Human Immunodeficiency Virus Transmission Risk in Analytical Treatment Interruption Studies: Relational Factors and Moral Responsibility

Liza Dawson^{*}

Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Analytical treatment interruption (ATI) is becoming common in human immunodeficiency virus (HIV) cure-related research, but its use is controversial. ATI raises concerns about risks of HIV transmission to sexual partners of study participants. Researchers may have difficulty addressing these risks, given that study participants' private behavior is implicated, the partners are not enrolled in the research, and behavioral HIV risk mitigation strategies usually fall outside the study objectives. This analysis argues that researchers should assume some responsibility for partners' risks, based on the importance of partner relationships for the study participants themselves, and out of concern for the partners' welfare. Adding this responsibility is reasonable since the risk is created in part by research procedures, and since concern for third parties is often part of professional standards for healthcare providers. Study participants and their partners also bear some responsibility. Specific recommendations for measures to address risk are discussed.

Keywords. HIV; research ethics; analytic treatment interruption; HIV clinical research.

The use of analytical treatment interruption (ATI) in human immunodeficiency virus (HIV) cure-related research is becoming increasingly common. While there is debate about circumstances in which this approach is appropriate, there is widespread agreement that some research questions cannot be answered without interrupting antiretroviral therapy (ART) [1].

Because HIV is almost certain to rebound following treatment interruption, transmission risks will emerge as well. The timing of rebound is uncertain, and even with close monitoring, there may be a point at which viral rebound has already begun but has not been identified. Studies in primates indicate that HIV transmission may be particularly great during a period of increasing viral load, as in an acute infection. Therefore, the possibility of a new unidentified viral rebound causing HIV exposure to sexual partners of study participants is a real concern. Addressing transmission risks in a study that includes an ATI may be difficult—first, because behavioral risk reduction strategies fall outside the scope of the research, and second, because study participants' sexual partners are typically not part of the study.

US ethical guidelines and regulations for human research do not directly address obligations to nonparticipants in research [2] (with the exception of group harm), and in the past, non-participant concerns have been controversial [3]. In US human subjects regulations, obligations to study participants are related to direct exposure to risks and burdens of research. In biomedical research, compared to behavioral studies, there has been less attention to participants' relationships and social context. In fact, bioethics as a field, and research ethics oversight in particular, has been criticized for viewing individual autonomy and self-interest in isolation from other factors, in particular the fact that individuals value relationships, group membership, and other aspects of social life that cannot be defined strictly by autonomous self-interest. Feminist scholars have pushed for a more inclusive and relational bioethics account of personality and self-interest. If a person's relationships are part of their life plan and even their personality, some argue, then they deserve consideration [4] in balancing obligations to individuals and groups [5].

Based on a broad conception of individual interests, including one's relational interest in not harming a sexual partner, it is reasonable to claim that researchers should assist participants in studies that include an ATI in their efforts to avoid exposing partners to risk of infection. While researchers are not responsible for individuals' private behavior, they are responsible for the viral rebound which complicates and imposes burdens on that private life. Obligations to address nonparticipant risk can therefore be framed, to some extent, as part of a primary obligation to subjects themselves. HIV-infected individuals are likely

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Correspondence: L. Dawson, PhD, MA, Walter Reed Army Institute of Research, 503 Robert Grant Ave., Silver Spring, MD 20910 (liza.dawson.civ@mail.mil).

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to be concerned about transmission of HIV to others. Recent qualitative research demonstrates that fear of transmitting HIV is a substantial psychological burden [6]. Therefore, researchers should make commitments to mitigate the burden of possible unintentional transmission of HIV in studies that include ATIs.

The claim that researchers must bear some responsibility to mitigate nonparticipant risk might raise alarm about a “slippery slope.” Would researchers then be responsible for every secondary effect that research might engender? These fears of ethical overreach can be allayed by recognizing that the ATI case is unusual. The viral rebound is indisputably caused by a research procedure; rebound is predictable, and viral load has a quantifiable relationship to HIV transmission. Considering research more generally, effects of research on nonparticipants are usually much more speculative and indirect. Therefore, assigning responsibility in this case does not imply a broad-based claim that researchers always bear responsibility for nonparticipants; the issues must be evaluated on a case-by-case basis, and assignment of responsibilities should rest on evidence about risks and not mere speculation.

