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Ethical considerations in HIV cure research: points to consider

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Abstract

Purpose of review—Research directed toward an HIV cure presents ethical as well as scientific challenges.

Recent findings—International guidelines, regulations, and the medical literature provide helpful guidance on protecting research participants.

Summary—This review presents points to consider for researchers, sponsors, oversight committees, community advisory boards, and HIV advocates to help resolve ethical challenges that are particularly complex or difficult or that are not adequately addressed by current ethical guidelines. The points to consider are: collaborative partnership among international scientists from both the private and public sectors, as well as engagement of HIV-affected communities, social value, scientific validity, fair selection of participants and study sites, a favorable and acceptable risk–benefit balance, independent scientific and ethical review, informed and voluntary consent, and respect for enrolled patients and communities. To prevent therapeutic misconception, participants' comprehension of key features of the study may need to be assessed. Participants who suffer study-related adverse events should receive appropriate medical care and compensation. If interventions are shown capable of curing HIV, sponsors and international funding agencies should plan how to make them available and affordable in resource-poor countries.

Keywords

ethics; HIV cure; research

INTRODUCTION

A cure for HIV would be a significant and widely influential benefit for the world, but research directed toward an HIV cure must carefully address ethical considerations to protect human participants. International guidelines, regulations, and the medical literature

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Conflicts of interest

The authors have no conflicts of interest.

provide helpful guidance [1,2,3■■,4■■]. This article offers points to consider for those who are designing, conducting, reviewing, or evaluating HIV cure research, focusing on the difficult and complex ethical issues that may not be resolved by the straightforward application of current ethical guidelines and practices.

ETHICAL CONSIDERATIONS IN CLINICAL RESEARCH

Innovative HIV research is aiming to find effective ways to eradicate HIV from the body – to find a cure for HIV. Even in patients on antiretroviral therapy (ARV) who have undetectable viral loads, HIV remains latent in the body. HIV cure research aims to further our understanding of this viral latency and to find well tolerated and effective means of eliminating HIV reservoirs or controlling HIV replication in the absence of antiretroviral therapy. If latent reservoirs of HIV as well as replicating virus could be eliminated, HIV-infected persons would not need lifelong ARV, which has considerable long-term adverse effects. Finding a cure for HIV would not only 'improve the health and quality of life for those with established infection' but would also have important benefits to society by reducing the risk of virus transmission and ultimately allowing resources to be shifted to other pressing societal needs [5]. If made widely accessible in resource-poor countries and communities, an HIV cure could also reduce disparities in HIV care.

Clinical research on HIV latency, eradication, and possible cure poses substantial ethical challenges. Although the potential benefit to humanity of curing HIV would be enormous, benefit to research volunteers, especially in the early trials, is likely to be small or nonexistent. In addition, there are unknown and possibly significant risks associated with the range of interventions and studies currently being discussed and, in some studies, with the discontinuation of effective and well tolerated antiretroviral therapies for extended periods of time. As the hope for a cure may be great, it will be imperative to assure that those who volunteer understand and willingly accept these risks and uncertain benefits.

International guidelines, regulations, and the medical literature provide guidance that should be followed in all ethical translational and clinical research, including HIV cure research [1,2]. Significant work on the ethics of HIV-related research, including that from UNAIDS/WHO and the US HIV Prevention Trials Network on ethical issues in HIV prevention research may be particularly useful [3■■,4■■]. These established guidelines provide an ethical foundation for research directed to a cure for HIV. However, the innovative nature of HIV cure research presents novel challenges to research ethics, and ethical standards and oversight for HIV cure research must be as rigorous and cutting-edge as the science.

In this article, we offer points to consider for those who are designing, conducting, reviewing, or evaluating HIV cure research to assist with the ethical issues that are likely to be particularly complex or thorny and may not be resolved by the straightforward application of current ethical guidelines and practices. The specific ethical issues pertinent to any given study – and how they will be resolved – will depend on the intervention being studied and the protocol details. The points to consider summarized in Table 1 can help

investigators, sponsors, regulatory bodies, community advisory boards, and patient advocates assure that important ethical issues in HIV cure research are not overlooked.

Although we recognize that there are significant ethical complexities involved in preclinical HIV cure research, research with animals, and decisions about priorities and allocation of limited healthcare resources, in this article we focus only on issues related to clinical research with humans.

In all clinical research including HIV cure research, balance must be achieved between the important goal of generating useful knowledge about human health and the need to protect those who volunteer to participate. Table 1 summarizes ethical considerations particularly salient in HIV cure research, using an established framework for ethical research [6■■].

