consider health promotion and social marketing campaigns to raise awareness about HIV prevention needs for partners of ATI trial participants	Risk of stigma for people who participate in ATI trials
Monitor participants	
Frequently monitor HIV viral load and restart ART as needed to protect partners[9, 85]	Risk of reducing scientific or social value (eg, early termination of ATI)
Develop a decision tree or algorithm to guide the use of STI monitoring for each participant during ATI. Monitor for STIs[21] and provide or refer to any necessary treatment for participants and their partners. Delay ATI, or restart ART, as needed to protect partners (eg, if a participant is unwilling to be treated for a diagnosed STI)	Risk of imposing unjustified burdens, risks, or restrictions for participants; risk of reducing scientific or social value (eg, recruitment challenges due to STI monitoring, early termination of ATI after STI diagnosis), or reducing diverse representation
Encourage additional STI monitoring and treatment for participants and partners outside the trial (eg, regular use of standard test and treat services offered by health departments or charitable organisations)	No major ethical limitations or tradeoffs
Monitor trial results	
Establish independent SMC to review interim trial data (eg, safety of cure-related trial intervention, partner safety)	Risk of reducing scientific or social value (eg, early trial termination)
Select appropriate trial sites	
Select sites with regular and robust community engagement experience with community-based organisations that have the capacity to discuss ATI trials and partner protections. Select sites with community advisory board to advise on emerging partner protection issues[9]	Risk of reducing scientific or social value (eg, if selective site selection leads to recruitment challenges), or diverse representation; risk of limiting access to ATI trials
Select sites that have relationships with community HIV clinicians[73–76] and provide continuing medical education about the need for partner protections in ATI trials	No major ethical limitations
Practise good communication and build trust	

	Potential ethical limitations and tradeoffs
Practise good communication and build trust with participants and their partners throughout the trial to enable open and individualised decision making[13] about partner protections	No major ethical limitations or tradeoffs
Ensure prompt management of any HIV acquired during ATI—conduct ATI trials only when partners who acquire ATI-related HIV will be treated promptly and maintained on treatment	
Select appropriate trial sites	
Select sites with access to long-term, quality HIV prevention services and treatment in the community and established relationships to ensure linkage to and retention in effective prevention and care. Consider preferentially selecting sites where HIV stigma in the community is also low, as this could further reduce the risks of any acquired HIV infection during ATI	Risk of reducing scientific or social value (eg, if selective site selection leads to recruitment challenges), or reducing diverse representation; risk of limiting access to ATI trials
Conduct swift referral to ART through established referral practices	
Be prepared to link partners who acquire HIV to local HIV treatment provider. To ensure prompt treatment, proof of an ATI-related HIV acquisition should not be required	No major ethical limitations

Columns list basic considerations for protecting partners and underlying justification, possible ways of implementation, and potential ethical limitations and tradeoffs. ART=antiretroviral treatment. ATI=analytical treatment interruption. P3=Prototype Partner Protection Package. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. SMC=study monitoring committee. STI=sexually transmitted infection.