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PAPER

Ethics of treatment interruption trials in HIV cure research: addressing the conundrum of risk/benefit assessment

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ABSTRACT

Though antiretroviral therapy is the standard of care for people living with HIV, its treatment limitations, burdens, stigma and costs lead to continued interest in HIV cure research. Early-phase cure trials, particularly those that include analytic treatment interruption (ATI), involve uncertain and potentially high risk, with minimal chance of clinical benefit. Some question whether such trials should be offered, given the risk/benefit imbalance, and whether those who choose to participate are acting rationally. We address these questions through a longitudinal decision-making study nested in a Thai acute HIV research cohort.

In-depth interviews revealed central themes about decisions to join. Participants felt they possessed an important identity as members of the acute cohort, viewing their bodies as uniquely suited to both testing and potentially benefiting from HIV cure approaches. While acknowledging risks of ATI, most perceived they were given an opportunity to interrupt treatment, to test their own bodies and increase normalcy in a safe, highly monitored circumstance. They were motivated by potential benefits to themselves, the investigators and larger acute cohort, and others with HIV. They believed their own trial experiences and being able to give back to the community were sufficient to offset participation risks.

These decisions were driven by the specific circumstances experienced by our participants. Judging risk/benefit ratios without appreciating these lived experiences can lead to false determinations of irrational decision-making. While this does not minimise vital oversight considerations about risk reduction and protection from harm, it argues for inclusion of a more participant-centered approach.

INTRODUCTION

Going beyond treatment to cure

Antiretroviral therapy (ART) is highly beneficial for people living with HIV, leading to a near-normal lifespan.¹ Starting ART as early as possible after infection is associated with better immune recovery and lower HIV burden,² and viral suppression is associated with a low risk of transmitting HIV to others.³ Thus, ART is the standard of care for people living with HIV. However, ART also has

limitations; it suppresses but does not eliminate HIV from the body. The virus remains in a latent state, and if ART is discontinued, viral load (VL) normally increases ('rebounds'). Inconsistent ART adherence can lead to drug-resistant HIV strains. Long-term use can have side effects, including organ dysfunction, neuropsychiatric effects⁴ and cardiovascular disease.¹ Clinical care for the millions of HIV-positive people, particularly in developing countries, constitutes a tremendous logistical challenge and resource burden on fragile healthcare systems. Finally, HIV remains a highly stigmatised disease that impacts human rights, and stigma is a major barrier to engagement in HIV prevention and treatment. In short, curing rather than treating HIV remains an important scientific and clinical goal.

As described by Margolis and colleagues,⁵ the field of HIV cure research is complex and rapidly evolving. Current studies are early-phase, first-in-human trials that aim to generate knowledge relevant to an eventual cure for HIV, understood either as elimination of all replication-competent virus in the body ('sterilizing cure') or as long-term remission ('functional cure').⁶ A small but increasing number of cure trials also involve analytic treatment interruption (ATI), in which participants are taken off ART to test the effects of the intervention used; viral rebound after ART discontinuation supports lack of efficacy.

The risk/benefit ratio puzzle of HIV cure trials

A number of commentators, including contributors to a recent special issue of the *Journal of Medical Ethics* devoted to the ethics of HIV cure trials,⁷ identified what they consider the core ethical challenge of HIV cure research studies, including those involving ATI.^{8–14} In such trials, participants are very likely to have no direct medical benefits and face uncertain and potentially high risks from the study intervention, invasive procedures and loss of therapeutic benefits from ART.¹⁵ In the introduction to the special issue, Eyal argues that, at the very least, this is *prima facie* a 'bad deal' or 'bad gamble' for participants. Further, participants' decisions to join may draw doubt on their rationality, generating a 'risk/benefit ratio puzzle' as to how anyone truly informed about cure trials could prudently choose to participate.⁷ Dresser also raises the important



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question of whether it is ethical for researchers to run such studies and for ethics boards to approve them because of their unfavourable risk/benefit ratio, and since participants seem likely to be worse off for participating.¹⁵

