



Ethical issues in HIV remission trials

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Purpose of review

Several promising experimental pathways exist for long-term control of HIV in the absence of antiretroviral therapy (HIV 'remission') and are now being tested in early clinical studies. These studies can be invasive and pose a host of distinctive risks to participants, as well as to nonparticipants, especially to participants' fetuses, and sexual partners.

Recent findings

Ethical analyses of these studies have mainly focused on the risks to study participants. They recommend, and some investigators implement, procedures to mitigate risks for participants or to offset them with direct, indirect, and nonmedical benefits. They also suggest ways to keep participants' consent highly voluntary and informed. Rarely do ethicists propose keeping the social value of studies high. Of these recommended responses, only the latter, rarer proposals help address the risk to nonparticipants, as would some novel ways to address that risk.

Summary

HIV remission studies pose a number of ethical dilemmas. Many current investigative approaches put the participant at significant risk, but well established guidelines exist for mitigating this risk. Ethical issues that are not being fully addressed include risk to nonparticipants and the need to consider the societal value of studies, for example, their prospective impact on the global HIV burden.

Video abstract

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Keywords

analytic treatment interruption, HIV cure-related studies, human subjects research, immunotherapy, research ethics

INTRODUCTION

A sterilizing cure – complete eradication of all replication-competent HIV in an individual – has most likely been achieved in one case; however, this case would be challenging to replicate and, with current technology, impossible to scale. Therefore, current HIV cure-related research focuses primarily on achieving a long-term functional cure, or 'remission'. We define remission as undetectable viremia for a given period (yet to be defined) without antiretroviral therapy (ART), and without either CD4+ T-cell loss or HIV symptoms or potential for HIV transmission [1^{••}].

An ethical challenge in many early-phase HIV cure-related studies is the high risk to individual participants from toxicity, invasive diagnostics, and analytical treatment interruptions (ATIs). These risks accrue to individuals who are typically otherwise healthy and stable on ART, in contrast, for example, to risky early-phase studies of cancer [1^{••},2,3,4[•]]. There is no standard set of ethical guidelines governing these risks to the individual, but

current guidelines apply to any experimental therapy.

In this perspective, we summarize these standard risks, but also discuss issues that are more unique to studies of HIV remission. For example, as there is no standard biomarker for a remission study, many if not most studies include an ATI, which poses risks not only to the participant but

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Curr Opin HIV AIDS 2018, 13:422–427

DOI:10.1097/COH.0000000000000489

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KEY POINTS

- Many studies that seek to achieve HIV remission create risks for study participants as well as to some study nonparticipants (namely, sexual partners and fetuses).
- Potential strategies to address that risk ethically include mitigating the risk, special participant selection criteria, informed consent, community engagement, enhancing benefits to participants, and relying on the social value of studies.
- Although each of these strategies helps somewhat, some of the risks involved require studies of especially high social value to be justified.
- Such high social value can only come from studies to develop interventions with a real chance of a large denture at the global burden of HIV, and hence potential for global scalability.

also to his or her sexual partners. In addition, as the main beneficiaries of any remission strategy are expected to be those who cannot access life-long ART, it seems reasonable to advocate for a scalable intervention that can be distributed globally when deciding which strategies to pursue.

PERSONAL RISK

The risks of remission studies accrue to active arm participants, placebo arm participants, and nonparticipants, including sexual partners and fetuses.

Risk for active arm participants

Risks to active study participants in remission studies come from toxicities and invasive diagnostic exams, as well as ATIs. First, many of the drugs currently trialed for HIV remission have known toxicities. This is accentuated by the growing appreciation that rapidly emerging advances in cancer immunotherapy have direct implications for achieving an HIV remission [4[¶]]. In particular, checkpoint inhibitors such as anti-programmed death-1 (anti-PD-1) – now standard care for metastatic melanoma and other cancers – are being carefully moved into the HIV remission arena. Anti-PD-1 therapy can cause autoimmune diseases of the skin, gut, and other organs, and fatal reactions are possible [5,6]. Other interventions for boosting immune response in cancer and potentially in HIV (either for a sterilizing cure or for remission) involve the use of gene modified T cells and gene editing approaches; known and unknown toxicities are major concerns for these approaches as well [7].

Combination therapies are now seen as the most promising approaches [8], but create an added layer of uncertainty – how do partly known effects interact? [9]. Additional risks and burdens come from invasive diagnostics.

In the absence of a viable biomarker for the reservoir, many cure-related trialists are appropriately measuring the impact of their intervention by interrupting ART. In sterilizing cure studies, in which the goal is to simply determine if an active infection persists, the resulting complications are theoretically manageable with frequent monitoring and a clear plan to resume ART should the virus rebound [10]. But in remission studies, the goal is not to determine if the virus is present, but rather to determine if the immune system can respond to the rebounding viremia and eventually bring it down to low or undetectable levels. These so-called set-point ATI studies need to allow for a period of high-level viremia that is expected to be transient [6]. Thus, in many remission studies, ART resumption might be preceded by adverse results, for example, acute retroviral syndrome, selection of drug-resistant HIV, immunodeficiency and irreversible harm to immune system, and reseeding of the reservoir [11[¶]]. It should be noted, however, that recent studies indicate that when treatment interruptions are done carefully and in a monitored setting, they need not be associated with either the emergence of a drug-resistant virus, or manifest expansion of the viral reservoir [10,12–15].

