Ethical and Practical Considerations for Cell and Gene Therapy Toward an HIV Cure: Findings from a Qualitative In-Depth Interview Study in the United States

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Abstract

Background: HIV cure research involving cell and gene therapy has intensified in recent years. There is a growing need to identify standards, safeguards, and protections to ensure cell and gene therapy HIV cure research remains ethical and acceptable to as many stakeholders as possible as it advances on a global scale.

Methods: To elicit ethical and practical considerations to guide cell and gene therapy HIV cure research, we implemented a qualitative, in-depth interview study with three key stakeholder groups in the United States: 1) biomedical HIV cure researchers, 2) bioethicists, and 3) community stakeholders. Interviews were transcribed verbatim. We applied conventional content analysis focused on inductive reasoning to analyze the rich qualitative data and derive key ethical and practical considerations related to cell and gene therapy towards an HIV cure.

Results: We interviewed 13 biomedical researchers, 5 community members, and 1 bioethicist. Informants generated considerations related to: perceived benefits of cell and gene therapy towards an HIV cure, perceived risks, considerations necessary to ensure an acceptable benefit/risk balance, cell and gene therapy strategies considered unacceptable, additional ethical considerations, considerations for first-in-human cell and gene therapy HIV cure trials. Informants also proposed important safeguards to developing cell and gene therapy approaches towards an HIV cure, such as the importance of mitigating off-target effects, mitigating risks associated with long-term duration of cell and gene therapy interventions, and mitigating risks of immune overreactions.

Conclusion: Rapidly evolving cell and gene therapy towards an HIV cure is accompanied by a host of ethical and practical challenges. To minimize risks to potential participants and facilitate the translation of scientific advancements from the bench to the clinic, cell and gene therapy HIV cure research must be thoughtfully developed and implemented. To protect the public trust in cell and gene therapy HIV cure research, ethical and practical considerations should be periodically revisited and updated as the science continues to evolve.

Background

Human immunodeficiency virus (HIV) cure research involving cell and gene therapy (CGT) has intensified in recent years. Such efforts aim to completely eliminate HIV from the body or confer sustained drug-free viral suppression. Fundamentally, cell therapies involve delivering living cells inside the human body, while gene therapies involve delivering genetic material (1). Timothy Ray Brown – the Berlin patient – was the first person cured of HIV following a risky allogeneic stem cell transplant from a donor with a double Δ32 mutation (2,3). His HIV cure represented a monumental scientific breakthrough that was only replicated a decade later when Adam Castillejo – the London patient – underwent a similar procedure (4–6). Timothy and Adam's cures have energized the HIV cure research field. Several investigators are trying

to replicate these cures using CGT as a means of avoiding allogenic transplants. To date, over 35 clinical trials involving CGT to achieve an HIV cure have been completed (7).

The field of CGT is fast-moving and raises several ethical and practical concerns. The first generation of CGT HIV cure interventions present many uncertainties, toxicities, and participant burdens. A cautionary tale remains the 1996 X-linked severe combined immunodeficiency (SCID) clinical trial in Europe, after which 25% of participants developed T cell acute lymphoblastic leukemia due to vector insertion near a proto-oncogene (8,9). Three years later, in a similar event in the United States, Jesse Gelsinger, a volunteer in a gene therapy clinical trial for a rare metabolic disorder who had until then survived through dietary restrictions and medical therapy, died from an intense inflammatory response that led to systemic organ failure. This tragedy led to a close examination of the pace of clinical investigation in the field and substantially delayed many research efforts (10). Decades later in 2018, He Jiankui announced he used clustered regularly interspaced short palindromic repeats (CRISPR) to create the first gene-edited babies in an attempt to prevent their HIV infection (11). This was widely considered an ethical failure and the effort received widespread condemnation (12).

Considering these paradigmatic cases, the field of CGT has made much progress in safety and the responsible conduct of research over the last two decades. Likewise, the regulatory environment has evolved to accommodate a recent surge in CGT research globally (9). Since 2017, the CGT field has produced several U.S. Food and Drug Administration (FDA) approved therapeutics in multiple disease areas, such as sickle-cell disease and lymphoma, among others (9,13). Investigational CGT HIV cure strategies encompass several different approaches that aim to make cells resistant to HIV infection, increase immunity, or disarm HIV [11]. Common gene editing platforms remove the C – C chemokine receptor type 5 (CCR5) and make cells refractory to HIV. These include CRISPR, transcription activator-like effector nucleases (TALENs), and zinc finger nucleases (ZFNs), among others (14). An increasing array of CGT approaches are derived from the oncology field, such as chimeric antigen receptor (CAR) T cells that seek to improve the adaptive immune response against HIV (15). Some studies also require the interruption of antiretroviral treatment (ART), termed analytical treatment interruption (ATI) to determine the effect of the intervention on the immune system.

There are a growing number of CGT HIV cure clinical trials being implemented globally. While CGT will continue to present challenges in terms of efficacy and human safety, a growing tool box of recent and future scientific advances provide cause for optimism (1,15). As CGT HIV cure research intensifies, the application of CGT to scientific endeavors aimed at finding a cure may heighten ethical complexities (16). To elicit ethical and practical considerations to guide CGT HIV cure research, we implemented a qualitative, in-depth interview study with three key stakeholder groups in the United States: 1) biomedical CGT HIV cure researchers, 2) bioethicists, and 3) community stakeholders. Our objective was to understand stakeholder perspectives around CGT and generate ideas on desirable standards, safeguards, and protections to ensure CGT HIV cure research remains ethical and acceptable to as many stakeholders as possible as it advances.

Methods

Participant Recruitment

We used purposeful sampling to select key informants. We recruited biomedical researchers actively working in the field of CGT towards an HIV cure, community members, including people living with HIV (PLWH) who have previously participated in CGT research as well as community advocates working in the field of HIV cure research, and bioethicists. An External Advisory Group listed potential informants who represented academic institutions, community advisory boards (CABs), government, and the pharmaceutical industry. All participants were recruited based on prior familiarity with CGT towards an HIV cure. We conducted in-depth interviews to identify ethical and practical considerations to guide future implementation of CGT HIV cure research (17). The study's principal investigator (K.D.) sent formal e-mail invitations to potential informants. Email correspondence indicated the purpose of the study and contained our institutional review board (IRB)-approved informed consent form, blank demographic sheet, and sample interview guide. Interview acceptors received a Health Insurance Portability and Accountability Act (HIPAA)-compliant virtual conferencing weblink over which the interview was conducted.

Data Collection

Two trained researchers (K.D. and J.K.) conducted all interviews in English with fidelity to the IRB-approved interview guide (**Table 1**). Interviews lasted between 30 – 60 minutes, and all informants agreed to be audio recorded. Community members received compensation in the form of an electronic US $20 e-gift card following their interviews. Informants from academic institutions, government, and pharmaceutical companies did not receive compensation.

Data Analysis

Interviews were transcribed by a professional, web-based transcription company. One research team member (J.K.) reviewed all transcripts for accuracy against the audio recordings. We then destroyed audio recordings after cross-checking transcripts for quality. Because this was a formative research project, we employed conventional content analysis focused on inductive reasoning to analyze the qualitative data (17). We distilled the interview data to derive key themes and generate ethical and practical considerations related to CGT towards an HIV cure.

