AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 31, Number 1, 2015

DOI: 10.1089/aid.2014.0219

The Ethics of HIV "Cure" Research: What Can We Learn from Consent Forms?

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Abstract

The advent of HIV ''cure'' research has generated enormous attention, but also concern about its potential to engender false hope, leading to overestimation of benefits and underestimation of risks, and about recruiting relatively healthy participants to studies with uncertain or serious risks. Currently, little is known about potential ethical problems in the ways that informed consent for HIV cure research is described to potential participants. As a first step to address this question, early phase, HIV ''cure'' research consent forms were analyzed to assess how study aims and potential risks and benefits are presented. Thirteen consent forms from a diverse group of clinical studies were selected to represent the major categories of cure research, including 11 interventional (gene transfer, vaccine intensification, treatment interruption, and latency reversing) and two observational. Consent forms were coded using seven categories, abstracting data on study purpose and design, participant selection criteria, presentation of risks and benefits of participation, and potential return of research results. Findings demonstrate variation and deficiencies that merit attention, but that can largely be addressed by turning to existing guidance about early phase research and specific study designs from other research contexts. The most challenging of these is ensuring that clear, specific, and consistent language is used to describe study aims, risks, benefits, and possible return of results. Informed consent for HIV ''cure'' research represents an opportunity to apply relevant existing guidance, measure the effectiveness of its application, and develop standardized best-practice policies for consent forms and processes.

Introduction

The NIH Clinical Trials database includes more than 100 current or completed early phase clinical trials devoted to some aspect of HIV cure research. Consent forms explain that people on antiretroviral therapy (ART) with undetectable virus via standard testing can still have a small amount of virus in cell reservoirs, and that this virus can reactivate if ART is stopped. Cure trials aim to minimize or eradicate virus in these reservoirs. These clinical HIV cure studies include gene editing, therapeutic vaccines, ART intensification studies, latency reversing strategies, and combination approaches.[1]

In this high profile, rapidly evolving field, when media hype can magnify even very preliminary results,[2] it may be difficult to maintain a capacity for balanced ethical oversight. Bioethicists Lo and Grady warn that the ''ethical standards and oversight for HIV cure research must be as rigorous and cutting-edge as the science.''[3] They offer ethical points to consider that focus attention on considerations of study design, participant recruitment, and implementation.[4] Several authors highlight the need to balance assessment of risks and benefits, including special dilemmas raised by recruiting neonates into clinical trials,[5] and possible shifting assessments that may be required when fairly healthy individuals are recruited to trials with uncertain and in some cases serious risks.[6,7] Finally, a number of authors[7–9] comment on the importance of language and the power of the word ''cure.'' As Eyal and Kuritzkes write, ''the word cure must be used with great caution, to avoid providing false expectations to participants—especially in early phase studies in which definitive cure is unlikely.''[7] Although replacement terms have been suggested,[10] it is unclear whether any will stick, since ''cure'' is now firmly entrenched in our lexicon. The Forum for Collaborative HIV Research (The Forum),[11] a public-private partnership, has convened multidisciplinary working groups to address challenges in HIV cure research and develop recommendations for investigators and oversight groups.

In concert with these efforts, this article offers an analysis of 13 consent forms to identify potential ethical problems in the ways informed consent for HIV clinical cure trials is

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being handled. It focuses on what is disclosed to participants in the consent forms: how forms characterize the studies, the kinds of participants needed, the methods employed in the research, risks and benefits of trial participation, and possible return of research results to participants. Key ethical issues and concerns are summarized.

Materials and Methods

Sample selection

During 2014, The Forum's HIV Cure Working Group #3 provided 13 consent forms for analysis, selected by them to represent the main categories of HIV cure study design. Ultimately, the Working Group assembled a list of over 100 studies from the NIH clinical trials website for use at their June 17, 2014 ''HIV Cure Project'' meeting in Washington, DC. As Table 1 shows, the 13 consent forms represent seven of 10 clinical trial categories on th list. Of the 13 consent forms, 11 studies were open and two were completed at the time of this analysis. Although not selected systematically from all HIV cure trials, they represent a broad diversity of study designs.