Risk for placebo arm participants

A placebo arm can be key to interpretable findings, and hence to defensible research. Yet participants in placebo arms of remission trials can face the risks of diagnostics or of ATI with no therapeutic prospect from the intervention being tested [16[¶]]. Placebo arms are easiest to justify when there is no risk for those randomized to that arm from diagnostics and no ATI is planned. But some assume that when an ATI is unavoidable, placebo arms are illegitimate [17], whereas others only recommend proceeding with special care [16[¶]]. No consensus exists on that question [16[¶]].

Risk for sexual partners

Interrupting therapy and allowing even transient episodes of high-level viremia poses clear risks to nonparticipants. A study participant's ATI and the acute viremia that results in some remission studies deprive his or her sexual partner(s) of a highly efficacious protection from infection [18]. It thus exposes them (and their other sexual partners, and

Table 1. Summary of discussion

Attempted ethical responses to the risk	Risk			
	Affecting active arm participants	Affecting placebo arm participants	Affecting sexual partners	Affecting fetuses
Mitigation risk for participants	✓	✓	–	–
Mitigating risk for nonparticipants	?	?	✓	✓
Special selection criteria	✓	✓	✓	✓
Informed consent	✓	✓	?	?
Community engagement	?	?	–	?
Enhanced benefits	✓	✓	–	?
Social value	✓	✓	✓	✓

The table lists attempted ethical responses to risks from remission studies and categorizes how relevant each response is to the risks to various populations.

their partners, and so forth) to the risk of being infected.

Risk for fetuses

A study participant’s ATI would also deprive her fetus of the protective effect of ART and put it at risk of becoming infected with HIV. In some gene therapy remission studies, germ-line changes that would risk fetuses and even their progeny are also possible.

PROPOSED ETHICAL RESPONSES TO THE RISK

Several strategies seek to address ethically the risks from remission studies to each of these populations (refer to Table 1 for a summary of the discussion).

Mitigating risk to participants

The most obvious ethical response to a risk is to build in safeguards that reduce the hazard that any adverse event will occur or contain its consequences [19–21]. Many strategies have been proposed to reduce the risk faced by study participants. These include, among other things, very intense mathematical modeling and greater use of animal models before turning to human participants [19]; excluding invasive diagnostics from the study procedures [22]; replacing intense, one-time administration of large doses of toxic interventions with a gradual increase in dosing [9]; frequent monitoring and, in the case of ATIs, predetermined CD4+ and HIV RNA thresholds for resumption of ART [11[¶], 16[¶]]; and preparing to provide new lines of ART should drug resistance emerge [16[¶]]. For mitigating risk to placebo arm participants, one strategy is strict reliance on historical controls [17], though it risks confounding study results.

As important as mitigating risk to participants is, it does not address the ethical complications arising from risk to nonparticipants.

Mitigating risk to nonparticipants

Much less standard in research ethics is addressing risk from trials to people who are nonparticipants [23], nevertheless some strategies do exist. For example, in HIV remission studies with an ATI that put sexual partners of participants at risk for transmission, study procedures may include counseling on safe sex practices or provision of preexposure prophylaxis to stable sexual partners of study participants [11[¶]]. Isolating study participants whilst deemed infectious is regularly used in challenge studies [24], and bioethicists have proposed isolation for infectious disease research more broadly [25]. However, in the HIV context, isolation may curb personal liberty too much compared with the magnitude of risk.

A common strategy for averting transmission to fetuses is excluding pregnant women from the study and asking ones of a reproductive age to use two forms of contraception. But this strategy may dissuade female patients from participating in studies.

Special selection criteria for study participation

Many studies try to avoid risk by recruiting participants who are at low risk [e.g., in the case of remission studies with an ATI, excluding candidates with a history of centers for disease control and prevention category C clinical events (1993) or those with cutaneous Kaposi’s sarcoma [11[¶]]]. Again, this strategy need not address protection of nonparticipants (except when the exclusion criterion serves both purposes, e.g., excluding from these studies candidates with a record of a high viral load

setpoint). Significantly, other studies respond to the risk by focusing recruitment on candidates who are in important ways at high risk. A high portion of remission studies [26] and about half of current gene-therapy-based HIV cure-related studies [26], are specifically done in HIV-infected cancer patients. First, as described earlier, similar strategies are being used to fight cancer [6], and there is greater hope for a therapeutic effect for cancer, HIV, or both, in that population. Second, one could argue that if worst comes to worst, it is ethically preferable to have shortened the life of a terminal or highly advanced patient (because of her cancer comorbidity) than the life of someone who is otherwise healthy. Indeed, a bold proposal is to focus specifically on patients who are at the end of their lives [27[■]].