A research team member (J.K.) compiled all de-identified responses into a single master document for manual coding. To realize the full potential of the qualitative data, the research team analyzed the data by question blocks. We carefully reviewed responses to each question to re-familiarize ourselves with the data. We then extracted salient quotes and ascribed themes and codes. Our resultant codebook was inductive and contained code names, code descriptions, and examples. Research team members (K.D. and J.K.) double-coded the data and organized text segments into emergent themes. During the coding process, we expanded and reduced codes and themes as needed. We resolved discrepancies by

discussion and consensus during virtual meetings. The lead author (K.D.) summarized the key themes and wrote narrative summaries to contextualize the data. All co-authors reviewed the data.

Ethics Statement

This study received IRB approval from the University of North Carolina at Chapel Hill (UNC-CH) IRB (study #19-0522). All informants provided verbal consent to be interviewed.

Results

We invited 38 potential informants, of whom 19 agreed to be interviewed (50% response rate). We interviewed 13 biomedical researchers, 5 community members, and 1 bioethicist. These included 16 cisgender men and 3 cisgender women. Of these, 16 were White/Caucasian, 1 was Black/African American, 1 was mixed race, and 1 was Asian (**Table 2**). Interviewees worked in the field of HIV for a mean of 24.1 years (SD = 10.5 years), and in HIV cure-related research for a mean of 14.3 years (SD = 9.7 years).

Perceptions of CGT and Benefit/Risk Considerations

Interview topics included: 1) perceived benefits of CGT towards an HIV cure, 2) perceived risks, 3) considerations necessary to ensure an acceptable benefit/risk balance, 4) CGT strategies considered unacceptable, 5) additional ethical considerations, and 6) considerations for first-in-human (FIH) CGT HIV cure trials.

Perceived Benefits of CGT Towards an HIV Cure

We asked informants to describe potential benefits of CGT for an HIV cure. Perceived benefits included the greater likelihood of achieving a complete cure when compared with other HIV cure strategies under investigation, the prospect of developing “one-shot” cures that could be globally scalable, and scientific advancements that could benefit other molecular genetic diseases.

The bioethicist (#14) stated CGT approaches aim at being “one-and-done” therapies could be more attractive to PLWH because they would not require lifelong treatment if proven effective, although this would not be true if PLWH would not be protected against HIV re-infection.

I think the distinction is between one and done therapies… that are really like, "Okay, we do this intervention and, once we're through it, you're done. You don't have to worry about your HIV anymore… You don't have to continue to take antiretrovirals" versus something where we're talking about continued lifelong therapies… I can imagine that if there were something that could be one-and-done, and that were reasonably safe, there would be a lot of people who would be very interested in doing it for themselves. – Bioethicist (#14)

Community members also identified possible benefits of CGT research towards an HIV cure. One community member (#16) believed CGT will be required to achieve a cure for HIV. If effective, CGT may result in making cells resistant to HIV, thereby preventing future HIV infection (#08). Another community member (#05) believed CGT strategies could go to the root of the problem to fix what is broken.

I also just think that [CGT is] a better way, you know, more complete and better way to really get into the body… to change what's wrong and fix HIV… From the get go, it's going to go in there, the gene therapy, and change what's broken.

– Community member (#05)

Two community members (#05, #16) described possible clinical benefits, short of a cure, that may emerge from clinical trials. These community members both witnessed unexpected, significant increases in their CD4+ T cells following a non-curative CGT intervention which did not occur after a long periods on salvage HIV treatment regimens.

It's been 10 years since I was in the trial. A secondary side effect, or secondary outcome of the trial, which was that my T-cells were doubled. I mean, nobody knew that was going to happen. So, I mean that's something that we need to consider, is what are those secondary outcomes that may come out of a gene therapy trial, that we would not expect it.

– Community member (#05)

It might be a great adjunctive benefit if you don't get a cure. I know people that were, myself included, basically on salvage regimens and at the end of their treatment rope with resistance… [who] have had perhaps an unintended benefit that they do better than they had… before [while] on medications.

– Community member (#16)

Biomedical researchers discussed the need for cutting-edge approaches to curing HIV, since other strategies under investigation have not yet proven effective at keeping HIV suppressed without ART. Three biomedical researchers (#02, #09, #11) stated CGT has great potential to lead to complete elimination of HIV. They described the strong scientific rationale for attempting to replace the immune system with cells that would become resistant to HIV.

The things we've tried in the past haven't really worked terribly well. [W]e need new technologies [and] new abilities to alter the immune system or alter how HIV is able to hide in the body for us to get a cure. – Biomedical researcher (#09)

The potential longevity of CGT was another appealing feature.

If there were to be a single shot in the arm that was more accessible, more palatable, more likely carried out in such individuals, that would be a boon to them and to their partners or whomever they might spread virus to.

– Biomedical researcher (#03)

Finally, a biomedical researcher (#06) described how scientific advancements in CGT could lead to cures for other molecular genetic diseases.

There's a lot of other genetic diseases and some cancers where the targets of the therapy are very difficult to find, and I think HIV… could provide a lot of benefit for the ways that we target [treat] other people with other viruses and other molecular genetic diseases. – Biomedical researcher (#06)

Perceived Risks of CGT Towards an HIV Cure

Community members and biomedical researchers also described possible risks of CGT HIV cure research. Perceived clinical risks related to immediate side effects, such as off-target editing or immune reactions, and longer-term risks, such as developing cancer. Further, community members were concerned about raising false hopes. Biomedical researchers mentioned the possibility of transmitting HIV to sexual partners if there was viral rebound during an ATI if the intervention was unsuccessful, and the financial costs associated with CGT.

Community members were concerned about both short-term and long-term clinical risks of CGT. They mentioned off-target editing and risks of developing cancer later in life as most salient to them. A biomedical researcher (#19) mentioned the theoretical risk of insertional oncogenesis, a deoxyribonucleic acid (DNA) mutation that could lead to cancer.

You have those off-target edits, which can be causing cancer, and that might not happen for 20 years.

– Community member (#08)

I think that the risks that everybody talks about is cancer or malignancies being, you know, caused by changing a piece of the DNA. – Community member (#05)

There's something called insertional oncogenesis, that just the idea of a viral vector integrating itself into the host DNA could induce a malignancy, by knocking out a tumor suppressor gene or something. – Biomedical researcher (#19)

Besides clinical risks, community members' narratives centered around the risk of creating false hopes and expectations in the community.

I think when gene therapy reaches the level of being able to cure cancers, to being able to cure HIV, it's going to be seen like a miracle. But it could also create false expectations. And I think the process of getting to that day, that's a risk, creating these false impressions. 'Cause even when I talk that way… it's easy to create false hopes and false impressions, and I think that causes more damage… over time, which may be collaterally worse than the actual cure you get to in the end.