Collaborative partnership

Finding a cure for HIV will require the collaboration of international scientists from both the private and public sectors, as well as the engagement of HIV-affected communities. Collaboration between academe and industry and among for-profit companies that are traditional competitors may accelerate the development of standards and methodologies to identify reservoirs of latent infection, allow early detection of viral replication in serum, or identify those patients likely respond to interventions or be more susceptible to adverse effects [7]. Sharing such discoveries would benefit all investigators working on HIV cure research; advancing this common good, however, may require some scientists or companies to forego short-term advantages over competitors.

Communities of people infected with and affected by HIV should be engaged in helping to determine HIV cure research priorities, limits of acceptable research risk, and reasonable strategies for recruitment and inclusion.

Social value

Research directed toward an HIV cure should be organized in ways that foster scientific progress and move the science forward in useful ways. HIV cure research will proceed along many different approaches and will require diverse scientific expertise and frank and constructive interchange of ideas and findings. As the field advances, there may be a tension between sharing knowledge openly in pursuit of a common goal and keeping trade secrets essential to the development of a commercial product.

Timely publication of study results, including negative findings and adverse events is important to move valuable scientific findings forward. In this cutting edge and rapidly moving scientific area, publishing serious adverse events and negative findings is critical to avoid harm to patients and inappropriate diversion of research resources, even when not publishing may be regarded as providing shortterm business advantage to sponsors [8].

Academic principal investigators should have full access to primary data and the right to publish scientific findings, and as always, should take responsibility for their publications [9]. Timely and full dissemination of scientific discoveries will accelerate progress toward the humanitarian goal of curing this fatal infection.

Scientific validity

Each HIV cure study should be designed to provide a rigorous answer to the valuable scientific question, as determined by the review process described below. Priorities developed by the International AIDS Society for HIV cure research include identifying and testing agents capable of interrupting viral latency and persistence and the molecular pathways that initiate and maintain latent virus, and ways of manipulating the immune system to cure HIV. Studies should have sound scientific design, an adequate sample size, and reliable statistical plans.

Fair participant selection

The selection of participants and study sites must be equitable, while also consistent with the imperative to protect participants and carry out a scientifically rigorous study. The implementation of this general principle will depend on the specifics of the study. If the study involves a highly invasive and risky procedure, such as bone marrow transplantation, the study sites must have the expertise and facilities to carry out the procedure safely and to address reasonably foreseeable complications. Early studies of proof of concept should be conducted at sites capable of careful ethical review, timely data collection, and frequent monitoring of participants. Ultimately, if the promise of cure is to be meaningful in resource-poor countries, it is also important to ensure that studies are planned and carried out in a timely manner to evaluate the efficacy and safety of the interventions in these settings.

Eligibility and exclusion criteria will depend on the specifics of the study. In certain studies, it will be appropriate to enroll healthy persons whose viral loads are undetectable on highly active antiretroviral therapy. Early studies should enroll only those who have the capacity to voluntarily consent for themselves. HIV cure studies should include women, including women of reproductive age, if rigorous data are to be gathered on the effectiveness and safety of the intervention for them, including implications for reproductive health.

If well designed trials show that HIV cure can be safely achieved in adults, the results cannot be extrapolated to children. Thus, if children and adolescents are to benefit from HIV cures, they must also be research participants. Difficult dilemmas can be posed by the countervailing ethical guidelines of protecting vulnerable children from the risks of research and including them to provide an evidence basis for their care. Because children are vulnerable as clinical research participants, the level of risk in pediatric HIV cure research should be carefully scrutinized and limited compared with the research risks that competent adults may agree to. Regulations and guidance suggest enrolling children in HIV cure research only when the anticipated level of risk is a minor increase over the risk they would experience in clinical care or if the research project offers a clinically meaningful prospect of direct clinical benefit to the child participants [10].

Adherence to follow-up is crucial to determine the effectiveness and safety of interventions directed at cure. Therefore, in studies to demonstrate proof of principle and in pivotal clinical trials, participants should be excluded if they have conditions that could significantly compromise adherence, such as homelessness and substance use.

Risks and benefits

Anticipated risks and potential benefits of research projects must be clearly described in each protocol, and the risks must be minimized and acceptable in relation to the prospective benefits. Early phase clinical trials, such as dose-finding studies and short-term safety studies, will not offer personal benefit to participants. Studies could also pose significant or uncertain risk to participants, for example, those designed to mobilize latent virus. Certain cure studies will ask participants who have undetectable viral loads while on antiretrovirals to stop taking these well tolerated and effective drugs for extended periods. The risk of viral rebound must be carefully monitored and procedures in place to reinstitute antiretrovirals when this occurs. If it is possible that participation in an early HIV cure study could make individuals ineligible for later studies or future beneficial interventions, these risks should be taken into account.

