

# COMMUNITY RECOMMENDATIONS FOR CLINICAL RESEARCH INVOLVING ANTIRETROVIRAL TREATMENT INTERRUPTIONS IN ADULTS

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**TAG**

Treatment Action Group

## INTRODUCTORY SUMMARY

- Combination antiretroviral therapy (ART) is now recommended for all people with HIV. Suppression of HIV viral load to undetectable levels by ART greatly benefits individual health—causing lifespans for many people with HIV to approach those of comparable HIV-negative individuals—and eliminates the risk of most forms of HIV transmission.
- Scientists working to develop a cure for HIV infection sometimes need to conduct clinical trials in which participants are asked to temporarily interrupt ART, which contradicts the recommendations and guidelines for people with HIV under medical care.
- The use of analytical treatment interruptions (ATIs) in the setting of research is widely considered to be a necessary step for developing a cure for HIV infection or therapies with the potential to reduce the need for ART. There is also widespread, but not universal, agreement that ATIs in clinical trials can be acceptable, as long as steps are taken to maximize the safety of participants.
- Researchers are currently developing recommendations on the use of ATIs in collaboration with other stakeholders (including community representatives), based on a consensus workshop held at the Ragon Institute in Boston on July 9, 2018. The BEAT-HIV Martin Delaney Collaboratory Community Engagement Group is also generating a position paper on HIV cure research and ATIs.
- In 2014, Simon Collins, from the treatment information and advocacy organization i-Base in the United Kingdom, led a collaborative effort with TAG and Project Inform to develop community recommendations on the use of ATIs in clinical research for adults<sup>1</sup> (<http://www.treatmentactiongroup.org/hiv/Treatment-interruption-recommendations-2014>).
- With the support of the Elizabeth Taylor AIDS Foundation, TAG has undertaken a survey of community advocates and a review of parameters in current research involving ATIs in adults, in order to offer an updated community-based perspective and set of recommendations on the topic.
- The science and ethics of ATIs in HIV cure research are the subject of an increasing amount of literature.<sup>1,2,3,4,5,6,7</sup> This report aims to contribute to the ongoing discussion and to add to the information available to people with HIV who may be interested in supporting this research as study participants.

## BACKGROUND

The medical management of HIV infection has been transformed by the advent of combination ART capable of effectively suppressing viral replication. When ART combinations involving three drugs first came into use in the mid-1990s, there was uncertainty about how best to balance the benefits of treatment with potential risks posed by drug toxicities. This uncertainty manifested in disagreements among experts and shifting guidelines regarding when people with HIV should initiate ART and whether ART should be taken continuously or could be used intermittently to maintain health.

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In 2018, the accumulated evidence clearly shows that the benefits of HIV suppression by ART vastly outweigh the risks. Guidelines now recommend the initiation of treatment as soon as possible for all people with HIV.<sup>8,9</sup> Two very large international clinical trials have contributed significantly to these developments: Strategies for the Management of Antiretroviral Therapy (SMART) and Strategic Timing of Antiretroviral Therapy (START).

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<sup>1</sup> The use of ATIs in pediatric HIV research involves consideration of a range of issues that are distinct from adults, both in terms of biology and policy, and is beyond the scope of this report. The IMPAACT Network, which is conducting the only current trial that includes the possibility of an ATI in infants (P1115), has established a specialist advisory body that is providing input on the ATI parameters.

The SMART trial specifically investigated whether ART could be used intermittently to maintain CD4<sup>+</sup> T cell counts above a threshold at which opportunistic infections are rare.<sup>10</sup> A total of 5,472 participants were randomly assigned to either continuous ART or a 'drug conservation' strategy that involved interrupting ART until CD4<sup>+</sup> T cell counts fell below 250, then restarting ART until an increase to over 350 was achieved.

The results showed that, although the overall rate of events was relatively low, the risk of serious illness and mortality was more than doubled among those receiving intermittent ART: opportunistic disease or death occurred in 120 out of the 2,720 participants, as compared with 47 of the 2,752 participants on continuous ART. The average length of follow up was 16 months.

The incidence of major cardiovascular, kidney, or liver disease was also significantly lower in recipients of continuous ART, as were instances of grade 4 adverse symptomatic events. A substudy that included 1,225 participants found that quality of life was inferior among those randomized to intermittent ART.<sup>11</sup>

Subsequent analyses revealed that the risk of negative outcomes in SMART was significantly associated with biological markers related to inflammation, particularly interleukin-6 (IL-6) and D-dimer.<sup>12</sup> Rising viral load during ART interruptions drove increases in inflammation levels.

***Since the SMART results were published, there has been an accumulation of additional evidence supporting the benefits of viral load suppression by continuous ART.***

A follow-up study reported that the risk of illness and death remained slightly elevated in the SMART interruption arm even after participants were assigned to restart treatment. The researchers noted that lingering consequences of the elevated inflammation that occurred during ART interruption might have contributed.<sup>13</sup>

The large size of the SMART trial and the strength of the evidence favoring continuous ART lend considerable weight to the results. Some researchers initially attempted to find flaws in the findings,<sup>14</sup> but these criticisms did not stand up to scrutiny.<sup>15</sup> Broadly similar outcomes have been reported in a randomized trial in West Africa<sup>16</sup> and in several observational studies.<sup>17,18,19</sup>

It's important to note that, prior to SMART, a number of smaller studies involving intermittent ART suggested that the approach might be a safe way of maintaining CD4<sup>+</sup> T cell counts. However, in at least some cases, deaths occurred that were not considered by investigators to be related to the ART interruption.<sup>20</sup> In one trial, deaths due to cardiovascular disease (CVD) were reported, but the link to interrupting ART was uncertain.<sup>21</sup> It required a trial the size of SMART to clearly demonstrate that the inflammation accompanying viral load rebound is associated with an array of health complications beyond the opportunistic infections that were thought to be the most serious consequences of HIV infection.

Since the SMART results were published in 2006, there has been an accumulation of additional evidence supporting the benefits of viral load suppression by continuous ART.