– Community member (#08)

Likewise, biomedical researchers also described both short-term and long-term clinical risks of CGT. Immune reactions, such as cytokine release syndromes (CRS) expected with some CAR-T cell interventions, were perceived as a real possibility. Three biomedical researchers (#02, #11, #12) mentioned the risk of developing later malignancies.

If you put gene-modified cells into the body, there is a potential to have one or two… of those cells become malignant, and that would be hazardous. – Biomedical researcher (#02)

Biomedical researchers and community members were also concerned about possible unknown risks of CGT. These unknown risks will require careful vigilance, particularly as there may be interparticipant variations.

I think the risks are the ones … that we don't know about... Any time you do something that's unknown, you can't quantify or qualify risks. There's no crystal ball… It's only going to be after many years of accumulated experience that we really know. Likely, it's going to be very heterogeneous with respect to the risks, in terms of interindividual variation. We just have to walk forward, like anything else we do in the clinic, with our eyes wide open. – Biomedical researcher (#03)

One biomedical researcher (#09) was concerned about the risk of transmitting HIV to sexual partners during ATIs and unsuspected viral rebounds.

The real risk is someone becoming viremic without knowing and then could potentially transmit the disease to somebody else… To me, that is the most tangible risk in this type of therapy... But… the only way we know if it works, is by taking people off their medicine… To me that's the scariest adverse effect… is that somebody unwittingly transmits the disease to somebody else because of the trial they're on. – Biomedical researcher (#09)

Ensuring Acceptable Benefit/Risk Balance

We queried informants about possible ways to ensure acceptable benefit/risk parameters in early-phase CGT HIV cure trials. Informants described the difficulty of objectively assessing benefit/risk ratios and recommended minimizing risks to participants while maximizing possible benefits to science and humanity.

The bioethicist (#14) provided three suggestions to ensure acceptable benefit/risk profiles: 1) minimizing risks as much as possible, 2) learning as much as possible from the trial, and 3) being transparent about the potential risks to allow participants to make informed decisions.

I think here the question is really, have we minimized the risk? Is it really, really good science? Are we being honest with people so they can make informed decisions? – Bioethicist (#14)

A community member (#08) described the difficulty of assessing benefit/risk ratios in early-phase CGT trials, comparing the exercise to “walking a tightrope.” Further, risk toleration is greatly reduced as a result

of highly effective ART. Constant consideration around acceptable benefit/risk is therefore required.

I don't know if you ever really do achieve that… So I always think of it as walking a balance bar or walking a tightrope… [In] the case [of] cure research…, there's gonna [be] less acceptable risks… And so that's stuff that we're gonna have to constantly monitor… Don't assume that you have a risk-benefit ratio, and it's taken care of… it needs constant vigilance.

– Community member (#08)

Biomedical researchers converged on the difficulty of making benefit/risk assessments. They described how these evaluations rely on their biological intuition based on the specific mechanisms of action being investigated. They also commented that the field of CGT HIV cure research will need better biomarkers or metrics to assess benefits and risks.

[I]t is very difficult to really, fully assess a cost benefit ratio to make decisions like that. I think a lot of it has to [do] more with biological intuition, in terms of, based on the underlying mechanism of action associated with a curative approach, we can surmise that… it's not likely to be harmful… But I think until we have better cure biomarkers, it's going to be difficult to come up with really robust metrics to make yea or nay decisions about going to the clinic. – Biomedical researcher (#19)

To ensure acceptable benefit/risk profiles, biomedical researchers recommended collecting as much safety and efficacy data as possible, particularly at the pre-clinical stage. They also stressed the need for an incremental scientific approach, adequate regulatory reviews, and robust risk mitigation strategies as part of clinical protocols. Researchers will also need to consider potential benefits to otherwise healthy PLWH compared with standard ART.

I think having as exhaustive data as possible, looking at the safety of the approaches, as well as how well it's likely to work…. But I think if the so-called efficacy, or how well it's working in the cure, if that's very high, and we think that it's feasible to administer these therapies in one way or another and the toxicity is low, I think it just comes down to what the benefit is for an otherwise healthy person living with HIV. – Biomedical researcher (#06)

In addition to weighing the possible benefits to PLWH, a biomedical researcher (#09) considered the potential benefits of a curative CGT strategy to humanity.

For HIV disease, this is truly altruistic. The people who participate in our trials, they're not doing it because they think they're going to get cured. I think in the long run they're doing it because they hope there is a cure… I think from a risk-benefit point of view, it doesn't make sense. But from a humanity point of view, somebody who's angry at their disease and how it's… stigmatized them, caused them to take all these medicines, I do think they do want to fight back a little bit and say, "Okay, I want to work towards a cure." – Biomedical researcher (#09)

CGT Strategies Perceived to be Unacceptable for Human Testing

There was a convergence of opinions regarding two CGT HIV cure strategies considered to pose too much risk and to be unacceptable for human testing: germline editing and allogeneic stem cell transplants in otherwise healthy volunteers.

First, informants identified gene modifications that would affect the germline to treat or cure HIV as unethical. They referenced the recent episode of embryos being gene edited using CRISPR-Cas9 by He Jiankui in China.

I think that needs to be a very solid moratorium [on editing the germline in HIV], even though it's been broken… I'm against the germline therapy, simply because of the implications that we are not even yet aware of, and I think it's jumping the gun... I do not think we are ready to start messing with our germline. – Community member (#08)

Germline editing [towards an HIV cure]…, at this point, I think should be a no no… Definitely with the tools and the understanding that we have now, we shouldn't even think about doing germline editing and the stuff that [He Jiankui] did with the CCR5 editing with the babies. [It is] totally irresponsible and insane. – Biomedical researcher (#19)

Informants also converged around the unethicality of conducting allogeneic stem cell transplants in otherwise PLWH, unless there was an underlying malignancy warranting such a risky procedure.

Except for people with cancer, you wouldn't want to do a bone marrow transplant on a healthy person, right? Wow, it can lead to the cure in a relatively small percentage of the people that get it, there the risk reward doesn't make sense because there's a 30-40% chance you can die. That's never a good risk reward benefit… It's an area where we know much less because there are no proven stem cell therapies. – Biomedical researcher (#09)

A community member (#05) said he would not tolerate any procedure that could lead to debilitation or hastened death. In turn, a biomedical researcher (#07) and community member (#08) commented that unacceptable risks would depend on individual volunteers or scientists. Further, a biomedical researcher (#12) was adamant that science should not be restrained as long as experiments were conducted within ethical boundaries.

I think that, while we keep our ethical considerations and approval, everything is game. I don't think we should limit science. We should protect subjects [participants], but we should not limit science. And a lot of people, under the disguise of protecting patients, they're really biased. And sometimes it's just as simple as not accepting a new technology.

– Biomedical researcher (#12)

Additional Ethical Considerations for CGT Approaches Towards an HIV Cure

We asked informants to provide additional ethical considerations for developing CGT HIV cure research. Most of the considerations given were not unique to this field and included: strong scientific rationale, safety maximization, fair participant selection, and distributive justice. Community members stressed the need to maximize long-term scientific benefits for the HIV community.

