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"We Need to Deploy Them Very Thoughtfully and Carefully": Perceptions of Analytical Treatment Interruptions in HIV Cure Research in the United States—A Qualitative Inquiry

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Abstract

Strategies to control HIV in the absence of antiretroviral therapy are needed to cure HIV. However, such strategies will require analytical treatment interruptions (ATIs) to determine their efficacy. We investigated how U.S. stakeholders involved in HIV cure research perceive ATIs. We conducted 36 in-depth interviews with three groups of stakeholders: 12 people living with HIV, 11 clinician-researchers, and 13 policy-makers/bioethicists. Qualitative data revealed several themes. First, there was little consensus on when ATIs would be ethically warranted. Second, the most frequent perceived hypothetical motivators for participating in research on ATIs were advancing science and contributing to society. Third, risks related to viral rebound were the most prevalent concerns related to ATIs. Stakeholders suggested ways to minimize the risks of ATIs in HIV cure research. Increased cooperation between scientists and local communities may be useful for minimizing risk. Further ethics research is necessary.

Keywords: perceptions, treatment interruptions, HIV cure research, United States

Introduction

Antiretroviral therapy (ART) alone will neither cure HIV[1–4] nor end the epidemic worldwide. Strategies to control the virus in the absence of ART are needed, spurring research in the United States and around the world.[5] However, strategies will require analytical treatment interruptions (ATIs) to determine efficacy.[6,7] There is currently no established diagnostic test to accurately predict the likelihood that a viral rebound is imminent.[8] There are also unresolved ethical questions about how best to ensure that study participants know about ATI risks in the context of research.[7,46] These risks include the potential for HIV drug resistance, heightened HIV transmission, and an increased HIV reservoir.[9–13] Due to the well-documented benefits of complete ART adherence,[14,15] stopping ART for research purposes remains one of the most controversial topics in HIV cure research.[16,17]

Several cases of HIV remission suggest the uncertainties involved in HIV research toward a cure. Only one person, Timothy Brown, achieved a sterilizing cure following interruption of treatment and close monitoring for signs of virologic rebound. He underwent an allogeneic stem cell transplant from a donor homozygous for the CCR5 gene deletion.[18] The VISCONTI cohort participants were all treated with suppressive ART during early HIV infection for at least 2 years, and have remained virologically suppressed

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following treatment cessation for years, despite the lack of protective human leukocyte antigen alleles.[19] In contrast, the Boston patients experienced virologic rebound following an extended time off ART. They received an allogeneic stem cell transplant from donors heterozygous with the CCR5 gene deletion, followed by reduced conditioning.[20,21] The Mississippi child received ART at 30 h of age, continued ART for 18 months, became lost-to-follow-up, and no longer received ART for a period of time. She remained without detectable provirus while off treatment for over 2 years, until a medical visit demonstrated rebound.[22] These cases illustrate the uncertainty in HIV remission research.

ATIs have also been used in a wide range of studies toward an HIV cure, including those involving acute or primary infection,[19,23–30] chronic infection,[31,32] immune-based interventions[33,34] and, to a limited extent, gene modification.[35] ATIs have not been used extensively in studies involving latency-reversing agents[36–38] or in pediatric research[39] (Table 1).

Given the controversial nature of ATIs, we investigated how stakeholders involved in U.S. HIV cure research perceived ATIs. Stakeholders were people living with HIV (PLWHIV), clinician-researchers, and policy-makers/bioethicists. Clinician-researchers and policy-makers/bioethicists were involved in HIV cure research, and PLWHIV were connected to HIV cure research networks. While surveys have been conducted to assess patient willingness to undergo ATIs,[40–42] there is a lack of data about stakeholders' perceptions of ATIs in the context of HIV cure research. Our study examined perceptions of ATIs among U.S. stakeholders involved in HIV cure research.

Materials and Methods

Participants

We used in-depth interviews that allowed us to solicit candid opinions from individual stakeholders.[43] Qualitative research can identify rich narratives and lived experiences not captured in quantitative research. We conducted interviews with three groups of purposively selected stakeholders: PLWHIV, clinician-researchers, and policy-makers/bioethicists. The latter two groups had professional experience with HIV cure research studies. These three groups of stakeholders were selected to provide perspectives on ATIs. PLWHIV discussed their role as potential study participants who could be eligible for ATI studies in the future. Clinician-researchers discussed their role as past, current, or potential study organizers and/or as HIV clinicians. Policy-makers/bioethicists discussed their normative role reviewing ATI protocols. We selected these three groups of stakeholders since they were important decision-makers in HIV cure research, and have direct influence on studies involving ATIs. All PLWHIV were on ART at the time of the interview and were recruited from a previous online convenience survey on willingness to participate in HIV cure research in the United States.[42] Clinician-researchers and policy-makers/bioethicists were recruited by email using a convenience sample. Policy-makers/bioethicists were recruited from regulatory agencies or institutional review boards involved in regulating or reviewing HIV cure research in the United States.

Data collection

The lead author conducted the interviews, which lasted between 30 and 75 min, from September 2015 to January 2016, either by telephone or in person. All interviews were conducted in English and audio-recorded, except for one participant who declined recording, but accepted note-taking. The interview guide included questions regarding ATI perceptions, motivations for undergoing or conducting ATIs, concerns around ATIs, and considerations for the effective and ethical implementation of ATIs in the United States. Respondents were provided a fact sheet explaining the study objectives. Interviews were conducted until saturation occurred, with consideration to ensuring the purposive sampling scheme.

Ethics statement

The University of North Carolina at Chapel Hill IRB approved the study (study #14-2672). Respondents provided their oral informed consent to participate. Oral consent was IRB approved and documented. No compensation was given for participation in interviews.