The START trial recruited 4,685 people with HIV whose CD4<sup>+</sup> T cell counts were above 500, and compared immediate initiation of ART to deferring treatment until CD4<sup>+</sup> T cell counts fell below 350 (or health complications requiring ART occurred). The benefits of immediate ART were readily apparent: endpoints of serious AIDS-related events, serious non-AIDS-related events, or death from any cause occurred in 96 participants (4.1%) in the deferred ART group, as compared with 42 participants (1.8%) in the immediate group. The Data Safety Monitoring Board (DSMB) overseeing START recommended that the trial be stopped early and all participants offered ART.<sup>73</sup> A subsequent pooled analysis of data from both START and SMART has underscored the advantages of continuous ART.<sup>22</sup>

Researchers have also looked at how an individual's cumulative exposure to detectable levels of HIV viral load affects risk of illness and death, finding that greater exposure equates to greater risk.<sup>23,24,25</sup> Most recently, cumulative exposure to HIV viral load has been shown to be significantly associated with risk of heart attacks.<sup>26</sup>

Complementing the individual health benefits of ART, there is now convincing evidence that the maintenance of undetectable viral load can prevent sexual transmission of HIV infection,<sup>27,28</sup> which has led to the transformative ‘Undetectable = Untransmittable’ (U=U) movement.<sup>29,30</sup>

## ATIS

The newfound clarity regarding the importance of viral load suppression is the backdrop against which ATIs continue to be explored in the context of research. Understandably, there are concerns about potential risks to research participants and, in some cases, their sexual partners.

Furthermore, with so much emphasis on public health campaigns promoting the importance of initiating ART and maintaining adherence, there is also the possibility of confusion caused by mixed messages: ART interruptions being strongly advised against in regular medical care, but still undertaken in some clinical trials.

*The majority opinion among scientists, research regulators, community-based advocates, and other stakeholders is that carefully performed ATIs are still permissible.*

The justification for conducting ATIs is that they are essential to the development of therapies that aim to induce long-term control of HIV in the absence of ongoing ART and, ultimately, a cure for the infection.

Animal models, particularly macaques infected with simian immunodeficiency virus (SIV), can be informative and provide a rationale for moving experimental interventions into human trials, but they’re far from perfect in predicting how an approach might work in people.

The majority opinion among scientists, research regulators, community-based advocates, and other stakeholders is that carefully performed ATIs are still permissible.

Social science studies have begun to explore the opinions of people with HIV regarding participating in trials with ATIs, and results to date suggest that many individuals are willing to take on the risk, frequently citing the altruistic goal of contributing to the development of better treatments or a cure.<sup>31,32</sup> It has also been argued that the self-agency of people with HIV should be respected when it comes to decisions about taking on risks associated with ATIs (or cure research generally).<sup>33</sup>

The two most common types of ATI trial designs are:

- Extended interruptions (often of fixed duration; for example, 12 or 16 weeks) that allow some degree of viral load rebound, with the goal of measuring how effectively viral load is subsequently controlled once it declines to a steady state, which is referred to as the set point.
- Time to viral load rebound above the limit of detection (or other specified viral load threshold) after ART interruption.

The second type—sometimes referred to as a monitored antiretroviral pause (MAP)<sup>2</sup>—is believed to have a lower risk for participants, as ART can be rapidly reinitiated as long as monitoring for viral load rebound is performed frequently.

Recently, however, there has been a shift toward designs that allow fairly high peaks of viral load rebound and then measure set points. The shift has been driven by results of experiments in the SIV/macaque model demonstrating that certain interventions induce containment of viral load for extended periods, but only after a significant burst of SIV replication occurs following ART withdrawal. Examples include a study of therapeutic vaccines combined with a TLR7 agonist (an immune-modulating agent).<sup>34</sup>

Rare individuals with HIV who exhibit post-treatment control of viral replication after ART interruption have also been documented; in some cases this control followed a transient spike in viral load.<sup>35,36</sup>

These examples have raised the concern that the effect of a therapeutic candidate could be missed if ART is restarted too quickly after viral load rebound.

The scientific literature specifically addressing the safety of ATI trial designs in the context of cure research is as yet fairly limited. A recent study led by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) reported no persistent detrimental effects of an ATI performed during a clinical trial of the broadly neutralizing antibody VRC01.<sup>37</sup> Various measures of the HIV reservoir and immune dysregulation did transiently increase during the ATI, but returned to baseline when participants resumed ART. The one exception was a possible biomarker of inflammation, the chemokine RANTES, which remained significantly elevated when analyzed an average of 363 days after restarting. The study did not obtain samples from the central nervous system (CNS), and thus could not address one of the concerns that has been raised about ATIs, which is the potential to increase HIV levels and/or inflammation in the brain (some evidence of this possibility has been documented in the SIV/macaque model<sup>38</sup>).

Several additional published studies have also noted no irreversible increases in measures of the HIV reservoir after ATI,<sup>39,40,41,42,43</sup> although one report from a trial involving an unusually long (48 week) interruption warned of a potential persistent elevation in levels of integrated HIV DNA after ART restart.<sup>44</sup>

At the 22nd International AIDS Conference (AIDS 2018), Jillian Lau and colleagues from Monash University presented a poster describing a systematic review of treatment interruptions in clinical trials.<sup>45</sup> A total of 42 studies (representing 1,597 participants) were categorized as ‘cure-focused’, and, of these, six reported adverse events, the most serious of which was a death from a heart attack, which occurred in a placebo recipient in a therapeutic vaccine trial involving a 24-week ART interruption.<sup>46</sup> The other noted complications were the development of drug resistance, acute retroviral syndrome, thrombocytopenia, AIDS defining events, and HIV-related events/symptoms. The review is in the process of being published, so more details on the specific trials and the ATI designs that they employed will be forthcoming.<sup>47</sup>

Jintanat Ananworanich, an investigator studying individuals in Thailand who start ART during the earliest stages of HIV infection, has noted that there can be social harms associated with ATIs in this context. When ART is begun very quickly after HIV acquisition, the process of seroconversion to HIV-antibody-positive can be curtailed, causing individuals to test negative on standard diagnostic tests. If they later undergo an ATI, viral load rebound can change their antibody test status by prompting seroconversion to HIV-antibody-positive. In Thailand, testing HIV-positive can be an impediment to employment.<sup>48</sup>

***There has been at least one reported case of HIV transmission to a sexual partner during an ATI, in a therapeutic HIV vaccine trial known as the LIGHT study.***

There has been at least one reported case of HIV transmission to a sexual partner during an ATI, in a therapeutic HIV vaccine trial known as the LIGHT study. The safety results were presented as a poster during the R4P conference in Chicago in 2016,<sup>49</sup> including the information that “while counseling was performed throughout the trial, one patient transmitted HIV infection during the ATI period. This transmission was confirmed by a phylogenetic analyses of the viral strains obtained from the patient and his partner.” The study investigators emphasized the importance of clearly and repeatedly conveying information regarding the risk of transmission during ATIs in future trials, and recommended that pre-exposure prophylaxis (PrEP) be offered to sexual partners “wherever possible.”

