Secondary HIV Infection and Mitigation in Cure-Related HIV Trials During Analytical Treatment Interruptions

To the Editor—We are writing to express concerns regarding facts reported in 2 recent *Journal of Infectious Diseases* articles [1, 2] pertaining to the ANRS-LIGHT study, conducted in 18 clinical sites in France between September 2013 and May 2015. Initially, we were delighted to see the authors implemented several inclusion criteria that we believe were likely to ensure safety of participants during the analytical treatment interruption (ATI) that occurred during the trial, for example a nadir of $CD4^+$ T-cell count of ≥300 cells/mm^3 and an initial $CD4^+$ T-cell count of ≥600/mm^3 [3]. However, other aspects are dismaying, including the detailed identifying information about the index participant and partner. We fear it is possible to identify both persons from the elaborate medical and nonmedical history provided. After contacting the study Principal Investigator, Dr Lelièvre, through a European colleague, it appears there were no consents to disclose this information. Thus, we feel strongly that it was inappropriate to include such comprehensive, potentially identifying details.

Although not strictly forbidden by exclusion criteria delineated in the protocol summary, which we obtained with Dr Lelièvre's cooperation, according to the first published article [1], the participant in question had "chronic depression (for which he refused to take treatment) and poorly managed diabetes mellitus". We believe it was inappropriate to enroll into an ATI trial a participant with poorly managed diabetes mellitus. Moreover, we are concerned about the chronic untreated depression described in this case. We suggest the best practice in such cases is to administer validated measures to assess acute symptoms of depression or other mood disorders in order to ascertain whether a participant is an appropriate candidate for studies involving ATIs. Furthermore, we firmly believe participants enrolled in HIV cure-related research should have access to adequate psychosocial assessments and mental health support.

Also concerning to us was information provided about the sexual practice reported by the participant that resulted in the secondary HIV transmission, in this case reported to be cunnilingus. The authors note this route of transmission "is not considered a risky act. However, (…) other sexual relations could have taken place (…). Our case report shows that even well-informed patients/activists can harm themselves". While we believe it is unproductive and unnecessary to perseverate on the purported route of transmission, we feel it is imperative to note that the article implies blame, and thus inadvertently stigmatizes the participant for the occurrence. This seems to us insensitive and dangerous and, as an unintended consequence, may present untoward challenges for enrolling participants into future trials, especially in the United States where this article has been widely disseminated among community activists.

We believe prevention of secondary HIV transmission to sexual partners is one of the most critical ethical issues surrounding the use of ATIs in HIV cure-related trials [4]. In the first article, Lelièvre and Hocqueloux [1] stated that, whenever possible preexposure prophylaxis (PrEP) should be prescribed to the known partners of all study participants. Unfortunately, Lelièvre's second article [2] almost exclusively addressed why PrEP may not be 100% effective in eliminating the risk of secondary transmission during ATIs. Many of his points are well taken, such as pharmacokinetic issues surrounding PrEP use in women, sexual relations with casual partners, and the absence of data indicating whether PrEP as currently administered is effective against sudden viral rebound. Further, we acknowledge that, due to social and structural barriers, PrEP is not widely accessible in many US states or across all of Europe, and was not available in France in 2015 when the ANRS-LIGHT trial was conducted. While PrEP may not be a magic bullet that prevents all cases of secondary HIV transmission, we firmly believe it is unproductive to abandon efforts to ensure access during trials involving ATIs by dwelling on why PrEP is not perfect or universally available. The landscape of HIV-related health equity is such that additional data and efforts to maximize PrEP access will remain paramount in the foreseeable future. At present, when accessible, PrEP is a powerful tool in our armamentarium to prevent secondary HIV transmission during an ATI, especially when combined with repeated counseling on the risks of transmitting HIV during an ATI and the use of barrier protection [3]. Ensuring access to PrEP may also help reduce the risk of legal liability on the parts of trial participants or investigators, particularly in litigious societies such as the US.

Many HIV advocates have focused on whether trial sites should provide PrEP, how this might be funded, and the many complex implementation difficulties presented, such as those imposed by the realities of sexual encounters with casual partners. One solution to implementation issues in the US may be that most HIV cure research sites are located in metropolitan areas where health care and PrEP services are readily available, and provided by the same institution conducting clinical trials. While we understand HIV cure-related research is already an extremely complicated endeavor, it is nevertheless essential that, at a minimum, we repeatedly counsel

DOI: 10.1093/infdis/jiz262

participants and provide written information about the risk of transmitting HIV during ATIs, as well as written counseling, testing, and referral information for their sexual partners. If possible, we strongly encourage coordinated assessments and warm transfers between trial sites and PrEP sites. For example, having PrEP providers meet referred partners in person at trial sites would ensure that they are linked to qualified PrEP sites.

Many of us in the US activist community see provision of PrEP to sexual partners of study participants as our next essential step in ensuring that HIV cure-related trials involving ATIs are ethical. The unfortunate HIV seroconversion of a participant's partner in the ANRS-LIGHT study is a stark reminder that secondary transmission is a very real possibility that affects real people. Rather than espousing an attitude of defeatism, our prevention efforts require advocacy and effective collaboration between researchers and affected communities.

Notes

Acknowledgments. We thank the following members of the Martin Delaney Collaboratory for HIV Cure Research Community Advisory Board (CAB) members for their cooperation and approval of the contents of this manuscript: Delaney AIDS Research Enterprise, David Evans and Moises Agosto-Rosario; Collaboratory of AIDS Researchers for Eradication CAB, Jeff Taylor; Immunotherapy for Cure CAB, Charles L. Christen; Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication CAB, A. Toni Young; defeatHIV, Delaney Cell and Genome Engineering Initiative, Michael Louella, Laurie N. Sylla and Manuel Venegas; and Beyond Antiretroviral Therapy, Delaney Collaboratory to Cure HIV-1 Infection by Combination Immunotherapy CAB, Christopher Roebuck.

Potential conflicts of interest. L. D. is Executive Director of AIDS Action Baltimore, Inc. (AAB). AAB has received grants from Gilead Sciences for PrEP education in Baltimore African-American men who have sex with men and transgender communities, annually from 2015 to the present. All other authors declare no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 21 March 2019; editorial decision 15 May 2019; accepted 5 June 2019; published online August 22, 2019.

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