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Participant experiences in a combination HIV cure-related trial with extended analytical treatment interruption in San Francisco, United States

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Abstract

Background: There is limited systematic information available about the perspectives of participants enrolled in intensive combination HIV cure-related trials inclusive of an extended analytical treatment interruption (ATI).

Objective: To assess and understand experiences of people with HIV involved in a combination HIV cure-related trial with an extended ATI.

Methods: The trial included five interventions and was followed by an ATI lasting up to 52 wk. From 2022 – 2023, we conducted in-depth interviews with study participants following

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Authors' contributions

KD led data analysis and wrote the first draft of this manuscript. SON assisted with data analysis. JAS conducted all participant interviews. All authors reviewed the manuscript for intellectual contents and approved the final version of the manuscript.

Disclosure statement

K.D. provides advisory services to Gilead Sciences, Inc. J.S. is a member of Merck KGaA's Ethics Advisory Panel and Stem Cell Research Oversight Committee; a member of IQVIA's Ethics Advisory Panel; a member of Aspen Neurosciences Clinical Advisory Panel; he was also a member of a Merck Data Monitoring Committee. None of these activities are related to the content of this manuscript.

their extended ATIs. Interviews were audio-recorded, transcribed, and analyzed *via* conventional thematic analysis.

Results: We interviewed seven participants. The majority were male, White, and non-Hispanic, with a median age of 37 years. Trust in the research team, scientific altruism and hope of becoming a post-intervention controller were key motivators for joining the trial. Interviewees reported being satisfied with their decision to participate in the trial and the extended ATI. Most recounted feelings of worry related to viral rebound during the ATI. Participants reported both defeat and relief with ART restart. Four faced challenges with protecting partners from HIV during their ATI, such as trying to find out if their partner(s) were using pre-exposure prophylaxis.

Conclusions: Our findings demonstrate potential improvements for future ATI trial participant experiences, such as more robust resources for psychosocial support and partner protections. Dedicating greater effort to understanding participant ATI experiences can inform the design of future participant-centered HIV cure trial protocols.

Keywords

HIV cure research; analytical treatment interruptions; participant experiences; socio-behavioral research; combination trials; people with HIV

Introduction

In the last decade, intensified efforts have been dedicated towards finding a cure for HIV that could either eliminate the virus from people with HIV (PWH) or keep HIV durably controlled in the absence of antiretroviral treatment (ART) [1]. Examples of HIV cure strategies under investigation include latency reversing or permanent silencing agents, immune-based approaches, and cell and gene therapies [2]. Due to the complex interplay between the HIV reservoir and the immune systems of PWH, cure-related research strategies will likely need to be combined to generate sustained ART-free control of HIV [3,4]. Such combinations of interventions may improve the likelihood of efficacy, but also increase clinical risks and burdens above standard-of-care ART [3]. HIV cure trials also often require an analytical treatment interruption (ATI), which is a highly monitored pause of HIV treatment often lasting for several months or more. This is because there is no established biomarker [5] that can predict durable ART-free control. ATIs are therefore used to determine whether an intervention had the intended effect. Prolonged ATIs lasting weeks to months can result in psychological risks to trial participants, such as increased worries of viremia, inflammation, and the elevated risk of onward HIV transmission to sex partners [6–8]. Yet, little is known about the direct experiences of PWH who are enrolled in these trials.

Trial risks and burdens may not only be related to physical risks and burdens, but also to key psychological and social factors. Relevant psychological factors are the potential to experience psychological distress, specifically anxiety, while interrupting ART as part of HIV cure trials. Social factors include changing sexual behaviors (e.g., use of condoms) or advocating for use of pre-exposure prophylaxis (PrEP) for sex partners given participants are off ART and may experience viral rebound posing a risk of transmission to them. While

oversight bodies require the monitoring of physical adverse events, it is important to assess secondary psychological and social adverse events.

Ethical considerations related to ATIs include the need to justify their utility, manage participants' expectations, minimize risks, ensure adequate informed consent, and engage the community [9–13]. An ATI consensus statement published in 2019 underscored the need to assess and understand participant experiences to guard against psychological and social harms [11]. While social-behavioral sciences research within HIV cure trials is growing [14–18], few studies have examined the perspectives of participants following an extended ATI. A study implemented in Belgium found overall satisfaction with a short-term ATI trial, but that PWH greatly under-estimated the emotional impact of being off ART [19]. Another short-term ATI study in Thailand revealed that PWH were willing to interrupt ART in a safe environment but were disappointed with the rapid viral rebound they experienced [20]. Therefore, participant experiences during ATIs remain an important area of study.

This study examines the experiences of PWH who underwent an extended ATI as part of the "*Combinatorial Therapy with a Conserved Element DNA Vaccine, MVA Boost Vaccine, TLR-9 Agonist and Broadly Neutralizing Antibodies*" (NCT04357821) trial (hereafter referred to as the "UCSF-amfAR trial"), implemented at the University of California, San Francisco (UCSF) from 2020 to 2023.

Methods

Parent trial

The UCSF-amfAR trial was a single-arm, proof-of-concept experimental study aimed at inducing sustained ART-free HIV control in PWH and exploring how long participants could remain virally suppressed off ART. The rationale for the study was based on a combination of interventions that showed efficacy in non-human primate models. It involved a combination of five interventions: 1) A conserved element (CE) HIV DNA vaccine administered in combination with interleukin (IL)-12 at Weeks 0, 4 and 12 by electroporation, a technique that uses short high-voltage pulses to help increase cell membrane permeability, improving the likelihood that the DNA will be introduced into cells; 2) Modified Vaccinia Ankara (MVA)-boost vaccine administered at Week 20; 3) combination broadly neutralizing antibodies (bNAbs) 10–1074 and VRC07-523LS administered at Week 24 and 34; 4) lefitolimod, a toll-like receptor (TLR)-9 agonist administered weekly from Weeks 25 to 33; and 5) ATI beginning two days following Week 34 and lasting up to 52 wk.