## CURRENT TRIALS

At the time of this report, 34 current clinical trials and observational studies listed in the [clinicaltrials.gov](https://clinicaltrials.gov) registry cite the inclusion of an analytical treatment interruption (see Table 1). The principal investigator of one other trial has reported that an additional ATI phase is now under consideration.<sup>50</sup>

The information in registry entries about the specific ATI criteria is typically limited, but the most common requirement for CD4<sup>+</sup> T cell count at entry is either above 500 or 450. Not all trials specify a requirement for the lowest ever CD4<sup>+</sup> T cell count (CD4 nadir), but among those that do the most frequent is a count above 200.

Exclusion criteria related to clinical status and history vary, but there are common themes:

- Hepatitis B and C co-infection (with some allowance for resolved infection).
- History of AIDS-defining/CDC category C events (in some cases within a specific time frame; for example, during the prior three years).
- CVD.
- History of cancer (often with exceptions for basal cell or squamous cell carcinoma of the skin or low grade anal or cervical dysplasia).
- Neurologic, renal, or liver disease.

In terms of approaches to assessing viral load during the ATI, nine studies cite measuring set points and eight studies fall into the category of time-to-rebound designs (one trial is evaluating both).

ART restart criteria differ based on the type of ATI design, with examples including:

- Two viral loads >200 copies/ml and/or CD4<sup>+</sup> T cell count <350.<sup>51</sup>
- Two viral loads >10,000 copies/ml, CD4<sup>+</sup> T cell count <350, evidence of disease progression.<sup>52</sup>
- CD4<sup>+</sup> T cell count <350 cells or two viral loads >200 copies/ml or above set point level (if documented).<sup>53</sup>
- Two viral loads >50 copies/ml or stage B or C AIDS-defining events or any serious non-AIDS clinical event at least potentially related to ATI.<sup>54</sup>
- Two viral loads >1000 copies/ml at least one week apart, two CD4<sup>+</sup> T cell counts <350 at least two weeks apart, CD4<sup>+</sup> T cell decline >50%, CDC B, C progression, pregnancy, or acute retroviral syndrome.<sup>55</sup>
- Viral load >50,000 copies/ml for ≥4 weeks, >30% decline in CD4 or count <350, acute retroviral syndrome.<sup>35</sup>
- Viral load sustained >100,000 or CD4<sup>+</sup> T cell count <350 or less than 50% of baseline.<sup>56</sup>

**Table 1. Current Clinical Trials Involving ATIs\***

Trial	Additional description	Trial registry identifier(s)	ATI endpoint (if specified)	Entry CD4 <sup>+</sup> T cell count	CD4 <sup>+</sup> T cell count nadir	Sponsor(s)	Location(s)	Phase
<b>ANTIBODIES</b>								
Vedolizumab	Anti- $\alpha_4\beta_7$ integrin antibody	NCT03577782		>350	None specified (NS)	Hospitales Universitarios Virgen del Rocío	Spain	Phase II
Vedolizumab	Anti- $\alpha_4\beta_7$ integrin antibody	NCT03147859		>500	>200	Ottawa Hospital Research Institute	Canada	Phase II
3BNC117 + 10-1074	Broadly neutralizing antibodies	NCT03571204	Proportion of participants meeting ART restart criteria	>450	NS	NIAID	USA	Phase I
3BNC117 + 10-1074	Broadly neutralizing antibodies	NCT03526848	Time to viral load rebound and rate of viral load rebound	>500	>200	Rockefeller University	USA	Phase I
<b>COMBINATIONS</b>								
Maraviroc, dolutegravir, dendritic cell vaccine, auranofin, nicotinamide	CCR5 inhibitor, integrase inhibitor, therapeutic vaccine, anti-proliferative + HDAC inhibitor, <b>ATI under consideration</b>	NCT02961829 (closed to enrollment)		>500	>350	Federal University of São Paulo	Brazil	Not listed
ROADMAP: romidepsin + 3BNC117	HDAC inhibitor + broadly neutralizing antibody	NCT02850016	Time to viral load rebound	>500	>200	Rockefeller University	USA, Denmark, Germany	Phase IIa
iHIVARNA, MVA vector HIV vaccine, 10-1074, romidepsin, HIVACAR01	Therapeutic vaccines, broadly neutralizing antibody, HDAC inhibitor	NCT03619278 (not yet open for enrollment)	Proportion of participants with viral load below 50 copies/ml after 12 and 24 weeks of ATI	>450	>350	David Garcia Cinca	Spain	Phase I/IIa
GTU-MultiHIV B-clade + MVA HIV-B $\pm$ vedolizumab	DNA + viral vector vaccines $\pm$ anti- $\alpha_4\beta_7$ integrin antibody in people who started ART during primary or chronic infection	NCT02972450 (not yet open for enrollment)	Time to viral load rebound or ART resumption for any reason	>600	>300	Inserm-ANRS	USA, France, Germany, Italy, Spain, Switzerland, UK	Phase I/II
DCV3 + pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV + cytokine	NCT02767193 (not yet open for enrollment)	Proportion of participants with viral load below detection at 12 weeks	>450	>350 on average during year prior to ART	Judit Pich Martínez, Fundació Clínic per la Recerca Biomèdica	Spain	Phase I
peginterferon alfa-2b + 3BNC117 + 10-1074	Cytokine, broadly neutralizing antibodies	NCT03588715 (not yet open for enrollment)	Proportion of participants with viral load below 50 copies/ml after eight weeks of ATI	>450	NS	Wistar Institute	USA	Phase I
<b>GENE THERAPIES</b>								
VRX496	Autologous CD4 <sup>+</sup> T cells modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	Viral load during ATI	>350	NS	University of Pennsylvania	USA	Phase I/II
C34-CXCR4	Autologous CD4 <sup>+</sup> T cells gene-modified to express the HIV-inhibiting peptide C34	NCT03020524	Set point viral load	>450	>200	University of Pennsylvania	USA	Phase I
CD4 CAR + C34-CXCR4 + SB-728mR modified T cells	Autologous CD4 <sup>+</sup> T cells gene-modified to inhibit CCR5 expression and express the HIV-inhibiting peptide C34 and a chimeric antigen receptor (CAR)	NCT03617198 (not yet open for enrollment)	Set point viral load	>450	>200	University of Pennsylvania	USA	Phase I



SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression	NCT02500849	Viral load at weeks 2, 4, 6, 8, 10, 12, 14, 16, and 28 during ATI	>200, <750	NS	City of Hope Medical Center	USA	Phase I
<b>GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS</b>								
Stem cells gene-modified with Cal-1	Stem cells gene-modified with Cal-1 to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT03593187 (not yet open for enrollment)				Assistance Publique - Hôpitaux de Paris	France	Phase I/II
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified with Cal-1 to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02378922 (suspended)				Fred Hutchinson Cancer Research Center	USA	Phase I
Safety of transplantation of CRISPR modified CD34 <sup>+</sup> cells in HIV-infected subjects with hematological malignancies	Stem cells gene-modified to abrogate CCR5 expression using CRISPR technology	NCT03164135	Viral load during ATI	>200, <750	NS	307 Hospital of PLA (Affiliated Hospital of Academy to Military Medical Sciences)	China	Not listed
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shl-TAR-CCR5RZ)	NCT02337985				City of Hope Medical Center	USA	Phase I
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shl-TAR-CCR5RZ) + cyclophosphamide conditioning	NCT01961063 (closed to enrollment)	Viral load during ATI			City of Hope Medical Center	USA	Phase I
Gene-therapy-treated stem cells in patients undergoing stem cell transplant for intermediate-grade or high-grade AIDS-related lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-shl-TAR-CCR5RZ)	NCT00569985 (closed to enrollment)				City of Hope Medical Center	USA	Phase I
<b>OBSERVATIONAL STUDIES</b>								
ATI to assess HIV cure		NCT02437526 (enrolling by invitation only)	Time to viral load rebound			Mayo Clinic	USA	N/A
APACHE: Monitored antiretroviral pause in chronically infected HIV <sup>+</sup> individuals with long-lasting suppressed viremia		NCT03198325	Proportion of participants not meeting ART restart criteria after 12 months	>500	NS	Ospedale San Raffaele	Italy	N/A
ACTG A5345: Biomarkers to predict time to plasma HIV RNA rebound		NCT03001128	Time to viral load rebound >1,000 copies/ml	>500	>200	AIDS Clinical Trials Group	USA	N/A
HIV-STAR	HIV sequencing after ATI to identify the clinically relevant anatomical reservoir	NCT02641756 (closed to enrollment)	Phylogenetics of rebounding viral load, kinetics of viral load rebound	>500	>300	University Hospital, Ghent	Belgium	N/A
Impact of a short-term analytical treatment interruption and re-initiation of antiretroviral therapy on immunologic and virologic parameters in HIV <sup>+</sup> individuals		NCT03225118	Time to viral load rebound	>450	>200 or >100 if >450 for past three years	NIAID	USA	N/A



TESOVIR	Tracking and exploring the source of viral rebound after ATI	NCT03117985	Genetic cartography of viral load rebound	CD4/CD8 ratio >0.5	>200	Centre Hospitalier Régional d'Orléans	France	N/A
<b>STEM CELL TRANSPLANTATION</b>								
HIVECT	HIV eradication through cord-blood transplantation	NCT02923076	Viral load after ATI			Puerta de Hierro University Hospital	Spain	N/A
Maraviroc in HIV-1+ individuals requiring allogeneic hematopoietic cell transplant	CCR5 inhibitor	NCT03118661	Viral load after ATI, functional or sterilizing cure	>250	NS	Washington University School of Medicine	USA	Phase I
<b>THERAPEUTIC VACCINES</b>								
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985 (closed to enrollment)	Set point viral load	>600	>300	French National Institute for Health and Medical Research/ French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ ANRS)	France	Phase II
THV01	Lentiviral-vector-based therapeutic vaccine	NCT02054286 (closed to enrollment)	Set point viral load	>600	>300	Theravectys S.A.	USA	Phase I/II
Ad26.Mos.HIV + MVA-Mosaic	Adenovirus and modified Vaccinia Ankara strain vectors encoding mosaic HIV antigens in people treated during acute HIV infection	NCT02919306 (closed to enrollment)	Number of participants with viral load <50 copies/ml at 24 weeks after ATI	>400	NS	Janssen Vaccines & Prevention B.V.	Thailand	Phase I
<b>TOLL-LIKE RECEPTOR AGONISTS</b>								
Vesatolimod in ART-treated HIV controllers	TLR-7 agonist	NCT03060447	Time to viral load rebound, set point viral load	>500	NS	Gilead Sciences	USA	Phase Ib
<b>TREATMENT INTENSIFICATION/EARLY TREATMENT</b>								
VIRECURE: impact of extremely early ART to reduce viral reservoir and induce functional cure of HIV infection	Combination antiretroviral therapy	NCT02588820	Proportion of participants with viral load below detection at 1, 3, and 12 months post-ATI	NS	NS	David Garcia Cinca, Hospital Clinic of Barcelona	Spain	Phase III
Peginterferon alfa-2b	Cytokine	NCT02227277	Proportion of participants with viral load rebound >50 copies/ml during ATI	>450	NS	The Wistar Institute	USA	Phase II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	Combination antiretroviral therapy, VRC01 broadly neutralizing antibody	NCT02140255	HIV remission: no viral load above detection after 48 weeks of ATI	>25% and in normal age range	Not applicable	IMPAACT, NIAID, NICHD	Argentina, Brazil, Haiti, India, Kenya, Malawi, South Africa, Tanzania, Thailand, Uganda, USA, Zimbabwe	Phase I/II

\* In some cases (particularly in trials of gene therapies for HIV-positive people with cancers) ATIs will only be conducted if study participants meet certain criteria.

## SURVEY RESULTS

A survey of community-based advocates garnered 85 responses. The majority of respondents (90%) identified themselves as HIV treatment and research advocates. A large proportion (71%) reported membership of a community advisory board (CAB) or other similar bodies that review research protocols. 61% self-identified as people living with HIV.