Creating coding categories

Preliminary categories were developed after a review of all 13 forms. Additional categories were derived from the federal requirements for consent form content (e.g., study purpose, risks of participation); others were derived from two prior consent form analysis projects on ''benefit'' in gene transfer research consent forms[12] and the return of research results following whole genome/exome sequencing.[13] After a detailed, preliminary list of categories was created, each consent form was reviewed and coded. Categories were reduced by grouping into broader themes. Statements coded for the themes from each consent form were then entered into an excel spreadsheet. Themes were further reduced to create a final list of seven categories: (1) study goals; (2) study design; (3) other design elements including phase, dose-escalation, and use of comparison groups; (4) participant recruitment including exclusion and inclusion criteria, number of participants, and length of study and follow-up period; (5) risks of participation; (6) benefit; and (7) other topics, including what participants might expect regarding return of research results and placement of results into the medical record.

Table 1. HIV Cure Trial Categories and Corresponding Consent Form Study ID Numbers

HIV Cure Trial category	*Study ID*
Antibodies	
Antifibrotic	
ARTs in HIV controllers	
Gene therapies	01, 02
Gene therapies for HIV$^+$ oncology patients	
Latency-reversing strategies	07, 08, 09, 10, 11
Stem cell transplantation (SCT)	13
Therapeutic vaccines (Vaccine)	03, 04
Treatment intensification	06
Treatment interruption (TI)	05
Observational	12, 13

Coding risks and benefits

Material coded under risk included enumeration of the types of risks mentioned in the risk section and the number of lines of text devoted to each type. Although comparisons across consent forms were limited by different font sizes, margins, and varying use of extra spacing, the lines of text devoted to each risk type were used as a proxy for how much emphasis each was given. Because not all risk types are identified by every study, and uncertainty estimates varied in how and whether they were included, it was not possible to create quantitative uncertainty assessments. Instead, qualitative assessments and excerpts from the consent forms are presented when appropriate. A systematic assessment of the way consent forms handle uncertainty would have been preferable. However, this would have required a much larger number of consent forms, so that study presentations of uncertainty could be compared to other similar studies; furthermore, to assess clarity and adequacy, information from protocols and IRB reviews would be needed. Material coded under benefit included statements about the likelihood and nature of direct medical benefit, collateral benefit (e.g., monitoring, access to care), and benefit to society and to future patients. These statements were coded wherever they occurred in the consent forms. The entire ''benefit'' section text for each consent form was also included.

Analysis

All material coded under each category was reviewed across all of the consent forms to assess the depth and breadth of language used. Then material was reviewed by type of study design. That is, statements from the two gene transfer intervention trials were read together to assess similarities and differences, followed by statements from the two vaccine studies, and so on. Next, coded material was organized and read by each of the seven code categories. That is, all consent form statements on study purpose were read together, all statements on study design were read together, and so on. Similarities and differences across studies and categories were noted, and tables for each category were created. Questions raised during this process were addressed by returning to consent forms, and if necessary, recoding categories, particularly when assessing the prevalence of specific characteristics. For example, did every consent form mention benefit to society? How many studies reported having Certificates of Confidentiality? Finally, data were summarized within and between categories.

Results

Table 2 presents data on study purpose and design, anticipated risks, and the likelihood and nature of possible direct medical benefit from participation for each of the 13 studies. The table does not identify the individual studies (with title, institution, or PI). However, analysis of study titles reveals the overarching emphasis on establishing safety and tolerability. No title uses the word ''cure,'' although one includes the phrase ''…to reverse latent HIV infection,'' and another, ''…toward eradication of HIV.''

Table 2. Study Designs, Risk Types, and Likelihood and Nature of Benefit in 13 HIV Cure Consent Forms