The goal of the ATI was to observe the virologic set-point. Thus, high-level viremia was tolerated for up to 12 wk and lower-level viremia for up to 24 wk. The specific virologic criteria for ART restart were plasma HIV RNA level >50,000 copies/mL for 4 wk, >10,000 copies/mL for 6 wk, >2,000 copies/mL for 12 wk, or >400 copies/mL for 24 wk. Participants could also resume ART according non-virologic criteria including CD4+ T cell decline below 350 cells/mL, acute retroviral syndrome, sustained or high-level viremia, or acute COVID-19.

To be eligible for the UCSF-amfAR trial, participants had to be 18 to 65 years old at the time of screening, on continuous ART for at least 12 months, with a CD4+ T cell count ≥500 cells/mL, and with phenotypic sustainability to both bNAbs at baseline, as ascertained by the PhenoSense Assay (Monogram Biosciences, Inc.). Participants underwent extensive biological sampling and were closely monitored for safety. Since the UCSF-amfAR trial opened in February 2020, it overlapped with the COVID-19 pandemic. Proactive measures were taken to mitigate risks to trial participants [21] and allowed for COVID-19 vaccinations during the trial [22,23]. In addition, the trial team implemented a risk mitigation plan for sex partners of ATI trial participants [6], which involved a warm hand-off from the trial team such as accompanying the participant and/or their partner(s) to an on-site PrEP clinic or directly connecting them with local PrEP providers.

Participants and settings

Trial participants were prior volunteers in the UCSF SCOPE cohort (NCT00187512), which is a long-standing observational study. We recruited interviewees from the UCSF-amfAR trial. Our social sciences team, which was independent of those conducting the clinical trial team to encourage participants to speak openly about their experience, conducted all in-depth interviews after participants resumed ART. Participants provided oral consent for the interviews as approved by the UCSF Institutional Review Board (IRB). Interviews were conducted within one month after resuming ART. All participants in the UCSF-amfAR trial were eligible to be interviewed.

Data collection

Interviews were conducted from 2022 – 2023. A health psychologist (JAS) conducted all interviews by teleconference. Interviews lasted between 30 – 60 min. The interview guide contained questions about: 1) decision-making (e.g., reasons for joining the trial, influence of personal background on decision to participate, perceived risks and benefits, trial perceptions and expectations); 2) trial experiences (e.g., positive aspects, trial concerns and burdens, feelings about trial interventions, feelings and experiences with the ATI, feelings and experiences with ART restart, and concurrent COVID-19 pandemic); 3) behavioral factors (e.g., partner protections); and 4) reflections on trial experiences and recommendations to improve future trials (Table 1). Participants received $USD 50 as compensation.

Data analysis

After a professional service transcribed each interview verbatim, we reviewed transcript quality and removed potential personal identifiers. We then applied conventional thematic analysis [24] to guide a multi-step analytic process. The coding process was informed by inductive and deductive approaches. We first used the interview guide to derive the main code categories, then analyzed the responses by question blocks, allowing the analysis team (SON and KD) to review the range of responses received in a contextual manner. We coded the data manually in Microsoft Word. The codebook contained code (theme) names, descriptions, and illustrative quotes. A Research Associate (SON) prepared a preliminary list of codes. The lead author (KD) then led data analysis and expanded the codes or themes, examined patterns, and wrote narrative data summaries. The senior author (JAS)

subsequently verified the resultant analysis. The team resolved discrepancies *via* discussions and consensus.

Ethical considerations

The UCSF IRB reviewed and approved the UCSF-amfAR trial interview study.

Results

Participant characteristics

Seven of the ten UCSF-amfAR trial participants (median age 37 years) completed post-ATI interviews. Six identified as cisgender males and one as a transgender woman. Four self-reported being White/Caucasian (one declined to report race), and three identified as Hispanic/Latinx. Three participants declined to complete the post-ATI interviews due to time constraints ($n = 2$) and lack of privacy ($n = 1$). HIV rebound occurred at a mean of 15 wk post-ATI across all trial participants [25]. Five of the seven participants exhibited some evidence of post-intervention control, including one who did not experience viral rebound (Table 2).

Decision-making

Reasons for joining the trial.—Participants' motivations for joining the UCSF-amfAR trial centered around scientific altruism, including advancing HIV therapeutics research, and benefiting the HIV/AIDS community. Most described elements of trust with the UCSF research team. Two participants noted excitement about this specific trial, including the combination design. Two others strongly hoped they could become post-intervention controllers.

> Reading through and kind of going, you know, "This is exciting. This is groundbreaking. This is thrilling … This is the first of its kind … in the grand scheme of things, you know, towards the cure. – Participant #07

> It was basically like, "We might have something here, big." And it was framed as a cure[-related] study. Through my experience, there's this element of hope and faith that we can cure this thing [achieve post-intervention control]. – Participant #03

One interviewee was so motivated to participate in the trial that he relocated from another country. The COVID-19 pandemic started shortly thereafter, causing challenges with the immigration process, employment, and supporting his family abroad. Nonetheless, this participant remained committed to the trial throughout its duration.

> I feel that I did everything and all that I wanted. So, if I would have stayed in [home country], I would be thinking why I didn't go. So, I did what I wanted. I came and then I tried. – Participant #10

Influence of personal background on decision to participate.—A key factor was the history all participants had with the UCSF SCOPE cohort, from which the UCSF-amfAR trial recruited. All interviewees mentioned having established trusting relationships with the clinical trial team. Research participation and giving back to science were described as part

of a personal HIV journey. For some, the trial represented the culmination of their trajectory of contributing to clinical trials at UCSF. One participant with a scientific background did not view the trial procedures as invasive or burdensome. Another mentioned that he regularly donated blood for research, had a close relationship with his HIV care provider, and was a longtime HIV community activist.