Eyal suggests a spectrum of candidate solutions to address these concerns.¹⁶ For example, one could argue that a well-informed person should be permitted to consent to a trial that might look like a ‘bad gamble’ given that as autonomous adults, they are permitted to engage in bad gambles in other domains of life. Second, one could also reduce the risks of the study, for example, through careful participant selection, extensive health monitoring and other safeguards. A third approach is for researchers to enhance the benefit side of the equation, such as by offering financial compensation that would contribute to a more positive risk-benefit assessment of research.¹⁷ Another approach would address the problem by considering societal as well as individual benefits associated with research; that is, what initially looks like a bad gamble for individuals may not be a bad gamble overall.^{18–20} As such, the research could arguably be ethically permissible on these grounds, though one might still worry that participants are recklessly sacrificing themselves for the greater good. In all of these approaches to resolving the ‘risk/benefit ratio puzzle,’ the arguments largely leave unexplored the initial framing of participant decision making as a process where individuals weigh risks and benefits based on their own values and preferences. Our data from HIV cure research in Thailand, reported below, suggest an important variant on the ‘enhancing the benefits’ approach to the puzzle: that on closer inspection, participants find HIV cure research participation more valuable than one might expect, and therefore worth doing despite the risks.

In this paper, following Evans’ report on the carefully considered decisions of four HIV cure trial participants,²¹ and other similar investigations,^{20 22 23} we contend that a fuller depiction of cure research decision making, grounded in empirical data, is ethically relevant. As we have argued,²⁴ it is critical to undertake empirical investigations of those recruited to HIV cure trials (both those who choose to participate and those who decline), to assess their motivations, expectations and decision processes. These findings can then be used to develop effective ways to communicate about study goals and unknown risks associated with participation, particularly with planned ATI.²⁴ Further, such data can form frameworks to evaluate the salient features of participant decision making in subsequent research.²⁵

Here we present data from our social science and ethics study currently under way in Bangkok, Thailand. This interview study is embedded within a series of early-phase HIV cure trials, all of which include ATI. The trials recruit from a cohort of individuals, termed the SEARCH cohort.^{26 27} Starting in 2009, SEARCH clinical investigators began identifying and treating individuals at the very early stages of acute HIV infection. Cohort members were then followed at the Thai Red Cross AIDS Research Centre in Bangkok. The SEARCH clinical trial team, keenly aware of the ethical concerns associated with this research, invited our group to conduct a longitudinal decision-making study of SEARCH cohort members recruited to HIV cure trials. Our project is called the SEARCH HIV Cure Trials Decision-Making Study (hereafter the Decision-Making Study or DMS). No clinical investigators (members of the SEARCH or cure trial teams) have access to the data or the analysis files, and are not involved in the coding or interpretation of the interview data nor the interviews themselves. They are, however, queried as expert resources when the analytic team has questions about interpretation of

HIV or trial-related issues, and have participated in manuscript development.

THE SEARCH STUDY

Nearly 500 people are enrolled in the SEARCH cohort. The majority are well maintained on ART and have an undetectable VL. The cohort almost entirely comprises men who have sex with men (96%). The median age is 26, and participants are, on average, better educated than the general Thai population. SEARCH cohort members are recruited to HIV cure trials based on strict eligibility criteria, and should they not qualify or decline one invitation, they may be recruited for a subsequent trial. Because of early ART, they have lower HIV burden, a factor hypothesised to be important for reaching a functional cure of HIV.²⁸

THE DECISION-MAKING STUDY

We initiated our semistructured interview protocol with individuals in the SEARCH cohort who consented to participate in SEARCH 019, the first in the series of HIV cure trials that were initiated in 2015. Although the DMS includes individuals who have joined or declined subsequent HIV cure trials, here we focus on interviews with 12 participants in 019.

The SEARCH 019 HIV cure trial

SEARCH 019 was a randomised trial that compared the efficacy of adding vorinostat/hydroxychloroquine/maraviroc to standard-of-care ART in controlling HIV once treatment was interrupted. Participants, all Fiebig stage 3 or 4, were randomised into two study groups: 10 who received the three-drug regimen in addition to existing ART, and 5 who continued ART drugs only. Participants underwent ATI at week 10. VL was monitored weekly and ART was resumed when confirmed VL > 1000 copies/mL.²⁹ During the course of the trial, participants were recruited to optional procedures, which they could decline without impacting their ability to remain in the trial. The consent form informed participants that the trial included ATI and described the risks of the three experimental drugs in detail.

Of the 15 participants in SEARCH 019, twelve accepted our invitation to be interviewed. A compensation of 500 Thai Baht (approximately US\$15) was provided for the hour-long, face-to-face interview. At the time of the interviews, one had been withdrawn before ATI due to side effects of the three-drug regimen. All other participants had experienced viral rebound after ATI, knew of their rebound status and were either back on ART or soon to reinitiate ART (see table 1).

