Willingness to risk death endpoint in HIV cure-related research with otherwise healthy volunteers is misleading

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Abstract

This viewpoint article critiques two recent articles examining 'willingness to risk death' to advance HIV cure-related research. The 'willingness to risk death' endpoint sends the wrong signal to the HIV cure-related research community about ongoing research in otherwise healthy volunteers living with HIV. Socio-behavioural scientists have examined the acceptability of a 99% risk of death scenario, which is unrealistic and would not be acceptable by current regulatory and ethical standards. We believe that the field needs robust and relevant socio-behavioural research reflecting ongoing biomedical HIV cure-related trials. These studies will need to withstand regulatory and ethical scrutiny if cure or remission regimens are to proceed to the licensing stage. The HIV cure-related research community must continue to protect the public trust in the HIV cure-related research field and sustain societal value generated by such research. We call for the utmost prudence in designing biomedical HIV cure trials as well as in setting up socio-behavioural research experiments related to these complex trials.

Keywords: risk of death, willingness to participate (WTP), HIV cure-related research, otherwise healthy volunteers, socio-behavioural research

Introduction

We are writing to express our concern regarding two recently published articles assessing 'willingness to risk death' to advance HIV cure-related research [1,2]. We argue that the 'willingness to risk death' endpoint is misleading and potentially damaging to the field. We have developed our arguments in three points. First, the chosen variable ('willingness to risk death') sends the wrong signal about HIV cure-related research in otherwise healthy volunteers. Second, studies with 99% risk of death are not realistic and would not be approved to proceed due to stringent current regulatory and safety standards. Third, the field needs robust socio-behavioural research reflecting ongoing biomedical trials to assess risk tolerance in people living with HIV (PLHIV) as well as other stakeholders in order to forge a useful regulatory pathway towards a cure.

Willingness to risk death

Two recent socio-behavioural research articles examined 'willingness to risk death' among PLHIV in the US to be cured of HIV. Both articles employed standard gamble methodology [1,2]. The first article used a quantitative approach and found that 26% of PLHIV surveyed would be willing to take a 99% chance of dying to be cured [1]. Willingness to risk death was strongest among those with a stable job and financial stability, which seems an apparent contradiction since individuals with stable situations may likely be more risk averse. The second article employed a qualitative approach to examine the maximum chance a person living with HIV would risk for a cure [2]. Researchers asked PLHIV: '*If there was a 99% in 100 chance that you would die by taking this HIV treatment and a 1 in 100 chance that you would survive and be cured of HIV, would you take this treatment?*' Over one quarter of respondents reported being willing to take a 99 or 100% risk of death to be cured [2]. It is possible that these socio-behavioural studies were not attempting to show how realistic a risk a person living with HIV would be willing to undergo, but rather, a hypothetical example of two extremes. Researchers also acknowledged the potential for a social desirability bias in the sample of 22 PLHIV interviewed [2]. Nonetheless, these studies might also have used a format and language that confused participants. Notably, research literacy and numerical confidence are commonly over-estimated in surveys examining patient preferences.

1. Willingness to risk death sends the wrong signals about HIV cure-related research in otherwise healthy volunteers

We believe that the 'willingness to risk death' endpoint sends the wrong signal about the state of HIV cure-related research [3]. Early-phase HIV cure-related studies have an inverted ratio from the early days of the HIV epidemic [4]. Most of them follow a 'healthy-first' pharmacology model as opposed to the 'sickest-first' oncology model [4]. Contrary to the early 1980s when the armamentarium against AIDS was extremely limited and PLHIV had to take significant risks to stay alive, there are now many classes of highly potent, safe and efficacious fixed dose combinations of one pill administered once daily [5]. The safety threshold to move HIV cure-related experiments forward has become extremely high. The US Food and Drug Administration (FDA) now considers PLHIV as 'otherwise healthy volunteers' for the purpose of assessing risks and benefits [3]. Therefore, studies aimed at conferring sustained antiretroviral (ART)-free suppression must involve extremely low risk. Furthermore, the types of anticipated risks depend on the background standard of care and stage of disease in study volunteers [3]. The healthiest participants would arguably have the most to lose in terms of health and the least to gain from joining these studies [3].