> I had done a couple of previous experiments before. So I'm just, like, taking tissues or giving extra blood … I've still been going every few months to give my blood … It's just kind of what I do … Anyway, I've had a longtime primary care doctor [also infectious diseases doctor] … But she's always been very—I consider her a friend, as well as my doctor. – Participant #06

Two participants reported having risk-seeking personalities – one stated he would do whatever the trial staff asked. Another described excitement around this trial, even claiming willingness to sacrifice his life for an HIV cure.

> Cut me, slice me, dice me. I don't have a healthy fear of death so I'm just, like, sign me up. Let's do it … I feel like I know everyone there [at SCOPE] on a personal level. Like, they also have my best interests in mind. I'm not just a lab rat. It's, like, if I felt like that, I don't think I would have been as willing to participate on the level I've participated … When they were first introducing the electroporations, the idea and the concept and how it worked … For me I'm just, like, I'll do whatever you want. – Participant #02

> I've been a big risk taker my whole life, whether it be personally, business wise, leisure … When I came into the program, which was SCOPE, there was always talk about this trial, a lot of amazing things, a lot of excitement around it. – Participant #03

Perceived risks and benefits.—Most participants had a good understanding of trial risks. They viewed these as acceptable and appreciated the opportunity to have their questions answered satisfactorily. Close clinical monitoring during ATIs mitigated worries about their potential risks.

> So, the individual risks for the individual interventions, you know, like the electrophoresis [electroporation]. Bruising, inflammation, those sorts of things. Those can happen in regular life. It's not that big of a deal. It's certainly not a dealbreaker. As far as the [treatment] interruption … I knew I was in good hands. I was being monitored every week, so I wasn't concerned in the slightest. Had it not been weekly, I might have been concerned. But again, I knew that I was in excellent hands. I was in, probably, the best possible hands. So, I wasn't really concerned at all … Maybe if it was a monthly check in, that would've been concerning. But the fact that it was every seven days, checking in, making sure that everything was okay. That was really reassuring. – Participant #07

One interviewee explained that he was not worried about trial risks, specifically those surrounding the ATI, because he had faith in his body. However, another seemed to believe there were tangible, uncertain risks, but was willing to take them on regardless.

> I was willing to really risk. The risk piece, I'm like, "I'm good with that," right? I've hurt myself physically, in many ways, through sports I participate in. I can handle the give and take. So, my risk assessment is going to probably be a lot different than someone else's … I'm an "all in" type of guy. I'm like, "Let's do this." … So, my risk piece, I'm just like, "Whatever it takes, really." So, when I'm assessing it, it's like, "Would you pay the ultimate price of discarding this body for something bigger than you?" And then, I was just like, "Yeah." I made that decision before I came in." – Participant #03

Participants tracked their viral load and CD4+ cell counts during the ATI. Close clinical monitoring had associated psychosocial benefits (e.g., sense of pride, purpose, and optimism), which may have increased motivation to engage with a long and time-intensive study.

> It was really nice. I actually got to see them [trial team] with such regularity and have great conversations about everything … Because they were just there. They were just accessible … I was always aware of, kind of, where my numbers were and how I was doing, in relation to the study … There's a sense of kind of pride and purpose. That despite this study being for a cure for HIV, and that's the reason why I was in it, that I served, like, a purpose. A larger goal through that contribution. – Participant #02

Trial expectations.—Trial expectations were mixed among interviewees. One participant explicitly stated having no expectations of being cured of HIV because of the trial, explaining that they had done their own research and developed a grasp of trial procedures.

> This isn't the first attempt that's been made towards a cure, or towards an intervention, rather. So, I didn't expect much, given the fact that so many attempts have been made in the past … I knew that they knew what they were talking about. I had done my own research … But I had done some reading in the literature. – Participant #07

One interviewee recounted that his trial outcome differed from his initial expectations. This participant noted feeling like he had failed the research team and the HIV community when his virus rebounded.

> I definitely had expectations. I definitely went on a rollercoaster of emotions, for sure. And so I don't want you thinking that I was flippant, or laissez-faire about this, or didn't have expectations—because I absolutely did. I posted a lot on social media about this … I had this feeling of a lot of responsibility for all of these people. And to have to post that the experiment didn't work … I felt like a failure … It took me a couple of days. And I think I even got back on meds before I could post to everyone—because it's not just my family and friends that I had to tell, but it was also these people in these other countries—my little pen pals, who, you know—some of them feel so desperate for there to be a cure and really needed this to work. And they were even more invested in it than me, okay? It kind of didn't work. You know, so that was a hard post, and those were hard conversations to have. Yeah. That was—I mean, you know, I could have chosen, obviously, to

keep very private and never, ever post about that. So that would have all gone away, right? Like, that I did to myself. – Participant #06

Trial experiences

Trial concerns and burdens.—Participants noted their appreciation of the clinical research team's flexibility around trial visits (e.g., scheduling visits early in the morning), and providing transportation to/from the research site (e.g., ride shares). Three participants described specific trial burdens, including needing to take time off from work to attend trial visits, frequent blood draws that encumbered business travel, and income loss due to inability to travel during the trial. Two participants also shared unique participation burdens. The participant who relocated from another country had an internal conflict about whether to return home during the trial. Another froze his sperm prior to participation, to preserve reproductive viability.

Feelings about trial interventions.—Most interviewees described tolerating the experimental interventions well, except for one participant who found the immune-based interventions challenging. Another described becoming "anti-sympathetic" to the COVID "anti-vaxxers" during the trial. Additionally, he was pleasantly surprised about being able to relax on infusion days.