A further complication is that nonparticipant risks might bring up worries about researchers’ legal liability. However, based on precedent from clinical care, it is unlikely that courts would consider researchers liable. There are 2 different legal justifications for holding a person legally responsible for a harm to a third party: foreseeability, or a direct relationship among the parties. (For example, see *Seebold v. Prison Health Services, Inc.*, 57A.3d 1232 [PA 2012]; however, a full review of legal issues relevant to this topic is outside the scope of this article.) In studies that include ATIs, the researchers do not have a preexisting relationship with the nonparticipant. Regarding foreseeability, while viral rebound is very predictable, the risk behavior of individuals in their private sexual relationships is not. Individuals are counseled about risk reduction measures, and their sexual behavior is private and occurs outside the study, making it unlikely that any legal claim could be levied against the researchers. (For a related discussion, see “Removing one barrier to protecting sex partners in HIV remission studies with a treatment interruption” by Nir Eyal in this supplement [7].)

There are 2 additional claims of responsibility in the ATI case. First, apart from commitments to study participants, researchers also have an obligation directly to the nonparticipants. If, for example, an individual study participant was apathetic about transmission risk, researchers should still be concerned on behalf of partners potentially exposed. The basis of the responsibility to nonparticipants is analogous to the responsibility of medical professionals to families and contacts of their patients. While commitment to the patient is primary, physicians acknowledge some responsibility to advise patients about limiting risks to others, for example, sexual contacts of a patient diagnosed with a sexually transmitted infection [8, 9]. This responsibility is also formalized in public health practice, which

involves contact tracing for communicable disease [10]. Health providers’ responsibilities to other parties can be nuanced, as in the case of genetic counselors who may urge their clients to inform relatives about a hereditary disease risk so that they may avail themselves of genetic testing options [11, 12]. These examples illustrate that health professionals’ concerns extend beyond their primary patient or client. In each of these scenarios, the provider has acquired information that is valuable for mitigating risk or for aiding decision making by the third parties. In contrast, in the case of ATI studies, researchers have actually *created*, in part, the risk to third parties—thus implicating researchers in a higher level of concern for the welfare of the nonparticipants. This is not to say that researchers acquire legal liability, as noted above, due to the complexities of private sexual behavior, which is one of the necessary contributing factors in exposure to HIV risk. Nevertheless, concern about risks to other parties is arguably part of a professional standard of non-maleficence, and in healthcare generally, concern for the welfare of others who are connected to the index patient or client is recognized as part of the professional responsibility of medical providers. Establishing exactly how far the responsibility extends is often debated. (As will be noted below, researchers, unlike medical providers, are able to select study participants purposively to minimize risks to participants and their contacts. This is only one of several strategies that researchers may deploy in response to the creation of risks in the course of research—noted here as it differs from options available to medical providers.)

It should be acknowledged that the primary purpose of research is generating new knowledge, not providing clinical treatment to research participants. It could be argued that the typical duties of clinical care professionals are entirely distinct from those of researchers. However, in the course of doing research, researchers take on duties of beneficence and non-maleficence with regard to study participants. These duties are limited to the domain of activities encompassed in the research, for example, limiting risks, and in the case of clinical trials of treatment regimens, ensuring that treatments are in a state of equipoise as compared to the prevailing standard of care. While there are debates about how to frame the responsibility to look after study participant welfare, there is no doubt that researchers acquire these kinds of obligations when they enroll individuals in research.

When considering the nature of researchers’ responsibility, further nuances are important. The concept of responsibility has several different layers and implications. A person who behaves recklessly with regard to another person may be held responsible for resulting injuries. In this sense, responsibility is tied up in a causal chain. Another form of responsibility results from fiduciary obligations. For example, parents are responsible for care of their children if they become injured, not because they have caused the injury, but because of their duty of care. Because researchers are trying to mitigate a risk that is created

only partially by research participation, they cannot be fully responsible for the causal chain of events. However, their responsibility, as outlined above, is to help mitigate the risk created by research procedures, namely the ATI. Furthermore, researchers do not have an overall duty of care for nonparticipants in research—the responsibility researchers hold toward third parties in the case of research involving ATIs is specific and limited in scope. Assuming researchers have fairly informed study participants and provided assistance to mitigate transmission risks, they have discharged their responsibilities. If HIV transmission nevertheless occurs, they do not then acquire duties of care for treatment of HIV-infected partners.

