

The ethics of HIV cure clinical research among acutely infected adults: points for consideration

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Abstract

A better understanding of acute HIV infection is important for HIV research, including research towards a cure. However, recruiting and retaining acutely infected individuals to HIV cure clinical trials may present special ethical challenges. Significant gaps in current knowledge exist concerning their involvement in HIV cure research. The purpose of this paper is to address how the social contexts, personal dimensions, and other factors related to acute HIV infection may contribute to ethical challenges in HIV clinical research. We identify five ethical domains of potential concern, each related to a stage of research design, which may help guide acute HIV cure studies moving forward.

Methods

An intensive literature review focused on:

• Social and psychological/emotional experiences during acute infection

• The ethics of clinical research within HIV treatment, prevention, and cure-related studies

The aim of this review was to identify potential areas of ethical concern related to the involvement of individuals diagnosed during acute infection in HIV cure clinical research. Our goal was to develop a preliminary set of ethical points to consider regarding the recruitment, retention, and care of these research participants.

Background

Acute HIV infection refers to the first weeks following HIV transmission, a time when no antibody is detectable,¹ yet individuals are most infectious.²

While recent years have seen promising advances in the quest for a cure, one of the greatest remaining challenges is *HIV's ability to form reservoirs of latently infected cells*.³ Increasing interest in interventions to reduce and eliminate these reservoirs has led HIV cure researchers to focus on people diagnosed during acute HIV infection.

Acutely infected individuals treated with combination antiretroviral therapy (ART) may display certain research-advantageous immunological characteristics⁴ compared to patients diagnosed and treated at later stages of infection. Foremost among these characteristics may be *smaller latent HIV reservoirs*.⁷

In June 2015, the Treatment Action Group listed at least 12 HIV cure studies (see Figure 1) specifically involving individuals diagnosed during acute infection.⁸

Results

The social, behavioral, and psychological contexts of acute HIV infection

- Acute infection may represent an especially difficult, confusing, and overwhelming period. Diagnoses made during acute infection have been linked to experiences of distress, anxiety, depression,⁹ anger and guilt,¹⁰ decreased interest in sex,¹¹ and other morbidities, including alcohol or substance abuse disorders.¹²
- While patients diagnosed with acute and chronic infections may tend to have similar diagnosis experiences, including shock, hopelessness, and detachment,¹³ existing research suggests that acute experiences may be subtly, yet remarkably different. These differences may warrant special ethical attention for clinical research:
 1. Most acutely HIV infected individuals experience noticeable yet ambiguous ('flu-like') symptoms (see **Figure 2**) which may be misdiagnosed, leading to confusion.⁹ Such experiences may contribute to doubt, suspicion, or incredulity concerning care-providers and the medical system.
 2. Some predictors of HIV clinical outcomes (e.g., HIV phenotype) are pending at the initial diagnosis of acute HIV infection. Acutely infected individuals therefore may be provided with comparably less or less precise information about their prognoses.¹⁰
 3. Acutely infected patients may have a better understanding of the risk behaviors or sex partners that led to their infections, possibly leading to more clearly directed anger toward their partners.¹⁰
 4. Post-diagnosis, all HIV patients are bombarded with new and potentially overwhelming information and asked to make important decisions regarding their care. Due to their heightened infectiousness and the increased benefits offered by ART,¹⁴ these decisions are especially urgent for the acutely diagnosed.

Potential ethical issues and strategies for risk mitigation

We identified five primary domains of ethical concern related to adults diagnosed during acute infection in HIV cure studies. These domains, and potential strategies for mitigating associated risks, are described in **Table 1**. **Figure 3** links these domains to stages of clinical research design.

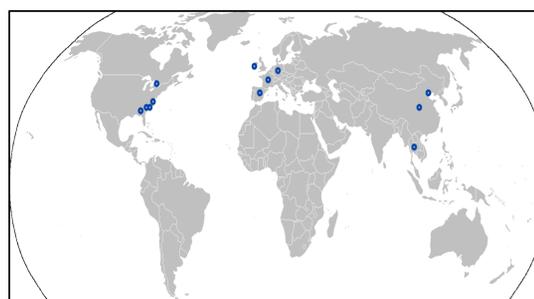


Figure 1. Locations of current HIV cure clinical research projects around the world involving acutely infected individuals.*