> I tolerated it [interventions] pretty well. It was easier than I thought. And it made me less sympathetic to anti-vaxxers … after, when the pandemic came and that became, like, to the forefront of people's minds. That the COVID vaccine was unproven medical thing. It made me very anti-sympathetic to that point of view … [And] Even, like, the days that were billed as very difficult days, which were very long days, for the eight-hour infusions. Those went by pretty quickly. It felt, I mean, those were nice because I was just there in the hospital bed … It was, you know, it was a long time. I just had to sit there and just receive the infusion … But there was a TV, and I kind of dozed off a little bit. And it was kind of a relaxing time. I think around that time, I was working quite a bit. So, it was nice to actually take the day off for that. And it was, yeah, kind of rewarding. You know, receiving this treatment that was so advanced and so tailored that I was really not paying anything … It was kind of satisfying or gratifying and exciting. – Participant #04

Apart from the ATI described below, the most concerning trial procedure for most participants was the electroporation used with the experimental DNA vaccine. Most expressed worry or surprise and experienced some level of physical pain with the electroporation, ranging from a "punch in the arm" to much sharper, visceral pain.

> We got to the part of the electroshock as part of the three sets of shocks that they administered … I thought they undersold that, underplayed that … I screamed the first time and my arm flailed. And then they're like, okay, the other side; same thing. And I will tell you, that was the most nerve-wracking part—was between that time and six weeks later when I had to do it again—I was really nervous about having to go through that again. Like, they told me it was going to be like a punch in the arm. And I just don't think that's an accurate description—because a punch in the arm seemed to me to be like a dull punch. You can hit me pretty hard in the

> arm, and I'm good with that if it's a big, dull poke. But I mean, had I thought about it further, I'd realize, oh, it's actually an electropulse going in. It's not going to be dull; it's going to be sharp and visceral … Like, you know, this is really—I have a high threshold of pain, but that threw me. So when I went in the second time, I actually didn't take anything; I just psyched myself up. – Participant #06

Feelings and experiences with ATI.—Participants reported a range of experiences around the ATIs. Two described being on the ATI longer than expected. Three reported feeling relief around not taking HIV medications and not having to worry about the side effects of ART (e.g., side effects on liver), with one describing a sense of liberation.

> So, it's one more free life, you know, you feel more free. And I think that for everybody it happens, it's much better to live without taking pills than taking pills daily. This is the point. – Participant #10

One participant described anxiety about acute retroviral syndrome while being off ART.

> What was anxiety-producing about it with me is, I didn't want the virus to spike. I was worried about, would I have a new seroconversion on this as it came back? And what if it spiked to 10,000, or, you know, 50,000 or whatever? Would I be laid up in bed? – Participant #06

However, others developed a keen scientific curiosity in observing their viral load levels during the ATI given the opportunity to receive weekly test results.

> There was always a level of interest. Kind of knowing the numbers, because for me, in my case, it [viral load] kind of serpentined. And it went, you know, like 300 copies, like 1,000, back down to a couple hundred copies … There was always, like, something to kind of look forward to. There was always some excitement about the levels … It was exciting, what was happening with the science. – Participant #04

Interviewees described emotional highs and lows during the ATI, coupled with periods of uncertainty about the outcome, thus comparing the ATI to a journey. One participant would have preferred weekly – rather than bi-weekly – viral load testing during the viremic period, having perceived an incongruency in the clinical monitoring plan.

> At some point, I looked at their plan … And, like, the virus had just come back. And they're like, okay, we skip to every other week for blood. I'm like, okay, could I actually ask y'all that we go every week for blood? Because it's a little weird that, all of a sudden, y'all are—at the heart of it, as the virus rebounding, you're saying, go every other week, or—you know, like, that makes no sense to me … I need it to know whether the virus is spiking; what's my body doing? Knowledge—that information is my medicine. Don't deny me my medicine. – Participant #06

The sustained post-intervention controller noted several stressors during the ATI. Ambivalent about the state of ART-free post-intervention control, and not labeled as cured or completely rid of HIV, this participant compared sustained post-intervention control to a perilous middle ground between being HIV negative and living with HIV on ART.

> It's just being suppressed without meds as opposed to being cured. Sort of the more, I guess, technically appropriate term is ART-free viral suppression. But it's a mouthful and it's all jargon … And it mostly sucks because, you know, the whole, like, I guess, like, fantasy is to, you know, get cured or suppressed or whatever, but then, you know, you can get superinfected which I never even considered. So, it feels more dangerous living that life than someone who's HIV negative and taking PrEP or, like, other people who are HIV positive and just taking their meds … So, yeah, it's, like, this unique inner turmoil … I feel like, how exciting. You've been off meds for so long and hasn't [haven't] rebounded and I'm, like, what does it mean? We don't know. – Participant #02

Overall, about half of those interviewed recounted specific episodes of anxiety related to becoming detectable for HIV. One worried about feeling HIV come back in his lymph nodes, but eventually considered this indicative of his body fighting the virus. For this participant, high viral load measurements (e.g., 10,000 copies/mL) were a source of worry. He described ongoing concern about illness and was ultimately disappointed when he did not achieve sustained post-intervention control.

> So for those times, you know, when I'd get that viral load, like, woo-hoo, you know, kind of celebrate. Go, body, go, you know. I'm feeling really good about it. But always in the back of my head, there was a lingering, like, oh, could it spike? Could I get sick? … So there was a little bit of—especially when I was first—the number was going up, and we didn't know how high it would go up. I think it went up to 1400 [copies/mL], and then dropped to, like, 12, and then spiked up to 1600, which is still basically nothing, or 1500 … I think real illness would come at, like, 10,000 … . Like, so if I'm at 800, that ameliorated a lot of my concern that, like, okay, I'm not going to get super sick. I'm not going to a hospital with this—because, like, it's only 800; you know what I mean? – Participant #06

Similarly, another participant expressed worry when his viral load started to increase exponentially.