Data analysis

We transcribed the recorded interviews verbatim. One researcher reviewed the transcripts for completeness and accuracy by comparing the audio recordings against the typed transcripts. To protect informants' identities, we redacted all personal identifiers. We used a combination of grounded theory (to understand the realities anchored in the view of respondents) and phenomenology (to capture the essence of a phenomenon or the lived experiences of individuals)[44] as our methodological approaches. We used applied thematic analysis[45] combining a priori and emergent codes to analyze the data. One researcher applied the thematic codes to the data, and a research assistant subsequently examined all codes and transcripts to determine agreement with the first coder. Discrepancies were resolved by discussions between the two coders to reach consistency in interpretation of the data. We used MAXQDA software (version 12.1.3) for analysis.

Results

We interviewed 12 PLWHIV, 11 clinician-researchers, and 13 policy-makers/bioethicists. PLWHIV (seven males and five females) were 18 years of age or older and were generally interested in HIV cure research. One (8.3%) PLWHIV experienced an ATI as part of an HIV cure clinical study and three (25%) experienced ATIs because of personal circumstances or nonadherence. We did not collect detailed demographic variables from the study participants.

Our qualitative data revealed four main themes across all three stakeholder groups. First, there was little consensus on when ATIs would be ethically warranted. Second, the most frequently perceived hypothetical motivators for participating in research on ATIs were advancing science and contributing to society. Third, risks related to viral rebound were the most prevalent concerns related to ATIs. Stakeholders suggested ways to minimize the risks of ATIs in HIV cure research.

Perceptions of ATIs

There were divergent responses in whether stakeholders thought ATIs should be conducted in HIV cure research in the United States. Approximately half of the clinician-researchers and policy-makers/bioethicists supported ATIs

Table 1. Notable Results from Human HIV Cure Studies Involving Analytical Treatment Interruptions

Study types	*Notable results*	*Select references*
Allogeneic stem cell transplants Strategy involves producing new HIV-resistant cells	Timothy Brown is the only known case of sterilizing cure following allogeneic stem cell transplant from donor homozygous for the delta-32 deletion in the CCR5 allele. Timothy Brown remains without viral rebound after treatment cessation to this day; it has been 10 years.	18
	Boston Patients received an allogeneic stem cell transplant with donors heterozygous for the delta-32 deletion in the CCR5 allele, followed with reduced conditioning. ATIs occurred at 4.3 and 2.6 years after the stem cell transplant, and participants experienced rebound viremia after 12 and 32 weeks of treatment. Both participants developed symptoms consistent with acute retroviral syndrome and one patient developed a new efavirenz resistance. The study showed that viral rebound could occur despite a minimum 3-$\log_{10}$ reduction in the HIV reservoir size.	20,21
Gene modification studies Strategy involves removing key elements the virus needs to invade cells	Limited examples until gene therapy interventions start showing signs of efficacy. Zinc-Finger Nuclease Study: Treatment interruption used after infusion of autologous CD4+ T cells in which CCR5 gene had been rendered dysfunctional with zinc-finger nuclease (ZFN). 6/12 participants underwent 12-week ATIs that began 4 weeks after infusion. Viral load became detectable in 4/6 participants 2–4 weeks after ART cessation and peaked at 6–8 weeks. ATIs were terminated prematurely in two participants. Viral load set point decreased in 4/6 participants who underwent ATIs.	35
ART during acute or primary HIV infection Strategy involves the acute phase of HIV infection (Fiebig I–IV)	Posttreatment Control Studies: Long-term therapy viral load control is possible in a minority of study participants. Study participants with low HIV DNA levels at ATIs are more likely to maintain viral control for long periods.	19,24–30
Pediatric studies Strategy involves infants infected with HIV	Viral Rebounds in Infants: Viral rebound following treatment cessation in infants. The Mississippi child had the longest HIV remission (27 months). Randomized clinical trial involving treatment interruption after 2-year ART initiated in early HIV in infancy showed limited durability of HIV remission (no infant had posttreatment viral control).	22,39
Chronic HIV infection Strategy involves people who have lived with HIV for a long time (>6 months).	Pooled analysis of treatment interruption studies from the AIDS Clinical Trials Group (ACTG) demonstrated that the size of the active HIV reservoir, as reflected by cell-associated HIV RNA (ca-RNA) and residual plasma viremia, was predictive of the timing of viral rebound after treatment interruption.	31
Immune-based approaches Strategy involves strengthening the immune response to enable destruction of newly infected cells	ATIs used to assess outcomes in immune-based trials—including changes in CD4+ counts and return to viral set points–with various outcomes. Examples include Vacc-4x Phase II, peptide-based randomized control trial (ATIs at week 28 for up to 24 weeks), or dendritic cell vaccine studies (ATIs at weeks 12 and 24 to assess decrease in viral load set point). Studies involving antibodies and ATIs are ongoing [VRC-01, 3BNC117, vedolizumab (anti-$\alpha^4\beta^7$ integrin antibody), among others], and most remain in the preclinical phase.	33,34
Latency-reversing agents Strategy involves forcing latent HIV out of resting state so the virus can be released and then cleared by the immune system	ATIs not widely employed with latency-reversing agents. Despite possible disruption of latency, latency-reversing agents have not been associated with a substantial reduction of the size of the replication-competent HIV proviral DNA reservoir to date. Following administration of latency-reversing agents (mix of vorinostat/hydrochloroquine/maraviroc) + ART versus ART alone in acutely infected individuals, all acutely treated participants had viral rebound after ATIs.	79–81
HIV reservoir studies Studies predicting the effect on HIV reservoir reductions on the likelihood of rebound prevention over time	The exact degree of reservoir reduction needed for viral suppression off treatment remains unknown. Findings indicate >2,000-fold reductions in the size of the replication-competent HIV proviral DNA reservoirs are required to permit the majority of HIV cure participants to interrupt ART for 1 year without rebound, but rebound may occur suddenly after multiple years. Above 10,000-fold reductions may be required to prevent rebound altogether. Furthermore, participant outcomes are highly variable and HIV reservoir assays remain limited. A large number of participants ($n=40$–150) will be needed to more accurately predict the reservoir-reducing potential and ATI outcomes of new therapies.	36,38

