Lessons learned from HIV antiretroviral treatment interruption trials

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Purpose of review
Clinical trials with an antiretroviral therapy (ART) interruption remains indispensable for assessing strategies for ART-free HIV remission. This review highlights the lessons learned from ART interruption studies so far, including the risks to the participants and implications for HIV remission.

Recent findings
Historically, analytic HIV treatment interruption (ATI) studies were commonly designed with a prolonged duration of ART interruption and with viral load set point as the primary outcome. For a variety of reasons, including participant risk, recent treatment interruption trials have frequently used time to viral rebound as the primary endpoint and have restarted ART once a predetermined viral load threshold is reached.

Through treatment interruption trials, investigators have tested the efficacy of therapeutic and curative strategies that showed promise in preclinical trials, including therapeutic vaccines, latency-reversing agents, and broadly neutralizing antibodies. In most populations, ATI trials have been well tolerated, with few adverse clinical events and no significant changes to the reservoir. Several reservoir predictors of HIV-rebound timing have been reported, with a subset of trials uncovering posttreatment controllers who can maintain HIV remission despite ART discontinuation.

Summary
Treatment interruption trials are a vital tool, but their optimal design remain uncertain and must balance participant risks with scientific rigor. The ability to predict the timing or extent of HIV rebound and identify mechanisms of posttreatment control may accelerate the development of novel therapeutics for sustained HIV remission.

Keywords
HIV, posttreatment controller, remission, reservoir, treatment interruption

INTRODUCTION
Antiretroviral therapy (ART) is effective in suppressing HIV viral load and reducing immune activation, but cannot eradicate the infection. There is intense interest in developing strategies that can lead to ART-free sustained HIV remission. Interventions that appear promising in preclinical or early-phase clinical studies will ultimately require validation through analytic treatment interruption (ATI) studies. HIV ATI trials have demonstrated that for most participants, plasma HIV rebound to detectable levels occurs in the span of a few weeks (Fig. 1) [1**] and ATI studies have been used to show that a sterilizing cure for HIV is indeed possible [2]. ATI trials have also been invaluable in testing the in-vivo efficacy of strategies for sustained HIV remission. The field of therapeutic vaccines serve as an illustrative example. A wide range of therapeutic HIV vaccines have been developed to enhance HIV-specific immune responses; several have shown induction of anti-HIV responses and clinical efficacy in animal models [3–5]. When tested in the context of human trials, however, similar efficacy in delaying viral rebound or altering viral load set point has not been demonstrated [6–13,14,15*]. Although ATI trials are valuable, they are associated with possible risks to participants and there is not yet consensus on the optimal design of ATI studies. In this review, we highlight key lessons learned from HIV ATI studies to date, with an emphasis on the evolution of ATI trials.
study designs over the past two decades, the potential risks to the participants, the search for predictors of viral rebound timing, and the identification of HIV posttreatment controllers.

TREATMENT INTERRUPTION TRIALS AS A THERAPEUTIC STRATEGY

Initially, HIV treatment interruption strategies were attempted mainly as a means of reducing participant exposure to antiretrovirals, with the hope that ATI would reduce side-effects, prolong the durability of the limited number of available regimens, and possibly boost anti-HIV immune responses [16]. However, the Strategies for Management of Antiretroviral Therapy (SMART) trial demonstrated that prolonged, repeated, CD4 count-guided treatment interruptions resulted in significantly increased risk of opportunistic infections, non-AIDS-defining events, and death [17]. Given these findings and the availability of better tolerated and easier to take antiretrovirals, treatment interruption as part of a therapeutic strategy was largely abandoned.

TREATMENT INTERRUPTION TRIALS TO TEST STRATEGIES FOR HIV REMISSION

As a mechanism to test immunologic HIV remission strategies, ATI trials have often involved predetermined lengths of treatment interruption (e.g. up to 24 weeks of treatment interruption) with variable primary efficacy outcomes based on the proposed mechanism of the intervention (e.g. the viral load set point, CD4$^+$ cell count, or meeting criteria for ART re-initiation) [6,10,18,19]. Through these trials, modest reductions in viral loads have been detected in a few therapeutic HIV vaccination studies [6,12,20–23], but their clinical impact remains uncertain.

