Representations and Willingness of People Living with HIV in Switzerland to Participate in HIV Cure Trials: The Case of Gene-Modified Cell Therapies

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Running head: Acceptability of HIV gene therapy cure trials

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ABSTRACT

Background. Recent advances made in cell and gene therapies for cancer suggest that they represent plausible strategies to cure HIV. However, the health risks and constraints associated with these therapies require a deeper understanding of the expectations of such treatments among people living with HIV.

Methods. We conducted 15 semi-structured in-depth interviews among patients from two HIV units in Switzerland. Following a conversation about their perceptions of research on HIV therapies, participants were provided with a trial description using a gene-modified cell therapy as a potentially curative approach. They were invited to discuss how they might consider participation in the trial. Content analysis was performed to identify core themes.

Results. Participants perceived the trial as burdensome and uncertain. Most were aware that cure was not guaranteed and 6 of 15 considered that they would participate. Two main concerns were expressed about potential participation: 1) the impact on the professional life and fear to be stigmatized because of this; and 2) the fact that stopping antiretroviral treatment would challenge the balance currently achieved in their lives. The decision to participate would depend on their understanding of the trial, the availability of sufficient information, and the relationship with healthcare professionals.

Conclusion. Involving people living with HIV in early stages of research would be crucial to improve their understanding of gene-modified cell therapies. It could also help adapt trials to address key factors, including the anticipation of stigma, that may discourage people living with HIV from participating in treatment research.

Key words: gene-modified cell therapies, HIV cure-related research, acceptability, decision-making, qualitative research

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INTRODUCTION

Finding a cure for HIV—whether in the form of vaccines, stem cell transplants, gene and gene-modified cell therapies, immune-based strategies or latency-reversing agents—has become a major interest in HIV research.[1,2] Two cases of remission have been reported, where patients received stem cell transplants from donors negative for CCR5, an essential co-receptor for HIV entry into cells.[3,4] Recently, gene-modified cell therapies (GMCTs) have been approved as curative treatments for certain cancers and primary immune deficiencies, and similar approaches are being investigated in an attempt to achieve remission and ultimately cure HIV. However, these therapies raise ethical questions as they involve analytic treatment interruption and inherent risks for patients' health, but without any demonstrated clinical benefits at the present time.[5,6] Mirroring these ethical questions, several studies have explored why people living with HIV (PLWH) would agree to engage in HIV cure-related trials (HCRTs),[1,7,8] particularly GMCT trials.[9] The main findings showed that trust in treating physicians, follow-up during trials, and perceptions of societal and scientific benefits constitute important levers for the participation of PLWH.[7,9,10-13] By contrast, the negative attitude of PLWH towards research,[9,14] perceived and/or actual health risks,[12,15] as well as types of HCRTs and their degree of constraint constitute barriers to participation.[8,16] Some results also suggest that despite weak evidence for direct clinical benefits, around 50% of PLWH would accept substantial health risks associated with participation in HCRTs.[15,17]

However, GMCT trials are still not well known and PLWH may not have a clear picture of what their participation would entail. In most studies, participants reported that they did not receive a clear description of such trials and their consequences, including adequate responses to questions such as: what should I expect from the treatment? what are the potential side-effects? Important concerns and reservations of participants were recently reported, particularly for GMCTs, due to such a lack of a detailed description.[9] We explored here the perceptions of PLWH on GMCTs to gain insight into how they would decide to participate or not in such a trial by providing them with a precise

description of the conduct of a GMCT trial. The study could provide useful information to inform strategies to improve participation in this type of clinical trial.

METHODS

Design

We conducted a qualitative study among 15 PLWH under treatment at the HIV units of the Geneva and Lausanne University Hospitals (Switzerland) between November 2019 and February 2020 to explore their perceptions of GMCT trials and eventual willingness to participate. Semi-structured in-depth interviews (60 to 90 minutes depending on the time spent by participants to read the study description) were conducted and analyzed to identify themes relevant to participation in such trials. The study followed the requirements of best practices for qualitative research (see the COREQ checklist in Supplemental Content1).