Second, in addition to researchers' responsibilities to participants and their partners, responsibility must also be assigned to participants and partners themselves. Given that transmission of HIV is known to occur when virus rebounds, individuals bear responsibility for using protective measures. The assignment of responsibility to multiple parties, including researchers, participants, and partners, is not a zero-sum game. Fulfillment of responsibility by one party does not absolve the others of their role. At the same time, it must be acknowledged that sexual partners cannot be held responsible if the study participants misrepresent their status and claim to pose no infection risk when in fact this status is uncertain.

A final word on assignment of responsibility to different parties: It is also true that oversight committees such as institutional review boards (IRBs) should review studies to evaluate risks and determine if they are acceptable. Their role is to enforce standards that are recognized as ethically appropriate given current knowledge of risks, burdens, and benefits of research. However, IRBs have no preexisting metric for determining obligations to nonparticipants because, as mentioned above, there is no regulatory standard, nor is there a consensus in the discourse on research ethics about how to handle this gray area. The proposals in this paper attempt to reason through the issues for a specific case, namely ATI studies. Should the facts or circumstances change significantly, a new assessment would be needed.

In practical terms, risk mitigation strategies should be offered by researchers, with a menu of options appropriate to the needs of the individuals enrolled in studies that include ATIs. Researchers should partner with, or refer participants to, providers for counseling, prevention methods for partners such as preexposure prophylaxis, and other supportive strategies. Another approach would be to enroll the nonparticipants in research and include provision of HIV prevention methods. However, enrollment of partners might not be appropriate for all studies or all participants. Many people do not have steady partnerships, or partners might not be interested in enrollment. Also, over the course of a study, partner status may change. Therefore, at a minimum, researchers' commitments to nonparticipant welfare are mediated through risk reduction measures provided to study participants.

The social milieu in which study participants experience the burden of worry about transmission risk is also relevant. Increasingly, individuals living with HIV are following clinical guidelines stipulating lifelong ART, and they are reminded that having an undetectable viral load provides virtual assurance that virus will not be transmissible ("undetectable = untransmittable") [13]. It may be difficult for study participants and their partners to discuss viral rebound and use protective measures in settings in which failure to take ART may be seen as a failure of personal responsibility.

As another method to reduce transmission risks, evidence-based inclusion criteria should be used to select for individuals who may be better able to navigate safe sex practices. For example, individuals with recurrent incident sexually transmitted infections other than HIV, or those who are struggling with substance use, may be engaging in sexual practices that could involve transmission risk. It is also critical to recognize that structural factors as well as individual characteristics affect individuals' risk of engaging in unprotected sex [14, 15]. Inclusion criteria should be based on evidence from behavioral and social science research [16] and not perceptions or anecdotes.

Using exclusion criteria to select individuals for research participation who are more likely to follow safe sex practices could be viewed as unfair, especially because some people have life circumstances that make it more difficult to follow safe sex practices, through no fault of their own. However, exclusion from research is a more salient concern about justice and fair access when research offers direct clinical benefit. In fact, HIV cure research is at a relatively early stage of development, and at present, none of the HIV remission studies to date have been clinically beneficial. (It is true that participants may experience psychological benefit and may value the compensation provided, extra attention from expert clinicians, or other experiences of research participation.) Hopefully at a future time point, HIV remission strategies will be more developed, offering clinical benefit to study participants and ultimately to patients. However, at this stage, given that research is largely nonbeneficial, the question of fairness in access to research does not outweigh concerns about the possibility of transmitting HIV to sexual partners, and a cautious approach to enrollment is warranted.

In sum, addressing risks and benefits in studies that include ATIs will entail addressing nonparticipant risks as part of researchers' overall ethical obligation to study participants and their communities. There are 4 layers of responsibility: (1) researchers' obligations to study subjects; (2) researchers' obligations to the partners; (3) subjects' responsibilities to partners; and (4) partners' obligations to practice safe sex in general. Researchers can discharge their ethical responsibilities in several ways: offering risk reduction measures to study participants; enrolling partners and offering prevention methods; and

using evidence-based criteria for enrolling individuals who are well-situated to handle these risks.

Notes

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