A recently introduced treatment interruption study design has been termed the intensively monitored antiretroviral pause (IMAP), where time to viral rebound would be used as the primary endpoint and ART is restarted as soon as the viral load has reached a predetermined threshold [24]. IMAP studies showed that allogeneic stem cell transplantation without CCR5-defective donor cells can significantly delay viral rebound, but does not lead to long-term HIV remission [25]. IMAP studies have also been used to assess the impact of HIV broadly neutralizing antibodies (bNAbs). For example, passive infusion of either of the CD4-binding site-targeting bNAbs, VRC01 or 3BNC117 were found to significantly delay the timing of viral rebound, while exerting strong selective pressure on HIV-1 emerging from latent reservoirs [26,27]. Finally, IMAP trials have been used to test both latency-reversing agents (LRAs) [28], therapeutic vaccines [15,29] and combinations thereof [30,31], showing modest effects on the timing of viral rebound. There is ongoing debate over the optimal viral load

FIGURE 1. Cumulative percentage of participants who maintained virologic suppression after treatment interruption based on two viral load thresholds: 200 and 1000 HIV-1 RNA copies/ml [1**].
threshold for ART restart, which must balance the participant risks associated with prolonged viremia with missing immune-mediated viral control that can occur after initial HIV rebound.

**RISKS OF ANTIRETROVIRAL THERAPY INTERRUPTION**

When first introduced, ART interruption studies were performed to assess the benefits of reduced ART exposure on disease progression and clinical events, especially in the era of more toxic and less effective ART. In the SMART study, the use of episodic ART guided by CD4+ count was associated with an increased risk of opportunistic disease or death [17]. However, there are important aspects of the SMART study that are not part of modern HIV ATI studies, including repeated cycles of prolonged ART interruption with limited monthly laboratory monitoring. Additional safety concerns for participants undergoing ATIs include the expansion of the HIV reservoir [32], HIV transmission to partners [33], immune activation/damage [34,35], acute retroviral syndrome [36], HIV rebound in the central nervous system [37] and emerging drug resistance, predominantly in participants on nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based ART regimens [25]. There are ways to mitigate the risks of treatment interruption studies. First, a secondary analysis of SMART participants with preserved CD4+ counts demonstrated that short-term treatment interruption of 16 weeks was not associated with significant increases in clinical events [38]. This finding is supported by reports from other ATI trials reporting excellent safety records with short-term treatment interruption [6,10,18,19]. In addition, the duration of participant exposure to high-level viremia is further limited by the IMAP study design with time to viral rebound as the primary outcome and reinitiation of ART with return of viremia. IMAP studies that have been performed with participants on a protease inhibitor or INSTI-based ART have so far been found to be well tolerated and without evidence of emerging drug resistance [15*,39,40]. Importantly, recent reports suggest that short-term treatment interruption does not lead to significant expansion of the HIV reservoir or prolonged immunologic consequences after ART reinitiation [40,41**,42,43].

It should be noted that there are circumstances that may increase participant risks during an ATI. As an example, Henrich et al. described two patients with lymphoma, both of who underwent allogeneic stem cell transplantation (HSCT). Both patients were found to have successful engraftment of the donor immune cells and undetectable HIV reservoirs after HSCT despite extensive sampling [44].

After discontinuing ART, the two patients remained aviremic for 12 and 32 weeks, but both experienced subsequent high-level viral rebound and symptoms consistent with the acute retroviral syndrome. In addition, one patient was found to have emergent drug resistance mutations in the setting of suboptimal ART adherence. However, it is important to note that the posttransplant immune systems for these two patients were functionally-naïve to HIV and the rapid rebound observed was akin to that seen in acute HIV infection. This would not be expected to be the case for most participants treated either in early or chronic HIV infection. In fact, treatment interruption studies of individuals treated during Fiebig 1, the earliest stages of acute HIV infection, have observed a very low rate of acute retroviral rebound syndrome [45]. In children, the effect of brief treatment interruption on the HIV reservoir is still uncertain, especially given the prolonged decay of the HIV reservoir with uninterrupted ART [46].

**BIOMARKER PREDICTORS OF HIV REBOUND**

The identification of HIV viral load as a biomarker predictor of HIV disease progression and therapeutic efficacy of ARVs was a major advance for the field [47,48]. The use of HIV viral load as a surrogate endpoint for clinical trials of ARV efficacy significantly accelerated the development of new anti-HIV therapeutics. A corresponding biomarker predictor of HIV rebound timing and posttreatment control after treatment interruption may similarly accelerate the development of strategies for HIV remission. Such a biomarker could be used as a surrogate endpoint for preclinical and early-phase trials to assess which interventions have sufficient potential to advance into treatment interruption trials. Several such biomarker predictors have been identified so far.