Participants and Recruitment

Patients were eligible if they were >18 years old, included in the Swiss HIV cohort study network, and sufficiently proficient in French to follow a conversation. Medical teams (treating physician and nurses) from the two HIV Swiss university clinics announced the study to eligible patients and ask for his/her agreement to be contacted by the research team. A research team member then approached patients by phone, explained the study in details and, if patients accepted to participate, scheduled the interview. The research team was responsible for sending the consent form to patients. A judgment sampling was applied on the basis of the eligibility criteria and the knowledge the medical team had of their HIV patients. The constitution of the sample considered three important criteria: time since diagnosis (<5 years/>5 years since HIV diagnosis); past experience with research (yes/no); and gender. Twenty-four patients were screened and invited to participate to interviews; nine patients declined participation. Recruitment stopped when researchers estimated that data saturation had been reached.

Data Collection and Analysis

Based on existing literature regarding the acceptability of a cure trial, an interview guide was developed. The guide was tested before the interviews and then slightly adapted after the first interviews. Interviews were conducted alternately by two researchers specialized in qualitative methods (SL and LV) who had been trained by clinical staff members to ensure that they understood all the terms used and could answer any questions from participants. Interviews comprised two parts: first, participants were invited to speak spontaneously about their perceptions of HCRTs and about what it would mean to them to be cured. They were then asked to read a 5-page patient information letter (PIL) of a fictitious cure trial involving a GMCT and discuss how they would decide to participate or not. The PIL was written by GMCT cure trial experts and included all information, side-effects and clinical ancillary benefits expected in a classic PIL (Supplemental Content 2). The trial design was based on administration of autologous HIV-specific chimeric antigen receptor (CAR) T-cells, similar to other globally registered studies (NCT03617198, NCT03240328, NCT04648046). Special attention was paid to the clarity and comprehension of information contained in the letter. We proposed the PIL to participants during the interviews and not before as we wanted to access their spontaneous reactions to the document. In addition, since the PIL described a fictitious cure trial, we did not want the letter to be accessible outside of the study context. As recruited participants were comfortable with French, they read the PIL alone (generally around 15 minutes). They were also free to ask the interviewer any questions if they had comprehension difficulties.

Audio recordings were fully transcribed and analyzed by using lexicographic analysis with IRaMuTeQ software (version 0.7 alpha 2, 2008-2014 Pierre Ratinaud). Lexicographic data analysis was complemented by analyses performed by three researchers specialized in qualitative methods (IG, SL and LV). These analyses consisted of identifying recurring themes that structured the participants' discourse (using the co-occurrence of words or expressions). Identified themes were then

interpreted by the researchers (IG, SL and LV) by using typical words or extracts proposed by the software. Time since diagnosis, gender, past experience with research, and willingness to participate as expressed during the interviews were considered in the analyses in order to determine whether specific themes were addressed by the participants. All results were then discussed with the entire research team.

Ethical approval was granted by the ethics committee of the canton of Geneva. All participants received consent forms explaining the purpose of the study 72 h before the interviews.

RESULTS

Participant Characteristics

All 15 participants were receiving antiretroviral therapy (ART) and had an undetectable viremia with a mean CD4 count of 725.4 ul (min = 231; max = 1140) measured up to 3 months before the interviews. CD4 count was missing for four patients; two participants were at AIDS stage. Mean age was 47.1 years (male=9); 5 were diagnosed <5 years ago, and 9 participated in the Simpl'HIV randomized 48-week clinical trial (evaluation of a simplified strategy for the long-term management of HIV infection).[18] The demographic characteristics of the 15 participants were similar to those of all treated patients in terms of age and gender.

Willingness to Participate

Six of 15 participants thought that they would participate in the described GMCT cure trial. Participants who had no research experience were more likely to accept (4 of 6). However, analyses showed that participants who thought that they would participate did not highlight specific themes compared to other participants.

Lexicographic Analysis

Participants evoked 11 sub-themes that were gathered into three main themes: a) living with HIV; b) treatments and interruptions; and c) the decision-making process (Figure 1; typical words and extracts are shown in Table 1). Whereas the first two themes were mainly associated with cure representations, the third was clearly associated with the reading of the PIL.