We asked a range of questions related to ATI trials, particularly on appropriate criteria for including or excluding participants.

On the overarching question of whether it is appropriate to include ATIs in HIV cure research, 61.7% were accepting of both set point and time-to-rebound designs, 14.8% selected only time-to-rebound, and a small proportion (4.9%) preferred only set point ATIs. Notably, eight respondents (9.8%) did not approve of the use ATIs in clinical trials. Most comments were supportive, such as the following example.

*"At this point, ATIs are the only way to prove the efficacy of any viral eradication/suppression strategy. With sufficient community input, I think it's possible to design acceptably safe trials."*

Opinions on the CD4<sup>+</sup> T cell count threshold for allowing entry into a set point ATI trial were split: in terms of the choices for specific cutoffs, most (20.5%) selected 500, consistent with the most popular criteria for current studies, followed by 350 (15.7%) and 700 (10.8%). However, the majority of respondents (37.3%) felt that the entry CD4<sup>+</sup> T cell count criteria should be based on the extent of the viral load rebound being allowed.

For time to rebound ATIs, there was a more distinct preference for the threshold of 500, which was chosen by a majority (30.9%). Flexibility based on the permitted level of viral load increase ranked next (27.2%), and a count of 350 was picked by 17.3%.

The most frequently selected nadir CD4<sup>+</sup> T cell count for either type of ATI design was 350 (23.2% for set point ATI, 32.1% time to rebound ATI). Although it is commonly used in current trials, 200 was less favored (15.9% and 16%, respectively). A substantial proportion of respondents recommended deciding CD4<sup>+</sup> T cell nadir criteria on the basis of the amount of viral load rebound (22% and 18.5%).

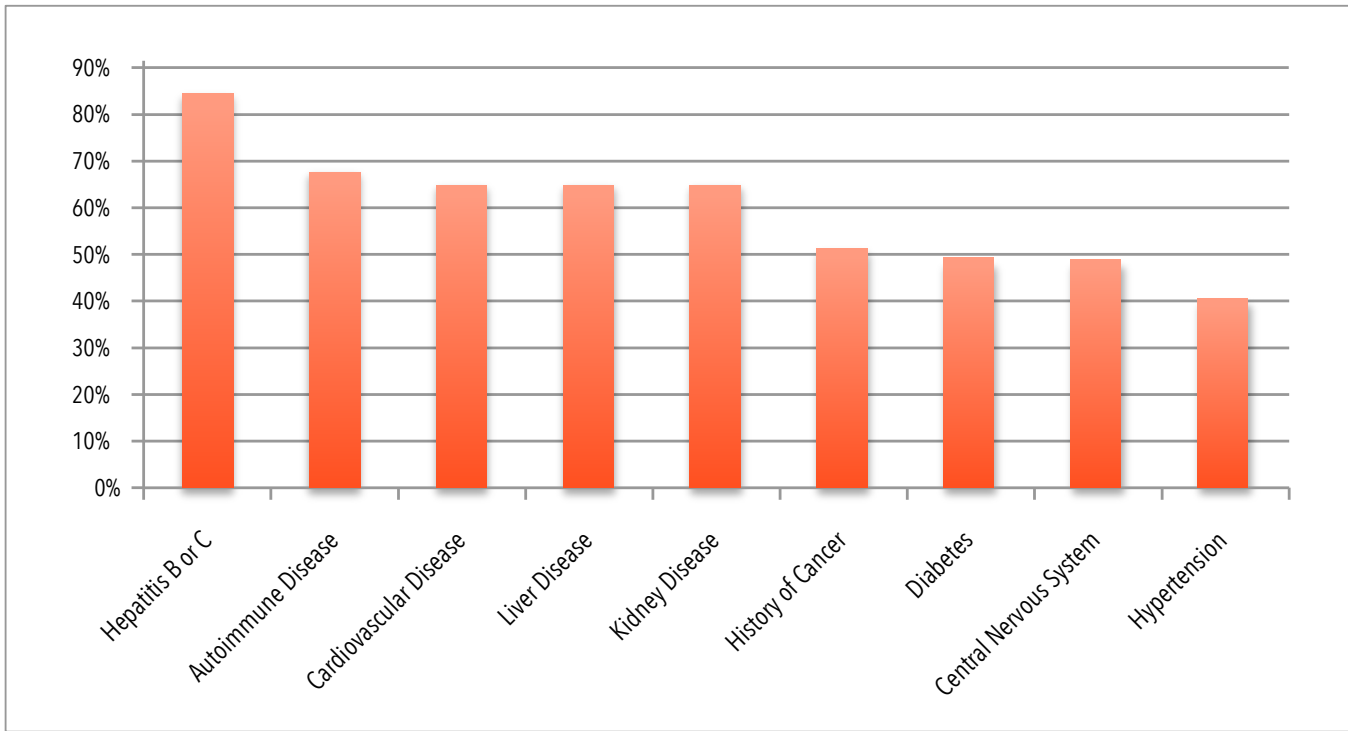
It was pointed out that some potential participants may not know their nadir, and that this shouldn't necessarily exclude them from trials.

*"There are people who we don't know their true minimum and some who hit their nadir >10 years ago who now have normal counts. Would absolutely include such individuals in studies."*

A large majority (84.3%) supported considering comorbidities when developing exclusion criteria for ATI trials.

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**Figure 1. The comorbidities cited as of most concern closely mirrored common exclusion criteria in current trials involving ATIs.**



The question of whether older age should be a factor was answered “no” by most individuals surveyed (56.6%). Several comments suggested that clinical health was a more important consideration than chronological age.

*“Only if there’s a clinically valid reason. Older long-term survivors in their 50s and 60s are often the most motivated cure study volunteers, so we shouldn’t exclude them without clinically valid reasons for doing so.”*

*“I think a ‘frailty’ definition is more important than a chronological age.”*

Smoking has been reported to be common among people with HIV, but is also strongly associated with negative health outcomes, leading to an emphasis on efforts to promote cessation.<sup>57,58</sup>

In response to the question of whether current smokers should be excluded from ATI trials, 20.5% said “yes,” an additional 25.3% selected only heavy smoking (one pack per day or greater) and 41% thought it shouldn’t be a consideration.

