Reply to Commentary: “Are HIV-Infected Candidates for Participation in Risky Cure-Related Studies Otherwise Healthy?”

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Abstract

We respond to Eyal et al.’s commentary focusing on how people living with HIV participating in HIV cure-related studies are defined. We argue that the types of participants enrolled in research cannot be dissociated from the study interventions, the types of anticipated risks, and the background standard of care. As the field of HIV cure research advances, more nuance and granularity will be needed to define research criteria and acceptable risk/benefit ratios for cure study participants, as well as specific tiered protocol designs that serve to protect various participant populations from untoward risks, especially in very early phase research with interventions known to have potentially serious toxicities. We highlight key lessons from the ACTIVATE study involving a latency-reversing agent, Panobinostat, for HIV cure study design involving “otherwise healthy volunteers”.

Keywords

otherwise healthy volunteers, HIV cure research, United States, people living with HIV, panobinostat

Eyal et al.’s commentary focuses on one aspect of our article: how people living with HIV participating in HIV cure-related research are defined. We believe that the authors have become lost in the semantics of the “otherwise healthy” criterion. The main point of our article is that if people living with HIV are described as merely “otherwise healthy” without an analysis of truly informed consent, altruism, and the value of the willingness of participants to enroll in these studies to move the HIV cure research field forward, we may lose the opportunity to undertake this valuable research. Of course, we are cognizant of the fact that more risk and toxicity will be tolerated in less healthy participants and the threshold of safety will increase with healthier individuals (Kuritzkes, 2016). Furthermore, the types of participants enrolled in research cannot be dissociated from the study interventions, the types of anticipated risks, and the background standard of care. Another key point in our article is that HIV cure research should not create additional medical or life vulnerabilities in HIV cure research participants.

We believe that there is a difference between healthy volunteers and people with HIV who are on stable antiretroviral therapy (ART), who would rebound if treatment was interrupted. Furthermore, the “otherwise healthy volunteer” criterion is a general policy for the purpose of assessing risks and benefits in HIV cure research (Forum for Collaborative HIV Research, 2014). The criterion has been established by the U.S. Food & Drug Administration (FDA) to preserve its paramount function of protecting participant

safety. The danger presented is the possibility of thwarting this important research. Yet we rely on the FDA to ensure a reasonable risk/benefit profile for all participants in clinical research. In fact, it is the FDA’s role to make HIV cure studies as safe as possible for people who are stable on ART and can have a near normal life expectancy. In reality, the “otherwise healthy” policy may not be as rigid as it appears. The FDA reviews investigational new drug (IND) applications on a case-by-case basis to ensure the safety of *every* investigation and has been flexible in permitting studies to proceed once stringent protocol safety features have been established based on the population and the interventional risk presented. It should further be noted that to do no harm to sicker patients, most latency-reversing agent protocols for HIV cure research in the United States—such as those used for ACTIVATE—include only people with confirmed

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HIV infection who have been on stable HIV regimen for several months, with a high CD4 count (usually ≥ 300 cells/mm³), low plasma viral load (< 50 copies/ml), no recent viral blip, and no comorbidity such as Hepatitis B or C.

In practical terms, we concur with Eyal et al. and are not in full agreement with a blanket “otherwise healthy volunteer” designation that does not also consider other important health factors. For example, inflammation, immune activation, and cardiovascular disease occur at a much higher rate in people living with HIV, despite long-term viral suppression (Nou, Lo, & Grinspoon, 2016). Nor should we discount the cumulative toxic effect of years of HIV treatment on people living with HIV, the cost of lifelong ART, and the stigma related to HIV infection that persists to this day.

However, unlike what the commentators implied, we do not suggest that people living with HIV in our study were not “otherwise healthy.” Our study assessed how stakeholders perceived hypothetical HIV cure research scenarios. Participants interviewed were infected with HIV but may or may not qualify for actual HIV cure-related studies. Respondents were asked how they perceived the notion of “otherwise healthy volunteers” in general. Most did not agree that people living with HIV on stable ART were “otherwise healthy,” believing that the scourge of HIV disease was always with them, like an unpredictable time bomb.

Furthermore, there are various participant populations who enroll in HIV cure research protocols who are not “otherwise healthy.” For example, those with treatment fatigue, with incomplete immune recovery, or with concomitant cancer in need of bone marrow transplants, as was the case of the only person who has been cured of HIV to date, Timothy Ray Brown, aka the Berlin patient (DiGiusto et al., 2013). Other HIV cure-related research protocols include participants at the end of life who are obviously in very poor health (Gianella et al., 2017). There is also a spectrum of HIV cure research modalities being investigated. As the field of HIV cure research advances, more nuance and granularity will be needed to define research criteria and acceptable risk/benefit ratios for cure research study participants, as well as specific tiered protocol designs that serve to protect various participant populations from untoward risks, especially in very early phase research with interventions known to have potentially serious toxicities. From a community perspective, we need applied, practical ethical considerations to review these complex HIV cure-related research protocols.

Finally, we agree with the commentators that the definition of study participants will affect clinical trial designs. The ACTIVATE study provided useful HIV cure research trial design lessons that will move the field forward and protect participant safety. We summarized these in Table 1.

Table 1. Lessons From ACTIVATE for HIV Cure Study Design.

- Ensure clear rationale for dose and interval of investigational product
- Initially enroll only a small number of study participants
- Stagger enrollment into two or more cohorts with progression, especially in dose escalation based on acceptable safety from earlier cohorts
- Consider known toxicities of a drug(s) in HIV cure study drug(s) selection and use lowest dose and duration necessary, including dose escalation strategies

We encourage HIV cure research investigators to avail themselves of the FDA during the pre-IND process in this regard to avoid clinical holds and wasted time and effort on all sides. Finally, we should never stop asking what makes HIV cure research ethical in any study population.

Author Contributions

K.D. conceived and designed the protocol; collected, assembled, and analyzed the data; and drafted the manuscript. L.S. served as study coinvestigator, participated in interpretation of the data, and reviewed the article for intellectual content. L.D. reviewed the article for intellectual content.

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Lynda Dee, JD, is an HIV/AIDS treatment activist and was a cofounder of AIDS Action Baltimore in 1987. She works with academia, industry, and government to expedite ethical drug

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