All DMS interviews (see online supplementary appendix 1) were conducted in Thai, audio-recorded and transcribed.

Table 1 Decision-Making Study participants’ background data

Number of participants	12
Mean years enrolled in SEARCH	3.8 years (range 2–6 years)
Gender	Male 10, female 2
Median age	28 (range 24–53 years)
Level of education	1 Primary 4 High school/basic technology school 1 Advanced technology school 6 Bachelor of Arts (BA) degree
Median days off antiretroviral therapy (ART) in 019 trial	36 (range 16–115 days)

Transcripts were then translated and checked for accuracy by both Thai and US-based team members. Participants responded to a series of semistructured questions about their experiences of being diagnosed with acute HIV and joining the SEARCH cohort, their HIV cure trial decision making and their trial experiences. To develop the initial codebook, the 12 SEARCH 019 interview transcripts were read by five members of the US team. Thirty-three codes were developed, defined and applied to the transcripts using the MAXQDA text program by two US team members (see online supplementary appendix 2). A separate audit of code reports was conducted by two other team members to assess their usability.

This preliminary set of findings, comprising only cross-sectional analysis of interviews from participants in one trial, is the first from a much larger set of longitudinal data about decision making by those recruited to join the cure trials. Here we focus on study participants' decision motivations and their perception of the risk/benefit balance, and report themes relevant to the ethical debates about enrolling individuals into HIV cure trials.

DECISION-MAKING STUDY RESULTS

We report results from the interview analysis in the order that questions were most often posed and discussed. The quotes reflect transcript data that were translated from Thai to English and checked and revised based on translation errors and interpretative challenges. After then making syntax changes as necessary to interpret the data, our team did not further modify the transcripts and associated quotes to refine the translation. In selecting illustrative quotes, we note the interviewee number in brackets.

Context of SEARCH acute cohort

SEARCH 019 participant assessments of the trial's risks and benefits were influenced by their acute status and experience as members of the SEARCH acute cohort in Bangkok. 'Cohort belonging' is thus one layer of the context in which HIV cure trial participants made their decisions about these trials.

SEARCH identity

Interview participants reported trust and confidence in the SEARCH team to optimally manage their HIV. Several felt lucky to find SEARCH shortly after infection and being encouraged to begin treatment quickly. They often contrasted the SEARCH experience with what they judged to be less personal care at overly burdened public hospitals. Every interviewee reported positive perceptions of the care provided by staff, especially the nurses who were often available at all hours for phone calls to answer questions and offer support.

Useful bodies for HIV science

Participants perceived other important aspects of being diagnosed at the earliest stages of infection, including the expectation for an improved chance for prolonged viral control after ATI, and the resulting value that researchers place on acute status in a research cohort. Several participants perceived that, as acutely diagnosed people, they had a better chance of prolonged ATI than others with HIV. Their bodies were thus described as providing reciprocal benefit to the participant, SEARCH and the HIV community, and several contrasted this with the many negative implications of HIV infection. Participants felt pleased to occupy this important category, regarding recruitment to a cure trial as being tapped to be 'representative' of a special group.

As one said, "Our bodies (referring to 019 participants) may be stronger than others because we took the drug at the first stage of infection and it may suppress the virus better" (Participant 04). Several talked about being happy to be used as 'guinea pigs'. This term was not pejorative, but rather depicted the opportunity to act as 'experimental items' for the benefit of science and society. One said, "We do not have many chances to be useful in the world... We are guinea pigs, that's right.... The guinea pig is useful... The main benefit may not happen to us directly but it will happen to other people definitely" (Participant 06).

Decision making for SEARCH 019

The 12 study participants recounted their motivations for joining SEARCH 019, their relative ease making the decision and thoughts after the trial ended. Their self-portraits were diverse, varying in the extent they expressed worry about the decision, were positive thinkers, or pragmatic about their circumstances, for example, 'Nothing is getting better if I am worrying about it' (Participant 04). One was a self-described 'serial participant' who incorporated the decision to participate into his identity as someone who enrolls in clinical trials, whereas two others made the decision to join with considerable trepidation. Participants reported that joining the trial was a decision they made independently, with one exception who cited strong family influence to 'do what is right' by participating (Participant 06).