[Insert Figure1]

Living with HIV. This theme comprised three sub-themes and was mainly representative of participants diagnosed <5 years ago, with no previous research experience. In a first sub-theme, participants evoked the impact of HIV on their social and professional life. HIV was described as something intimate and to be shared with only a limited circle of close friends and family. In this respect, anything that could make the disease visible, such as side-effects or repeated medical controls, was to be avoided. Associated with this fear of being identified as HIV-positive was a second sub-theme: fear of stigmatization. Here, participants underlined the public's misconceptions about HIV. They also compared HIV with other (chronic) conditions, such as cancer and diabetes, which they viewed as being potentially more deadly or more restrictive than HIV, in order to explain the special status of HIV in public opinion. Of note, women specifically evoked fear of stigmatization. Moreover, this sub-theme was evoked together with a third sub-theme: hope for a cure. Participants did not consider cure as an attainable goal in their lifetime, but rather as an expectation for future generations.

Treatments and Interruptions. ART was a key topic. In a first sub-theme specifically raised by those diagnosed >5 years ago, participants expressed their fear of ART interruption. For those who had experienced first-generation ART or had a late diagnosis, interrupting ART challenged the life balance that they had taken a long time to achieve. Their main concern was the possibility of retrogression. If they experienced important side-effects, if their viral load increased, or if they withdrew from the study, could they return to the same treatment and the same health state as before? The idea that an interruption could provoke ART resistance was also raised. In a second sub-theme, participants

(specifically evoked by those diagnosed >5 years ago and having had past experience with research) underlined the fact that following ART improvements, PLWH could live a rather normal life with some strategies to reduce the burden of the daily intake of ART. In a third sub-theme specifically evoked by women, participants explained that professional constraints imposed by treatments and participation in a cure trial (eg, repeated or unpredictable absences) would be important barriers to participation.

Decision-making Process. This last main theme was related to the strategies that participants would use to decide whether or not to participate. A first strategy, mainly evoked by those diagnosed >5 years ago and having research experience, would be to search for information in specialized journals and through their social network (eg, friends, family, other PLWH). A second strategy (mainly evoked by men) would consist of weighing up what participants perceived globally as risks and benefits, with the main risk being a deterioration of their health status due to the presence of serious side-effects or complications following infusion of the GMCT. Participants had difficulty explaining gene modifications and perceived them as being quite unpredictable and potentially leading to other physiological modifications, such as treatment resistance. Perceived benefits were of two types: clinically ancillary (ie, participants understood that a cure for HIV could not be guaranteed) and mainly societal (ie, advancing science) benefits. For the latter, participants recognized that their current stability with ART was the result of past research and thus they considered it normal for research to continue. Some explained that they would be proud to participate in such research and therefore bring their own contribution, but not at any price.

Finally, in a third sub-theme, participants evoked the patient-physician relationship as being crucial in the decision-making process. Participants expressed the need to receive complete and detailed information and to have the freedom to ask any questions on the HCRT. They considered healthcare professionals to be reliable and trustworthy resources to meet this need. Women mainly evoked this

last sub-theme. Concerning the patient-professional relationship, we observed that it was also mentioned in several other instances, such as when participants discussed the issue of ART, or living with HIV, or when they talked about sources of information. The relationship with the family physician or the physician at the HIV unit seemed to be particularly important and it came up regularly in conversations beyond the two former sub-themes.

[Insert Table1]

DISCUSSION

Few qualitative studies have focused on the perception and decision-making processes of GMCT trials for the cure of HIV.[9] To the best of our knowledge, no study has used a PIL to provide participants with a concrete representation of such a HCRT. In our study, 6 of 15 participants would be willing to participate in the GMCT cure trial described in the PIL. Because of the small number of participants, we can neither draw a conclusion concerning this result nor compare it to previous studies on the topic. Further, acceptance rates expressed by PLWH in acceptability research seems to differ between quantitative and qualitative studies[19] and may be influenced by a desirability bias.[14] Thus, it appears difficult to interpret such rates. Actually, when they were developing their thoughts and perceptions about the trial, participants perceived it as being cumbersome and risky. Moreover, interruption of ART, together with the resulting possible deterioration of health status, were important concerns for participation in GMCT cure trials.[9] In addition, the GMCT approach seemed to elicit specific representations in the participants' understanding of genetic modifications.[20] In particular, gene manipulation was associated with unpredictable changes in the body, changes that could lead participants to develop resistance to ART, among other issues. This result confirms that an understanding of scientific information remains crucial, particularly for GMCT, which can seem complex to the layman. As observed in our study, this understanding depends largely on the levels of communication and trust between PLWH and healthcare professionals.[7,16]

