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A collaborative, multidisciplinary approach to HIV transmission risk mitigation during analytic treatment interruption

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Abstract

Analytic treatment interruptions (ATIs) are currently the standard for assessing the impact of experimental interventions aimed at inducing sustained antiretroviral therapy (ART)-free remission in trials related to HIV cure. ATIs are associated with substantial risk to both study participants and their sexual partner(s). Two documented HIV transmissions occurring in the context of ATIs have been recently reported, but recommendations for mitigating the risk of such events during ATIs are limited. We outline a practical approach to risk mitigation during ATI studies and describe strategies we are utilising in an upcoming clinical trial that may be applicable to other centres.

Keywords: HIV, HIV cure research, HIV remission research, analytical treatment interruption

Introduction

HIV cure-related clinical trials aimed at inducing an antiretroviral therapy (ART)-free remission in people living with HIV (PLWH) often require analytic treatment interruptions (ATIs) [1]. During an ATI, ART is paused to determine if the study intervention has affected the time to or degree of viral rebound, and(or) if the intervention has induced sustained control of HIV. Most participants undergoing an ATI will experience viral rebound until ART is resumed. While different protocols prescribe different durations of viremia, it has been argued that a prolonged period of detectable virus during which HIV is transmissible is necessary to assess the ability of immune-based cure interventions to achieve sustained aviremia [2,3]. This approach is becoming increasingly acceptable [4].

Risks and challenges associated with ATIs in cure-related trials

In addition to carrying substantial risk to study participants, ATIs expose sexual partners of participants to the risk of HIV transmission [5]. Recently, this risk was highlighted following two transmission events during clinical trials of therapeutic vaccines in Europe [6,7]. In the first case, transmission occurred between a male research participant and female partner and was attributed to oral sex [6]; in the second case, transmission occurred between a male research participant and a male partner, although the mode of transmission was not specified [7]. As a result, there is an urgent need to understand and mitigate the risks faced by participants' sexual partners to prevent further transmissions during clinical trials [1]. These risks may also have an impact on future participants' willingness to contribute to HIV cure-related research [8].

Previous work has identified a number of specific challenges for both ATI participants and their partners, see Table 1. In brief, sexual partners of study participants are typically not directly informed of their risk of HIV acquisition and may not receive advice on how to reduce this risk [1,9]. These individuals are not considered study participants, and behavioural risk reduction strategies are often considered to fall outside the scope of this research [10]. As partners do not provide informed consent and are not directly engaged in a research protocol, many researchers rely on study participants to disclose information regarding the risk that their involvement in the ATI study might pose to their partners. Even when a partner seeks advice from the study team, this advice may be generic, lack active engagement, or may not be followed up. There is also a lack of information on the approach that may be most effective and(or) acceptable to partners.

Determining a 'standard of prevention' for ATI clinical trials

In light of these challenges, we have developed and implemented initial recommendations that could be used as a potential model for future ATI studies in settings similar to ours. This process involved close consultation between the biomedical study team, our community advisory board, socio-behavioural scientists, and bioethicists. The risk mitigation plan evolved over a series of meetings during which the goal of the effort was to minimise the risk of HIV transmission to sexual partners during ATIs. We modelled our approach after efforts within the field of HIV prevention, in which testing and disclosure within serodiscordant couples is encouraged [11] and a risk-reduction package (the 'standard of prevention') is typically provided to participants in clinical studies who are HIV-negative [12,13].

Our risk mitigation approach

We developed several mechanisms to address these challenges (Table 1). The first was identifying and recognising the limitations of exclusion criteria related to sexual activity for participants

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Table 1. Challenges and possible mechanisms to address challenges around engagement and HIV transmission risk mitigation for sexual partners of study participants in ATI trials