ART, antiretroviral therapy; ATI, analytical treatment interruption.

under specific conditions. A clinician-researcher stated the following: ''ATIs remain the best outcome measures that we have and we need to deploy them very thoughtfully and carefully.'' Clinician-researchers and policy-makers/bioethicists thought ATIs could be done only if participants were clearly informed about the potential risks of ATIs, including the increased risks of adverse events, the possibility of developing resistance to antiretroviral treatments (ARVs), or the risk of transmitting HIV to sexual partners. Clinician-researchers mentioned the need for intense frequent monitoring of the study participants to assess viral rebound and the need for resumption of treatment as soon as the viral load increases above a specific threshold. A clinician-researcher explained his rationale for supporting ATIs:

> ''I think they can be done cautiously and with very careful monitoring. Because if they're not done, I don't think [that] we will be able to convince anybody that we have achieved an ART-free remission… We really do have to move forward with ATIs as the key indicator of whether we have achieved what are striving for … But I think that if it is done carefully, it can occur. There is proof in the literature that ATIs can be done carefully and not expose people to risk.'' —Clinician-Researcher

One of the clinician-researchers believed that ATIs were helpful clinical endpoints to determine whether sustained ART-free remission has occurred. He explained that the success of interventions aimed at achieving ART-free remission will be judged by their ability to show clinically meaningful results. Another clinician-researcher said that ATIs may carry fewer risks than some of the HIV cure interventions under investigation. Similarly, some of the policy-makers/bioethicists believed that ATIs could be done, and ''would be just like any other risk in the study.'' A policy-maker/bioethicist said that biomedical scientists would need to take the risk profile of the intervention into account, including the impact of the intervention and its proven ability to deplete the HIV reservoir, as well as the scientific evidence of safety and efficacy at any given time.

In contrast, around half of the clinician-researchers and policy-makers/bioethicists thought ATIs should not be performed at all, due to concerns about their scientific and ethical justification. A clinician-researcher performing gene therapy research expressed concerns about using ATIs because of the almost guaranteed relapse if study participants stop taking therapy. He explained that limits of reservoir detection are not sensitive enough to determine whether the investigational intervention removed all latent HIV proviruses from the body. Another clinician-researcher explained that there might be no clinical benefit of reducing the size of the HIV reservoir. He explained that some HIV cure protocols rely on very sensitive assays, such as the quantitative viral outgrowth assay, making ATIs unnecessary, since contemporary assays can determine whether experimental agents had any effect on the size of the HIV reservoir. Similarly, a policy-maker/bioethicist mentioned that reservoir assays remain useful surrogate endpoints in trials that continue ART. Using surrogate endpoints would decrease the potential risk of ATI-related harms.

Many stakeholders said that latency-reversing agent monotherapy studies and pediatric studies should not use ATIs. Most clinician-researchers and some policy-makers/bioethicists noted that ATIs should not be used with latency-reversing agents alone because of insufficient effectiveness data. For studies involving latency-reversing agents alone, a clinician-scientist noted, ''it is best to rely on reservoir assays and not combine these experimental latency-reversing compounds with treatment interruptions, given the overall compounded risks.'' Second, some clinician-researchers and policy-makers/bioethicists stated that ATIs should not be used as part of pediatric HIV cure research, with either newborns or children. A clinician-researcher said that it is premature to implement ATIs in the pediatric population, explaining that there are risks of drug resistance with perinatally infected children who will need to take ART for the rest of their lives. If treatment is interrupted and resistance to the current regimen emerges, the children will have one fewer option for the rest of their lives.

While most PLWHIV perceived ATIs as too risky for them personally, they believed ATIs could still be useful in general. Some of them explained that they worked hard to achieve undetectable status. This was the case for around half of the respondents, who have been infected with HIV for a long time. Some PLWHIV had experience with early HIV drugs that were highly toxic and not as efficacious as current treatment, including azidothymidine and didanosine. They would not be willing to risk losing their undetectable status as part of an ATI. Others explained that their treatment options were already limited, and an ATI could induce further resistance. Some PLWHIV were proud of their high CD4+ count and would not be willing to risk clinically regressing or having a viral increase due to an ATI. Another subset of PLWHIV expressed anxiety with stopping treatment since their treatment has been lifesaving up to now, and they would not participate in HIV cure research if the protocol required an ATI. Table 2 summarizes perceptions on ATIs.

Motivations for undergoing or conducting ATIs

Advancing scientific progress and contributing to science and society emerged as the most frequently cited perceived hypothetical motivators for undergoing or conducting ATIs in HIV cure research across all three stakeholder groups. Scientific progress was a strong motivator for undergoing or conducting ATIs. A clinician-researcher expressed that, if a clinical protocol requires ATIs, ''we need to make sure that we are going to learn something.'' A policy-maker/bioethicist mentioned that ATIs would become more relevant when there are major breakthroughs in science, such as proof-of-concepts established in animal models. As the potential for direct clinical benefits or efficacy increases (e.g., HIV reservoir reduction), he explained, so would the appeal for implementing ATIs. The topic of drug holidays and treatment fatigue as motivating factors to undergo ATIs also emerged in some of the interviews. A policy-maker/bioethicist explained as follows:

> ''[Some] people have different reservations about taking drugs. For example, in the START trial, when they started enrolling, patients [participants] did not have trouble being randomized to delaying treatment. They found more people who wanted to delay treatment. My caution would be that we should not presume that all patients are really excited about being on treatment all the time. Some people may be glad to be off the drug for some time … People have different attitudes.'' —Policy-Maker/Bioethicist

Table 2. General Perceptions of Analytical Treatment Interruptions (People Living with HIV, Clinician-Researchers, and Policy-Makers/Bioethicists, $N=36$), United States (2015–2016)