The involvement of PLHIV in cure-related research must balance the ethical principles of beneficence and non-maleficence. Any potential risk of death would be justifiable only in exceptional

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cases, such as concomitant malignancies. The only two people cured of HIV represent paradigmatic cases. For example, Timothy Ray Brown, the Berlin patient, suffered acute myeloid leukaemia (AML) and received a double hematopoietic stem cell transplantation (HSCT), total body irradiation and full intensity conditioning to be cured of his leukaemia and HIV [6]. Similarly, after being diagnosed with Hodgkin lymphoma, Adam Castillejo, the London patient underwent HSCT, but did not receive irradiation and was given reduced intensity conditioning [7]. A third person, the Düsseldorf patient, may also be cured of HIV following an HSCT to treat his AML [8]. Risks associated with HSCT are obviously too high to be justifiable in PLHIV without malignant disease [9]. In fact, stem cell transplantations may be associated with severe complications, such as graft-versus-host disease (GVHD) or even death. A recent study has found an 81.1% (335/413) survival rate at 100 days after undergoing HSCT [10]. In the HIV cure research field, following this procedure, the Essen patient died 10 months later [11], and the Paris one 6 months later [12]. Most HIV cure studies, however, do not involve HCST since risks would not be justifiable in otherwise healthy PLHIV [13].

It is important to note a new translational research paradigm involving PLHIV at the end of life to advance HIV cure-related research [14,15]. For example, the Last Gift study participants are extremely altruistic individuals who have received a terminal illness and a life prognosis of 6 months or less [16]. They have elected to donate their body at the time of death to advance the understanding of the location of HIV in other body compartments besides being in blood [17]. In all cases, death is expected to be due to a terminal medical condition (i.e. solid cancer, cardiovascular disease, neurodegenerative illness) and not HIV infection or cure-related research participation [15]. All of these well-informed participants are aware that the present state of research will not be curative [15]. However, even when considering this end of life scenario, there are upper limits on allowable risks to advance this type of research [15].

2. A 99% risk of death scenario is unrealistic and not acceptable by current regulatory and ethical standards

In the early-phase of HIV cure-related research, participant safety must remain paramount. A 99% risk of death gamble is unrealistic and fails to take into account research regulatory and ethical frameworks. The reality is that the risk gamble must be kept to an absolute minimum. The US FDA and Institutional Review Boards (IRBs) would not allow protocols with a high probability of unnecessary and unjustified risk to move forward. In the 99% risk of death scenario, the risk to benefit ratio would be unfavourable and the proportionality requirement would clearly be violated. Further, it is highly probable that no sensible HIV cure biomedical researcher would test such potentially risky interventions.

Risk aversion in clinical research originated with the establishment of ethical codes of conduct that govern clinical research. For example, the Nuremberg Code (1947) paragraph 21 states:

> *'No experiment should be conducted, where there is an a priori reason to believe that death or disability injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.'* [18]

Ethical codes are clear about the fact that researchers have an obligation to protect study participants from unjustified or excessive risks [19]. Following the principle of human primacy, the protection of volunteers in clinical research must prevail over the interests of science and society [19].

Regulatory bodies governing clinical research remain extremely cautious and risk averse. Clinical trials are meant to establish safety (i.e. whether clinical benefits outweigh the risks) and efficacy (i.e. whether the intervention effectively prove the hypothesis being studied). The US FDA Investigational New Drug (IND) application process must describe the risk-benefit assessment that will be used to safely test interventions in people, including risk evaluation and mitigation strategies (REMS) to ensure interventions remain as safe as possible in the case of serious safety concerns [20]. The FDA has also established a number of guidance documents to determine acceptable benefits and risks [21]. Only when potential benefits outweigh risks can experimental interventions be allowed to proceed. For example, additional pre-clinical research may be requested before testing an intervention in research participants. Protocols may also be changed to reduce or gradually increase the doses of an experimental product to which volunteers are exposed, and/or may restrict some populations from participating to minimise harm. The FDA has placed HIV cure-related clinical trials on hold due to the disproportionate risks, such as in the ACTIVATE trial [22]. Other trials have been halted due to untoward toxicities in non-human primates and participants, as in those involving anti-PD1 products [23,24]. These examples should represent learning moments for the HIV cure-related research field. Checks and balances are necessary and important not only to protect the safety of participants in HIV cure-related trials, but also to preserve trust in research [19,25]. One can only imagine the terrible toll on participants' loved ones, and the HIV community as well as the chilling effect on a given research area if someone was to die as a result of clinical trial participation. A general public outcry may ensue, causing clinical trial regulations to undergo more extensive reviews, as was seen in the case of Jesse Gelsinger's death in a gene therapy trial in 1999 [19]. Thus, all HIV cure studies are ethically obliged to minimise potential harm to study participants. Table 1 summarises some of the safeguards that are in place in the HIV cure-related research field.