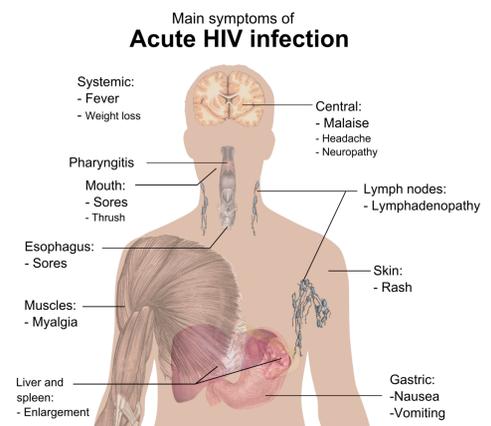


Figure 2. Acute retroviral syndrome**

Ethical concerns by stage of research

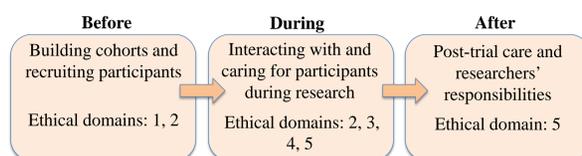


Figure 3. Stages of research (before, during, or after data collection) paired with possible domains of ethical concern as described in Table 1.

Table 1. Ethical domains, potential points of concern, and possible ways to mitigate risks

Ethical domains	Potential points of concern	Some possible ways to mitigate risks
1 Identifying, building, and interacting with acute HIV research cohorts and communities	- Defining and monitoring groups at 'higher risk' - Responsibility for HIV seroconversion among monitored populations - Stigmatizing or further marginalizing already vulnerable groups	- Identifying acutely infected individuals through cohort alternatives (e.g. referrals from testing centers or primary healthcare providers) - Provide 'standard of prevention' - Application of a robust human rights framework - Community engagement activities and participatory research practices
2 Recruitment and voluntary informed consent	- Attaining informed consent soon after diagnosis - Therapeutic or curative misconception - Recruitment by care-providers	- Whenever possible, recruitment and consent should not take place immediately following an HIV diagnosis - Provide immediate mental health services - Staged consent procedures or re-consenting at set intervals - Non-clinical personnel should approach patients about research participation opportunities, not their primary caregivers ¹⁵
3 Transmission risks and partner involvement	- Structured or analytic treatment interruption and risk of partner infection - The effects of research participation on interpersonal (especially intimate) relationships - Social harms (e.g. stigmatization and discrimination)	- Inform partners of potential infection risks - Provide condoms to couples and/or PrEP to participants' partners; - Seek partner consent - Treat participants (and their partners) on a case by case basis - Take social harms and relationship-related risks seriously and include these during informed consent
4 Interactions and interventions with participants	- Risk of HIV re-infection - Undue pressure for participant retention (participants as 'precious resources')	- Inform participants about risks of re-infection - Ensure participant understands rights to discontinue study involvement at any time
5 Ancillary and continuing (post-trial) care and researcher responsibilities	- Mental health issues, substance abuse, other comorbidities including acute retroviral syndrome - Responsibilities for ancillary and continuing participant care	- Care should be provided when: participants have no viable alternatives, the care is relatively inexpensive, the participants would otherwise suffer, participants and researchers have an established relationship, and/or when the researchers owe a debt of gratitude. ¹⁶ - Mental health issues should be expected and resources for services should be provided

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Conclusions

- Acute HIV infection is an important period of HIV disease progression from multiple perspectives: individual well-being, public health transmission prevention, and development of HIV cure clinical research.
- Globally, HIV cure studies are at an early stage and the involvement of human subjects (especially the acutely infected) is just beginning. Therefore, it is imperative to move quickly to distinguish serious ethical worries from merely speculative ones.
- Current evidence suggests that acute HIV infection may introduce special ethical concerns that should be addressed during research design and ethical approval processes.
- Despite the widely accepted scientific importance of acute infection, significant gaps in current knowledge exist. Further research is required concerning:
 - a) how the social, psychological, and behavioral contexts of acute infection may impact recruitment, retention, and care of participants; and
 - b) how these issues may best be addressed in HIV cure clinical research protocols.
- These points of consideration and potential avenues for risk mitigation (see **Table 1**) may provide an initial foundation for ethical guidelines focused on research with people diagnosed during acute HIV infection.

Acknowledgements

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