Topics	*Stakeholder types*	*Quotes*
ATIs can be done	Clinician-researcher	''They can be done. … [We] need to explain the risks and how they will be monitored and we need to resume treatment immediately if we reach a certain threshold. We need to explain resistance and give them options. … There are people out there who are ready to take a break from their meds if it would help figure out some answers''
	Clinician-researcher	''To put a finer point on that discussion, ATIs are by far the outcome measure of choice if we were to study interventions. Every other measure is really a surrogate. Of course, what we want to do is stop therapy, so there is no better test. That being said, the current LRAs that we have in the pipeline, the likelihood of seeing anything useful is too low and I don't think ATIs should be part of these trials given the low efficacy of these drugs ex vivo. We are not seeing complete elimination of the reservoir, and knowing how the reservoir behaves, we have guarantee that the virus will return at some point. ATIs in this context do not help us much in advancing the field given the modest effects ex vivo, while we know that they carry some risks to patients; I don't think that's acceptable. This does not mean that we won't have combination approaches that would be more promising in the future. ATIs are the best outcome measure that we have and we need to deploy them very thoughtfully and carefully''
	Clinician-researcher	''They can be done under close monitoring as long as the participants understand the potential risks. I think that ATI increases the risks of cardiovascular events in people who are HIV-positive. If [you] start with someone who is healthy and have low risk of cardiovascular event and if [you] monitor them closely and put them back on treatment as soon as they rebound to say 10,000 copies/mL, then I think it's acceptable as long as the participant is informed of the risks and agrees/accepts the risks. The risks are smaller than some of the risks associated with the procedures we are talking about''
ATIs should not be done	Clinician-researcher	''My personal opinion is that it should not be done at all until we have more evidence due to risks of drug resistance because perinatally infected children take ART for a lifetime. If they interrupt therapy and develop resistance right now, we don't have any other options. They are still facing lifelong therapy and this gives them one less option. … Until we have a systematic way of taking people off treatment and monitor closely what is happening, then I don't think that we are going to understand what is happening after treatment interruption''
	Clinician-researcher	''I am very concerned about treatment interruption … If you take these patients off therapy, you find out that you did not take out all the virus, but … you reset sort of the entire reservoir back to its originally full level; once the reservoir reactivates and recedes, it sort of goes back to 100% and you have sort of lost your … benefit. So I worry that there is a danger in these ATIs. So one thing that [name of laboratory] is working on is to develop even more sensitive ways to measure the reservoir so that we can really limit ATIs to patients that [who] you truly believe are probably cured so that we don't put people in an unnecessary risk of losing the … benefit that they've gained by participating in a trial''
Perspectives of PLWHIV	Persons living with HIV	''It would be too risky if I had to stop taking my ART medications''
		''My T-cells have maintained at around 350 for the past 10 year going off my treatment at this point might be too risky''
		''With being undetectable I think it would be reckless to stop HIV therapies that make you not contagious which prevents the spreading of HIV''
		''I'm scared to stop treatment. I would not participate if I have to stop my medication. I may die''

PLWHIV, people living with HIV; LRAs, latency-reversing agents.

A PLWHIV explained that she/he went off treatment because it was mandated by the stem cell transplant HIV cure research protocol in which she/he participated. He would not have been able to join the study if he had refused to be off treatment. In this case, there was a desire to comply with the study requirements and to help science. Other PLWHIV interviewed mentioned that helping society and generating scientific evidence would be the most important motivators for them. For example, a PLWHIV said, ''the motivational thing would be to help find a cure.'' Another PLWHIV would be motivated by the scientific evidence and high prospect of cure: ''If I saw the evidence that it [a cure] is likely, it would persuade me..'' Yet another PLWHIV stated the following:

''If you are healthy and you are virally suppressed, seeing how the immune system will attack that HIV and not increase would be a great thing. [It] would be an interesting thing to see that they are other things that I can do to stay virally suppressed other than take medications.''—Patient-Participant

A PLWHIV explained her prior experience with treatment interruptions outside the clinical research context. Because she previously maintained a stable CD4+ count off treatment and became rapidly undetectable after resuming treatment, she would not be afraid to go off treatment again:

''[T]hey took me off the medications for three years. And for three years, my CD4+ count never dropped below 550. So for me, including my story, that would be something that I would be willing to do because I know what it looks like to be off medication for three years.''—Patient-Participant

Some PLWHIV also mentioned that financial incentives motivated participation in ATI-related studies. A couple PLWHIV mentioned monetary compensation as a motivator for joining HIV cure studies involving ATIs. A patient-participant stated the following: ''One motivator would be money. It would be less expensive not having to take meds for 6 months.''

Another patient-participant was motivated by the opportunity of having a safer form of treatment interruption given his/her life circumstances:

''You had mentioned something about the burden of having to go without your medication for a certain time, to be in certain studies and… the only way I would consider that, and this is honest with my life, there was a period of time when I did not have a job, and I did not have insurance. … So, I was like, if at least I'm not gonna have the ability to access medication, let me be in a study that monitors me while I'm off medication and that's when I found this study … [at the] NIH where they were actually studying people who were off their medication, and that's pretty much the only circumstance that I can think of, unless I know I only got a certain number of months to live or something anyway…''—Patient-Participant

Table 3 summarizes perceived motivations for undergoing or conducting ATIs.

ATI concerns

Analytic treatment interruption concerns centered on the risks of viral rebound. Concerns about unknowingly transmitting HIV to sexual partners were expressed by clinician-researchers, policy-makers/bioethicists, and patient-participants.