Study ID and type	*Study design*	*Number of risk types: top risk types (most lines of text); other key risk types (lines of text)*	*Consent form statement on likelihood of benefit*	*Nature of benefit*
01 GTR	Phase I, infuse gene-modified cells back into participants, then introduce structured treatment interruption and monitor HIV viral levels	11 risk types: *Top:* Adenoviral vector (30); reproductive (27); gene modified cells (23); apheresis (18) *Others:* Antibody formation (13); viral drift (10); excluded from future research (9); TI (7); blood cancer (7)	"You should not expect any benefit. it is primarily designed to test safety."	Genetically modified cells resistant to HIV and produce additional resistant cells
02 GTR	Safety study, participants have stopped ART; three groups: no chemotherapy or two doses of chemotherapy, then infuse gene-modified cells and monitor HIV viral levels	10 risk types: *Top*: Gene modified cells (52); busulfan (chemotherapy agent) (50); neupogen G-CSF (32); apheresis (21); infusion of modified cells (20) *Others:* Excluded from future research (6); no ART (4)	"It is unusual for people who take part in an early trial like this to personally benefit from the experimental intervention."	Improve immune system, reduce HIV in bone marrow and WBCs, WBCs live longer
03 Vaccine	First-in-human, 5 groups: vaccine or placebo; vaccine + low dose IL-12 or placebo; vaccine + mid-dose IL-12 or placebo; vaccine + highest dose IL-12 or placebo; vaccine + highest dose IL-12 or placebo	13 risk types: *Top:* EP procedure (34); pregnancy (33); HIV DNA vaccines (31); IL-12 plasmid (26); pDNA vaccine (13) *Others:* Unknown frequency or theoretical: include mutagenesis and autoimmune (12); placebo (6); randomization (4)	"…there may be a direct benefit to you, but no guarantee can be made. It is possible you may get a treatment that will improve your immune response…and may control your viral infection better."	Control viral load better, extra stimulation to form immune response to HIV
04 Vaccine	Therapeutic intensification with two ART drugs, then randomized to either add or not add the vaccine intervention	10 risk types: *Top:* Maraviroc (ART) (41); raltegravir (ART) (28); DNA vaccine (17); pregnancy (15); injection (8) *Others:* HLA typing (5); exclusion from future research (3); rAD5 vaccine and exclusion from future research (2)	"If you take part, there will be no direct benefit to you."	See if proviral DNA decreases, if immune response increases
05 TI	After viral suppression, introduce treatment interruption and follow over time	13 risk types: *Top:* [5 procedures are optional] Brain MRI (24); colonoscopy (17); spinal fluid (13); lymph noted biopsy (12); mucosal secretions (6); leukapheresis [required] (13) *Others:* Pregnancy (11); sexual transmission (9); virus not controlled (8); questionnaire and discomfort with questions (4); confidentiality (2)	"It is possible that you will not gain any direct benefit from participating in this study."	Changes in CD4 count and amount of virus over time

(*continued*)

Table 2. (Continued)