Informants noted the need for a strong scientific rationale and hypothesis, and only approaches that could lead to a successful durable ART-free suppression regimen should be pursued. Informants recommended maximizing safety, a responsibility that often rests directly with scientists.

Then the main driver of all of this is the validity of the hypothesis, the rationale which is driving the program. That rationale is how we start to think about risk-benefit and ensuring that that rationale can be clearly discriminated from existing studies or published literature is absolutely key. If it can't be discriminated from those other studies, then what is the purpose of repeating it? – Biomedical researcher (#04)

Another ethical consideration relates to fair participant selection. Informants recommended recruiting volunteers who represent populations of interest and who are diverse in age, sex and gender, and race and ethnicity. Special safeguards should be in place for pregnant women, pediatric populations, and other vulnerable groups.

Other ethical considerations related to distributive justice. There must be a balance between providing HIV treatment and prevention access around the world and research funding dedicated to an HIV cure. Efforts should also be made to reduce the cost of CGT technologies as a matter of global access justice and equity.

So, you have always… in the background, a question about is it ethical about going into cure when people don't even have access to treatment and 15 million people are facing death from HIV? Shouldn't we be giving more money to get that treatment everywhere? – Community member (#08)

We also think about the cost and, if we have to make this universal therapy, how can we apply it to maybe resource-limited settings as well? – Biomedical researcher (#17)

Finally, a community member (#01) discussed the ethics of CGT development. Several companies conducted initial experiments in PLWH, only to move on to other disease areas when a CGT product demonstrated some safety or proof-of-concept. This community member (#01) recommended that CGT companies show a genuine commitment to stay in the HIV space and maximize long-term community benefits for altruistic PLWH.

Companies may decide that they don't want to continue to benefit [or]… that they don't want to continue to work in HIV because … it is hard… I can see why your business model might suggest you move on to another disease, but we need to think about some method [whereby] the whole community receives some later benefit from having helped these companies actually achieve the safety signal in their product that they needed to be able to move on to later work.

– Community member (#01)

Considerations for First-in-Human CGT HIV Cure Trials

Informants provided considerations for implementing FIH CGT HIV cure trials which included robust pre-clinical data, well-designed and supervised FIH trials, and observance of regulatory standards. Community members emphasized the need for early community involvement in clinical trial design and adequate compensation for study participants. Biomedical researchers recognized the limitations of current animal models and the need for constant improvements.

The bioethicist (#14) described the imperative for a compelling scientific rationale for implementing FIH trials. Similarly, a biomedical researcher (#12) stressed that nothing could replace FIH trials.

If there's a bunch of preclinical experience that can be done to narrow the window of uncertainty, then those should be done. But at a certain point… if there's nothing more than that we could do before going into humans to actually take the science forward, then you get presented with the million dollar question which is, "Are we willing to do this?" That is going to have to be a judgment of how compelling is the science [and] how compelling is the rationale to date, and weighing that against what are the risks we might be asking people to take. – Bioethicist (#14)

And at the end of the day, there's nothing like trying this in patients. It doesn't matter how much pre-clinical data you have. – Biomedical researcher (#12)

A community member (#08) emphasized the need to involve PLWH in clinical trial design from the start, as well as adequate compensation for early-phase trials that includes compensation for research-related injuries.

You should have the people of that population involved from the beginning…; patients really need to be involved at the trial level. If it's first-in-human you need to make sure that you have at least one person who lives with HIV involved at the get-go…, not a tad later on…, because I think they can help you with the acceptable balance of risks and benefits… Compensation needs to be thought about… if something goes wrong [the participants] should definitely be compensated.

– Community member (#08)

Biomedical researchers' narratives centered around the need for robust testing in animal models. There must be strong emphasis on safety standards together with signals of potential efficacy in humans. A community member (#08) stressed the need for careful peer review of pre-clinical data.

Everything plays to me around safety and then, if it's safe, I think to proceed, if you've checked preclinical development, you've checked that the genes are manufacturing, it is released. It's all this. It's clean. It's ready to be infused. Highest standards. Then together this body of evidence makes it ethical. – Biomedical researcher (#15)

We should insist before anything goes into humans that it is published, that animal data, or that pre-clinical data has been published, so that others can make independent judgments about the quality of the work, before it goes into humans… They [the investigators] can't just keep that data private. – Community member (#08)

Further, biomedical researchers discussed relying on regulatory authorities and processes, such as the FDA's investigational new drug (IND) application process or their respective Institutional Biosafety Committee (IBC), for guidance, as well as Data Safety Monitoring Boards (DSMBs).

It's like you check so many things to make sure that it's safe to proceed, it's ethical... We have [an] Institutional Biosafety Committee… reviewing that and we have the FDA that has clinical, preclinical, and CMC [Chemistry, Manufacturing and Controls] manufacturing reviewing that body of data..., so they should know when [to begin testing]. – Biomedical researcher (#15)

Nonetheless, several biomedical researchers pointed out limitations with current animal models, such as humanized mice and non-human primates, to predict future outcomes in humans. They also mentioned the need to continue improving these pre-clinical research models.

I actually think one of the key challenges for cell and gene therapy within the context of HIV infection, and actually, for the HIV cure field in general, is that there aren't really that many great choices for preclinical animal models... There's hardly anything where the model is satisfactory, in that it really recapitulates a lot of the key features of the host virus interaction in the real McCoy, a human being… I think a real key step, in terms of making sure that when we go into an infected individual [PLWH] with one of these therapies, that we're doing something where the benefit to cost ratio is satisfactory, is to really do everything we can to be beef up and develop these preclinical models, to make sure that we can rigorously evaluate them before we take them into the clinic. – Biomedical researcher (#19)

Safeguards and Risk Mitigation Strategies

Interview topics included: 1) general safeguards for developing CGT approaches towards an HIV cure, 2) safeguards for combining CGT approaches, 3) mitigating off-target effects, 4) mitigating risks associated with long-term duration of CGT interventions, 5) mitigating risks of immune overreactions.

General Safeguards for Developing CGT Approaches Towards an HIV Cure

We asked informants to describe general safeguards that should be in place for developing CGT approaches towards an HIV cure. Considerations centered around the specificity of the CGT product, manufacturing and transportation safeguards (e.g., to ensure identity, purity, sterility, stability, and potency), thoughtful clinical trial design, clinical trial monitoring, robust training of research staff, and long-term monitoring.

Biomedical researchers described safeguards related the specificity of the CGT product to ensure that the intervention being tested only targets HIV. Manufacturing safeguards, such as basic biology and identity

testing, were also mentioned, but these were perceived to be straightforward.

Probably the major safeguard that I've looked at over the last couple of years is specificity. So, if I develop this therapy, whenever it's in your body, will it only recognize the cells that it's intended to recognize? So, I would say that's relatively easy for something for HIV, because HIV infected cells, and HIV itself, have these very specific proteins that we can target, and we can develop reagents against those. – Biomedical researcher (#17)

Several general safeguards centered around clinical trial design issues, including dose escalation and de-escalation rules, staggering trial participants, carefully monitoring trial participants for possible adverse events (e.g., off-target effects and hyper immune responses), and clear stopping rules in the event of intolerable toxicity. In addition to having narrow inclusion and exclusion criteria, a biomedical researcher (#15) recommended paying close attention to potential social and economic vulnerabilities of study participants, such as lack of medical insurance to reimburse for potential harm.