Close monitoring

Participants described the burdens of time and travel associated with the close monitoring required in SEARCH 019, but accepted this as necessary for risk mitigation. They report being confident that viral rebound would be caught very early and ART reinitiated. As one noted, 'I trusted this organization. I came mostly every week; they followed up on the results continuously. If my symptoms get worse, it can be detected fast and solved at an early stage' (Participant 03). When asked to describe potential study risks, five other participants (Participants 02, 05, 07, 09 and 10) explicitly mentioned the reassurance of careful monitoring after stating their perceived risks of viral rebound, drug resistance and side effects from the intervention. Many participants also perceived close monitoring as something already experienced as part of the SEARCH cohort. For example, one noted, 'If you come to participate in the [SEARCH] study, you will get more than participation. You will get blood tests often... It has benefits more than testing the drug' (Participant 06).

Optional procedures

For some participants, optional procedures such as MRI, leukapheresis and lumbar puncture were described as offering useful surveillance and potential health benefits at no cost. As one said,

"Please try to think—how many people get to use an MRI scan each year... It's a low number, right? My results can show the doctor what the virus does to my brain. I do the [leukapheresis] test. They take my plasma to check about it. It is a benefit to me, too" (Participant 07).

For others, optional procedures were a burden. Three SEARCH 019 participants refused all optional procedures. Comparing the decision to join the trial to the decision to participate in optional procedures, one said deciding to join, "...was easy. I decided immediately. If there is anything useful to me and the research center, I participate without any hesitation...except something that was too hard, for example, tissue collection; if it has a lot of effects on me, I will not do it" (Participant 05).

This underscores these participants' understanding that they have the autonomy to decline certain procedures even after joining the trial.

Anticipating going off ART

The large majority of participants demonstrated an understanding of the major risks of ATI, the likelihood of viral rebound and possibility of drug resistance in restarting ART. In addition, several mentioned time/travel burden, negative impact on work and privacy concerns. However, in light of the trial's intense monitoring, participants balanced risks against what they described as real benefits of stopping ART. Thus, ATI was classified as an exciting, rare opportunity to reduce treatment burden, increase a sense of normalcy and test their bodies in what they considered a safe environment with the sanctioning of their healthcare providers. Echoing the excerpt above from Participant 05, and other participants who were interested in using their bodies for scientific investigations, one said:

I want to stop the drug. I want to know, the same as the staff wants to know, how it will be if we stopped the drug. If we stopped the drug, will the virus increase? How long will it take to increase, one year or two years? I want to know, too... But I [was] confident if I participated and the virus rebounded, the study still takes care of me, so I can decide easily... [And] Because the study has told [me] that if there are any problems, the study is willing to be responsible or pay for the treatment for that symptom. It's okay. (Participant 02)

The strong appeal of being off an ART drug regimen was further described by another participant: 'I was very happy, was very excited. I turned off every [reminder] alarm. The alarm that I set for over a year, I was going to turn it off' (Participant 06).

When asked if they understood the risks of the study when they joined 019, several mentioned exposure to the experimental drugs and specific side effects. One participant said, "I was afraid of only one thing...taking one more drug, because I always check the news about people who were taking the anticancer drug [Vorinostat]" (Participant 05). This participant resolved that if he was randomised to the experimental group and his 'body was not strong enough,' he would withdraw if needed. Another participant declared himself 'lucky' to be randomised to the control group (Participant 06).

Relationships with others and society

Participants described benefits to self and to society in a variety of interrelated ways. Some described short and longer term 'wins' for both themselves and others: 'It will be my luck if I am cured. If not, I'm okay. More than that, I wanted the research to provide information for the future' (Participant 08). Although most stated that they did not expect a cure, they did hope for scientific advances:

The hope of infected people, we hope that in the near future, we will see the treatment, medicine, or vaccine that lets us not need to take the drug or kills the virus completely, and we have the vaccine for uninfected people that is the same as the Influenza vaccine which we inject into normal people for prevention. (Participant 07)

The same participant later described creating benefit for society through incremental scientific gains from early-phase research, as illustrated by this striking metaphor:

Even if there is not yet any conclusion, we are in the process. It's like we are on a conveyor belt—when the packaging comes out,

if it cannot be used and is thrown away, that package can provide guidance for a new package in the future. (Participant 07)

Some focused on helping the SEARCH team or the cohort. Many participants wanted to aid the research team who 'work so hard and always encourage [us]' (Participant 06). A few seemed motivated as well by a feeling of solidarity within the cohort, for example, 'Now I have my brothers and sisters and we talk and encourage each other' (Participant 07). Furthermore, because so few people are eligible for cure trials, this may translate into a feeling of responsibility to volunteer.