For recreational drug use, which might conceivably exacerbate certain risks associated with ATIs, such as CVD, 56.6% thought it should be cause for exclusion and 28.9% did not.

Replies to a series of questions regarding appropriate viral load thresholds for ATIs suggested that this sample of community-based advocates was wary of the higher rebound levels being used in some protocols. The uncertainty regarding this issue was also reflected in a higher proportion of “don’t know” answers compared with other questions.

For ATI trial designs measuring time to viral load rebound, the most frequent choices for the threshold to restart ART were “any detectable viral load” or >1,000 copies/ml (both 21.7%), followed by >10,000 copies/ml (19.3%), >50 copies/ml, and “don’t know” (both 15.7%).

There was greater hesitancy about recommending maximum allowable viral load levels for set point ATIs. The most popular selection was “don’t know” (30.5%), followed by, in descending order, >1,000 copies/ml (29.3%), 10,000 copies/ml (18.3%), 50,000 copies/ml (11%) and 100,000 copies/ml (2.4%).

***There was greater hesitancy about recommending maximum allowable viral load levels for set point ATIs.***

A majority believed viral load readings should be confirmed by a second test, which has become standard in ATI trials.

Several comments reflect the range of opinions and concerns expressed about viral load rebounds.

*“Resurgent replication is bad; it increases inflammation, which harms the immune system, major organs, and increases risk of transmission. Even low-level viral load (less than 1,000 copies/ml) has been shown in observational studies to be associated with harm.”*

*“I would discuss with both my primary care provider/infectious disease specialist and the clinical study team prior to enrolling if I needed to decide this for myself. To make this decision for the study as a whole, I suggest focus group discussion with HIV clinical specialists, HIV researchers, and HIV advocates/PLWH to review current data and recommendations, then discuss.”*

*“The bigger issue in my opinion is how to counsel participants about the fact that they may be infectious, and the effect on their sexual partners. And the legal ramifications of HIV criminalization, which varies by jurisdiction. We need reliable point-of-care testing—we should be trialing and validating those devices in these trials.”*

*“I’m not sold that there is really a ‘set point’.”*

*“Depends on the study. For example, pilot non-human primate trials have shown that subjects can rebound to high levels, but then achieve a baseline significantly below their previous set point, or even suppress virus altogether—they should be allowed to rebound to any level provided their safety isn’t compromised.”*

Quizzed on the degree of CD4<sup>+</sup> T cell decline during an ATI that should prompt reinitiation of ART, independent of any viral load measure, respondents most frequently chose a greater than 20% decline from the baseline CD4 cell T cell count (24.7%), with a drop to below 350—often cited in current trials—being the second most popular selection (17.3%). A 30% reduction from baseline, which a number of trials have used as an either/or option along with reaching less than 350, was picked by 16% of respondents. Additional choices included <500 (14.8%), <250 (13.6%) and “don’t know” (7.4%).

Because there may be a possibility of delayed adverse consequences of ATIs, we asked how long study participants should ideally be followed in a trial after restarting ART. A period of one year was considered appropriate by 37.8% of respondents, with 26.8% recommending two years and 20.7% finding six months acceptable.

To gain a sense of which possible or theoretical safety issues were of most concern, we requested that the following list be ranked from one to five (with one representing the least concern, five the most). The following list is in descending order based on the number of respondents ranking the issue as of most concern.

1. Risk of HIV transmission to an HIV-negative partner (57%).
2. Risk of developing resistance to a component or components of combination ART (46%).
3. HIV disease progression (40%).
4. Risk of increasing the size of the HIV reservoir (39%).

5. Central nervous system/brain viral load rebound (38%).
6. Acute retroviral syndrome (26%).
7. CVD/heart attacks (23%).

An additional concern described in a comment was the effects on mental health of a trial participant thinking they might be cured due to a lack of viral load rebound, only to later experience a viral load increase. This was described as “the anxiety of waiting for the other shoe to drop,” and it was noted that it has been reported by at least one research participant, Gary Steinkohl.<sup>59,60</sup>

The risk of transmission to an HIV-negative partner was most frequently ranked of greatest concern. Consistent with this, in response to the question “how important is it for research studies to include information about the potential for increased risk of HIV transmission during an ATI?,” the vast majority (86.6%) selected “very important.”

The question was also posed as to whether pre-exposure prophylaxis (PrEP) should be offered for provision to sexual partners during ATIs, with 79.5% replying “yes” and 14.5% choosing an alternate option, stating risk reduction counseling and referrals would be sufficient. One commenter pointed out that there are likely to be challenges associated with attempting universal PrEP provision.

*“I would love for PrEP to be offered to the partners of ATI participants, but do not believe this is realistic for many reasons, including unplanned encounters and multiple partner scenarios. I think counseling and referrals is the minimum that should be offered.”*

***The risk of transmission to an HIV-negative partner was most frequently ranked of greatest concern.***

At the end of the survey, we provided an opportunity to comment on several more general questions, and received a range of insightful feedback.

Do you have recommendations for ATI trials that are not covered by these questions?

*“Frequent patient feedback, INCLUDING personal, one-on-one interviews, should be an important part of this process.”*

*“I believe that all ATI trials should assess both time to viral rebound AND viral load set point in order to maximize value of the research relative to the risk undertaken by participants (unless impossible for some reason of overriding significance). This would help justify, from an ethical perspective, asking participants to take reasonable risks to advance the science.”*

*“Care should be taken to insure that sites conducting these trials have either intensive training or use new personnel to address transmission risk counseling and support. It is likely a reality that best practices don’t yet exist for this. Funds must be invested for this. These studies must include capturing of data about psycho/social harms analogous to what is being done in vaccine and other prevention trials.”*

*“Although ATIs are important part of finding a cure/vaccine, they must be done with great care, oversight, and ongoing supervision of both the trial process and frequent data collection from patients.”*

Do you have questions about ATIs that you would like to see answered?