Challenges	Mechanism to address challenges
Participant-level challenges	
Difficulty in following safe sex practices (i.e. condoms)	Study exclusion criteria (may be problematic)
Limited knowledge of HIV transmission risk	Standard informed consent Post-consent quiz or discussion to assess comprehension
Difficulty in accessing barrier protection	Study provides barrier protection at no cost
Difficulty in discussing ART pause and viral rebound	ATI study disclosure script
Multiple or anonymous partners	ATI study disclosure script Community engagement
Participant unwilling to disclose status or participation to partners	Very difficult to mitigate
Partner-level challenges	
Non-participant status	Encourage participants to invite partners to study visits
Partner unaware of HIV status	Encourage partners to undergo HIV testing
Lack of partner education on PrEP	Partner-directed PrEP education materials
Lack of partner navigation to PrEP	Partner-directed PrEP navigation
Known possible exposure to HIV for sexual partner during study	Partner-directed PEP navigation
Study-level challenges	
Development of context-appropriate approach	Close collaboration with community advisory board and patient community
Lack of consistent oversight/regulation regarding risk mitigation	Engagement of institutional review board and other regulatory bodies during study review/approval
Need for research team to provide consistent counselling	Transmission risk mitigation standard operating procedure and checklists
Limited knowledge of sexual practices of participants during ATIs	Nested socio-behavioural assessments of partner protection measures, potential social harms and prevention altruism
Limited data on HIV transmission risk mitigation plans in ATI studies	Greater transparency regarding risk mitigation strategies, with documentation in study protocols and research databases (i.e. ClinicalTrials.gov)

ART: antiretroviral therapy; ATI: analytic treatment interruption; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis.

before and during ATIs. We felt comfortable requiring a contraception plan to mitigate the risk of pregnancy in participants of reproductive potential owing to the possible effects of the experimental agents and treatment interruption on fetal development. However, in situations in which neither the participant nor partner is of reproductive potential, we recognised the difficulty of conditioning enrolment or ongoing participation on consistent use of barrier protection. Behaviour related to sexual practices can change over time in ways that a participant or the study team may not be able to predict. Even in cases in which a participant chooses not to use barrier protection during the ATI, we recognised that specific risk-mitigation approaches such as the use of pre-exposure prophylaxis (PrEP) or ART by their informed partners might be sufficient. For these reasons, we did not feel that we could rely on blanket exclusions, although there is support for using evidence-based criteria for enrolling individuals who are well suited to handle risks presented by ATIs [10]. There may also be instances where some participants should be restarted on ART if they demonstrate, after repeated counselling, that they cannot handle the risks associated with ATIs.

Regardless, we removed obstacles to barrier protection by proactively providing both male and female condoms and lubricant without charge to participants who wish to use them. It is unclear whether barrier protection was recommended or actually provided by the study group in cases in which transmissions have occurred [6,7].

We next addressed the challenges participants face with regard to disclosing their HIV-positive status and participation in ATI trials. Since it has been determined that Undetectable=Untransmittable (U=U) [14–19], many HIV-negative individuals rely on their

partner's adherence to ART and viral suppression below detectable levels for protection against transmission. During an ATI it is anticipated that participants' undetectable status will be temporarily lost while they are off ART. During this period they could transmit the virus to others; this risk is likely to be directly related to both the duration off ART and peak levels of viremia during rebound [17]. These issues are addressed in a recent consensus statement on ATIs [4]. ART adherence to prevent HIV transmission is increasingly framed as a matter of personal responsibility, therefore our team developed a disclosure script to facilitate participants' ability to disclose and describe the risk of HIV transmission to sexual partners during the ATI.

Additionally, we are welcoming participants to invite partners to study visits, and explicitly encouraging partner participation at a study visit at least 4 weeks prior to initiating an ATI. The purpose of this visit is to provide information and resources related to HIV PrEP, a safe and effective HIV prevention method recommended by the U.S. Centers for Disease Control and Prevention [20]. Direct provision of PrEP to partners by the study team may not be feasible in many research settings owing to the medical, legal, financial, and regulatory complexities of engaging third parties. At our site, both PrEP and post-exposure prophylaxis (PEP) currently require the collection of medical information, screening laboratory studies, adherence counselling, and periodic clinical and laboratory assessment (at baseline and 1 month for PEP and typically every 3 months for PrEP) to monitor for other sexually transmitted infections, ensure the safety of ongoing PrEP use, and rule out incident HIV infection. In many cases in the US, an individual's access to PrEP is determined by their insurance status and plan.