Despite the close relationships with the SEARCH team, participants nonetheless reported both voluntariness and feeling informed, as this individual revealed:

I walked in here by myself. I made the decision by myself. They did not force me. I can withdraw whenever I want... About the knowledge, they told me everything...what will I get from this study, what are the benefits, what are the disadvantages, what will happen after I stopped the drug... Will it have any long-term effects on me? (Participant 05)

DISCUSSION

The empirical data we present reveal why individuals decided to join the first HIV cure trial offered to Thai SEARCH cohort members. As such, they are relevant to the risk/benefit ratio challenge and associated ethical concerns about participation in HIV cure research portrayed in the recent *Journal of Medical Ethics* special issue.⁷ This study and the related conclusions do not address disagreements about the science of cure trials, or the validity and acceptability of the use of ATI within those trials. We defer to experts to debate those issues in other forums.

Our DMS finds that participation is considered by participants (on various grounds) to be sufficiently worthwhile to make it reasonable for them to join and remain in studies with ATI, at least in the particular cultural and social contexts of the Thai SEARCH cohort and the 019 trial. Our results similarly reveal how participants' understanding of their own decision making may be markedly different than the risk/benefit evaluation that has characterised HIV cure ethics discussions to date, and that is known to frame decision making within institutional review boards.^{30 31} That is because our participants value a wide range of potential benefits, and perceive an opportunity to benefit from what regulators characterise as the primary risk of trial participation. Thus, our participants' entire risk/benefit calculus is framed quite differently from that of most clinical researchers and regulators.

The category of benefits that commonly holds the most weight with scientists and ethicists is direct benefits,^{32 33} which are defined as the clinical benefits of the experimental agent and procedures that are scientifically necessary to test the experimental intervention under study. Our participants appreciated the risks of ATI, but they complicated the traditional concept of direct benefit in their reporting of the hopefulness engendered by going off ART. ATI was not interpreted *simply in terms of risk or benefit*, but as a complex act in which testing of one's body, the potential for restoration of normal life, and the deviation from trusted, clinical standard of care, was merged under the careful supervision of doctors and nurses. In fact, our data suggest that it is not uncommon for trial procedures or activities to embody both beneficial and harmful dimensions, even for the same participant.

Aspirational benefits are those directed to individuals and society that the research may eventually produce, and are commonly reflected in altruistic benefit attributions.^{32 34 35} SEARCH 019 participants also depicted themselves and their trial decisions in relation to others, identifying as members of the SEARCH cohort and as having a special physiology shared with those with acute diagnoses. While altruism and reciprocity were common themes, our participants' close relationships with SEARCH staff, in a context where HIV-positive status is approached with compassion and understanding, blur the boundaries between research, clinical care and community. While this boundary blurring raises some concerns in the clinical trial context,^{36 37} the positive meaning of these relationships for our participants should not be underestimated.³⁸ Their desire to be 'normal' and to be of use to society, and even to conceive of their bodies as 'special' in a positive sense despite HIV infection, illustrates how they redefine the meaning of research participation in the context of an illness that alters self-concept and poses quality-of-life burdens.

In addition to aspirational benefits, our participants reported other important, non-direct benefits. This is particularly evident in their improved sense of self-worth in relation to usefulness or normality, and their sense of being well cared for by the SEARCH team. As such, these outcomes might also be classified as inclusion benefits, that is, psychological and ancillary care-related benefits that arise from being a research participant.³⁹ These broader inclusion benefits have been perceived as insufficiently compelling to offset research risks.⁴⁰ Participants in the SEARCH 019 study, however, weighed various forms of benefit against study-related risks, and highly valued inclusion benefits in the benefit/risk calculus.

Our findings demonstrate that what participants perceive to have received from being in a trial, and by extension what makes participation worthwhile in light of perceived risks and study-related burden, may be different from the benefits that researchers may imagine they are providing. In this sense, our participants' appeals to what can be interpreted as direct, aspirational and inclusion benefits demonstrate an alternative that combines Eyal's proposals in which risks are mitigated, benefits to participants are increased (because indirect benefits are taken into account and ATI is perceived as a benefit) and societal benefits also figure into decision making. In addition, our participants used their trial participation to help make meaning of their HIV experience, their personal histories and the social meaning of HIV cure research through the contextual lens of interactions with the research team and other contingent factors. We thus demonstrate that the way participants experience and are motivated to engage in research is quite different from the perspective of researchers and regulators as they classify the same aspects of a trial into risks and benefits, in order to facilitate a risk-benefit calculus.