Clinician-researchers focused on the biomedical aspects of virologic rebound. One concern related to the lack of knowledge around the kinetics of viral rebound since virus can reemerge from single or multiple clones, leading to increased viremia. Additional concerns related to the repopulation of the HIV reservoir, virus diversification, and

Table 3. Perceived Motivations for Undergoing or Conducting Analytical Treatment Interruptions (People Living with HIV, Clinician-Researchers, and Policy-Makers/Bioethicists, $N=36$), United States (2015–2016)

Topics	*Stakeholder types*	*Quotes*
Scientific progress	Clinician-researcher	''And I do think if that we are gonna be doing ATI studies, we have to make sure that we are going to learn something–these should be done with great care''
	Policy-maker/ Bioethicist	''If it were me, it would be a breakthrough in science with a proof-of-concept in an animal model. Something really could have the potential for clinical benefit …''
ATIs are per protocol	Patient-participant	''Going off treatment was the protocol. Without going off treatment, I would not be able to participate in the study. That was the entire premise of the study. Well, I should not say that. Going off treatment, going off medication was the only way to see whether the premise of the protocol would work … My specific participation in the research protocol was predicated on coming off treatment. If I did not come off treatment, there was no protocol for me''
Helping find a cure/altruism	Patient-participant	''The motivational thing would be to help find a cure … Knowing that you are doing well and you are healthy and that you are a part of something that may help a lot of people in the future''
	Policy-maker/ Bioethicist	''Solidarity with the community. Wanting to help … Would be just like any other risk of the study … If [it's] part of the study and can benefit science and they want to help out the cause''
	Policy-maker/ Bioethicist	''These are for people who have a deep scientific or social interest in HIV research''
Past experience with HIV treatment or treatment interruptions	Patient-participant	''They took me off the medications for three years. And for three years, my CD4+ count never dropped below 550. So for me, including my story, that would be something that I would be willing to do because I know what it looks like to be off mediation for three years''
	Patient-participant	**''**I would have no problem interrupting treatment in a minute. When I started taking meds, I became undetectable almost immediately and I have been on the same regimen for 7+ years. So I think you got to reach the people who are like me''
Financial incentives	Patient-participant	**''**One motivator would be money. It would be less expensive not having to take meds for 6 months''
	Patient-participant	''For some people, money is a motivator''

impairment of the HIV-specific immune responses during relapse. Clinician-researchers discussed ways to minimize risks during ATIs, but recognized that risks could not be eliminated. A clinician-researcher mentioned the need to employ sensitive assays to detect recrudescence, which requires frequent study visits. Another clinician-researcher explained that if ATIs are employed, scientists will need to find ways to also enhance the immune system in a durable manner to prevent viral rebound.

From the perspective of most policy-makers/bioethicists, the lack of predictability and great scientific uncertainty around viral rebound was concerning. Policy-makers/bioethicists worried about the emergence of drug resistance, due to the threat to both the study participants and the broader public, particularly if the emergent resistance is not immediately recognized. Another concern related to the difficulty of making HIV cure cost-effective because of the need for frequent monitoring and viral HIV testing: ''Spontaneous failures can have a huge impact on when and whether interventions can become cost-effective.''

PLWHIV expressed concerns with the fact that they would unknowingly transition from being undetectable to being detectable, describing the phenonemon as ''a ticking time bomb.'' In terms of transmission risk, one PLWHIV asked about the personal burden she would feel of joining an HIV cure study that involved an ATI: ''Is it too much of a burden to be in a treatment interruption cure study knowing that you could potentially infect someone?'' PLWHIV also mentioned the risk of developing resistance to ARVs and the risk of developing opportunistic infections. A PLWHIV recognized that ATIs should not be recommended for heavily pretreated participants without numerous other options: ''[o]bviously, for people like me who are on salvage therapy, or third line regimen, I would not even recommend anybody to [undergo] ATIs.'' Most PLWHIV were concerned about switching medications if HIV resistance developed because of the challenges of getting accustomed to new regimens. Two PLWHIV raised concerns around criminalization laws for transmitting HIV in the context of ATIs. Table 4 compiles stakeholders' ATI concerns.

ATI considerations and safeguards

Clinician-researchers, policy-makers/bioethicists, and patient-participants offered extensive precautions to minimize the risks of ATIs. The most repeated consideration was the need for intensive and frequent monitoring during ATIs, particularly viral load and CD4+ count. The three groups of stakeholders mentioned the need for a back-up ART option available for study participants if resistance develops, establishing clear criteria for reinstituting antiretroviral treatment, such as predetermined CD4+ and HIV RNA thresholds, and providing clear and concise adequate information to study participants about the risks of ATIs.

Clinician-researchers focused on study design issues and clinical considerations, such as the need for a demonstrated substantial reduction in the size of the HIV reservoir before interrupting treatment. Clinician-researchers also stated that the research on sensitive measures of the HIV reservoirs must continue. A clinician-researcher mentioned that a matrix describing when ATIs may be appropriate would be useful, including scenarios when ATIs should not be implemented, such as pediatric studies and those involving latency-reversing agents alone. A clinician-researcher mentioned that scientists need to start thinking about how ATIs would actually work in the real world as opposed to an experimental setting, as these would require frequent HIV testing and an increased burden on healthcare systems.