Informed consent

With fully informed consent, it can be possible, rational, and permissible for a person to sacrifice selfish interests for the sake of a noble cause [28]. Taking risks in HIV-cure-related studies is a case in point [21,29[■]] – as is sacrificing a kidney for others. There are many indications that people living with HIV (PLWHIV) are enthusiastic to contribute to cure-related research [30,31,32[■]], and this is anecdotally familiar to many investigators.

Evoking the notion of a ‘therapeutic misconception’ in clinical studies, some commentators have warned, however, that cure study participants may be subject to a ‘curative misconception’ [33,34]. By that suggestive term they may have meant that study participants could be overoptimistic about the chance for and the benefits of being cured, of the paucity of study-borne side effects, or of the investigators’ goal to promote participants’ clinical interests. Additional work warned that consent forms in cure-related research can be misleading [35,36].

Activists and ethicists have implored for trusting cure-related study participants to make highly intelligent decisions on what is acceptable to them, both in general [37,38[■]] and in remission studies with an ATI in particular [39[■]]. Interviews may suggest that participants in cure trials have been informed [32[■]] and remain satisfied with their decision to participate in hindsight, even after suffering from side effects [37,39[■]]. Even PLWHIV who express theoretical high willingness to contribute to cure research seem responsive to risks and benefits [32[■],40].

Nevertheless, two specific complications about reliance on personal consent arise in remission studies. First, only empirical investigation can rule out the possibility of what one may call ‘curative

misconception #2’: both PLWHIV [41,42] and cure-related trial participants [30,31] are excited about a sterilizing cure far more than about mere remission. It is not impossible that in risky remission studies, some of the eagerness to participate reflects confusion between the two types of ‘cure-related’ research [43]. In other words, a misconception of remission studies as sterilizing cure ones may turn out to help drive participation in the former. Inasmuch as that is the case, remission study participants’ consent would be less than fully informed, somewhat undermining its justificatory contribution.

A second complication can arise even when a candidate participant’s consent is fully informed and voluntary. The participant’s consent does not address the ethical challenge of risk created to non-participants, for example, to the participant’s sexual partners.

Community engagement

To address risk to nonparticipants, some of the ethics literature proposes community engagement [25], and it has become common to interview PLWHIV and community advisory boards on these matters [16[■]]. However, in the area of risk of infection to nonparticipants like unstable sexual partners, the relevant community would need to be a large group of uninfected individuals, which is not a community that is easily reached or that has representatives.

Enhanced benefits

Several bioethicists recommend offsetting any remaining risks in cure-related studies by appealing to or enhancing the many potential indirect benefits of study participation, both medical and non-medical [40,42,44]. This has been proposed for addressing the risks from ATI studies [39[■],45[■]].

But these indirect benefits would be to the participants, and not necessarily to the party at risk. For example, a sexual partner at risk does not get anything when a participant gains in her medical care, social standing, or financial standing from trial participation.

Social value

To ensure that risks to all parties in HIV remission studies and cure-related research in general are justified, it remains necessary to ensure that these studies serve a very urgent social purpose, one that justifies placing some individuals at serious risks as is often unavoidable in this enterprise. Leading

antiutilitarian ethicists have opined that great importance for other individuals' health can also be near-sufficient for justification [46,47,48¹¹]. Here, satiating our scientific curiosity or making nonreplicable medical breakthroughs is not enough. We need to ensure that cure-related research in general and remission research in particular continues to pursue strategies that have potential for scalability on a global level, and a real chance of one day making a large dent at the global burden of HIV. Nowadays, HIV-infected individuals who are able to access, tolerate, and adhere to ART can expect to have a near-normal life span. A curative strategy that rids HIV-infected people with access to ART of the inconvenience, stigma, and personal costs still associated with taking it would be of value; however, the potential to generate immense societal value, and the surest ethical justification, belongs to trialing strategies that, if successful, would help promote access for the nearly 50% of PLWHIV around the world who are currently not accessing ART [49]. For this reason, and because the nature of the disease differs between rich countries and low and middle-income countries [50¹²], there is an ethical imperative to test remission strategies in low and middle-income countries [49,50¹³].

CONCLUSION

The strategies that would work for each type of population at risk are summarized in Table 1. As the table indicates, an unavoidable source of justification for the risks of HIV remission studies is the societal value of that science. This has practical implications for the choice of which strategies to prioritize for research and which countries to test them in.

Acknowledgements

We would like to thank Rebecca Kahn for her assistance with the study.

Solicited contribution for the issue: 'Progress in achieving long-term HIV remission' (eds. Jean-Daniel Lelièvre and Timothy Henrich).

Financial support and sponsorship

The current work was supported by NIAID grant NIAID grant R01AI114617 (HIV cure studies: risk, risk perception, and ethics), the amfAR Institute for HIV Cure Research (amfAR 109301), and the Delaney AIDS Research Enterprise (DARE; A127966).

Conflicts of interest

S.G.D. receives research support from Merck, Gilead, and ViiV Healthcare and is a scientific board member for

Bryologix and Enochian. Rest of the authors have no conflicts of interest.

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