*“1. There are compartmental issues; for example, CNS [central nervous system] versus blood versus lymphoid tissue. I hope that biopsies are done on tissues and that CNS samples are collected. 2. Also, screening for syphilis pre-ATI and during/after ATI should be done, as T. pallidum co-infection and re-infection is common among some sexually active MSM and T. pallidum penetrates the CNS and lymph nodes shortly after exposure, and this co-infection could affect time to viral rebound.”*

*“Long-term effects on secondary factors, such as lipids, kidney function, etc.”*

*“How sufficient are the methods in place in order to intervene rapidly in case of a rapid deterioration during treatment interruption?”*

*“Yes, the concept of health and wellness incorporated in ATIs studies need to acknowledge trial participants (and their partners, loved ones, and other affective communities) in more holistic terms—how will mental health and social support services be provided for those of us who will be confronting a detectable status again; and after many years of not being so? Our concerns are not only biological: how to maintain our health, how to keep our partners safe—they are also psychological: what is it to be detectable again, how do we deal with this status—and social: what does it mean to live with a detectable viral load (over the course of the study), how do we talk about this with our concerned loved ones?”*

Among the general feedback given, one respondent argued strongly that many of the detailed questions asked about ATI criteria can only be answered by scientific research, and questioned whether it was responsible to seek community input rather than wait for study results.

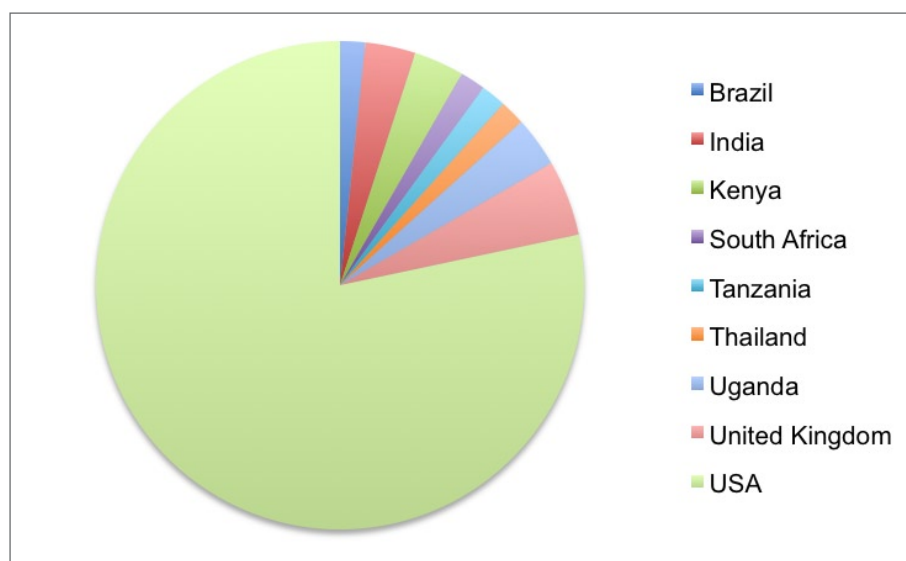
This point has some merit, but also highlights the overarching challenge of definitively establishing the safety of any given ATI approach. We now know from the SMART trial and other studies that lengthy CD4-guided ART interruptions are unsafe, but this required an extremely large sample size. The increased risk of illness and death associated with the approach was not detected in previous, smaller trials.

ATI trials typically enroll relatively small numbers of participants, with limited follow up, and therefore attempting to detect whether there might be some small difference in either short-or long-term risk associated with an entry CD4<sup>+</sup> T cell count criteria of 500 versus 700, or allowing transient viral load rebound to 1,000 copies/ml versus 50,000 copies/ml, will be extremely difficult, if not impossible.

In the absence of the ability to readily clarify these questions scientifically, researchers and other stakeholders—including regulatory agencies, funders, community advocates, and people living with HIV—are having to form opinions by evaluating the available evidence as best they can.

This informal survey, which was not submitted to an Institutional Review Board, aimed to capture a range of current opinions to inform the following set of recommendations.

**Figure 2. Survey respondent locations.**



## RECOMMENDATIONS

These recommendations represent TAG's attempt to synthesize the prior set offered in 2014 (<http://www.treatmentactiongroup.org/hiv/Treatment-interruption-recommendations-2014>) with more recent information and the opinions expressed by survey respondents. They're not meant to be proscriptive or to override the importance of input from community members not represented here, including community advisory bodies local to where trials are taking place.

We recognize that there is tension between the desire to maximize trial participant safety and the need to develop therapeutic and/or curative approaches that would improve upon the current standard of care. We also appreciate that the pool of potential research participants is finite, and that extremely conservative criteria for ATI trials might render trials difficult or impossible to enroll.

As basic principles, we believe the ethical conduct of ATIs requires:

- The use of study designs that minimize risks to participants, for example, by excluding those likely to be at highest risk of adverse outcomes.
- Provision of clear information that explains both documented and suspected possible risks of an ATI as part of the informed consent.

Potential trial participants need to be informed that:

- Interrupting treatment is not recommended in clinical guidelines.
- A treatment interruption may increase their risk of serious complications, including death.

Factors likely to influence risk include:

### 1. CD4<sup>+</sup> T cell count when interrupting treatment

**Recommendation:** For set point ATI designs involving extended interruptions, entry CD4<sup>+</sup> T cell counts should be at least 500. Higher counts should be employed whenever practical, as evidence suggests this would contribute to minimizing risk. For time-to-rebound ATI designs, an entry CD4<sup>+</sup> T cell count of 500 is also preferred, although lower counts (such as 350) may be appropriate depending on the frequency of monitoring and the viral load level used to trigger restarting ART. For both types of ATI design, the extent of viral load rebound allowed in the protocol should be a consideration when selecting the entry CD4<sup>+</sup> T cell count threshold.

### 2. The lowest ever CD4<sup>+</sup> T cell count (CD4 nadir)

*Lower CD4<sup>+</sup> T cell count nadirs are associated with faster declines in CD4<sup>+</sup> T cell counts when treatment is stopped<sup>20,61</sup> and a reduced likelihood of a return to the pre-interruption level when a person restarts treatment. In the SMART study, 18 months after restarting treatment, CD4<sup>+</sup> T cell counts remained, on average, 150 cells lower than when treatment was interrupted.<sup>13</sup>*

**Recommendation:** A CD4<sup>+</sup> T cell count nadir above 350 would be a reasonable threshold for ATI studies, but the criterion can be flexible depending on the magnitude of viral load rebound permitted in the trial design. Exceptions may be necessary in some circumstances, such as when potential participants have received interventions that transiently reduced CD4<sup>+</sup> T cell counts, or when information on the CD4<sup>+</sup> T cell count nadir is not available.