> We were seeing – essentially remaining undetectable. And then, going into being detectable … I was up and down, up, down. And then, we reached the point where I was starting to go up and rather exponentially … So, I'm pretty in tune with my body, especially this journey and the disease. So, really being able to feel like – I was like, "Something's going on here." A little bit of glandular stuff … But I could tell when things were starting to – something was starting to shift. – Participant #03

Only one participant did not express any worry with being off ART for an extended ATI.

One participant whose virus did not rebound as expected expressed confusion and uncertainty about the trial outcome and its causes. After resuming ART, he was surprised that no one could explain why was able to stay on an 18-month ATI.

> What they told me was that the point of this particular study was to see what would happen when the viral load rebounded and that never happened. Well, it sucks because no one really knows … no one wants to use the C word, the cured word, because going back to those other people that – people who thought they were

> cured. All these scientists said in the media and then, like, the virus came back. So it's, like, no one wants to use that word … And then, you know, it just keeps me in limbo. If people ask me what's going on … I have no idea. – Participant #02

Feelings and experiences with ART restart.—The trial protocol had pre-defined ART restart criteria that were being followed (see Methods). In addition, because of the close clinical monitoring during the ATI, ongoing conversations occurred between participants and the clinical trial team around whether to continue with the extended ATI. In other words, while the trial protocol was being followed, participants made decisions whether to continue with the ATI on a weekly basis based on their evolving feelings about the ATI.

Some interviewees described benefits of restarting ART. For example, one decided to resume ART after extensive discussions with the trial team, because ART resumption would result in a more effective response to the influenza and COVID-19 vaccines. Another considered resuming an active sex life as a benefit. However, one participant who had been off ART in the early days of the HIV epidemic described the stopping and restarting ART as "no big deal".

For those who had mixed emotions about ART restart, one was not ready to resume ART. He believed that his immune system was controlling the virus but felt instantaneous relief upon restarting. Another experienced both reassurance and disappointment with ART restart.

> Restarting medication was both a relief, and at the same time, it was kind of, almost a letdown. In the sense that I was really enjoying being off medication. I was really excited about the prospect of learning things from the study. And I was really invested in it. And so, I was kind of sad to see it come to the end of the study. So, it was a little bit disappointing, in that regard. But at the same time, it was quite a relief, as I was watching my numbers climbing higher and higher. The numbers of my viral load. So, yeah. It was definitely a relief to be back on. And it's nice being back on. – Participant #07

One interviewee explicitly stated that he did not view ART restart as challenging, while another hesitated to resume ART, wanting more time for his body to resuppress HIV. However, he acquired COVID-19 and restarted ART, and expressed his up-and-down experience as follows:

> We were seeing these ups and downs. It was like viral load going up, viral load going way down, viral load going up a little bit, down, going way up, kind of going down. And then … my personal doctor … everyone is like, "We want you to go back on meds." And I'm like, "No, I'm not going back on meds." And then, I got COVID … and my viral load started increasing pretty exponentially. And it was at that time that I was just like, "All right" … And thinking beyond myself and my body starting to basically move into viral load raising, which increases reservoir, which we don't want the reservoir to increase … I just made the decision. It was myself, and I just took the pill. And that was a big sense of defeat. And I went through the journey of, "Did I not wait long enough? Was this just part of the deal?" … So, it was a real emotional roller coaster. – Participant #03

As previously mentioned earlier, the participant whose virus did not rebound felt like he failed the trial and the HIV community when he restarted ART. However, he felt safe upon resuming medication.

> You know, especially, like, going back on meds was almost like I felt like I failed or I quit. Because who knows how much longer this could have gone on … I kept asking the doctors, like, well, is there any benefit? And they said, well, we've learned 99% of what we wanted to learn. So I don't even know what that means … I had a lot of friends who were, like, oh my God, you're so lucky. And I'm, like, well, I don't feel lucky. It actually feels worse … And I didn't even expect to feel this way, but, like, when I first took that one pill, like, I thought I was going to feel guilty but I was, like, I feel really relieved and I finally feel safe … I was the last one left on the study. – Participant #02

Concurrent COVID-19 pandemic.—The trial team had a robust COVID-19 risk mitigation plan in place during the trial (see Methods). The COVID-19 pandemic had unique and mixed impacts on the experiences of trial participants. One participant viewed the study as a benefit, reporting that they had much greater access to medical professionals during the pandemic, due to regular clinic visits, and appreciated that the research staff were also involved in COVID-19 research. However, in one instance, a participant raised concerns about having to test for COVID-19 prior to a trial visit, and this request seems to have caused a burden.

Given the novelty and significance of the trial, which was well known to many participants, in one instance, a participant elected not to vaccinate against COVID-19 in 2021 because he felt this limited his chances at ART-free viral suppression. He acquired COVID-19 and expressed remorse.

> When we went into this thing, I didn't vaccinate. I'm like, "Everyone's getting vaccinated, and they're pausing their treatments." I'm like … COVID didn't exist. I'm not getting the vaccination. You've got to – I'm not doing that … Yeah, and I was at a super spreader event in [location], and I came back. And I had [the] Delta [strain], and it throttled me. I think that was the first realization that "You're not invincible." There's a lot of factors and decisions that you made that other people respected. You're obviously – all eyes on … I think there was a little bit of ego in there around some invincibility and this super pumped immune system." – Participant #03

Behavioral factors

Partner protections.—Participants' comfort and experience in reducing the risk of HIV transmission to sex partners during the ATI varied considerably. Two participants managed partner protections without challenges. One was in a stable relationship and reported no concerns with their partner but was also careful not to overwhelm them with too much information about partner protections during the trial. Another had temporary partnerships during the trial but was aware of the need to use condoms and to find partners on PrEP.