The potential likelihood and magnitude of severity of risks are always considered when evaluating clinical studies. Severity is measured using the Division of AIDS (DAIDS) Adverse Events grading system [26]. Serious adverse events (SAEs) are those that could cause death or be life threatening, require hospitalisation, lead to persistent or substantial disruption in the ability to conduct normal life activities, i.e. disability, and(or) lead to congenital anomaly or birth defect [27]. According to the bioethicist David Resnik, clinical studies with a 1 in 100 chance of serious harm should not be allowed to move forward in order to balance the protection of study participants with the societal need to advance science [25].

Determining acceptable risk thresholds in clinical research requires a careful consideration of the interventions tested and the patient/participant populations that are to be included. DiGiusto and colleagues have described six possible categories of patient/participant groups in the context of cell and gene therapy HIV cure-related research, depending on HIV disease stage. These include: 1) healthy, virally-suppressed PLHIV on ART; 2) asymptomatic PLHIV who paused ART due to side effects or 'treatment fatigue'; 3) PLHIV without viral suppression and incomplete immune recovery; 4) PLHIV unable to control HIV on ART; 5) PLHIV with concomitant cancers such as lymphomas; and 6) PLHIV with cancer-requiring salvage HIV therapy. Greater risks could understandably be justifiable in those who have health issues such as highly treatment-experienced PLHIV on salvage therapy and those harbouring drug-resistant HIV with a concomitant cancer [28].

Table 1. Safeguards to help minimise risks in HIV cure clinical research (including risk of death)

Ethical trial design issues and requirements
- Ensuring strong level of pre-clinical evidence to move interventions forwards into human testing
- Ensuring clear rationale for the HIV cure studies to avoid redundancies (i.e. regimen, dose, duration and study population)
- Demonstrating a strong potential that the knowledge base will be increased as a result of specific early HIV cure-related studies
- Initially enrolling only a small number of study participants in trials
- Staggering enrolment into two or more cohorts with progression, especially in dose escalation based on acceptable safety from earlier cohorts or pre-clinical evidence
- Considering known toxicities of a drug(s) in HIV cure-related study drug(s) selection and using lowest dose and duration necessary, including dose escalation strategies
- If using combinations, ensuring a plan for rationally designed combinations and the ability to determine which drug is causing which result and/or reaction
- Considering drug–drug interactions related to antiretroviral treatment and other relevant drugs
- Observing conservative enrolment criteria and stopping rules and futility criteria to identify safety-related issues for participants and for possible future studies
- Utilising the most appropriate HIV reservoir assay(s) and minimising risks related to monitoring of study participants
- Creating clearly defined and appropriate study endpoints and well-characterised assays for assessing endpoints
- Creating long-term follow-up provisions for participants who have received drugs with known potential long-term risks, especially genotoxic, mutagenic or carcinogenic toxicity profiles

Selection of study population
- In preliminary studies, enrolling study participants on stable HIV treatment with high CD4+ counts and undetectable HIV RNA, and other robust inclusion and exclusion criteria

Informed consent issues
- Ensuring informed consent process fully addresses potential risks and intensity of studies, and convey no expectation of individual clinical benefit or curative prospect
- Avoiding the use of the word cure in the informed consent documents to prevent curative misconception
- Ensuring that the risk undertaken is understood by study participants and assessing comprehension as a component of the informed consent process
- Ensuring that the informed consent process is continuous throughout the HIV cure study (i.e. process consent)

Safety considerations
- Ensuring clear safety endpoints and frequent monitoring of study participants
- Implementing robust risk-mitigation strategies, such as stopping rules for treatment arms that fail to show an effect or are associated with development of serious adverse events
- Allowing scientific hypotheses to be tested while maintaining acceptable safety balance

Study conduct
- Promoting good recruitment and retention practices that do not promote unreasonable study expectations
- Providing fair compensation for study visits, but also ensuring incentives do not provide an undue inducement to participate in research

Considerations for HIV cure-related studies involving analytical treatment interruptions (ATIs)
- Creating frequent monitoring strategies during ATIs
- Enrolling study participants who have alternative cART regimens especially during ATIs in case resistance occurs during the study that would compromise their current cART regimens
- For additional safety considerations related to ATIs, see ATI consensus statement [40]

cART= combination antiretroviral therapy.