Policy-makers/bioethicists focused on the types of participants who should enroll in treatment interruption studies, such as those with an appropriate CD4+ count threshold before the ATIs. A policy-maker/bioethicist provided specific conditions for the effective and ethical implementation of ATIs, including minimum duration of ATIs to test hypotheses and counseling of study participants on HIV risk

Table 4. Perceived Concerns Related to Analytical Treatment Interruptions (People Living with HIV, Clinician-Researchers, and Policy-Makers/Bioethicists, $N = 36$), United States (2015–2016)

Concerns shared between clinician-researchers, policy-makers/bioethicists, and patient-participants
• Risk of transmitting HIV to others during an unsuspected relapse of viremia
Concerns from clinician-researchers
• Kinetics of viral rebound and viremia are unknown
• Virus can reemerge from single or multiple clones, leading to increased viremia
• Participants can be asymptomatic during viral rebound (e.g., Mississippi child)
• Risks of repopulation of the HIV reservoir, virus diversification and impairment of the HIV-specific immune response (during viral rebound)
• Assays must be sensitive enough to measure recrudescence and study visits must be frequent
• Need to find ways to enhance the immune system in a durable manner during analytical treatment interruptions
• Risks of analytical treatment interruptions can be minimized, but not completely eliminated
Concerns from policy-makers/bioethicists
• Unsuspected drug resistance could spread, causing public health problems
• People who have lived with HIV for a longer period of time may be more concerned with treatment interruptions because they have fewer treatment options available
• ''Spontaneous failures have a huge impact of when and whether interventions can become cost-effective''
Concerns from patient-participants
• Study participants can unknowingly go from being undetectable to being detectable (''ticking time bomb'')
• Risk of developing resistance to ARVs
• ATIs not recommended for patients on salvage therapy
• Increased risk of opportunistic infections

ARVs, antiretroviral treatments.

transmission during ATIs. Most policy-makers/bioethicists also wanted proven efficacy of the interventions in reducing the HIV reservoir size before ATIs. A policy-maker/bioethicist said that more research is needed to establish a relationship between reservoir assay results and time to viral rebound in clinical studies.

Most patient-participants, in turn, wanted adequate study designs, medical support, and monitoring during ATI protocols. For example, a patient-participant said the following:

> ''Just the constant follow-up is very important. Especially considering the sterilizing cure or the functional cure where the person would have to go off of their HIV treatment is a very scary concept. We need to make sure that folks who are participating in HIV cure research and who are being followed through are constantly being supported to make sure that they do not fall in between the lines and that their HIV viral load does not spike or anything like that.''—Patient-Participant

Other narratives centered on minimizing the burdens of frequent study visits, including inconvenience of study visits, which may be in tension with the need for close monitoring during ATIs. A PLWHIV mentioned that a back-up safety plan would need to be in place before joining studies involving ATIs. Table 5 compiles the considerations around ATIs from stakeholders' perspectives.

Discussion

Our findings examine perspectives of various stakeholders of HIV cure studies involving ATIs in the United States and complement the emerging willingness to participate literature.[40–42] The research also extends the HIV cure social sciences literature by focusing on ATIs in the United States.

Our study revealed variability in perceptions of ATIs in the context of HIV cure research in the United States. From our interviews, there was an inherent tension between clinician-researchers and policy-makers/bioethicists about whether ATIs were appropriate in HIV cure studies. Some believe they were justified under specific conditions that required frequent close monitoring. Around half of the clinician-researchers and policy-makers/bioethicists believed that they should not be performed at all. This finding is surprising because HIV remission cannot be proven without ATIs. Opposition to using ATIs was strongest in studies using latency-reversing agents alone and pediatric HIV cure research. Our data are consistent with quantitative surveys that showed that PLWHIV place high value on viral suppression as it reduces the risk of HIV transmission[42] as well as disease progression. Study narratives also revealed that PLWHIV who have lived with HIV for a long time and had more difficulty becoming undetectable with older drugs appeared to be less willing to undergo ATIs. This is also consistent with survey results that showed less willingness to undergo ATIs among people self-perceived to be medically vulnerable.[40,42] Moving forward, it will be important to adopt a patient-centered approach when assessing the need for ATIs, as there appear to be tensions between conservative attitudes among PLWHIV toward ATIs, and a more liberal acceptance of ATIs among some other research stakeholders.

Table 5. Considerations for Effective and Ethical Implementation of Analytical Treatment Interruptions (People Living with HIV, Clinician-Researchers, and Policy-Makers/Bioethicists, $N = 36$), United States (2015–2016)

Considerations shared between clinician-researchers, policy-makers/bioethicists, and patient-participants
- Provision of adequate information to study participants about potential risks during informed consent process
- Intensive and frequent monitoring (e.g., viral load, CD4+ count)
- Need back-up regimen for study participants in case ARV resistance develops during ATIs
- Provision of clear criteria for reinstituting antiretroviral treatment, including predetermined CD4+ and HIV RNA thresholds

Considerations from clinician-researchers
- Continued research to obtain sensitive measures of the HIV reservoir, including tissues
- Development of matrix for when treatment interruptions may be indicated and not indicated (e.g., indicated with early ART, therapeutic vaccinations, or if scientists think they cured someone, and not indicated with latency-reversing agents, TLR agonist studies, and pediatric studies as they face prospect of lifelong ARV)
- HIV reservoir reduction of 2 logs or less will not delay time to viral rebound by much; need at least 3–4 logs worth reduction for at least 1 year of ART-free remission
- Development of clear criteria for viral rebound endpoint versus viral set point endpoint are needed
- Accounting for patient-to-patient variability and stochastic nature of viral rebound
- Risk reduction related to monitoring analytical treatment interruption
- Determination of whether control arms should undergo treatment interruptions
- Considerations for how ATIs would be implemented in the real world as opposed to experimental setting as this would require frequent HIV testing (functional cure is more likely than sterilizing cure)

Considerations from policy-makers/bioethicists
- Determination of which participants to enroll in treatment interruption studies, including appropriate CD4+ threshold before ATIs
- Use of minimum duration of ART to test hypothesis
- Counseling of study participants on risk of HIV transmission during treatment interruptions
- Additional research to establish relationship between reservoir assays and time to viral rebound determinations

Considerations from patient-participants
- Adequate support to study participants enrolled in treatment interruption protocols
- Minimize burdens related to frequent monitoring visits (e.g., convenient parking at research sites)

TLR, toll-like receptor.