In some studies, participants may be asked to undergo invasive procedures solely for research purposes to advance science. To document that reservoirs of HIV infection are eradicated by an experimental intervention, for example, researchers may want to biopsy liver, bone marrow, or lymph nodes. Although research participants may have previously received these procedures as part of their clinical care, they need to understand that in this setting these research procedures are not for their personal benefit. Review bodies should determine that such research biopsies are necessary to achieve an important scientific objective and are carried out in ways that minimize risks to participants [11].

With some interventions proposed in HIV cure research, such as extended administration of histone deacetylase inhibitors, participants face possible long-term risks, such as an increased risk of carcinoma. In contrast, in other studies the research intervention may not pose additional risks beyond those in standard clinical care. For instance, in patients receiving a bone marrow transplantation for treatment of HIV-related lymphoma, transplantation from donors who are homozygous for the CCR5 gene variant 32 (CCR5 D32/D32), who do not express CCR5, may pose no additional risks beyond the risks of the clinically needed transplantation.

Independent review

The study protocol must undergo coordinated scientific and ethical review, approval from appropriate ethics committees, institutional review boards, and regulatory agencies. Such oversight helps assure that the results of the study will be valid and that humans will be adequately protected. In addition, the study should be reviewed by appropriate community advisory boards to assure that risks are appropriately identified and that concerns of participants and their communities are addressed.

Informed consent

Participants must give informed and voluntary consent to participate in HIV cure research. Because HIV research involves innovative interventions and unknown, potentially serious long-term risks, participants will be best protected if they give informed and voluntary consent for themselves, weighing for themselves the risks and potential benefits of participation. Participants must be fully informed that potential negative effects of some

interventions are largely unknown and some of the effects may only be detected in the longterm. In early studies, informed participants will need to decide whether to assume risks and inconvenience in order to advance scientific knowledge and benefit future patients. Therefore, participants, particularly in early studies, must be aware that as the investigational intervention is highly unlikely to have a direct benefit, following analytical treatment interruption, participants should resume their antiretroviral therapy. Participants must be made aware if participation in early studies could negatively influence their eligibility for later studies or for receiving beneficial interventions. Because the assessment of risks and benefits in these early studies is a complex and value-dependent decision, patients who lack decision-making capacity and need surrogate permission should not be enrolled. In HIV cure clinical trials whose interventions may pose significant long-term risks, HIV-infected patients who are eager for a cure might have unrealistic expectations of personal clinical benefit or fail to appreciate long-term risks. To guard against such therapeutic misconceptions, it may be appropriate to require a more extensive informed consent process than is customary, including formal assessment of the participant's understanding of key features of the protocol [12]. Review of the protocols and consent forms by community advisory boards will also help to ensure that study descriptions are understandable to participants and that participant concerns are addressed.

Consent should be an ongoing process and not a one-time event before a study begins. New knowledge that might change the assessment of risks and benefits of the study or participants' willingness to continue should be reviewed and investigators may need to reconsent participants. Generally, in such highly innovative research, investigators should try to interact with participants as partners, keeping them well informed about results as they are presented and published and other new developments in the field. Remuneration or payment to participants should be appropriate to reimburse expenses and recognize participant time and contribution, but should not be so high as to distort participants' judgment about risks and benefits [13]. If invasive procedures are carried out solely for research purposes, the amount of compensation should be discussed with appropriate review bodies, including advisory boards and patient advocacy groups, and should be consistent with compensation for similar procedures carried out solely for research purposes in other studies.

Respect for enrolled participants and communities

Throughout the study, participants' clinical situation should be carefully monitored, and steps taken to minimize negative effects of rebounding virus or serious adverse events. Protocols should include well thought out stopping rules to protect the safety of participants and the integrity of the study. Solid procedures for protecting the confidentiality of participants' data and clinical status should be in place. As described above, participants should be informed about findings from their and other relevant studies.

Compensation for study-related injury Sponsors should put in place appropriate protections for persons who are injured as a result of study participation. Participants who suffer study-related adverse events should receive appropriate medical care according to international standards at no cost to them. Such compensation for injuries is particularly important if

participants develop serious medical conditions, such as cancer, as a direct and proximate result of study interventions.

Posttrial access to interventions that are demonstrated to cure HIV infection

In order to make a difference in the world-wide epidemic, some HIV cure clinical trials will be carried out in high-prevalence populations that pose challenges because of poverty or lack of resources in the community. Sponsors and international funding agencies should plan proactively how to make interventions demonstrated to cure HIV infection available and affordable in these challenging settings, provided that such access is consistent with priorities of the country or region [14]. For persons who have concurrent conditions such as substance abuse or homelessness, supplemental strategies that have been developed and demonstrated to increase adherence to medication regimens may be needed to achieve cure.