Ultimately, the final decision of whether to undergo a risk belongs to the prospective participants after the informed consent process has taken place. All clinical trial risks should be clearly defined in informed consent forms in a way that is easily understandable to study participants. Early socio-behavioural studies have shown that PLHIV may have difficulty recalling clinical risks of early-phase HIV cure-related clinical studies and may overestimate the potential for clinical benefits [24,29,30]. It remains imperative to ensure that potential risks are clearly communicated to and understood by study participants.

3. Robust socio-behavioural research should reflect ongoing biomedical studies to assess risk tolerance and forge a useful regulatory pathway towards an HIV cure

We assert that the HIV cure-related research field requires robust socio-behavioural research reflecting ongoing biomedical studies to forge useful and customary pathways towards a cure. Such research should support the clinical development of regimens with acceptable risk and safety profiles. Side-effects may result either from the intervention performed, invasive study procedures or the HIV-1 viral rebound associated with analytical treatment interruptions (ATIs) in some protocols [24]. Others may include social, psychological or financial risks [3,24].

Socio-behavioural research in PLHIV has shown a highly variable level of willingness to undergo risks to advance HIV cure-related science [24,31]. When asked what would be considered unacceptable risks, several PLHIV have cited permanent or irreversible side effects, hospitalisation, debilitation and death [24] – all of which would qualify as SAEs. However, a subset of them did not place an upper limit on acceptable risks, which brings to the fore a host of potential regulatory and ethical questions to be addressed [24].

Moving forward, socio-behavioural research will need to focus on the potentially desirable product characteristics of future HIV treatment or remission options, particularly given the advent of long-acting ART formulations, which will blur the boundaries of what HIV remission means [32]. The comorbidities that make HIV management more difficult in older PLHIV [33,34] will also require considering the acceptability of drug–drug interactions to treat these concomitant conditions. The unanswered questions relating to unmet needs for all PLHIV [35] also include psychosocial issues. In order to become standard of care, an HIV cure or remission regimens will need to be safe while keeping PLHIV virally suppressed in the absence of ART. These interventions should also be scalable to be accessed by countries with the greatest unmet need for viral suppression.

Ultimately, socio-behavioural research should inform on a realistic regulatory pathway towards an HIV cure. Supportive behavioural and social science research (BSSR) should aim at strengthening biomedically-focused clinical trials and interventions that are acceptable to the HIV community [36], including helping prioritise strategies under development, and refine approaches and regimens to augment their acceptability. In addition to understanding PLHIV's willingness to undergo risks, we need to obtain a better understanding of the attitudes of HIV care providers and their willingness to refer patients to HIV cure trials, particularly those involving ATIs [36,37]. Socio-behavioural science should encompass more than thought experiments, and truly reflect the state of translational HIV cure-related research, ongoing biomedical studies and the current state of the HIV epidemic.

Conclusion

In summary, while we cannot deny that all clinical trials have potential risks, including death, we believe that the 'willingness to die endpoint' to advance HIV cure science is clearly misleading

and unethical. A gamble theory testing 99% 'willingness to risk death' is an incorrect approach, because it does not represent a fair gamble for otherwise healthy PLHIV with families, jobs and financial stability. HIV cure-related studies must withstand regulatory and ethical scrutiny if any cure or remission regimen is to receive ultimate FDA approval. Importantly, we must avoid transmitting erroneous safety signals to communities of PLHIV and respect that the patient's perspective must remain of paramount importance in assessing preferences and tolerance for risks [32,38]. As a research community, we must continue to protect the public trust [39] and sustain the societal value generated by biomedical HIV cure-related research [19]. For all the above reasons, we call for the utmost prudence in designing biomedical HIV cure-related trials as well as designing socio-behavioural research experiments related to these complex trials.

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Conflicts of interest

The authors have no competing interests to declare.

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