The worst fear is the fear of the dose. So, you have to pick a first dose, and that's the most frightening, most sleep-losing part of this. What is the first dose? Because we can quickly adjust that. We can quickly make changes, but the first person dosed is going to receive the dose that we thought from all of our reading, writing, calculating, everything else, that we thought was safe. So, I'll tell you that's the stomach acid producer right there, is the first dose. – Biomedical researcher (#04)

The inclusion criteria are significant. You want to know who is safe to treat and who is not, [and] where you are adding more risk… So I think there's certain populations [who may lack medical insurance] that are vulnerable.

– Biomedical researcher (#15)

Well for gene therapy… monitoring off-target effects, genetically sequencing and looking for off-target effects is critical. In terms of cell therapies, you're going to need to monitor the immune response and make sure that you don't get a cytokine storm type response. I think those are the main concerns. You could also have an anti-drug or anti-antibody type response, which will limit the efficacy, but it's not so much a safety concern; it's more of an efficacy concern.

– Biomedical researcher (#11)

A biomedical researcher (#04) discussed the importance of carefully training research staff on mitigating risks from novel CGT therapies. Medications should also be readily available to reverse possible complications.

We conduct onsite training. We make sure that we have medical experts available to these sites who are professionally dealing with those complications already and understand them. And we make sure that the sites have ready access to the medications needed to reverse these syndromes. – Biomedical researcher (#04)

Because CGT interventions may have long-term side effects, the importance of longitudinal clinical monitoring also emerged as an important safeguard. Research teams should employ mitigation strategies for worst possible outcomes.

If one is going to do a gene therapeutic approach, [and] I'm not sure if this still holds true, but it used to be you had to monitor those patients for life. But there is that risk that, because you're manipulating the genome in some cells, that a cell that's hanging around for quite a bit of time could suddenly, or over time, go bad [or] become malignant. [Y]ou got to watch for a very, very long time with these gene therapy approaches because there could be very long-term side effects.

– Biomedical researcher (#02)

In team research, you have to have that person is willing to say, "Okay, what's the worst possible outcome? Are we doing everything to mitigate the risk for that? And are we willing to accept the outcome if that risk comes to fruition?"

– Biomedical researcher (#07)

In addition, a biomedical researcher (#15) considered the cumulative body of scientific evidence as a safeguard. Another biomedical researcher (#07) discussed monitoring for potential conflicts of interest of investigators. A community member (#08) emphasized the need for ongoing community involvement across fields of research because CGT innovations may originate from other fields, for example, cancer.

Safeguards for Combining CGT Approaches

Moreover, we inquired about possible safeguards for combining CGT approaches. Several informants described how a cure for HIV will likely require a combination regimen as opposed to monotherapies. Possible safeguards for combining CGT approaches included ensuring individual product components are safe, determining potential harmful combinatorial or synergistic effects, combining individual safeguards, and relying on robust regulatory safeguards. Informants also emphasized the need for transparency around potential known and unknown risks, as well as robust community involvement around combinatorial CGT research.

The bioethicist (#14) perceived that a lot of CGT approaches are already used in combination. Informants also explained that a cure for HIV will likely require combining different approaches, much like combination ART for HIV treatment.

I would actually have thought that a lot of… candidate interventions might actually be combined cell and gene therapies. Whether it is autologous cells that are taken out, medically manipulated, [i.e.] modification of the CCR5 receptor [or] whatever it might be, and then reinfused back…, that's a combination of cell and gene therapy, or whether it is somehow… off the shelf stem cells that are genetically modified, I would imagine that a lot of potential interventions might be in effect combined interventions. – Bioethicist (#14)

Informants included making sure that individual CGT products were safe and carefully determining potential harmful combinatorial or synergistic effects as potential safeguards for combining CGT.

You just might want to make sure that they're both safe, and… you obviously want to determine if there's a synergistic effect which can be lethal, can be dangerous, but also could be effective. – Community member (#05)

Biomedical researchers discussed how combinatorial CGT approaches will require combining existing safeguards. For example, gene editing components will require measurement of off-target editing, while CAR-T cell components will require monitoring for potential toxicities.

When we think about multiple gene therapy approaches, usually we're thinking about multiple approaches that go into the same cells. So, for instance, if we have a CAR-T cell product where we've reprogrammed those T cells to seek out and destroy infected cells, we'll often also gene edit those cells for CCR5 so that those cells don't themselves become infected. So in that regard, it's a combination, but it's also the same cell product, so we can sort of combine the safety assurances that we have. So, for the CCR5 editing, it would be measuring the rate of off-target editing, and for the CAR-T cells, it would be proving that they're not toxic, and they're able to be controlled in the blood stream, if necessary. – Biomedical researcher (#06)

Biomedical researchers also described how CGT products may be combined with non-CGT modalities, for example, latency-reversal agents, as part of an HIV cure research regimen. Research teams would need to provide safeguards for both interventions when designing research protocols.

Biomedical researchers perceived that regulatory guidelines were robust enough with regards to combinatorial HIV cure research. They cited the FDA's published guidance for combining investigational products. A biomedical researcher (#12) cautioned about the need for continued vigilance around favorable benefit/risk profiles of combination regimens. The types of favorable combinations may also depend on the health status of patients/participants.

I think it depends on the status of the patient and the risk-benefit ratio… it's all about risk-benefit. Should I try, let's think about three different type of gene therapies together... on a patient that is stable enough for [anti]retrovirals for years? Probably not... But would I treat a patient that is sick all the time? Yeah. – Biomedical researcher (#12)

Additional safeguards for combining CGT products included carefully informing participants about the possible risks of combinatorial CGT, transparency, and robust community involvement.

Mitigating Off-Target Effects of CGT Interventions

Biomedical researchers offered possible ways to mitigate the risks of off-target effects of CGT interventions. These included better targeting of the CGT product during the engineering process,

extensive testing for possible off-target effects, monitoring for potential off-target effects in the entire body (including tissue sampling), and long-term follow-up of study participants.

Biomedical researchers described how CGT technologies are improving their targeting of HIV during engineering. For example, gene editing and viral vector technologies are becoming more specific. Some technologies (e.g., CAR T cells) already have well-defined targets, and robust specificity testing is in place for these.

We work extremely hard to make sure that we are as on-target as possible. That's in the process engineering. If you look at our final product, about 80 – 85% of the vector sequences are only in the target[ed] cells. So, the spill over into other cells is absolutely minimal. – Biomedical researcher (#04)

At least for CAR therapy for HIV…, the target's pretty well defined. We're going after [the] HIV envelope; we're going after something that's solely HIV… I'm pretty sure we could design therapies that are on-target.

– Biomedical researcher (#09)

Biomedical researchers further discussed extensive testing for off-target effects that are required as part of research efforts. Elaborate off-target diagnostic tests are now available, but may need to be standardized across protocols (#06). Further, off-target testing should investigate where the off-targeting occurred, the possible risks of off-targeting, and the frequency of off-targeting.