Four participants noted facing challenges with protecting their partners from HIV during their ATI trials. One stated that the need for partner protections became more difficult as the ATI progressed, creating discomfort with physical intimacy as a result of the risk of transmitting HIV while off ART. For another, asking whether partners were on PrEP was difficult, as the participant was “out of practice” with such conversations. This participant had a partner without HIV who took emergency post-exposure prophylaxis (PEP), provoking anxiety and need for additional support. Another participant engaged in condomless sex while attempting to conceive a baby with a woman who needed to go on PrEP which harmed their relationship. The participant had underestimated the challenges associated with the ATI.

> So, I’m dealing with the relationship piece, and then, a month of getting the test, and my partner is negative, and it’s going to stay that way. The challenges in the relationship there, and then, navigating my body … It’s been a real challenge for my partner during this journey, which I completely underestimated … I am in a relationship with a woman. And we have attempted to conceive during the time leading up to this … We were really arriving into this place where my partner is longing to try and conceive again. And that essentially requires unprotected sex … And that occurred right as I became detectable. So, once again, my partner had to go on to PrEP. She had to go through testing at that time, testing afterwards. It was a huge process for us and our relationship … It really affected our relationship, the trust piece. Essentially, I just had to take full ownership, like, “You’re right. I should’ve said, ‘No, we’re not doing this right now.’ But I didn’t … The practicality and the realness began to subside the deep elements of hope or ego, or just blind ambition, and the realness started coming into effect. – Participant #03

The post-intervention controller whose HIV did not rebound noted the difficulties in describing the nuance around what ATIs mean for transmission, and how this makes the rather elegant Undetectable=Untransmittable (U=U) equation less clear.

> You know, just trying to be cautious and, like, considerate of their safety. So I was trying to be, like, give a really forthright, exhaustive explanation of everything. It’s not black and white. So it was a real [swear word] boner killer, you know what I’m saying? … Yeah, it’s, like, I’m not allowed to be a part of, like, either side of the fence. I’m not allowed to be part of, you know, people who are positive or negative. I’m by myself, in the middle. It’s much harder being like this than what I was – because I lived as an HIV positive person for almost a year, so I remember how that felt. This is much worse. – Participant #02

Reflecting on trial experiences and recommendations.—HIV cure trials with ATIs may inadvertently trigger various emotional reactions. One participant emphasized the need for mental health support during the trial since becoming detectable for HIV fueled many emotions and reignited past psychological trauma.

> And I did speak to the team that I interface with regularly. I do feel like moving forward, whether you’re gay, straight, bi, however you choose to identify, single, partnered, there’s a really big component around the emotional support piece …

> But that stuff really needs to be addressed around navigating people's individual situations and their emotional stability during a time that's really trying, not only for them, but for partners and for people that [who] care about them. Because once the hope of the cure starts to fade, and you're detectable, and you're navigating this, and intimacy shifts, it just really fuels a lot of things for people. I should just speak for myself. It fueled a lot of stuff for myself and my relationship … My mental mindset is – the mental piece is huge. It helps the body. And it's always underestimated, in my opinion. – Participant #03

Two participants recommended helping people navigate the nuances of the trial and the field of HIV cure research in general. Given that HIV cure research likely has the largest knowledge gaps in terms of general awareness and understanding at the societal level, many family members and friends of trial participants could not grasp the relative risks of the trial and believed that the trial was potentially life-threatening.

> Everyone thought I was going to die from this. It was a little weird. I mean, doesn't that sound stupid? I tried to tell people that it was fairly benign … But people's imaginations really got away with them. Even my partner, I think, at one point got a little wicky-wacky … I was bedridden for those few days. And I was feeling really, really shitty, and this was really hard. And I think my husband got a little panicked. He got a little scared, and I think he scared our friends and family … Everyone lost perspective a little bit on that … It's a highly nuanced—right. And how do you explain that? So most of these people have zero understanding of HIV, except, oh my God, it'll kill you, right? And so then you try to explain that you're going off your meds. And people are like, well, how long does he have to live now that he's going off his meds? Like, he'll be dead in three weeks, right? … I realized I didn't have the tools to adequately communicate. – Participant #06

Additional quotes related to the above themes can be found in Supplementary Table 1.

Discussion

The UCSF-amfAR trial participants we interviewed completed a highly novel and intensive HIV cure trial with an extended interruption of HIV treatment. We found unique psychological and social factors at play throughout the trial from start to finish. The fact that most participants were motivated to join the trial by the desire to benefit HIV cure science did not come as a surprise [14–16,19,20,26–30]. What appears significant in our setting is that participants were prior volunteers in the UCSF SCOPE cohort and consequently had developed trust with the research team in the years and even decades preceding the trial. This level of trust may have underpinned participants' willingness to accept the high risks and complexity of the trial and made their overall experience generally positive, as participants noted they felt like partners in research, closely tracking their viral loads alongside the research team. Further, our findings appear consistent with a prior hypothetical study in which a minority of PWH did not place an upper limit on acceptable risks to achieve HIV cure [31], and a short-term ATI study where nearly one in five did not perceive risks of being off ART [15]. Close clinical monitoring – considered an ancillary or inclusion benefit [32] – appeared to have mitigated worries around trial risks as participants entered

the trial. These results highlight the importance of considering both potential risks and benefits from participants' perspectives.

Relatedly, the role of trust and partnership is known to be a strong facilitator for recruitment and retention in other HIV cure trials [17,19,26,33,34]. However, ethically, trust should not unduly distort risk perceptions of HIV cure trials, particularly in otherwise healthy PWH [35] who may have much to lose health wise by enrolling in such research. Consequently, HIV cure research teams should carefully anticipate the trial expectations and the challenges involved with recruiting PWH who are more risk-averse, less trusting of clinical research, or with full-time responsibilities – factors that will make participation more challenging for other PWH.