Study ID and type	*Study design*	*Number of risk types: top risk types (most lines of text); other key risk types (lines of text)*	*Consent form statement on likelihood of benefit*	*Nature of benefit*
06 TI	Phase I/II proof of concept study. After viral suppression, introduce treatment interruption and follow	8 risk types: *Top:* Nevirapine (68); lopinavir/ritonavir (27); blood draw (12); taking 3 ARVs earlier than usual (7); *Others:* Stop ARVs (4)	''This study may be of no direct benefit to your baby.''	Control amount of HIV in your baby's body
07 Latency reversing	3 dose groups of disulfiram (antialcohol drug), to reduce latent HIV infection, people on ART	4 risk types: Antabuse (45); reproductive (27); phlebotomy (12); side effects would stop participation (3)	''…study will not provide you with any direct benefit. It is hoped that it will reduce total amount of HIV in the body, but this may not happen. The intervention will not result in a cure.''	Reduce total amount of HIV in body; ultimate aim to develop cure for HIV, though likely to take many years
08 Latency reversing	Pilot safety and efficacy study, vorinostat (VOR) given to reduce amount of dormant HIV in immune cells, people on ART	6 risk types: *Top*: Vorinostat (33); contraception/pregnancy/breast feeding (14); sigmoidoscopy (9); other risks (8)	''We cannot guarantee or promise that you will receive personal benefit…the study drug is not expected to cure you of HIV infection.''	Test if VOR may reverse HIV, reduce amount of dormant HIV in immune CD4 resting memory T cells
09 Latency reversing	Study impact of valproic acid and/or Fuzeon [ART) on decreasing latent infection, people on ART	7 risk types: *Top*: Enfuvirtide (Fuzeon-ART) (54); valproic acid (34); leukapheresis (24); pregnancy (23); unmask HIV (9)	''Little chance you will benefit from being in the research study,'' not expected to cure but ''first step toward that far-away goal.''	Decrease cells infected with HIV; eradicate hidden virus, may someday eliminate HIV
10 Latency reversing	Phase I/II placebo-controlled, dose escalation study of romidepsin to decrease latent infection, people on ART	7 risk types: *Top*: Leukapheresis (28); pregnancy and infertility (24); romidepsin and could reactivate virus (10); blood draw (9)	''Not designed to directly benefit you…it is extremely unlikely that a single dose of the study drug will lead to curing HIV.''	Virus should reproduce and new HIV will kill cells hiding to it
11 Latency reversing	Phase I/II study of effect of vorinostat (VOR) on decreasing latent infection, people on ART	8 risk types: *Top*: Vorinostat (58); pregnancy (27); leukapheresis (24); blood draw (9); detectable viral load (5) *Others:* Infertility (5); confidentiality (5)	''There is little or no chance you will benefit from being in this study.''	Viral load changes after VOR
12 Observ	Compartmental analysis: Enroll individuals on ART and measure drug and viral levels in gut and lymph tissues	4 risk types: Lymph node biopsy (31); colonoscopy (22); anoscopy (12); blood draw (2)	''No benefit is assured by participating in this study.'' [Consent Form has no separate benefit section]	Measure drug and HIV levels in lymph nodes and gut after ART
13 SCT Observ	Study of HIV reservoir dynamics and diversity: Enroll individuals post-stem cell transplant (SCT), optional collection of tissues and treatment interruption	5 risk types: [3 procedures are optional] Analytical treatment interruption (40); rectal biopsy (30); cerebral spinal fluid sampling (22); leukapheresis (13); Nonphysical risks including return of results and not putting in EMR (17)	''Taking part in this study may not make your health better…we hope information learned…will help doctors learn how to improve the control of HIV infection. However, there is no guarantee or promise that this will happen.''	Improve control over HIV

GTR, gene transfer research; TI, treatment interruption; Observ, observational study; ART, antiretroviral treatment; WBC, white blood cells; IL-12, interleukin-12; ARV, antiretroviral.

Basic study characteristics

Study participants. All 13 studies recruit HIV-positive individuals with documented long-term suppression of viral replication. Twelve recruit adult participants and enroll at single or multiple sites in the United States, Australia, and Thailand, anticipating between five and 60 participants, with a median of 24 (mean of 27) per trial. An international pediatric study, by the NIH IMPACCT Network, will enroll 440 infants born to HIV-infected mothers, with a small subset followed for up to 5 years after HIV status is confirmed.

Study designs. Two of the studies are observational: one is a compartmental analysis of HIV reservoirs in lymph node and gut tissues; the other explores HIV dynamics and diversity in individuals after chemotherapy or stem cell transplantation for malignancy. Eleven are interventional, focusing on different ways to improve immune response to HIV, to ''help clear latent HIV'' (study 07) or ''completely remove HIV'' (study 04). They include two gene transfer trials; two therapeutic vaccine studies; two of which are solely treatment interruption (TI) studies, one for adults and one for infants on ART with good viral suppression; and five experimental latency-reversing trials (see Table 2). These interventional studies employ diverse study designs and length of participant involvement: two are first in human trials, two are phase I trials, and three are phase I/II trials (others have no phase designations). Eight involve different dose groups or placebo comparisons and five follow participants after TI (including two that are solely TI studies and three that employ TI after interventions). Participation lasts 4 weeks to 1 year or more. Several studies request long-term follow-up, up to 15 years. Subject payments also vary, from no payment to nearly $2,000.

How are risks and benefits of participation described?

Risks: Risk types. Consent forms list type of risk in no consistent or logical order. Risk sections include between four and 13 different risk types (see Table 2), with an average of eight types. Unsurprisingly, more risk types are included in the gene transfer and therapeutic vaccine studies; the fewest numbers of risk types are in observational studies and one latency reversing study. Risk descriptions include from 81 to 217 lines of text, with the greatest amount in trials that offer genetic interventions via gene transfer or HIV DNA vaccines, including risks associated with the interventions and the vectors that deliver them as well as risks of associated procedures, reproductive risks, and others.