For gene editing, there are a lot of assays right now that various groups are developing with greater and greater sensitivity to measure any off-target effects. I think those assays are all really great, but I think it's getting into somewhat of an overkill... I would say if I'm not able to keep up with them... [Having] a better idea of… what the best assay is and really getting to a point where we can standardize what that assay is for clinical trials is going to be very important… Different groups are going to have different gene editing protocols in clinical trials, and they'll each have their own off-target assay, and the ability to compare one to other is going to be tough. – Biomedical researcher (#06)

A biomedical researcher (#02) mentioned the need for monitoring off-target effects in vital organs throughout the body, as well as long-term follow-up of trial participants.

With in-vivo [inside the body] therapy, you don't have the opportunity to selectively hit one population of cells because all cells are equal partners for potentially being hit. So there you have to look for gene modification of the type that you've introduced in cells that are off-target. You would look for it by not just drawing blood, but also by taking careful biopsies of the places in the body where those genes might go. – Biomedical researcher (#03)

There have been chimeric antigen receptors used in cancer studies that, for some reason, targeted cardiac tissue, and that caused problems. The therapy itself had an off-target effect and that's something you have to worry about, too, so that's where your safety testing comes in. – Biomedical researcher (#02)

Further, three biomedical researchers (#10, #12, #19) challenged the concept of off-target effects. A biomedical researcher (#10) described how every drug has off-target effects. Informants stated that it may be best to reframe the conversation in terms of benefit/risk assessments.

Off-target is an interesting concept, because every drug has off-target effects… Sometimes we get down the rabbit hole of thinking that precision is everything, and maybe we set our standards a little too high as a result. You take Tylenol, it has off-target effects: as well as getting rid of your headache, it's doing things throughout your body… So, I feel the conversation has got a little distorted, it's got away from risk benefit, and it's obsessing with on-target and off-target… – Biomedical researcher (#10)

Another biomedical researcher (#19) described how even 100% on-target editing may carry some risks, such as immunological consequences derived by completing removing the CCR5.

Mitigating Risks Associated with Long-Term Duration of CGT Interventions and Immune Over-Reactions

We asked biomedical researchers to describe ways to mitigate risks associated with the long-term duration of CGT interventions. They explained that the desired duration of a CGT intervention depends on the specific product being tested and that there are engineering methods to control the duration of CGT interventions.

Biomedical researchers described how the optimal duration of CGT interventions depends on the specific CGT intervention or mechanism of action being tested. For example, transient approaches may be preferred for gene editing (e.g., CRISPR-Cas9). In turn, durability may be a preferred feature for immune-based or adeno-associated virus (AAV) approaches.

It just depends on the different types of cell and gene therapy. If your gene therapy is using… gene editing machinery, [like] CRISPR-Cas [that] goes in and cuts the gene out, then that activity is and should be very transient, but it creates a lifelong effect… You don't want to be doing gene therapy to disrupt CCR5 with a gene therapy vector that will hang around for decades; you want to go in with a very transient gene therapy… Other types of therapies, …you could think about using an AAV vector to go into a cell and be producing… an HIV entry inhibitor or something that should act as a vaccine, there you actually want to have long term production. – Biomedical researcher (#10)

Biomedical researchers mentioned ways to control the duration of CGT interventions, such as genetic ways to control or eliminate manipulated cells (#02). Another option would be to create a safety switch; however, this switch may also carry safety issues (#17), work prematurely (#09), or provide a false sense of security (#04). ART re-initiation is another way to shut down the CGT intervention by removing the HIV target (#09).

If you have a gene editing procedure that occurs, it needs to be quenchable, it needs to be easily controllable. That's a real critical thing. It needs to have a very effective on/off switch. That's really critical… Some of the gene editing and cell therapy stuff that we would do, that really isn't a concern because it would be a one-time thing. With the ex-vivo gene editing to get rid [of] core receptors, you could

administer a mature Cas9 enzyme or protein into those cells to do the editing work, it does its work once, and that's it. It's a done deal. It gets degraded. It won't even be around to any of the work anymore.

– Biomedical researcher (#19)

Obviously, the longer we can keep the therapy working, the better the chance that it actually has to provide therapeutic benefits. The converse obviously, is that if things go awry, how can you stop the therapies? There's a variety of these suicide strategies that have been put forward that you could do that… For HIV it's probably more feasible than in cancer... For HIV, we certainly have the ability to get rid of the antigen by re-establishing ART again. That's a great tool that we have for HIV that they don't have for cancer: we can start people back on their medicine again and then the target of the cell therapy goes away, and that probably is going to go a long way to get rid of any adverse reaction we have.

– Biomedical researcher (#09)

We then asked biomedical researchers for recommendations on immune overreactions resulting from CGT interventions. CRS were perceived to be important risks associated with CAR-T cell therapies. CRS can, however, be mitigated by pharmacological approaches, for example. corticosteroids or interleukin inhibitors.

Most biomedical researchers believed the risk of immune overreactions mattered a great deal when testing CGT interventions. These could lead to a lifetime of steroid use or even death (#07). A biomedical researcher (#10) recounted the pivotal Gelsinger episode.

Jesse Gelsinger... basically died because he had a massive immune response to a high dose of adenoviral vector, and that started this escalation that couldn't be stopped. So, as we are tweaking our immune responses, I feel we always need to remain vigilant for the unexpected. – Biomedical researcher (#10)

I think the immune overreaction matters a lot, even though the CAR T cells didn't really have much toxicity… That's something that we need to follow up on and really dig into as closely as possible… It becomes a very complicated ethical area if you know that something so terrible is doing something so good for you. – Biomedical researcher (#06)

CRS was perceived to be a significant risk with CAR-T cells because these engineered cells are designed to turn on an immune response (#02). Biomedical researchers recommended using established grading systems to measure the intensity of immune overreactions, such as the American Society for Blood and Marrow Transplantation (ASBMT) scale to grade CRS in addition to the ASBMT Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading system to grade neurotoxicity. Besides actively monitoring for CRS, additional risk mitigations included testing for antigenicity and immunogenicity of CGT interventions (#19), using pharmacological approaches to reduce inflammation (#10), and sustained vigilance are recommended (#10).

Adverse immune responses are absolutely monitored for, and you have people standing by with syringes full of anti-interleukin-6 and other mitigating effects so that, if you see that, you can stop it… Let's just make sure that we don't become so arrogant that we think that this is all going to go the way we expect [and] that we remain vigilant for these unexpected and very serious consequences of us trying to manipulate the immune system. – Biomedical researcher (#10)

CRS really comes about due to high antigen levels. The good thing about HIV that you can't say about cancer is that you can actually put people back on their ART… This is a way to bring down the viral antigen and so, therefore, you can reduce the chances of CRS. But then there's also again, and we have this written in our clinical protocol, other therapeutics that you can take to control CRS. So like Tocilizumab, corticosteroids. – Biomedical researcher (#17)

Two biomedical researchers (#04, #17) advised involving oncologists with extensive experience dealing with CAR-T cells and CRS on research teams. There must also be an infrastructure in place to deal with adverse side effects (#17). While immune overreaction is an important risk of CGT interventions, there are established grading systems and protocols in place to mitigate their risks. Nevertheless, a high level of vigilance is warranted.