The question that remains is whether our participants made a rational choice.

The complex motivations (including altruistic ones) driving HIV research participation may not take the form of the same objective risk-benefit calculus undertaken by experts, nor is that calculus conducted similarly by all participants. In fact, as Buchak argued, 'it is not as if each individual in the society gets to experience the average wellbeing [or risk].⁴¹ What matters is how each individual person fares...and [how] each subject holds that the risky strategy is better for him....' Further, Buchak posits a model for rational but divergent participant preferences using risk-weighted expected utility maximisation, which incorporates three psychological components to decision making: the

individual valuing of the anticipated consequences of the decision, perceptions of how likely consequences are to occur and the extent that the participant values the worst-case against the best-case scenario. Thus 'risk-inclined individuals' may make a rational choice for themselves based on higher consideration of potential benefits than for potential risks, even with an understanding that the chance for the benefit is low. From our view, this is how we see our participants demonstrating a rational choice. Further, our data provide support for Buchak's call to include preferences in determining rationality of decision making.

Participant preferences about participating in research do (and should) involve an array of considerations that arise from and are enacted within specific contexts in which cure trials are offered. Our research findings reveal how individual choices may appear irrational when one employs a narrow view of what reasons ought to count in research participation decisions. When the context of specific cure trials is brought in, the decisions of our participants appear rational because their appraisal of factors such as ATI differs from experts; more consequences figure in their decisions than appeared from the outside; and the standard of practical rationality against which these choices are evaluated needs to adapt to include considerations *beyond* consequences. For example, our participants sometimes seem to be forming and expressing new goals and identities *through* research participation, rather than framing the choice to participate as means to achieve fixed preferences established in advance.

Even if attention to participant preferences and lived experiences helps render research participation in HIV cure research more reasonable, should those experiences also be taken into account when ethically assessing whether a trial should be offered? Regulators, HIV researchers, advocates and bioethicists need to consider whether and how participants' perceptions of and experiences in HIV cure research fit into their ethical and regulatory judgments. Some commentators acknowledge participant perspectives in terms of rational decision making, but discount their ethical import by framing them as inclusion benefits, which are difficult to predict and often person specific,⁴⁰ or by acknowledging their import, but dismissing their ethical salience.¹⁷ In contrast, our data indicate that the potential for a more normal life, enhanced self-worth and contributing benefits to the HIV community were anything but insignificant for SEARCH 019 participants. They seem to play a major role in making trial participation attractive, acceptable or meaningful.

And yet clinical HIV researchers are better positioned than most potential participants to understand the risks of ATI, especially in relation to the clinical treatment option of uninterrupted ART. Third parties (e.g., regulators, ethics committees, bioethicists) have a responsibility to independently determine whether a trial is ethical and compliant with relevant regulations. Among their obligations is to place a cap on the level of clinical risk research participants undertake when there is no prospect of direct medical benefit, such that some individuals are not imperilled for the sake of the greater good. While we agree that these considerations are important, and in fact our data support much stronger influences of possible benefits than risks for our participants, our data also support Buchak's conclusion⁴¹ that thinking about research ethics in terms of narrowly defined participant rationality might not be the best criterion around which to centre debates about cure research ethics, as it might sidetrack the research community from evaluating such research in light of other morally relevant criteria.⁴² For those facing perplexing questions about how to design and whether to approve cure research, our findings may allay some anxieties; ATI might indeed be a clinical risk to participants (and/or increase the risk

of infection to others), but is also appreciated as a reprieve from the burdens of HIV-positive status and treatment, and as part of an opportunity to contribute to the HIV community—both locally and across time. One could, for example, include such information in informed consent processes, without implying that such positive aspects of trial participation will be experienced by all participants. After all, one is supposed to mention *potential* benefits and risks, including less likely ones. Alternatively, other ethical considerations might be more salient as a result of these findings; for example, the reassurance participants get from prior relationships with clinical researchers and from clinical trial monitoring suggests that cure research ethics might want to reflect on how such practices are presented to and understood by prospective participants. In addition, our findings suggest that contexts in which HIV-positive status is highly stigmatised can combine with cultural expectations to be considerate of others (in Thai, *'krenng-jai'*), generating potential concerns about participant vulnerability and the fairness of subject selection.⁴³