Our study uncovered hypothetical motivators for undergoing ATIs, including advancing scientific progress and contributing to science. These mirror the social science literature on HIV cure research,[40–42] yet reasons associated with willingness to undergo ATIs may be more diverse.[41] Our findings corroborate what was noted in similar research, in that, appealing to scientific altruism for ATI-related study participation may have a positive impact on study accrual.[40] The topic of advancing scientific progress as a motivator from the perspectives of all three types of informants is interesting, as it relates to the ethical criteria of scientific utility.[17,47–50] For ATIs to be justifiable, they must sufficiently contribute to improving scientific knowledge.

At the same time, among PLWHIV, there was considerable tension between motivations of altruism, advancing scientific progress, and anxiety about stopping treatment. PLWHIV interviewed displayed ambivalence to discontinuing their medications. This reflects a previous report on patient-centered HIV cure research.[51] Decisions to undergo ATIs cannot be dissociated from patients' experiences with their past or current HIV regimen.[51] In general, there was a low level of acceptability and high risk aversion toward ATIs from the perspective of PLWHIV in our study, although one PLWHIV had undergone temporary treatment cessation as part of an HIV cure clinical study (i.e., ATI) and three due to personal circumstances or nonadherence. This finding appears contradictory with quantitative surveys around willingness to interrupt treatment, where the majority of respondents reported being ''very willing'' or ''somewhat willing'' to interrupt ART.[40–42] Qualitative research may offer more nuance around reported motivations to undergo ATIs. Undoubtedly, decisions to undergo ATIs are individual choices, and may depend on how each individual patient-participant perceives his/her health status, in consultation with his/her HIV care provider. Study participants must understand that the investigational intervention may not be curative and there is risk of viral rebound, before undergoing an ATI. Individuals who have consented to participate in staged trials where an ATI is a later part of the protocol should have the potential risks associated with ATIs re-reviewed with them before undergoing the ATI, and should reconsent to the ATI before implementation.

Furthermore, a couple of PLWHIV interviewed mentioned financial incentives as being potential motivators to join studies involving ATIs. As with all clinical research, study reimbursements should recognize participant time and contribution, without creating undue inducement or distorting participants' judgments about risks and benefits.[47,52] Biomedical scientists should pay attention to the ethics of incentives in securing HIV cure research participation involving ATIs.[53]

Most of the ATI concerns expressed in our study related to the risks of viral rebound. Clinician-researchers focused on the biomedical aspects of rebound. Policy-makers/bioethicists raised public health and cost-effectiveness issues. Patient-participants emphasized the potential for clinical deterioration, the burdens of participation, and concerns related to switching treatment regimens. The biomedical risks of viral rebound have been documented in the literature and make the risk–benefit ratio of ATI studies less favorable. They include concerns around participant safety,[6] emergence of drug resistance,[23] risk of HIV transmission,[9] cardiovascular risks,[54] immune activation[54] and replenishment of the HIV reservoirs,[55] CD4+ decline, and viral rebound,[22,56] among others. These risks increase in likelihood with the duration of the ATIs. Furthermore, ART-resistant virus requires more challenging regimens, in turn augmenting adherence issues.[23] Some biomedical scientists recommend using intensively monitored antiretroviral pauses (IMAPs), which result in a reduced duration of viremia. Yet IMAPs can result in as many as three viral load tests per week, resulting in unmanageability of study visits and inconvenience for study participants.[57] Should technology ever advance to a point where frequent home testing for viral rebound markers is feasible, frequent testing during ATIs could become less burdensome and more feasible, cost-effective, and acceptable. Biomedical researchers are also intensely investigating biomarkers that will predict viral rebound[6,58] to minimize ATI-associated concerns.

The perspective of policy-makers/bioethicists on cost-effectiveness of ATIs is interesting and reflects an emerging cost analysis literature for various HIV cure scenarios.[59,60] Policy-makers/bioethicists also raised the topic of scientific uncertainty in the application of ATIs distinct from risk.[61,62] As revealed by our study, uncertainty has implications for recruiting study participants involving ATIs. How the uncertainty and risks surrounding ATIs are communicated to potential study participants may be of key importance. Yet informed consent guidelines around disclosure of scientific uncertainty remain unclear for the field of translational and clinical research as a whole.[63–66]

Some PLWHIV's concerns centered on risks of transmitting HIV to others and anxiety with switching ART regimens. These findings are consistent with quantitative surveys that revealed that risks of transmitting HIV to others discourage participation in HIV cure research.[41,42,67] Changing ART regimens is a critical choice for PLWHIV, as evidenced by similar patient-centered research.[51] Furthermore, our study did not reveal any possible perceived benefits of ATIs, such as the relief from possible side effects of the drugs.[17] Policy concerns around laws criminalizing transmission can also be consequential, particularly in an era where legal revisions may be needed.[68]

Finally, stakeholders provided considerations for the effective and ethical implementation of ATIs in HIV cure research in the United States. While the considerations are not exhaustive, and most are already being implemented in HIV cure protocols,[12] they may add to existing points of considerations and ethical safeguards around ATIs.[16,17] Clinician-researchers discussed study design issues, including the requirement for a strong scientific rationale. Their considerations reflect a growing basic and clinical science knowledge base around measurements of HIV reservoirs before ART cessation[36,38,69] and the use of immunologic mechanisms to control rebound.[37] Policy-makers/bioethicists mentioned possible precautions to protect study participants, including the most appropriate type of participants to enroll in ATI studies, and counseling on risks of HIV transmission during ATIs. Study participants focused on the role of support and minimizing personal burdens of increased monitoring study visits.[70] It may be useful for the HIV cure research field to develop guidelines for when and how to implement ATIs in various types of studies. Clearly, there should be a strong scientific rationale and some evidence of potential efficacy before implementing ATIs. As technology advances and our ability to measure the HIV reservoir, identify biomarkers of

success or failure, and interpret results improves, guidelines and considerations for ATIs will continue to evolve. HIV cure researchers implementing ATIs may also benefit from surveying other medical research fields where treatment interruptions have been applied, such as medication-free research in schizophrenia[71] or treatment cessation in solid organ transplantation research.[72]