Discussion

This qualitative interview study probed key informants on possible ethical and practical considerations for developing CGT towards an HIV cure. Our study revealed that CGT approaches may confer scientific comparative advantages compared with other HIV cure research strategies under investigation. For example, CGT HIV cure strategies have the potential to become one-time regimens that could eventually be scaled-up globally [11], although it is unclear whether they will be able to protect against HIV reinfection risk (18). Further, we must remain extremely cautious in our description of expectations for early-phase CGT trials to avoid the risk of therapeutic or curative misconception (18–20).

To ensure acceptable benefit/risk balance, CGT research teams must maximize scientific benefits, while minimizing risks as much as possible. There should be transparency regarding known and unknown risks to allow PLWH to make informed decisions about whether or not to participate (19,20). Research teams should also carefully counsel trial participants around which short-term or long-term risks to look for following a CGT intervention. Involving HIV clinicians who are not directly engaged in the research and who do not harbor the risk of curative misconception in helping their patients think through participation decisions is another strategy to help ensure an ethical risk/benefit ratio. Whenever possible, participants should be advised to discuss trial participation with their primary care physicians.

Like most early-phase trials, initial CGT experiments are not expected to confer direct clinical benefits to participants; therefore, the value of the scientific knowledge to be gained must justify the risks (21). The psycho-emotional benefit of altruistically contributing to the science of HIV cure discovery should be factored into the risk/benefit ratio, along with the low likelihood of clinical benefit to participants in early studies. The ethics of translational research for CGT products may require heightened considerations

when compared to other HIV cure research approaches, particularly with regard to their specificity, risk profiles, and irreversibility (22–24). Additional ethical considerations raised by our study – although not unique to CGT research – included robust pre-clinical evidence to move products into human testing (15,25,26), strong scientific rationale for pursuing CGT approaches, ethics of CGT development that includes a sustained commitment to the HIV field, fair participant selection (23), robust informed consent (27), nonmaleficence and protection of participants from excessive risks (28), and distributive justice (29). Interestingly, most ethical issues examined in our study parallel those found in recent Institute of Medicine workshop proceedings on CGT, ethics, and governance [33,34].

Our study also provided insight into the scientific, participant-level, and societal challenges of developing CGT towards an HIV cure and the long-term social acceptability of relevant research (29,30). Community members in our study emphasized the need for early, sustained, and robust community consultation in clinical trial design and reviews of CGT protocols. These findings align with recommendations made in two separate systematic reviews on increasing patient acceptability of CGT research across various disease areas (8,31). Providing the community with opportunities to offer input and engage in meaningful dialogue around the use of CGT towards a cure for HIV should be a priority (32), not only to increase awareness about ongoing trials, but also to understand factors that affect how communities of PLWH perceive such research. Acceptability of CGT will likely be tied to perceived risk levels and invasiveness of interventions (8). Acceptability research (33) revealed important misconceptions and mistrust around CGT HIV cure research in the United States. For example, several PLWH believed a cure for HIV had already been achieved and was systematically being withheld from the poor, while others believed that only participants who were desperate should participate in CGT trials. Given the complexity of the science, there will also need to be effective communication strategies for the public that simplify information about CGT research and its goals. Moving forward, perspectives of PLWH who participate in CGT will also be important to understand.

A strength of our paper is the identification of safeguards and risk mitigation strategies for developing and implementing CGT approaches. Informants carefully described considerations related to clinical trial design, research oversight, long-term monitoring of trial participants, and constant vigilance. A major concern with CGT has been the risk of off-target effects, but highly sensitive tests are now available to detect and mitigate these effects (19,34). Additionally, some biomedical researchers recommended reframing off-target conversations in terms of benefits/risks assessments. The desired duration of CGT interventions will depend on the specific strategy under investigation. For CAR-T cells, research teams will need to carefully monitor for CRS and neurotoxicity using established guidance.

Our summary of possible ethical and practical considerations for cell and gene therapy towards an HIV cure can be found in **Table 3**. This list is not exhaustive and may not reflect the views of all stakeholders involved in HIV cure research.

Limitations

We acknowledge limitations of our study. Our sample size was small and was self-selected. Thus, we may have been biased towards individuals supportive of CGT strategies towards an HIV cure. As we move forward with CGT HIV cure research, we will need to remain cognizant of dissenting opinions. Further, we acknowledge that our sample lacked diversity with respect to race and ethnicity and sex and gender, as most informants were White/Caucasian males; this is a major limitation of our study. After 19 interviews, we may not have reached saturation, the point when no new information emerges (35). We did not delve into ethical considerations related to interrupting HIV treatment, as these are thoroughly reviewed elsewhere (36–40). Our research was not designed as a consensus study; therefore, additional stakeholder engagement will be necessary to generate consensus on ethical guidance for CGT HIV cure research. Despite these limitations, our study generated detailed considerations to guide the blossoming research of CGT towards an HIV cure.

Conclusion

Rapidly evolving CGT towards an HIV cure is accompanied by a host of ethical and practical challenges. To minimize risks to potential participants and facilitate the translation of scientific advancements from the bench to the clinic, CGT HIV cure research must be thoughtfully developed and implemented. Our qualitative data identified nuanced ethical and practical considerations towards the goal of achieving a cure for HIV through CGT. To protect the public trust in CGT HIV cure research, ethical and practical considerations should be periodically revisited and updated as the science continues to evolve.

List Of Abbreviations

AAV	Adeno-Associated Virus
ART	Antiretroviral Treatment
ASBMT	American Society for Blood and Marrow Transplantation
ATI	Analytical Treatment Interruptions
CAPS	Center for AIDS Prevention Studies
CAB	Community Advisory Board
CAR	Chimeric Antigen Receptor
CCR5	C-C Chemokine Receptor Type 5
CGT	Cell and Gene Therapy
CIRM	California Institute for Regenerative Medicine
CMC	Chemistry, Manufacturing and Controls

CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated
CRS	Cytokine Release Syndrome
DARE	Delaney AIDS Research Enterprise
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FIH	First in Human
H+APR-PS	HIV + Aging Research Project – Palm Springs
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IBC	Institutional Biosafety Committee
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
IND	Investigational New Drug
IRB	Institutional Review Board
PLWH	People Living with HIV
SCID	Severe Combined Immunodeficiency
TALENs	Transcription Activator-Like Effector Nuclease
UCSF	University of California San Francisco
UNC-CH	University of North Carolina at Chapel Hill
ZFN	Zing Finger Nucleases

Declarations

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Availability of Data and Material

All relevant quotes have been included in the results section and in Supplementary Table 1.

Author's Contributions

K.D. drafted the initial version of this manuscript.

J.K., H.P., M.L., L.S., J.Sh., L.D., J.T., J.A.S., M.J.P., S.G.D and J.Si. reviewed the manuscript for intellectual contents.