We acknowledge the limitations of our data: it comes only from those who chose to participate in the clinical trial, from a unique acute HIV cohort in Thailand, and is based on translated materials (though the interview translations, both literal and cultural, are independently checked by three native Thai speakers). We must continue to explore the impact of SEARCH and Thai cultural norms on decision-making processes. Though we explored trial perceptions and decision-making influences during the interviews, we did not conduct a systematic assessment of their knowledge about the clinical trial risks. In addition, these interviews occurred when most participants had returned to ART after viral rebound. Undoubtedly, they reframed components of their decision making based on these trial experiences. We will explore this in future interviews. Moving forward, our study is conducting interviews at two or more time points during each subsequent SEARCH cure trial, with those who chose to participate and those who declined. This allows us to reduce retrospective bias, determine changes to perceptions of the risk/benefit balance over time and make systematic comparisons across participants (who would be hypothesised to be risk inclined in the cure trial context) and decliners (who would be hypothesised to be risk avoidant in the cure trial context) and different types of cure trials. Finally, to explore the impact of the specific Thai context, we plan to replicate our DMS in other locations.

To date, ethical discourse about early-phase HIV cure research has been dominated by concerns about 'bad gambles' and a narrow vision of research participant rationality. One important contribution of qualitative research is the ability to identify and address previously neglected but ethically relevant aspects of cure research. In such a complex research setting, oversimplifying what constitutes a morally relevant consideration is in and of itself an obstacle to progress. Evidence about what actually matters to cure research participants provides an important corrective, ensuring that third-party concerns do not operate on hidden and mistaken assumptions about what is at stake for participants. Such findings also move us towards a triangulated approach to cure research ethics: one that is simultaneously informed by the perspectives of researchers, participants and third-party regulators and bioethicists.

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Data sharing statement Due to concerns about maintaining confidentiality of our interviews, and their small numbers, we are not making those interview transcripts available.

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REFERENCES

- Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet* 2013;382:1525–33.
- Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med* 2013;368:218–30.
- Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493–505.
- Treisman GJ, Soudry O. Neuropsychiatric Effects of HIV Antiviral Medications. *Drug Saf* 2016;39:945–57.
- Margolis DM, Garcia JV, Hazuda DJ, et al. Latency reversal and viral clearance to cure HIV-1. *Science* 2016;353:aaf6517.
- Deeks SG, Lewin SR, Ross AL, et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. *Nat Med* 2016;22:839–50.
- Eyal N. The benefit/risk ratio challenge in clinical research, and the case of HIV cure: an introduction. *J Med Ethics* 2017;43:65–6.
- Tucker JD, Rennie S, and the Social Ethical Working Group on HIV Cure. Social and ethical implications of HIV cure research. *AIDS* 2014;28:1247–50.
- Lo B, Grady C. Working Group on Ethics of the International Aids Society. Ethical considerations in HIV cure research: points to consider. *Curr Opin HIV AIDS* 2013;8:243–9.
- Eyal N, Kuritzkes DR. Challenges in clinical trial design for HIV-1 cure research. *Lancet* 2013;382:1464–5.
- Sugarman J. HIV cure research: expanding the ethical considerations. *Ann Intern Med* 2013;159:490–1.
- Sugarman J. Ethics of Curing HIV: Roundtable Discussion Talk. *7th IAS Conference on HIV Pathogenesis, Treatment, and Prevention*. Kuala Lumpur, 2013.
- Sugarman J, Lewin SR, Henrich TJ, et al. Ethics of ART interruption after stem-cell transplantation. *Lancet HIV* 2016;3:e8–e10.
- Garner SA, Rennie S, Ananworanich J, et al. Interrupting antiretroviral treatment in HIV cure research: scientific and ethical considerations. *J Virus Erad* 2017;3:82–4.