### 3. Background health

*CVD. In the SMART trial, and some prior ART interruption studies, CVD—including fatal heart attacks—was among the most common serious complication. The inflammation associated with viral load rebound is almost certainly the key contributing factor.*

**Recommendation:** Baseline cardiovascular evaluations should be conducted to reduce the possibility that individuals at risk of a heart attack are enrolled into ATI trials, particularly those allowing prolonged viral load increases. A history of CVD or a high risk based on a validated assessment tool, such as the Framingham Risk Score, should be exclusion criteria.

*Liver disease. Based on the results from SMART, people with hepatitis B or C face a higher risk of complications from interrupting ART.<sup>62</sup>*

**Recommendation:** Hepatitis B or C co-infection should be exclusion criteria for ATI trials, as is currently common practice. The safety of treatment interruptions in people with a history of hepatitis B or C that has been cured is not known; some trials allow participation by individuals with resolved infections, but this may warrant further investigation.

*Other comorbidities. Detectable viral load has been shown to impair control of comorbidities such as diabetes and hypertension.<sup>63</sup> Active autoimmune disease requiring immunosuppressive treatment is also likely to be incompatible with participation in ATIs.*

**Recommendation:** The presence of comorbidities such as diabetes, hypertension, autoimmune, and kidney disease should be exclusion criteria for ATI trials.

*History of comorbidities. The majority of current studies involving ATIs take a cautious approach by excluding individuals with histories of cancer, neurological diseases, and AIDS-defining/CDC category C events. In some cases, a timeframe is cited, for example, during the past three years. For cancer, there are sometimes exceptions for less serious diagnoses, such as basal cell or squamous cell carcinoma of the skin or low-grade anal or cervical dysplasia. Clinical trials of stem transplantation for people with HIV and cancers represent a special case requiring tailored criteria.*

**Recommendation:** Exclusion of individuals with histories of serious comorbidities appears to be reasonable for minimizing risk. Outcomes among participants allowed into trials based on serious comorbidities occurring outside a given timeframe should be carefully evaluated to ensure safety and provide guidance for designing eligibility criteria for future ATI trials.

*Age. Older individuals had a significantly increased risk of mortality in SMART.*

**Recommendation:** Older individuals (such as those over 50 years of age) should be cautioned that they may face greater risk from ATIs than their younger counterparts, and this possibility should be evaluated in studies. The risk is likely to be lower for time-to-rebound ATI designs that restart ART as soon as viral load becomes detectable.

*Smoking. Smoking was also significantly associated with mortality in SMART and could be considered as an exclusion criterion. Two completed trials of the broadly neutralizing antibody 3BNC117 that included ATIs specifically excluded “current cigarette use in excess of one pack per day,”<sup>64,65</sup> but smoking is rarely cited in the listings of current ATI trials. However, a slight majority of survey respondents favored excluding either smoking or heavy smoking.*

#### 4. The level of viral rebound during the ATI

*There is consistent evidence documenting an association between viral load rebound and markers of immune activation and inflammation. Immune activation markers have been shown to be predictive of disease progression in untreated HIV infection,<sup>66,67</sup> and the inflammatory biomarkers IL-6 and D-dimer were strongly associated with a risk of illness and death in the SMART trial.<sup>12,68</sup>*

**Recommendation:** ATI designs involving frequent monitoring and immediate ART reinitiation when viral load becomes detectable avert inflammatory consequences and are widely considered to represent the safest approach. These designs are recommended for minimizing risk, but may not be suited to assessing the efficacy of some interventions (such as therapeutic vaccines and gene therapies).

Set point ATI designs allow rebound to higher levels (in some cases to over 100,000 copies/ml for short periods) without immediately restarting treatment, and there is greater concern about potential risks under these circumstances. Careful, frequent monitoring is recommended for set point ATI designs, and stricter criteria for entry into this type of trial is justified. As the number of set point ATI trials increases, evaluation for any adverse clinical consequences is essential, both during the ATI and for as long as possible afterward.

The possibility of using of biomarkers of inflammation (such as IL-6 and D-dimer) as additional screening tools to enhance safety should be investigated.

#### 5. The CD4<sup>+</sup> T cell count level used to restart treatment in the study

*Restarting ART at higher CD4 counts should contribute to minimizing risk.*

**Recommendation:** The commonly used criteria of a decline to less than 350 or a 30% drop below baseline levels have been deemed acceptable by regulatory agencies. These parameters are recommended as a minimum, but the highest threshold that is logistically feasible should be preferred.

#### 6. The duration of the ATI

*The length of an ATI is likely to influence risk, with shorter interruptions likely being safer. An analysis of data from the SMART trial, conducted to assess the safety of an ATI design for a therapeutic vaccine trial, suggested that there is a low risk during the first 16 weeks of ART interruption.<sup>69</sup> However, it remains possible that some of the increased risk of illness and death documented in SMART represents a delayed effect of inflammatory events that occur earlier during the ART interruption.*

**Recommendation:** ATIs should ideally be restricted to 16 weeks or less, although the criteria for restarting ART may be more important for maximizing safety than the potential duration of the ATI.

### HIV transmission

*If viral load rebound occurs during an ATI, the risk of transmitting HIV is increased.*

**Recommendation:** Participants must receive clear and frequent counseling and referrals to PrEP and prevention services for partners as a minimum, and access to PrEP for sexual partners should be facilitated whenever possible.

### Interrupting ART regimens containing drugs with long half-lives

*A complex problem associated with interrupting ART is the potential variation in the amount of time different antiretroviral drugs stay in the body after the last dose. For example, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are known to persist for longer than most other antiretrovirals. An extended period*

*of suboptimal levels of an individual antiretroviral can promote the development of HIV resistance to that drug.<sup>70,71</sup>*

*As yet there is no standardized approach to ART cessation in ATI trials. Recent examples of approaches taken by researchers include switching NNRTI-based regimens to protease inhibitor- or integrase inhibitor-based regimens either two<sup>35</sup> or four weeks<sup>72</sup> prior to the ATI.*

**Recommendation:** Strategies for minimizing the risk of resistance to components of ART regimens with long half-lives must be employed in ATI trials, and efforts should be made to standardize approaches where possible. Attention should also be paid to any concomitant medications study participants are receiving that have interactions with particular antiretrovirals, as these medications might require dose adjustments in the case of ART regimen alterations and/or during ATIs.

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