All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The Institutional Review Board of the University of North Carolina at Chapel Hill approved this empirical research ethics study (study #: 19-0522). All interview participants included in this study provided informed consent.

All methods were carried out in the accordance with relevant guidelines and regulations.

Consent for Publication

All participants provided informed consent to publish de-identified data.

Competing Interests

K.D. provides socio-behavioral and ethics support to the California Institute of Regenerative Medicine (CIRM)/City of Hope, the defeatHIV Collaboratory (UM1 AI126623) and the BEAT-HIV Collaboratory (UM1AI126620). K.D. has ongoing socio-behavioral sciences and ethics collaborations with the Delaney AIDS Research Enterprise (UM1AI126611).

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Tables

Table 1: IRB-Approved Interview Guide: Ethical and Practical Considerations for Cell and Gene Therapy Towards an HIV Cure

Interview Guide

- First, thank you so much for your time.
- Can you please describe your involvement in HIV-related research?

Perceptions of CGT and Benefit/Risk Considerations

- What might be some of the benefits of cell and gene therapy approaches towards an HIV cure?
- What might be some of the risks of cell and gene therapy approaches towards an HIV cure?
- How do we ensure cell and gene therapy HIV cure research approaches remain within acceptable benefit/risk parameters?
- Are there cell and gene therapy strategies that you would consider too risky or unacceptable for human testing? Can you please explain?
- What are some additional ethical considerations for developing cell and gene therapy approaches towards an HIV cure?
- What ethical criteria should be used specifically when evaluating first-in-human (FIH) cell and gene therapy HIV cure research protocols?
- How do we determine when we have enough pre-clinical evidence to move cell and gene therapies into human studies?

Safeguards and Risk Mitigation Strategies

- What general safeguards should be in place when developing cell and gene therapy approaches?
- What safeguards should be in place when combining cell and gene therapy approaches?
- What are some of the ways to mitigate risks when developing cell and gene therapy approaches?
  - What are some of the ways we can prevent off-target effects?
  - What are some of the ways we can control the duration of the intervention?
  - What are some of the ways we can prevent potential immune over-reaction?
  - What are some of the other ways to prevent adverse effects?

Table 2: Demographic Characteristics of Key Informant Interview Participants (United States, 2020 – 2021)

Participant Number	Sex	Race/Ethnicity	Informant Type
01	Male	White/Caucasian	Community Member
02	Male	White/Caucasian	Researcher
03	Male	White/Caucasian	Researcher
04	Male	White/Caucasian	Researcher*
05	Male	White/Caucasian	Community Member
06	Male	White/Caucasian	Researcher
07	Female	White/Caucasian	Researcher
08	Male	White/Caucasian	Community Member
09	Male	White/Caucasian	Researcher
10	Male	White/Caucasian	Researcher
11	Male	White/Caucasian	Researcher
12	Male	White/Caucasian	Researcher*
13	Male	Black/African American	Community Member
14	Male	White/Caucasian	Bioethicist
15	Male	White/Caucasian	Researcher
16	Male	White/Caucasian	Community Member
17	Female	Other, Mixed Race	Researcher*
18	Male	White/Caucasian	Researcher*
19	Male	Asian	Researcher

*Biomedical researchers who work in the pharmaceutical industry

Table 3: Summary of Possible Ethical and Practical Considerations for Cell and Gene Therapy Towards an HIV Cure

· Research teams should maximize the possible clinical and scientific benefits of CGT approaches towards an HIV cure. Perceived benefits included the prospect of developing "single-shot" regimens that could be less burdensome (although CGT may not prevent against re-infection), as well as scientific advancements that could lead to curative innovations for other molecular genetic diseases.

· Research teams should minimize the possible clinical and non-clinical risks of CGT approaches towards an HIV cure. The possibility of unknown clinical risks will require careful and sustained pharmacovigilance. The risks of unintentional HIV transmission to sexual partners, therapeutic or curative misconceptions, and financial burdens of CGT should be minimized as well.

· To ensure acceptable benefit/risk parameters, research teams should use an incremental scientific approach, ensure adequate regulatory review, minimize risks as much as possible, be transparent about potential risks, collect as much safety and efficacy data as possible, and maximize possible long-term benefits to humanity (knowledge/risk calculus) (41). There appears to be convergence on the unethicality of editing the germline and conducting allogeneic stem cell transplants in otherwise healthy PLWH. Research teams should remain attuned to unacceptable risk thresholds for individual study participants.

· Additional ethical considerations for developing CGT HIV cure research approaches – although not unique to the field of CGT – include strong scientific rationale, fair participant selection, robust informed consent, distributive justice, and equity issues. Research teams should carefully inform trial participants about what adverse events to look for following a CGT intervention. CGT researchers should try to maximize long-term benefits for the HIV community.

· Considerations for implementing FIH CGT HIV cure trials – although not specific to this field – include a compelling scientific rationale for moving into human testing, robust pre-clinical data despite limitations of current animal models, close observance of the regulatory process, and involvement of PLWH in trial design. For a comprehensive FDA summary regarding *Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, see: https://www.fda.gov/media/87564/download.

· Safeguards to developing and implementing CGT approaches towards an HIV cure may include, but are not limited to, clinical trial design considerations for example, narrow inclusion and exclusion criteria, low initial trial enrollment, dose escalation and de-escalation rules, staggering trial participants, careful monitoring for potential side effects that include long-term side effects, and clear stopping rules in the event of intolerable toxicity. CGT product specificity, manufacturing and transport safeguards (e.g., to ensure identify, purity, sterility, stability, and potency), robust research staff training, accumulating a scientific body of evidence over time, and monitoring for potential conflicts of interest of investigators are also of paramount importance.

· Possible safeguards for combining CGT approaches may include but are not limited to, ensuring individual components are safe, determining potential harmful combinatorial or synergistic effects, combining existing safeguards, continued investment in pre-clinical work, ensuring favorable benefit/risk profiles, transparency about risks, and community involvement. See FDA Combination Products Guidance Documents, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents.

· Possible risk mitigation strategies for off-target effects may include but are not limited to, improved targeting during engineering, extensive testing for off-target effects, such as location of off-targeting, risks of off-targeting, and frequency of off-targeting, careful monitoring in the entire body, including both blood and tissue sampling, ensuring that trial participants clearly understand possible long-term risks so they know what to look for over time, and long-term participant follow-up. See FDA Guidance on *Long-Term Follow-Up After Administration of Human Gene Therapy Products*, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products.

· Possible risk mitigation strategies to control the long-term duration of CGT interventions depend on the strategies being investigated, for example, gene editing may warrant transient approaches while immune-based approaches may warrant more frequent monitoring and control. Carefully

designed strategies to control the durability of a CGT investigational product, such as genetic manipulation, safety switches or ART restart.

· Possible risk mitigation strategies for immune overreactions, also called cytokine release syndromes, a risk factor associated with some CGT interventions (such as CAR-T cells) include active monitoring, using the ASBMT consensus grading system and established pharmacological protocols to reduce inflammation, like cortical steroids. Possible risks of neurotoxicity should also be monitored and carefully mitigated.

Supplementary Files

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- 2BSupplementaryTable14APR21.docx