What motivates participation in HIV cure trials? A call for real-time assessment to improve informed consent

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Abstract

HIV cure research, a diverse set of studies aimed at eradicating or greatly reducing HIV in latent reservoirs, has become a strategic priority for global AIDS research. However, in early-phase HIV cure research there are ethical challenges related to the uncertainty around potential risks and the risk–benefit balance. Similar to clinical trials in other disease areas, these concerns may impact clinical trial participants' comprehension and decision making. Here we suggest attention to the terminology used to describe HIV cure research that may promote therapeutic misconception, and exploration of the decision-making influences and processes of those who accept and decline participation in HIV cure trials. These data will facilitate efforts to improve protocols and informed consent based on an understanding of participant preferences and needs.

Keywords: HIV cure, decision making; clinical trials

'I believe that everybody expects to be cured of HIV, at least in 10 years. But the definition of HIV cure and expectations are different for everyone.'

Young adult Thai male with HIV [1]

Curing HIV has become a strategic priority for global AIDS research [2]. The NIH Clinical Trials database includes more than one hundred current or completed early phase clinical trials devoted to some aspect of HIV cure research [3]. These highly diverse studies employ a variety of approaches to eradicate HIV in latent reservoirs, including gene editing, therapeutic vaccines, ART intensification studies, latency reversing strategies and combination designs. Each features very different study designs and types and sources of potential risks. Many require participants to have demonstrated long-term viral suppression. Some introduce 'structured treatment interruption,' where ART is withdrawn under controlled conditions to examine the impact of a particular intervention [3].

The exciting prospect of clinical research aiming to cure HIV has also generated numerous commentaries on ethical aspects of these studies including developing an acceptable risk–benefit balance, and in some cases, focusing on how much risk and uncertainty is acceptable before a clinical trial can proceed [4–7]. Commenting on the potential for direct medical benefit for participants, Dubé and colleagues [8] describe HIV 'cure' trials as 'proof-of-concept studies designed to evaluate novel paradigms to reduce persistent HIV-1 reservoirs, without any expectation of medical benefit.' Evans [7] focuses on trial-related risk for participants who are relatively healthy, and Eyal and Kuritzkes [9] ask, 'Is it ethical to invite patients to volunteer for studies that replace safety with great uncertainty?'

Such commentaries focus attention on how participants in early-phase HIV cure research may balance perceived risks and benefits and manage uncertainty. The HIV clinical research community must grapple with these concerns, and address such practical questions as: within the constraints of applicable regulations, how much individual risk should be allowed in clinical trials for individuals who are 'healthy' on ART, especially when there may be major public health implications? How are benefits characterised and valued [10]? To offset risks for participants, what chance (if any) for direct medical benefit is sufficient? What about indirect benefits, such as enhanced care access (real or perceived), improved social support, and psychological benefits from participation? How should altruistic motivations and aspirational benefits to future patients be valued? How can research teams and institutional review boards make informed decisions when so much uncertainty exists about potential harms, benefits and participant preferences?

These issues are not, of course, unique to HIV. The ethics of early phase clinical trials, including the implications of how risks and benefits are presented and understood, has long been a focus of both conceptual and empirical bioethics literature (for examples, see [10–12]). Concerns about insufficient participant comprehension undermining informed consent have been studied in many clinical areas (see [13]). These concerns are especially relevant for early phase trials and for clinical areas with limited treatment options and a severe disease manifestation or progression. A phenomenon raising particular challenge to participant comprehension of trial risks and benefits is therapeutic misconception, first described by Appelbaum and colleagues in 1982 [14], and defined subsequently as when, '… individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial' [12]. Therapeutic misconception is orientated around deficiencies in understanding and knowledge of the research that may stem from the participant, the informed consent materials, and/or the clinical trial team. A contrasting framework is therapeutic optimism, which refers to a research participant's optimism for the best personal outcome, and does not necessarily compromise the decision-maker's autonomy or stem from a misunderstanding or lack of information [15,16]. In addition, trials have been shown to present a valued opportunity for participants to express optimism for better outcomes for themselves and others with the disease [17,18].

The potential impact of therapeutic misconception and optimism on clinical trial decision making deserves (and receives) continued attention (for example [19–21]). In HIV cure research, existing ethical concerns about acceptable risk–benefit balance, and uncertainty regarding levels of risk and benefit, will naturally lead

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to important questions about participants' clinical trial decision making and the informed consent process. And yet, determinations about how clinical trial participants 'should' make their decisions are fraught with challenges, notably that such recommendations may not be informed by evidence about the decision-making influences and processes of the population in question, and may assume rational, cognitively based decision making, when a large body of research suggests otherwise (as widely publicised in recent best-sellers such as Kahneman's *Thinking, Fast and Slow* [22]).

If efforts to improve informed consent processes are to be applied to best effect, there is a need to understand what motivates people to participate in HIV cure research and when and how they make decisions. Here we suggest addressing an area of 'low hanging fruit' regarding the terminology used to describe HIV cure research, and then present a longer-term need to explore decision making so the HIV cure community can make judgements and develop interventions based on an understanding of participant preferences and needs.

Attend to terminology that may promote therapeutic misconception

Decision-making influence may come in unexpected ways. Isles and Pearn's clinical trial commentary discusses the impact of descriptors and acronyms used to describe a range of clinical trials, where the use of positive descriptors may exert undue influence on the perception of potential participants [23]. In HIV, several authors discuss the potential for the word 'cure' itself to create misunderstanding and raise unrealistic expectations for potential personal benefit from participation in trials. Tucker and colleagues [24] consider three conceptual frameworks to replace 'cure' in describing current research: sterilising/functional cure, sustained virological response (SVR), and clinical remission. They opt for 'clinical remission,' a term long familiar in cancer research and clinical care, which appropriately 'denotes improvement with some uncertainty' [24]. Dubé and coauthors [8] concur that 'language used to describe clinical research represents a powerful opportunity to educate volunteers,' recommending the term 'experiment' as more appropriate than HIV 'studies' or 'clinical trials.' Finally, Volberding [25] points to the broader, potentially negative impact of over-hyped media attention, where inappropriately positive terminology is used to describe very preliminary trial results.