- 15 Dresser R. First-in-human HIV-remission studies: reducing and justifying risk. *J Med Ethics* 2017;43:78–81.
- 16 Eyal N. How to keep high-risk studies ethical: classifying candidate solutions. *J Med Ethics* 2017;43:74–7.
- 17 Largent E. For love and money: the need to rethink benefits in HIV cure studies. *J Med Ethics* 2017;43:96–9.
- 18 Nycum G, Reid L. The harm-benefit tradeoff in "bad deal" trials. *Kennedy Inst Ethics J* 2007;17:321–50.
- 19 Wikler D. Must research benefit human subjects if it is to be permissible? *J Med Ethics* 2017;43:114–7.
- 20 Gilbertson A. *Unanticipated participant benefits in HIV cure clinical research: A qualitative analysis*. Durban, South Africa: International AIDS Society Towards an HIV Cure Symposium, 2016.
- 21 Evans D. An activist's argument that participant values should guide risk-benefit ratio calculations in HIV cure research. *J Med Ethics* 2017;43:100–3.
- 22 Dubé K, Evans D, Sylla L, et al. Willingness to participate and take risks in HIV cure research: survey results from 400 people living with HIV in the US. *J Virus Erad* 2017;3:10.
- 23 Dubé K, Taylor J, Sylla L, et al. 'Well, It's the Risk of the Unknown... Right?': A Qualitative Study of Perceived Risks and Benefits of HIV Cure Research in the United States. *PLoS One* 2017;12:e0170112.
- 24 Peay HL, Henderson GE. What motivates participation in HIV cure trials? A call for real-time assessment to improve informed consent. *Journal of Virus Eradication* 2015;1:3.
- 25 Henderson GE. The Ethics of HIV "Cure" Research: What Can We Learn from Consent Forms? *AIDS Res Hum Retroviruses* 2015;31:56–63.
- 26 Ananworanich J, Schuetz A, Vandergeeten C, et al. Impact of Multi-Targeted Antiretroviral Treatment on Gut T Cell Depletion and HIV Reservoir Seeding during Acute HIV Infection. *PLoS One* 2012;7:e33948.
- 27 de Souza MS, Pinyakorn S, Akapirat S, et al. Initiation of Antiretroviral Therapy During Acute HIV-1 Infection Leads to a High Rate of Nonreactive HIV Serology. *Clinical Infectious Diseases* 2016;63:555–61.
- 28 Hurst J, Hoffmann M, Pace M, et al. Immunological biomarkers predict HIV-1 viral rebound after treatment interruption. *Nat Commun* 2015;6:8495.
- 29 Journal of the International AIDS Society. In: Kroon E, Ananworanich J, Eubanks K, Intasan J, Pinyakorn S, et al. eds. *Effect of vorinostat, hydroxychloroquine and maraviroc combination therapy on viremia following treatment interruption in individuals initiating ART during acute HIV infection*. Geneva, Switzerland: INT AIDS Society avenue de France 23, 2016.
- 30 Resnik DB. The Role of Intuition in Risk/Benefit Decision-Making in Human Subjects Research. *Account Res* 2017;24:1–29.
- 31 Corrigan O. Empty ethics: the problem with informed consent. *Sociology of Health and Illness* 2003;25:768–92.
- 32 King NM. Defining and describing benefit appropriately in clinical trials. *J Law Med Ethics* 2000;28:332–43.
- 33 Friedman A, Robbins E, Wendler D. Which benefits of research participation count as 'direct'? *Bioethics* 2012;26:60–7.
- 34 Convey MR, Dickson-Gomez J, Weeks MR, et al. Altruism and peer-led HIV prevention targeting heroin and cocaine users. *Qual Health Res* 2010;20:1546–57.
- 35 Seelig BJ, Dobelle WH. Altruism and the volunteer: psychological benefits from participating as a research subject. *Asaio J* 2001;47:3–5.
- 36 Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS Med* 2007;4:e324.
- 37 Lidz CW, Albert K, Appelbaum P, et al. Why is therapeutic misconception so prevalent? *Camb Q Healthc Ethics* 2015;24:231–41.
- 38 King NMP, Henderson GE, Stein J. Relationships in research: a new paradigm. in: *Beyond regulations: ethics in human subjects research*. Chapel Hill, NC: University of North Carolina Press. 1999:1–18.
- 39 Lantos JD. The "inclusion benefit" in clinical trials. *J Pediatr* 1999;134:130–1.
- 40 King NM, Churchill LR. Assessing and comparing potential benefits and risks of harm. *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:514–26.
- 41 Buchak L. Why high-risk, non-expected-utility-maximising gambles can be rational and beneficial: the case of HIV cure studies. *J Med Ethics* 2017;43:90–5.
- 42 Shaw D. The right to participate in high-risk research. *The Lancet* 2014;383:1009–11.
- 43 Thailand Family Law Center. Demystifying Kreng Jai 2012. <http://www.thailand-family-law-center.com/demystifying-kreng-jai/> (26 May 2016).