Moreover, most trial participants we interviewed understood that the trial was designed to answer a scientific question, and the combination intervention would not necessarily lead to HIV cure, or even sustained post-intervention control. Scholars have fore-grounded the importance of avoiding the "cure" terminology in informed consent forms and study-related materials [36–38], to reduce the risk of curative misconception. On point, one participant spoke openly to the media about his participation and recognized it as a scientific experiment [39]. This participant did not expect to be cured, and he said the trial team helped him manage expectations [39]. However, he was invested in staying undetectable and viewed his involvement as "a lesson in patience, perseverance, resilience, being comfortable with the unknown and, yet optimism" [39]. Most participants nevertheless understandably had therapeutic optimism, or the hope for a positive outcomes, which is generally not considered to be ethically problematic [40]. Yet, as the ATI lengthened, it is possible that some participants developed a growing sense that the trial might result in the best positive result. This phenomenon could be described as 'curative hope'. One participant who documented his journey publicly noted feeling like he had failed the research team and the HIV community when his virus rebounded. This feeling of failure was similarly recently noted in an extended ATI trial conducted in Philadelphia, United States [34]. Although participants were disappointed by having to restart ART, they reverted to their contributions to science and were satisfied by their ability to give back to research towards an HIV cure.

Nonetheless, even with positive trial outcomes, participants can be left with several unanswered questions. For example, the participant whose virus did not rebound was ambivalent about the reality of ART-free viral control and expressed confusion and uncertainty about his status. HIV cure research teams will need to grapple with issues of interpretability of trial outcomes, as these also seem salient from participants' perspectives. As we learned in this study, participants may experience discomfort with the uncertainty associated with a state of post-intervention control.

Another noteworthy finding from our study is that more than half of those we interviewed faced non-trivial challenges associated with partner protections during their ATI, even though the UCSF site had clear processes in place for dealing with HIV transmission risk mitigations [6]. The San Francisco PWH community is relatively knowledgeable about U=U, and PrEP acceptability is high in the demographic of participants who were enrolled in the UCSF-amfAR trial. Despite these factors, we noted several stressors, such as having

to revive old conversations around condom use, nervousness around being able to pass HIV to sex partners, awkwardness of trying to find out if partners were on PrEP, difficulty navigating fertility desires during the ATIs, uncertainty around whether to have sex during the ATI, and having to take oneself out of the U=U community altogether. Our findings are in sharp contrast with those of a prior short-term ATI study in which the fear of transmitting HIV did not emerge as a prominent concern [15]. However, the worry about transmitting HIV to sex partners emerged in prior studies [19,41–45], and could be exacerbated with prolonged ATIs. Findings from our study support efforts to develop evidence-based partner protection measures during ATIs that should be adapted to local contexts [8]. The UCSF-amfAR trial was conducted in San Francisco, United States, where PrEP is widely available. However, in other settings where PrEP is not as easily accessible, we recommend PrEP be provided free of charge to participants' partners without HIV and with close navigation and psychosocial support. We also recommend paying special attention to specific groups, such as cisgender and transgender women, where gender and power dynamics will be critical when negotiating partner protections [46–48]. Mitigating the risk of onward HIV transmissions during ATIs can help protect the field of HIV cure research and honors four decades of research and implementation in HIV prevention.

Based on our study results, it is possible that participants' worries are heightened in extended ATI trials, compared to short-term ATI trials. Both extended and short-term ATI trials require clinical monitoring and ongoing conversations with the trial team; however, extended ATI trials seem to involve more dynamic processes due to the need to monitor the fluctuating viral load following rebound. Extended ATI trials may also be accompanied with heightened stressors and uncertainties around risk to self (e.g., clinical risks) and risk to others (e.g., transmitting HIV) than short-term ATI trials. ATI-related worries appear to be mitigated by frequent trial visits and interactions with the trial team. Nevertheless, robust risk mitigations may also require psychosocial support at specific trial milestones (e.g., informed consent, ATI initiation, viral rebound, ART restart). Of note, no participant in the UCSF-amfAR trial received psychosocial counseling after restarting ART. Nevertheless, psychosocial counseling will likely need to become a standard in future ATI trials as they grow in size [46] and complexity. Overall, a recurring theme from these studies appears to be that the mental, emotional, and psychosocial impact of HIV cure trials with ATIs should not be underestimated [16,17,19,20,27,34].

Table 3 summarizes our findings and considerations.

Limitations

Our participant sample was predominantly male and White/Caucasian, consistent with those enrolled in the parent UCSF-amfAR trial. Our sample was also biased towards PWH with good access to health care, in a highly resourced setting, and with high tolerance for risks and who had prior relationships with the trial team due to their involvement in the UCSF SCOPE observational cohort. Interviews took place at only one clinical research site. For these reasons, our results are not generalizable to other PWH who participate in ATI trials. More research will be essential to understand the experiences of PWH who represent diverse groups with respect to race, ethnicity, sex, and gender [46,49], risk aversion, and

resource-limited settings. Due to the small sample size, it is possible that we did not achieve thematic saturation [50]. In addition, we only conducted one in-depth interview per trial participant following ART restart, and our results may be affected by recall or retrospective bias. These limitations notwithstanding, our results have internal validity with respect to PWH who participated in the UCSF-amfAR trial and our findings provide some important nuances in participants' perceptions and experiences that can inform the design and conduct of future trials.

Conclusions

Findings from this study underscore the need for increased and dedicated efforts to support PWH undergoing intensive ATI trials, particularly in the areas of mental health and partner protections. Additional socio-behavioral research should be conducted in different settings and cohorts of PWH and included as part of trial design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Post-ATI in-depth interview guide – participant experiences UCSF combination HIV cure trial (San Francisco, CA, USA, 2022–2023).

