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## Background

An important feature of some HIV cure research designs is the need to interrupt antiretroviral therapy (ART) to assess time to viral rebound or predictors of rebound. We investigated perceptions of and willingness to undergo analytical treatment interruptions (ATIs) among potential HIV-positive volunteers as part of HIV cure-related studies in the United States.

## Methods

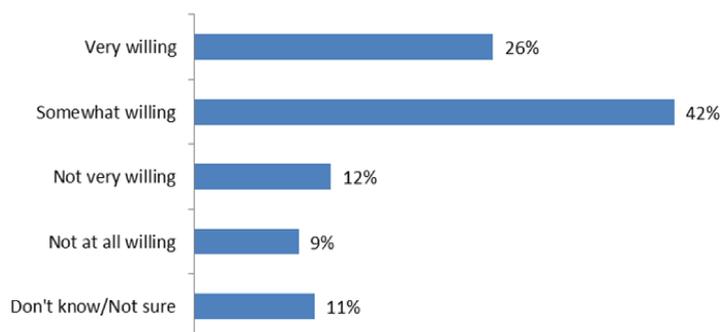
We completed a cross-sectional survey with 400 American adults living with HIV (22% females; 77% males; <1% transgenders) in September – October 2015. The sample was ethnically diverse and 38 U.S. states were represented. We also conducted key informant interviews with 12 people living with HIV and implemented 10 focus groups in 4 U.S. regions (Seattle, WA, San Francisco/Los Angeles, CA, San Diego/Palm Springs, CA and Chapel Hill/Durham, NC. We asked potential HIV-positive volunteers to provide their thoughts on the topic of treatment interruption.

## Results

### Results from U.S. Survey on Willingness to Take Risks in HIV Cure Studies

In the sample of potential HIV-positive volunteers, 98% [95% CI: 93, 100]; n = 400) were currently taking antiretrovirals. Almost half 44% [39, 49%]; n = 399) reported they had ever participated in an HIV treatment study and 7% [2, 12%]; n = 400) said they had ever been part of a HIV cure-related study. Of the survey respondents, 26% [21, 31%] were very willing to interrupt treatment, 42% [37, 47%] were somewhat willing, 12% [7, 17%] were not very willing, 9% [4, 14%] were not at all willing and 11% [6, 16%] were unsure (n = 359). Close to two thirds (65% [60, 70%]; n = 350) reported that no more HIV treatment ever would be the definition of cure to them..

### Willingness to Stop HIV Treatment as Part of an HIV Cure-Related Study (n=359)



### Motivations to Undergo Treatment Interruptions

Motivations for undergoing analytical treatment interruptions included: desire to help find a cure and for forward scientific progress, past experiences with treatment interruptions and compensation/financial incentives. A subset of potential volunteers considered treatment interruptions to be “too much risk” and expressed concerns about the possibility of viral rebound and development of resistance to antiretroviral drugs.

Themes	Quotations
<b>Protocol Mandates Treatment Interruption</b>	<i>“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. (...) 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” – Patient-Participant</i>
<b>Helping Find a Cure for HIV Infection</b>	<i>“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” – Patient-Participant</i>
<b>Past Experience(s) with Treatment Interruption</b>	<i>“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 medication for three years” – Patient-Participant</i>
<b>Financial Incentives</b>	<i>“One motivator would be money. It would be less expensive not having to take meds for 6 months” – Patient-Participant</i>

## Results (continued)

### Concerns around Treatment Interruptions

The table below summarizes the main concerns around treatment interruptions among the sample of potential HIV-positive volunteers. Given the risk of transmitting HIV to others during a treatment interruptions and an unsuspected viral rebound, a potential volunteer asked if it was too much of a burden to participate in a HIV cure study requiring treatment interruption.

#### Concerns around Treatment Interruptions from Patient-Participants

- Unknowingly going 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
- Risk of transmission to others during an unsuspected relapse of viremia

### Considerations for Ethical and Effective Implementation of Treatment Interruptions

The table below summarizes the various considerations given by key informants to ensure that treatment interruptions are implemented in an ethical and effective manner in HIV cure studies involving humans.

#### Considerations for Effective and Ethical Implementation of Treatment Interruptions

- Robust informed consent process before and during study participation; provision of adequate information to study participants about potential risks of analytical treatment interruptions
- Proper counseling to study participants on potential risks of HIV transmission during analytical treatment interruptions
- Adequate support to study participants enrolled in treatment interruption protocols
- Intensive and frequent monitoring (e.g. viral load, CD4+ count)
- Back-up regimen for study participants in case antiretroviral resistance develops
- Provision of and criteria for reinstating antiretroviral treatment
- Sustained research efforts to obtain sensitive measures of the HIV reservoir, including tissues
- Need criteria or matrix for when treatment interruptions may be indicated (e.g. immune-based therapies; early antiretroviral treatment) and when they are not (e.g. latency-reversing agents; toll-like receptor (TLR) agonists)
- Treatment interruptions are not indicated for infants as they face a prospect of lifelong antiretroviral treatment and need all treatment options possible
- Determination of when treatment interruptions and viral rebound should be a study endpoint (including time to viral rebound or viral set point)
- Clarity on whether control arms should undergo analytical treatment interruptions
- Procedures to account for tremendous patient-to-patient variability and stochastic nature of viral rebound
- Better consensus on which participants should enroll in treatment interruption studies
- Appropriate CD4+ threshold prior to analytical treatment interruption
- Planning for antiretroviral restart for clinical issues, pre-determined CD4+ or HIV RNA threshold
- Minimum duration of ART to test hypothesis
- Availability of acceptable antiretroviral treatment alternatives beyond current regimen
- Criteria for defining therapeutic success after treatment interruptions

## Conclusions

As a functional cure may be defined as ART-free remission, analytical treatment interruptions could become a clinically meaningful measure for cure. To ensure ethical utilization, it will be important to continue understanding stakeholders’ perspectives while minimizing risks of treatment interruptions. Further, study results underscore the need to better educate potential study participants about the possible risks of analytical treatment interruptions as part of HIV cure-related studies.

## Recommendations

In addition to the above considerations:

- ✓ Treatment fatigue should not be used as a way to attract volunteers in HIV cure-related studies that involve an ATI.
- ✓ To prevent sexual transmission of HIV to sexual partners during an ATI, both standards of care and standards of prevention should be applied for the study participants and his/her sexual partner(s), including adequate counseling.
- ✓ Particular care should be taken when setting financial incentives for HIV cure studies, and must balance the need for a diverse participant population and the obligation of frequent study visits and tests with the potential for coercion.
- ✓ More formative research is needed about perceptions, motivations, concerns and ethical guidance surrounding treatment interruption as part of HIV cure-related research.

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