Likelihood and severity of risks. Information about likelihood and severity may begin with common, relatively mild risks and end with rare, serious, or possibly fatal outcomes. Four of the five latency reversing trials describe risks from ''unmasking HIV'' or ''reactivating the virus,'' resulting in ''detectable viral load.'' One study defines these as ''theoretical'' risks that have not been seen; another describes them as ''possible, though unlikely.'' When severity or frequency of risk is unknown, uncertainty may be disclosed. Table 3 provides examples of uncertainty disclosure related to gene transfer intervention, DNA vaccines, and treatment interruption.

Risk of treatment interruption. As noted above, the use of TI to examine the success of an intervention is employed by five of the 13 trials. Data on the outcomes of TI are well documented[14–16] and inform risk descriptions. One consent form (study 13) devotes considerable text and specificity to risks and uncertainty, providing a list of 10 potential risks of TI, each with estimates of severity and frequency and percentages (e.g., ''likely, >50%'' or ''rare–serious, <5%''), noting that for two risks, likelihood is unknown, and that risks of ''infection and death'' will increase with longer periods of TI. In contrast, the other four studies devote much less text to TI and use nonspecific likelihood terms such as ''may,'' ''it is possible,'' or ''there is a risk.'' For example, study 01 (p. 11) states, ''[I]f your HAART therapy is stopped, the level of HIV in your body may increase, your CD4+ T-cells may decrease, or the type of HIV you have may change…Viral rebound with an increased risk of HIV transmission is possible.'' The pediatric study (06, p. 9) notes that HIV virus ''…may rise again to detectable levels…could also lead to your baby's body becoming resistant to ARVs.''

Other risk types. Across all interventional studies, sections describe risks associated with intensification of ARV treatment, study drugs, and related procedures (leukapheresis, apheresis, electroporation, and tissue biopsies). All studies with adult participants include women of reproductive age but exclude pregnant women; all but one of the adult interventional studies include long sections on reproductive risks for participants, detailing clear warnings about known and unknown risks. Two also warn of possible infertility risks. Other rare or ''unknown or theoretical'' risks related to study interventions include antibody formation, viral drift, mutagenesis, and blood cancer; three studies also list possible exclusion from future cure research. To address concerns about privacy and confidentiality, three studies acquired Certificates of Confidentiality. Some identify loss of privacy or confidentiality as a risk, whereas others address this in a separate section; and one notes the need for protection from media attention often experienced by participants in gene transfer studies.

Benefits. Nature and likelihood of direct benefit. These early phase, exploratory trials describe their main objectives as safety and tolerability, and their ''benefit'' sections generally state that there is no or very little prospect of direct medical benefit. However, long-term aims are often presented in lofty terms that may be interpreted as possible, even likely direct benefit to participants. These include, for example, ''to prevent HIV from killing CD4+ T cells'' (01), ''to achieve HIV remission'' (06), and ''to eradicate hidden virus…unmask or flush out the latent HIV in your cells'' (09). Seven studies also refer to results from promising laboratory or prior clinical studies. All identify potential surrogate endpoint changes that may be familiar to HIV trial participants from clinical care or media reports, such as ''modify CCR5 protein'' or ''viral load changes,'' which will be monitored closely; a few describe clinical endpoints, such as ''improve the body's ability to fight infection'' and ''remain healthy.'' In addition, three consent forms describe collateral health benefits from close monitoring while in the trial. Thus, as demonstrated in Table 2, there are multiple, potentially conflicting messages about the nature versus the likelihood of direct medical benefit.