Limitations

We acknowledge several study limitations. The validity of our study would have been strengthened if ATI perceptions were assessed as part of ongoing clinical studies. Our approach was exploratory, with interviews focusing on hypothetical ATIs. More research is needed around perceptions in the context of specific HIV cure research modalities,[17] and as part of actual HIV cure clinical studies involving ATIs. We also used a small convenience sample and the data are not representative of diverse PLWHIV populations, clinician-researchers, and policy-makers/bioethicists in the United States. We interviewed three types of stakeholders and significant groups were not represented, including HIV care providers not involved in HIV cure research, pharmaceutical companies, and funders. Furthermore, biomedical HIV cure researchers may have had a professional interest in studies involving ATIs, and their opinions may have been biased. Future research should include interviews with HIV clinical researchers or clinicians not involved in HIV cure research, or clinical researchers in health areas other than HIV with experience implementing ATIs. As in most qualitative research, it is difficult to ascertain bias in our sample and self-selection likely affected the responses. We did not provide information about ATIs before the interviews. Each study participant was interviewed only once. Longitudinal data collection would be useful as well.

The study could have been strengthened by collecting detailed demographic information, as it is likely that age, race/ethnicity, sex/gender, time since HIV diagnosis, experience with HIV treatment, and professional experience affected perceptions of ATIs. We could have included specific questions on the topic of informed consent surrounding ATIs. Scholars have recommended that informed consent forms should clearly explain the lack of direct personal benefit, the purpose of ATIs, and the contraindications for clinical care.[16,48] Biomedical scientists should also pay attention to participant's motivations for enrolling in ATI studies,[73] use the word ''cure'' cautiously, if at all,[74] and demonstrate attention to and specificity in risk descriptions.[63] Other underexplored topics in our study were the interplay between standards of care,[17,61] and prevention standards[75] in the context of ATIs, particularly given that one of the most prevalent concerns expressed by respondents around ATIs was the risk of transmitting HIV to others. Secondary HIV transmission events have been known to occur in the context of therapeutic HIV vaccine trials involving ATIs.[76]

Last, our study did not include unintended societal consequences of ATIs. ATIs could lead to the trivialization of ART by patients opting for treatment holidays. Finally, our findings are not generalizable and perspectives on ATIs may be context dependent. Capacity for HIV cure clinical research and viral load monitoring, health systems, treatment cascade, and access issues may affect perceptions around ATIs around the world, or even in various less affluent locations within the United States. Table 6 proposes possible future social sciences and ethics directions related to ATIs.

Table 6. Possible Future Social Sciences and Ethics Research Questions Related to Analytical Treatment Interruptions

Perceptions of ATIs
• How do stakeholders perceive different types of ATIs—for example viral load increase versus viral set point ATIs?
• How do stakeholders perceive the lack of predictability with viral rebounds?
• What are the implications of variable HIV infectious status on perceptions around ATIs?
• How do PLWHIV perceive the risk of becoming detectable for HIV during an ATI?
• How to PLWHIV perceive the risk of testing HIV positive or HIV negative as a result of participating in ATI studies?
• How do (serodiscordant) couples perceive ATIs?
• How do different stakeholders (e.g., HIV clinicians, HIV researchers not involved in HIV cure research, clinical researchers in other medical fields, funders, and representatives from pharmaceutical industry) perceive ATIs?
Motivations for undergoing or conducting ATIs
• What motivates participants to undergo ATIs as part of ongoing clinical studies?
• What is the role of altruism in undergoing ATIs?
• How does the one's experience with HIV treatment influence motivations to undergo ATIs?
Concerns around ATIs
• What are some of the concerns of various stakeholders around ATIs in the context of specific HIV cure clinical studies?
• What are some of the concerns of study participants around ATIs at various time points during *actual* study participation (e.g., informed consent versus follow-up visits)?
Considerations and ethical issues surrounding ATIs:
• What are some of the considerations for ATIs in the context of specific HIV cure clinical studies?
• What level of evidence must there be on potential efficacy to justify ATIs?
• How do we communicate risks and scientific uncertainty around ATIs to HIV cure study participants?
• What provisions should be in place for primary sexual partners of study participants undergoing ATIs?
• How do we assess the existence of curative misconception in the context of ATIs?
• What are some of the considerations for the effective and ethical implementation of ATIs in resource-limited settings, where treatment cascade issues may be greater?
• What are some of the possible unintended consequences of ATIs?

Conclusion

In conclusion, we explored perceptions, motivations, concerns, and considerations related to ATIs in HIV cure research in the United States. Our study bridged the social sciences and biomedical considerations around ATIs.[77] Studies using ATIs should be implemented with caution, allowing community engagement from diverse stakeholders. Stakeholder perspectives on ATIs may influence study design, regulatory approval, informed consent, and safeguards.[78] ATIs will likely continue to remain important for assessing clinical outcomes in specific HIV cure research protocols.[23,57] In terms of policy implications, there are cases when ATIs would not be indicated at this time. Overcoming challenges associated with ATIs will require further multidisciplinary cooperation.

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Availability of Data and Material

Datasets analyzed in this study were collected by researchers using a standardized interview guide customized to each category of stakeholders, namely (1) person living with HIV (PLWHIV), (2) clinician-researcher, and (3) policymaker/bioethicist.

Consent for Publication

The Non-Biomedical Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill approved the study (study #14-2672). All study participants were adults and provided informed consent.

Authors' Contributions

K.D., S.B.G., S.R., and A.S. conceived and designed the study. K.D. collected and assembled the data. K.D. and research assistant contributed to analyzing and interpreting the data. K.D. drafted the article. S.B.G., S.R., J.D.T., A.S., B.J.W., D.E., L.D., L.S., and J.T. reviewed the article for intellectual content. All authors gave their final approval.

Author Disclosure Statement

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