Communities and individuals who participate in HIV cure research should receive fair benefits for their participation

During the planning and implementation of HIV cure research, issues such as technology transfer, active collaboration with community-based organizations and healthcare providers, and community education need to be discussed.

CONCLUSION

Ethical HIV cure research should include considerations important to all clinical research, those more particular to HIV intervention research, and the specific challenges that inhere in testing interventions to cure HIV. A cure for HIV would be a significant and widely influential benefit for the world, but the process of identifying and testing possible interventions to cure HIV must proceed with careful attention to ethical considerations essential to protecting human participants in clinical research. These points to consider will hopefully facilitate this important effort.

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Papers of particular interest, published within the annual period of review, have been highlighted as

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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KEY POINTS

- Researchers, sponsors, oversight committees, community advisory boards, and HIV advocates need to address collaboratively the ethical challenges in research directed toward an HIV cure.
- To assure scientific progress, researchers must publish study results in a timely manner, including negative findings and adverse events.
- In HIV cure clinical trials whose interventions may pose significant long-term risks, the informed consent process should include formal assessment of the participant's understanding of key features of the protocol.
- To assure equitable posttrial access to interventions that are demonstrated to cure HIV infection, sponsers and international funding agencies should plan how to make them available and affordable in low-resource settings that bear the greatest burden of the epidemic.

Table 1

Points to consider in HIV cure research

Principles	Applied to HIV cure research	Challenges
Collaborative partnership	Finding a cure for HIV will require the collaboration of international scientists from the private and public sectors, as well as engagement of HIV-affected communities and other stakeholders	Public–private sector collaboration is needed
		Scientists from different specialties and geographic areas will need to work together
		The voices and input of those infected with and affected by HIV are critical
Social value	Research directed toward an HIV cure should be organized in ways that foster scientific progress and move the science forward in useful ways. Research relevant toward finding a functional or sterilizing cure for HIV can build on the IAS road map for HIV cure research	Preclinical and animal studies are necessary to provide a foundation for clinical trials
		All findings from HIV cure research, including negative findings, are important to disseminate
Scientific validity	Each HIV cure study should be designed to provide a rigorous answer to the valuable scientific question related to curing HIV	Stepwise and deliberate design is necessary to ensure safety and dosing and demonstrate proof of concept before wide-scale clinical trials are initiated
Fair selection of participants	The selection of participants and study sites must be equitable, also consistent with the imperative to protect participants and carry out a scientifically rigorous study, and guided by considerations of the equitable distribution of the benefits and burdens of HIV cure research	Early phase studies should enroll male and female adults who can provide their own consent and who are willing to assume risk for the benefit of others. HIV cure studies will include HIV-infected persons who are stable on long-term antiretrovirals, those who are sick with HIV-associated illnesses such as lymphoma, and healthy volunteers. Studies with children and adolescents should follow with promising interventions found well tolerated in adults. Sites should be selected that have the scientific, logistical, and ethical capacity to conduct the specific trial
Favorable risk–benefit balance	Research risks must be minimized and acceptable in relation to the prospective benefits to study participants or of the knowledge to be generated	In early trials, participants will assume risks without the prospect of direct benefit. Risks are uncertain and could be significant. Risks include those associated with interventions being studied, the risk of viral rebound after stopping long term antiretroviral therapy, the risks of research procedures that might be invasive, and the risk of possible long-term adverse events
Independent review	Each study protocol should undergo coordinated scientific and ethical review, approval from appropriate ethics committees, institutional review boards, and regulatory agencies	Multiple levels of review and oversight will be essential to assure scientifically and ethically appropriate research acceptable to relevant communities

Principles	Applied to HIV cure research	Challenges
Informed consent	Participants should give informed and voluntary consent	Special effort should be made to assure that participants in early studies understand the potential risks and lack of direct benefit. Understanding should be carefully assessed especially because of the possible distorting influence of a desire for a cure
Respect for enrolled participants and communities	Individuals who accept the risks associated with finding a cure for HIV should be carefully monitored, have their rights protected, receive compensation for any research related injuries. Plans should be in place regarding how interventions found safe and effective will be available and affordable to research participants and communities	Monitoring systems should be in place to allow rapid intervention for individuals whose virus rebounds or who suffer adverse events. Medical care should be provided for those who suffer any research related injuries. Discussions and planning for making successful interventions available should start early in the clinical trial process