Because clinician scientists are not immune to therapeutic misconception and highly optimistic beliefs about clinical trials [12,26,27], the need to clarify and revise the HIV cure language extends to professional use as well as when describing these trials to patients and communities. The input of community leaders and advocacy organisations about language preferences should be highly prioritised, and replacement terms should be explored with patients to evaluate their acceptability.

Explore trial decision making

There are well-established decision-making and health behaviour theories that provide a systematic framework to conceptualise and explore health-related behaviours relevant to clinical trial decision making. For example, the Health Belief Model (HBM) [28,29] is a commonly used conceptual framework to understand why individuals do or do not engage in health-related actions. Dimensions of the HBM include perceived susceptibility (a perception of personal vulnerability or risk), illness severity and burden, perceived benefits of the health-related behaviour, and perceived barriers to achieving the desired health outcome. The model includes cues to action (e.g. the offering of trial participation) that might spur a health-related decision, together with influences of social, demographic and personality factors. Several resources that describe social science relevant to decision studies are shown in the Resources panel.

The use of decision frameworks and theoretical models can inform studies nested within clinical trials to better understand the processes of decision making, influences on decisions that are made, and post-trial decision satisfaction. Furthermore, it may be useful to explore potential participants' hopes and expectations as distinct decision-making influences [30]. Specific examples of decision-making topics are provided in Table 1.

We encourage clinical trial teams to collaborate with social scientists to integrate decision-making studies in their trials. In contrast to studying responses to hypothetical scenarios or retrospective studies of trial participants, the current situation in HIV cure research offers a unique opportunity to investigate participants' experiences as they are unfolding, *in real time*. Concurrently, collaborative research teams can determine how to ensure that a nested decision study provides important feedback to the clinical trial team while taking care not to disrupt or threaten the clinical trial process [31].

In developing decision-making studies in these early days of HIV cure research, community engagement is especially vital to ensure that the decision study focuses on domains and asks specific questions that are most relevant to the participant experience. Longitudinal or comparative studies that follow participants from consent to trial end will provide especially important information on perceptions of 'cure' over time and address ongoing, real-world ethical concerns [12,32]. Such studies can also be used to inform decision-making interventions and generate (and later test) hypotheses related to study adherence and maintenance of participation. In addition, exploring perspectives of individuals who qualify for a trial, but decline participation provides valuable input into trial design and recruitment.

Panel 1. Resources

National Cancer Institute, Cancer Control and Population Sciences. Health Behavior Constructs: Theory, Measurement, and Research [Internet]. 28 April 2008. Available from: http://cancercontrol.cancer.gov/brp/constructs/index.html (accessed November 2014)

Creswell JW, Klassen AC, Plano Clark VL, Smith KC for the Office of Behavioral and Social Sciences Research. Best practices for mixed methods research in the health sciences. National Institutes of Health; August 2011. Available from: http://obssr.od.nih.gov/mixed_methods_research

National Cancer Institute. Theory at a Glance: A Guide for Health Promotion Practice. 2nd edn. NIH Publication No. 05-3896. US Department of Health and Human Services; 2005.

CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement. Principles of Community Engagement. National Institutes of Health publication #11-7782. Washington, DC: US Department of Health and Human Services; 1 August 2011. Available from: http://www.atsdr.cdc.gov/communityengagement/ (accessed November 2014).

Institute of Medicine. *Health and Behavior: The Interplay of Biological, Behavioral, and Societal Influences*. Washington DC: National Academy Press; 2001. Available from: http://www.nap.edu/openbook.php?record_id=9838

searchHIV: Social and Ethical Aspects of Research on Curing HIV. Available from: http://searchiv.web.unc.edu (accessed November 2014)

Table 1. Aspects of clinical trials decision-making for exploration

Decision-making topic	Relevant questions
Decision-making processes	1. Who is involved in making the decision? Are there cultural and societal norms that play a role in decision making? 2. How is the decision made, i.e. how is the 'evidence' (information and/or emotion) weighted? How is uncertain information regarding benefits, risks and burden internalised? 3. When is the decision made? At time of the primary informed consent encounter, before, or after?
Influences on decision making	1. What is the impact of the person's experience with HIV on his/her trial decisions? 2. What does the participant expect will happen during the clinical trial, in terms of logistics, benefits, burden, and harms? What are the information source(s) and motivations that underpin those expectations? 3. What does the participant hope might happen during the clinical trial; what are the influences of emotion and optimism? What are the information source(s) and motivations that underpin those hopes? 4. What would participants consider as meaningful benefits and harms? How does this compare with investigators?
Decision satisfaction during and after the trial	1. How is decision satisfaction related to prior decision-making influences, if at all? 2. Does the participant express decisional regret? In what areas? 3. Is satisfaction and/or regret associated with the trial meeting the participants' expectations? The trial outcome? Individual benefits, perceived or real?

Better understanding the perspectives, experiences, and decision making of clinical trial participants and decliners will not make the ethical challenges any less challenging. It should, however, lead the HIV cure community to more informed choices about how to address the challenges that face us as we aim to enhance the potential societal benefits of cure research while best protecting participants and patient communities. It is vital to protect the public trust in research on HIV cure so that any future interventions arising from it are not tainted with negative reputation that could undermine effectiveness [9].

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