UCSF Combination HIV Cure Trial In-Depth Interview Guide – Post-Analytical Treatment Interruption (ATI)
SECTION I: INTRODUCTORY QUESTIONS – PERSONAL BACKGROUND
● Are you back on your HIV medications?
● What was it like to be off your HIV medications for X days/weeks/months and now being back on them?
● What was the overall feeling you had while pausing your HIV medications? Were your expectations met or not? Please explain.
● What was the best part about being in this trial? What was the worst part? Do you have any concerns having completed the study?
SECTION 2: KNOWLEDGE FACTORS
● Why you were asked to stop taking your medications?
● What did you learn about the trial that you did not know when you started?
● How do you think your participation impacts what we know about HIV cure-related research?
● At this time in the trial, how do you feel about the combination of interventions that you received?
SECTION 3: DECISION-MAKING FACTORS
● Stepping back, how satisfied are you with your decision to participate in this study? What were the risks in your view?
● What were the benefits? How do you weigh them?
SECTION 4: PSYCHOSOCIAL AND PARTNER FACTORS
● Overall, how are you feeling emotionally, right now, after you finished the treatment interruption?
● How did your viral load change during the study?
● Did you have any sexual partners during the study?
● What resources, information, or people, did you leverage to talk about risks of sex while off your HIV medications?
● What do you consider acceptable partner protection measures during the HIV treatment interruptions (e.g., PrEP referral for partners, etc.)? Is there anything else the study trial could have done to support you with partner protection?
SECTION 5: CONCLUSIONS
● Do you have any recommendations to improve the conduct of future clinical trials like this one?

Table 2.

Demographic Characteristics of UCSF combination HIV cure trial participants (San Francisco, CA).

Participant Identification Number	Age	Sex Assigned at Birth	Race and Ethnicity	Duration of ATI (days)
Post-ATI Interview Accepters				
02	<50	Male	Declined to Answer, Hispanic	>300 days
03	>50	Male	White, Non-Hispanic	200–300 days
04	<50	Male	White, Hispanic	200–300 days
05	>50	Male	White, Non-Hispanic	100–200 days
06	>50	Male	White, Non-Hispanic	>300 days
07	<50	Male	White, Non-Hispanic	200–300 days
10	<50	Male	White, Hispanic	>300 days
Post-ATI Interview Decliners *				
01	<50	Male	White, Hispanic	100–200 days
08	<50	Male	Declined to Answer, Hispanic	100–200 days
09	<50	Male	White, Hispanic	100–200 days

* 01 and 09 declined post-ATI interview due to time constraints. 08 declined post-ATI interview due to lack of privacy to conduct interview. To maintain confidentiality, only birth sex is indicated, as there was only one transgender individual in the study.

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Table 3.

Summary of considerations for implementing combination HIV cure trials with extended ATIs.

Decision-Making Factors
● PWH may have several motivations for joining complex combination HIV cure-related trials, such as mix of scientific altruism, trust in the clinical research, and hope of achieving post-intervention control. It is important to guard against potential therapeutic or curative misconception when enrolling participants in HIV cure-related trials.
● PWH's backgrounds may influence their decision to participate (e.g., prior research participation or relationship with research team, time availability and resources to participate, personality types). Strategies will be needed to engage individuals in HIV cure-related trials who may not be as trusting of the clinical research establishment, with full-time responsibilities, or who are more risk-averse.
Trial Perceptions and Expectations
● Most participants perceived the likelihood of trial risks, although one participant was unable to accurately appraise risks. Close clinical monitoring mitigated potential worries around risks during the trial. Most participants perceived some trial benefits (e.g., psychosocial benefits such as sense of pride, purpose and optimism).
● Most participant had an accurate appraisal of the trial's purpose and no expectation of being cured. However, it is possible that PWH still hope to be cured or achieve sustained post-intervention control. For participants whose HIV do not rebound, there can be confusion or uncertainty about their trial outcome.
Experiences with Combination HIV Cure Trial
● Trial teams should find a balance between the frequency of clinical monitoring visits and providing peace of mind for participants, and accommodate trial visits to participants' unique circumstances when possible (e.g., travel schedules). There should be innovations in trial conduct to reduce trial intensity and burdens (e.g., home-based viral load test).
● There will be heterogeneity in how participants experience experimental interventions and procedures during the trial. There should an emphasis on safety and emotional health when undergoing experimental interventions.
● ATIs should be considered like a journey, on both physical and emotional levels. ATIs can be anxiety-provoking for participants who experience uncertainties around viral rebound. ATIs may not be as life-changing for participants who take daily pills for other medical conditions. Trial teams should carefully manage expectations around the state of durable ART-free control. Even the lack of viral rebound may not necessarily result in relief but can be a source of worry due to ongoing uncertainty. There should be a robust psychosocial infrastructure in place to take care of participants' needs before, during and after ATI trials.
● Participants will experience ART restart differently (e.g., sense of relief, defeat). Research teams should emphasize that participants have not failed the trial when resuming ART, but have helped answer scientific questions. Customized approaches may be needed to support participants with ART re-adherence behaviors post-ATI.
Psychosocial Factors
● Becoming and remaining detectable for HIV during ATIs can be a stressor. ATIs are accompanied with viremia-related worry, which will likely increase with higher viral load measures. Viremia-related worry may be lesser for individuals with prior experience with prior HIV detectable status, but will need to be thoughtfully considered in the era of U=U.
Behavioral Factors
● There can be many challenges associated with partner protections during ATI trials (e.g., conversations around condom use, trying to find out if partners are on PrEP, helping partners navigate PrEP, dilemma around whether to have sex, taking oneself out of U=U. etc.). Evidence-based partner protections support in the context of ATI trials are needed for participants and partners.
Logistical Factors and Study Conduct
● Research teams should offer as much logistical support and flexibility to participants as possible. The importance of mental health, emotional and psychosocial support systems around each participant should not be under-estimated.

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