Recent research suggests that distrust among study participants is becoming a concrete issue.[9,7,21] Therefore, a key priority of researchers and clinicians should be to preserve this trusting relationship.[7,21] This is particularly important as HIV-related GMCTs remain largely misunderstood by PLWH[9] and can lead to particularly negative perceptions, such as fear of gene modifications. Public and patient involvement approaches,[22,23] consisting of involving patients and lay people from the community in the early stages of research development, could be a way to reinforce this trusting relationship. Indeed, including insight from PLWH when developing research projects could help to generate new ideas and anticipate and overcome barriers to participation.[24] It could also result in a better access to information for PLWH and an increased involvement and consideration.[25] Such an approach, integrated in the UNAIDS/AVAC Good Participatory Practice guidelines,[26] has been successfully implemented in HIV preventive research and PrEP-related clinical trials and has been found to be beneficial to both researchers and PLWH involved.[27-29] Similar initiatives should be conducted for GMCT research.

Another important result concerned the fear of stigmatization, which was evoked as both a constraint for participation and a motivation to be cured. The fact that participants doubted that their involvement would go unnoticed in their work and social life was clearly associated with the fear of disclosure of HIV status and thus of stigmatization.[30] However, the anticipation of stigma is not specific to GMCT cure trials and similar reactions were observed in HIV vaccine trials.[31,32] When participants raised the hope of a cure in our study, it was also associated with the desire to escape stigmatization. This result shows that despite both the evolution of knowledge about HIV and the apparent mentality changes, stigma remains very concrete in the life of PLWH[33,34] and is a key factor to consider when setting up clinical or curative studies.[35]

Finally, the desire to participate in order “to advance science” was evoked as the main societal benefit. In contrast to previous research highlighting altruistic motives in PLWH participation,[36] our

participants evoked willingness to make a personal contribution to the fight against HIV, rather than to improve the future of other people, and the latter may not be considered as a genuine altruistic motive.[37] In addition, when participants evoked these societal benefits, they often mitigated them by adding a clinical benefit (perhaps they could be cured in the end) or by specifying that it would not be at any price. The question of altruistic motivation is at the center of ethical issues raised by GMCT cure trials[38] and our study confirms that when provided with concrete information (ie, the PIL), participants are less likely to participate for self-sacrifice, as suggested in research in other domains.[39]

The main strength of this study is that it complements current knowledge on the perception of GMCT cure-related trials by PLWH. When interpreting the results, the following limitations need nevertheless to be considered. First, interviews concerned PLWH who attended two Swiss HIV consultations. Despite possible generalizability issues, our findings were congruent with the published literature. Second, we focused on perceived willingness to participate and not actual participation. Thus, we cannot state that participants would in fact accept or decline participation in a real GMCT study.

In conclusion, our findings show that PLWH overall do not have a clear and comprehensive understanding of GMCT cure-related trials. Indeed, when provided with a concrete summary of how the trial would proceed, participants were less likely to express altruistic motives. Our results also confirm that PLWH perceptions about GMCT are deeply anchored in their personal struggle with HIV. Both stigmatization and the fear of losing a personal life balance built over time represent strong barriers to participation in HCRTs. These barriers, as well as the unfamiliarity of PLWH with GMCTs, should be considered when implementing these trials. As proposed, a patient-public involvement approach could allow researchers to consider these barriers in the early stages of cure-related trial development and to increase PLWH familiarity with these new techniques.

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Figure Legend

Figure 1: Themes emerging from textual analyses and corresponding typical words and excerpts. Percentages in parentheses represent the proportion of analyzed texts related to each theme and sub-theme.