For these reasons, and consistent with standard of prevention practices in HIV prevention trials [21], we decided that providing hands-on, aggressive PrEP navigation would be the most appropriate, effective, and feasible approach. This would be achieved through several mechanisms: provision of written information on PrEP resources to participants and their partners using study-developed information sheets, availability of a study physician to discuss issues related to PrEP with participants and their partners, repeated transmission counselling, and direct referral of partners to one of several clinical sites in our community at least 4 weeks before the participant's ATI. This referral will include a 'warm hand-off' from the study team, which involves accompanying the participant and partner to an on-site PrEP clinic or directly connecting them with local PrEP providers, not just merely making referrals to other locations. In the case of a known possible exposure to HIV, the study team will promptly facilitate PEP access for sexual partners of ATI study participants via established pathways at the institution. These procedures have been incorporated into the study operations manual and documentation by the study team is a protocol requirement.

Limitations

Our intent is to provide a practical starting point to mitigate the risks of HIV transmission to non-participant sexual partners. However, we acknowledge several limitations to our approach. First, we rely on the willingness of participants to disclose personal health information to sexual partners. Situations in which a participant is unwilling to disclose their HIV status or ATI study participation to others may be difficult to anticipate or identify and are particularly problematic. Second, our approach does not address issues of disclosure with regard to multiple or anonymous partners. Third, unless PrEP is available to all people at risk of HIV, it will remain difficult to devise a plan that will address all possible scenarios. Fourth, we acknowledge that our approach may not work in settings like rural areas of the US or other countries with limited PrEP availability [22], including resource-limited settings, where an increasing proportion of HIV cure-related studies are likely to be conducted in the future. Our studies are based in a community in which there is widespread understanding about HIV transmission risks, there is universal access to treatment, and PrEP is strongly supported by all stakeholders. This is not the case in all settings. In some it may be both feasible and appropriate for a study budget to include the cost of prevention (including PrEP and PEP) when it is not accessible via local clinical infrastructure. This will again depend upon the study team, participant needs, and local context. Researchers must work closely with their own communities and stakeholder groups to create plans that are appropriate to cultural norms, gender and sex dynamics; and issues related to stigma, structural, and intimate partner violence. The unique risks and challenges faced by women and people of colour regarding PrEP access, use, and (or) referral are also of particular importance.

Future directions

While we await the development and validation of improved research assays, ATI studies are likely to remain the gold standard for assessing the impact of immune-based interventions aimed at inducing sustained ART-free remission of HIV infection [1,2]. More research will be needed to understand participants' values, motivations and practices to avoid unintended transmission events during ATIs, a term coined 'prevention altruism' [23]. Efforts should be made to study the experiences and preferences of sexual partners of research participants to further inform risk mitigation strategies. Potential strategies are also likely to expand

in the near future, as a variety of delivery modalities, for example long-acting injectable formulations or implantable devices for PrEP, become available. Until all who are at risk of HIV know their status, are aware of the benefits of PrEP, and are able to access effective methods of HIV prevention, we believe that our multifactorial approach provides a reasonable method to mitigate HIV transmission during ATIs in settings such as ours.

Supplementary materials

The authors are pleased to make the materials referred to in this article available upon request. Please contact Michael Peluso (michael.peluso@ucsf.edu) or Steven Deeks (steven.deeks@ucsf.edu) to request the most recent version of these materials. A list of current or upcoming studies including ATIs can be accessed at www.treatmentactiongroup.org/cure/trials/. Studies including ATIs are specifically noted in the table on this site.

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Conflicts of interest

DC, JT, RH, RLR, JS, and KD have no interests to declare. LD is Executive Director of AIDS Action Baltimore, Inc. (AAB). AAB has received grants from Gilead Sciences for PrEP education in Baltimore among African-American men who have sex with men and transgender communities, annually from 2015 to the present. MJP receives research grant support from the UCSF Resource Allocation Program (Gilead HIV Cure Mentored Scientist Award). SGD receives research support from Gilead Sciences, Merck & Co. and ViiV. He has consulted for AbbVie.

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