Table 3. Example Descriptions from Consent Forms of Unknown "Theoretical" Risks

Study ID	*Excerpts from risk sections*
02 GTR	"There may be adverse effects that are presently *unknown and unforeseeable*…Possible consequences of [intervention] are unknown. It could have no effect or a positive effect…[It] could also possibly cause cancer, or even spread to your reproductive organs and be passed on to any future children you may have. However, to date no such events have been reported…so this risk is still theoretical…a test to monitor this [will be run at various times points during the study].
03 Vaccine	"*Unknown frequency or theoretical risks:*…insertion of the vaccine DNA into your body's DNA could possibly lead to cancer, or into the DNA of bacteria or virus in your body (which has unknown consequences). This can be serious, but is expected to be rare if it ever occurs. None of these possible risks of DNA vaccines has been seen in laboratory tests or in animals or humans so far, but you need to be aware of these possible risks."
13 Obser.	"The exact risks or severity of adverse events associated with analytical treatment interruption in patients with HIV who have undergone bone marrow transplantation are not known." (p. 12)

Societal benefits. Benefit to society is described in all 13 consent forms, defined as creating generalizable knowledge. For example, one states, "[Y]our participation may benefit the community, scientists, and doctors who work with HIV by providing new information about the treatment of your disease" (08).

How is return of research results addressed?

The consent forms reveal diverse approaches to return of research results (see Table 4). Three consent forms do not mention any possible return. Of the remaining 10, three types of return of results are mentioned: (1) return of screening results, (2) return of study results, and (3) return of results from future research on stored specimen. Additionally, five consent forms mention return (or not) of *genetic* results, and one mentions return of aggregate study data. Lastly, only five of the 13 consent forms mention the possibility (or not) of placing results in a participant's electronic medical record (EMR).

Discussion: What Are the Ethical Issues in HIV "Cure" Research?

HIV research has generated a range of ethical issues, from access to therapies in the early stages of clinical testing, to the role of communities and advocacy groups in trial design and conduct, to fairness in application of different standards of care in research and implementation of HIV treatment advances in health systems.[17–20] Given the profound stigma and vulnerability associated with HIV, special ethical guidance was developed for researchers[21] and research networks.[22] The advent of HIV "cure" research has generated broad questions about what studies should take place and who should be asked to participate. Indeed, the literature that frames this consent form analysis raises concerns about study oversight, especially when relatively healthy participants are recruited and treatment interruption is used to assess the effectiveness of early interventions. Controversy surrounds determinations of when to move from bench to bedside, who to select as the first trial participants, and whether to employ the "sickest-first (oncology) model or the healthiest-first (pharmacology) model"[23–26] (p. 384). Despite interest in these important questions, this article focuses on only one ethical issue in HIV cure research: the quality of consent.

A consent form analysis has clear limitations. As argued in a recent commentary,[27] to improve informed consent in HIV cure trials, there is a critical need to explore what motivates participation, and how risks and benefits are perceived. Interviews with participants and those who decline or who are excluded from enrollment would provide important data on the processes of informed consent. Data gathered from other stakeholders would provide perspectives about potential risks and benefits. Longitudinal or comparative studies would offer data on perceptions of "cure" over time and in different contexts and address ongoing, real-world ethical concerns. Nevertheless, these 13 consent forms provide a starting point to identify the ways that informed consent for HIV cure research is being handled across quite heterogeneous studies.

This analysis does not reveal ethical issues that are unique to HIV cure research, and in this regard, we might conclude that HIV research is no longer "exceptional." Studies whose primary goal is to determine safety and tolerability expose participants to uncertain and potentially high levels of risk in the absence of likely benefit. This is not exclusive to HIV cure research.[26,28,29] Phase I studies are sites of well-described ethical dilemmas.[30] Empirical bioethics research on early phase trials in oncology and other diseases focuses on the danger that participants may misunderstand the

Table 4. Diversity in Approaches to Results

Use of results	*Number of consent forms that mention results, EMR, sharing, or commercial use*	*Number of consent forms with no mention*
Return of results from screening for study	5 will return	8
Return of results from study	3 will return, 4 will not return	6
Return of results from future research	1 will return, 3 unlikely to return, 2 will not return	7
Electronic Medical Record (EMR)	3 will place results in EMR, 2 will not	8

potential for benefit and underestimate the likelihood of risk.[31–33] Many scholars have written about the difficulty in communicating about uncertain and unpredictable risk to trial participants,[34,35] made all the more difficult by the scientific and linguistic complexity revealed in risk sections of consent forms (see Table 3).