Table

Table1: Computer-assisted textual analysis and summary of results

Themes and subthemes	Typical words	Typical excerpt
Living with HIV		
Impact of HIV on social and professional life	Life, friends, losing consciousness, nausea, work, social, fatigue, family, embarrassing, anxiety, to affect, to suffer	“I have my family who totally accepted me, most of my friends, too. [...]On the other hand, I don't talk about it with my employers, for example.” (man, <5 years, no experience with research) “Weight loss it's not serious, but risk of stroke, nausea, pain, swelling ankles, all these things, flu-like illnesses, all these things will be visible. Or they will require repeated and frequent absences. So, I'm thinking more about work.” (woman, >5 years, past experience with research)
HIV, a disease like no other: stigmatization	Disease, AIDS, insurance, cancer, die, impression, catch, HIV, fear, diabetes, malaria, miracle, prep	“It's the dirty disease, so after a while people say: this one will spit on me, I'm going to eat the cookie, I'm going to touch the other cookie, you are contaminated. At work I suffered indirectly from it when I said that.” (man, >5 years, past experience with research) “That's it, we live well with it, but I think it denies a bit the experience of the virus or it worries me, anyway. There's the stigma. Fortunately, I managed to avoid it more or less especially in my personal life.” (man, <5 years, no experience with research)
Hopes for a cure	Research, hope, to find, disease, future, to cure, to imagine, to share, solution, infection	“It gives me hope. I always say: as long as they find it once. Before I didn't foresee so much time in front of me, because we didn't know. I never thought I'd reach retirement, but I did, so it's starting to tickle me.” (woman, >5 years, past experience with research)
Treatments and interruptions		
ART interruption	Situation, current, effective, treatment, stop, heavy, danger, detectable, start again, play, drop, CD4	“If it doesn't work, it is reversible? I mean, I can start my treatment again without any worries? [...] if I try to take my medication again and it doesn't work, of course I will get totally anxious.” (man, <5 years, no experience with research) “I think it's dangerous to stop treatment for that long. I'm always afraid that the virus will mutate or I don't know what it can do, if I stop the treatment and start it again.” (woman, >5 years, no experience with research)
Alleviating ARTs	Take, treatment, day, times, forget, decision, cost, pills, count, gesture, exactly, head	“With what I'm taking now, I have nothing anymore. The first tri-therapy I had was heavy and uncomfortable [...] now it's just a couple of pills not really...yet it's still a lot of discipline.” (man, >5 years, past experience with research) “Often in the morning I'm not wide awake yet and I arrive at the office and I say damn it I forgot to take my treatment. Now I have 2 flacons at the office so I don't forget.” (man, >5 years, past experience with research)
Social and professional constraints to participation in cure trials	To wait, follow-up, hours, spending time, flexibility, work, office, boss, social, controls	“After a while, professionally for a boss, you still lose time to go to the consultation, it takes me half a day, so to speak, 2 or 3 hours.” (man, >5 years, past experience with research) "You're not supposed to be sick, how you're going to tell your employer: I'm going to be absent from such and such a day. I'm sick, but for my employer I'm not sick." (woman, <5 years, no experience with research)

The decision-making process		
Sources of information	Print media, specialized, journal, dossier, to consult, access, social networks, to analyze	“It's in the press, newspapers, websites, but if it's an information like drug advances, it's not something that attracts everyone's attention.” (man, >5 years, past experience with research)
Risks	Guarantee, health, cells, remove, risks, cure, protection, samples, side effects, dangerous	“I don't ask for a guaranteed cure, but if I am told that it will worsen my condition and that we don't know anything about it, clearly... During the next few years my grandchildren will grow up again. If I would be all alone, it would be different.” (woman, >5 years, no experience with research) “It's still a genetic modification, well, we're still dealing with something in the cells, it's genetic modification, it's going very far. [...] We can do what we want with the genes, but it will touch something almost deeper, in relation to the human body. " (man, >5 years, past experience with research)
Indirect benefits	To participate, study, research, advance, future, benefits, to help, science, personally	“That's also why I took part in the previous study, because for me it was important, I said it was my contribution to advance science. After advancing science with all these risks, no, it's not.” (woman, >5 years, past experience with research) “The benefit of participating in a study is to help humanity in the long term, not only yourself but others and our children in the long term, that is the benefit. But if I get rid of my antiretroviral it's a great benefit.” (woman, <5 years, no experience with research)
Patient–physician discussion	Physician, principle, opinion, discussion, explanation, clear, depend on, information, implications, consent	“I would need discussions either with researchers, physicians and others. I need to understand in detail what the implications are.” (man, <5 years, past experience with research) “You are given documents like this. I think you need an accompaniment in the information that is given so that you can get an idea of what is going on.” (man, >5 years, past experience with research)
Patient–physician trust	Trust, questions, asking, reassuring, options, confidentiality, to answer, support, to acquire, to communicate	“Normally I'm very skeptical about everything, but I trust the hospital and the doctors. There's so much information that we don't know, what's true and what's false, we can say anything on the internet, so I prefer to have the opinion of a specialist instead.” (woman, >5 years, no experience with research)

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