In this consent form analysis, both the gene transfer and the vaccine studies feature particularly challenging risk–benefit assessments, featured in a recent article in the journal *Gene Therapy*.[33] The authors describe the risk of off-target mutagenesis and random insertions, asking two questions about levels of variability and severity of risk that plague many early phase and first-in-human trials: how great a likelihood of this risk must exist before preventing a trial from moving forward, and how much risk and uncertainty are acceptable before a clinical trial can proceed? The question for this analysis is whether consent forms present the nature, likelihood, and severity of risk using clear and appropriate language. One exemplary study includes an extensive description of the risks of treatment interruption, also described in a recent publication by the investigators: ''…uncertain significance of virologic assays and potential risks of ATI, including viral rebound, the acute retroviral syndrome, or graft-versus-host disease exacerbation.…''[36] (p. 3). Yet many of the consent forms in this analysis failed to demonstrate attention to and specificity in risk descriptions. Every effort should be made to improve vague, noninformative language (e.g., likelihood statement such as ''may occur''). When uncertainty of risk prediction is unavoidably part of a first-in-human or proof-of-concept study, this should be stated and explained.

In contrast to concerns expressed in the literature about overestimation of benefit in HIV cure trials, the benefit sections in these consent forms minimize or deny any prospect for direct medical benefit related to participation, which is appropriate for early phase trials, and do not advertise themselves as ''cure'' studies. However, the consent forms also include optimistic statements about promising preliminary findings, inspiring future study goals, and surrogate endpoints that may be interpreted as possible individual medical benefits. Tensions between cautious statements about likelihood and encouraging predictions about the nature of possible direct medical benefit should be monitored, but are not unique and have been described elsewhere, for example, in an analysis of 321 early phase gene transfer consent forms.[12] In contrast to findings from that study, in which almost 25% failed to mention benefit to society as a study goal, every one of the 13 HIV cure consent forms identifies contributions to scientific knowledge as a major study objective. Thus, analysis reveals that these consent forms provide an appropriate foundation for discussion of benefit, including the scientific objectives of the research and the low potential for direct medical benefit.

One caveat remains. Among the 13 consent forms, there is great variation in how they treat the possible beneficial return of research results from the investigations and whether or how results might be incorporated into the medical record. The return of individual results to research participants, a particularly contentious issue in genomic research,[37,38] raises critical questions about the boundary between research and clinical care, and whether surrogate or clinical endpoints mentioned in the consent forms might be misconstrued to represent possible medical benefits. At the least, consent forms should be clear about the significance of such endpoints and the difference between clinically relevant results that may be returned and those that will not. In these early HIV cure trials, most results will be produced in research rather than in CLIA-certified laboratories, and many are employing assays or biomarkers of uncertain significance. This important issue, which should be part of institutional guidance and IRB reviews, is not addressed in any of the 13 consent forms.

The variation and deficiencies as well as the strengths identified in this article merit attention and provide a window on what is happening in this new field. Is specific ethics guidance for HIV ''cure'' research needed? In the case of federal oversight for recombinant DNA research, an oversight model was developed to produce ''generalizable guidance that can be of use to oversight bodies having local control…[and] from review of common questions and problems that have not been systematically addressed in less prominent areas of research''[23] (p. 386). The issues that are raised by HIV cure research consent forms are discussed in the literature on the ethics of research in genetics, oncology, and psychiatry; yet there could be value in creating a specific document and promoting discussion across fields. Recommended next steps include applying this guidance, measuring the effectiveness of its application in concert with consultation with relevant stakeholders, and developing standardized best-practice policies for informed consent documents and processes.

Acknowledgments

I am grateful for assistance in collecting the 13 consent forms from The Forum staff working with the HIV Cure Working Group #3 (Sonia Navani and Courtney Hutchison), from Karine Dubé at UNC, and to the 13 PIs who gave permission for their use. The following individuals provided helpful suggestions on the article: Myron S. Cohen, Timothy J. Henrich, Nancy M.P. King, David Margolis, Veronica Miller, Stuart Rennie, Holly Peay, and Joseph Tucker. Mary-Beth Grewe provided editorial assistance. The article is much improved thanks to the thoughtful comments of two anonymous reviewers. Support for the work was provided by R01 A108366-01 (Tucker & Rennie, PIs), ''Unintended and Intended Implications of HIV Cure: A Social and Ethical Analysis,'' and the Brocher Foundation.

Author Disclosure Statement

No competing financial interests exist.

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