In a pooled analysis of ACTG treatment interruption trials, participants who initiated ART during acute/early HIV infection and those on a NNRTI-containing regimen had significantly delayed viral rebound [1**]. Higher CD4 nadir, longer ART duration, and shorter duration of HIV infection have also been associated with modest delays in rebound timing [39]. A smaller HIV reservoir size has also been associated with delayed viral rebound. In the SPARTAC trial of early-treated participants, total HIV DNA levels were associated with time to viral rebound [49] and low baseline integrated HIV DNA level were significantly associated with viral load set point during treatment interruption in the Swiss–Spanish intermittent treatment trial (SSITT) [50]. In addition, viral remission for more than 7 months
was described in an individual who initiated ART during extremely early infection [51*]. Furthermore, the level of the expressed HIV reservoir as measured by cell-associated HIV RNA were also associated with delayed viral rebound after treatment interruption [15*,20]. Additional data supporting the assertion that reducing the HIV reservoir can delay HIV rebound are from reports of patients undergoing hematopoietic stem cell transplantation [25,52*]. Henrich et al. reported two Boston SCT patients who had at least 3 log10 reduction in the number of circulating cells harboring HIV proviral DNA after transplantation. Although most HIV-infected individuals will experience plasma viral rebound in a few weeks after ART discontinuation, these two patients did not have HIV rebound until 3 and 8 months after treatment interruption, despite harboring an immune system that was functionally naïve to HIV [25]. A second report showed similar findings in a patient who achieved HIV remission for more than 9 months after the stem cell transplant [52*]. However, this data also suggests that sustained HIV remission is unlikely to be achieved in the absence of complete eradication of the reservoir, CD4⁺ cells resistant to HIV infection, or a robust anti-HIV immune response. There is also some evidence that the host immune response can alter HIV-rebound dynamics after treatment interruption [6,53,54], although not all responses have been predictive [55], and this area remains relatively unexplored.

**THE IDENTIFICATION OF POSTTREATMENT HIV CONTROLLERS**

Treatment interruption studies have also been instrumental in identifying individuals who are able to maintain HIV suppression after ART discontinuation, a population known as posttreatment controllers (PTCs). These individuals have been most commonly identified from individuals who initiated ART during acute/early HIV infection [15*,56–60] or during early infancy [61,62], although they can also be identified in those who initiated ART during chronic infection [63,64]. The most comprehensive published assessment of HIV controllers so far has been through the VISCONTI cohort, which found that PTCs have a smaller HIV reservoir and compared with spontaneous HIV controllers, they maintain HIV suppression largely without protective human leukocyte antigen (HLA) alleles [59], and have detectable polyfunctional HIV-specific T cells [65]. However, our understanding of how PTCs achieve sustained HIV remission is largely incomplete due to how rare it is to identify these participants through any one research center or clinical trial. Although efforts are underway to identify PTCs [65], a concerted international collaboration is needed to identify the determinants of posttreatment HIV control.

**CONCLUSION**

HIV treatment interruption trials have been a vital tool in the evaluation of the efficacy of therapeutic vaccines, LRAs, bNabs and other interventions. Given the diverse portfolio of HIV curative strategies under development, such trials are only expected to rise in importance. Over the years, the design of treatment interruption studies has undergone an evolution towards shorter duration of treatment interruption and the use of timing of viral rebound as the primary endpoint. This reflects the ethical considerations of such studies [66], which weighs participant risk with a sufficiently robust testing of interventions for sustained HIV remission. However, the optimal design of HIV treatment interruption studies remains unclear, with controversies surrounding the appropriateness of a placebo arm and the ART restart criteria. Although the timing of HIV rebound has been well characterized and relatively uniform for individuals who initiated ART during chronic infection, there is far more uncertainty for those who initiated ART during acute/early infection as they are far more likely to become posttreatment controllers, complicating the interpretation of uncontrolled trials. Although treatment interruption trials are increasingly using the timing of viral rebound as the primary endpoint, the optimal viral load threshold for ART reinitiation has not been defined and will likely depend on the type of intervention. For example, therapeutic vaccines and other strategies that rely on a robust, but delayed immune response to rebounding virus may best be evaluated in trials that allow higher and more prolonged duration of viremia [12]. In addition, a lower viral load threshold for ART reinitiation may reduce participant risk, but will also likely fail to identify a subset of posttreatment controllers who exhibit transient viral rebound prior to subsequent viral control [64]. Furthermore, there remains uncertainty over the appropriate intensity of viral load monitoring after treatment interruption and whether the partners of participants should provide informed consent and/or be provided with preexposure prophylaxis if they are HIV uninfected.

In the end, the design of treatment interruption trials will likely need to be tailored to the specific intervention and the risks involved. Tackling these decisions will require a collaborative effort with input from all stakeholders, including academia, industry and the community. Finally, the identification of
biodemographic predictors of viral rebound kinetics and uncovering the mechanisms behind posttreatment control may accelerate the development of novel therapeutics for sustained HIV remission.

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Conflicts of interest

J.Z.L. has received research support and consulted for Gilead Sciences and Merck.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest ■ of outstanding interest

1. Li JZ, Etemad B, Ahmed H, et al. The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption. AIDS 2016; 30:343–353. This pooled analysis of AIDS Clinical Trials Group treatment interruption trials demonstrated that the majority of participants had viral rebound within 3–4 weeks and that levels of on-ART cell-associated HIV RNA and residual viremia were predictive of the timing of HIV rebound.


This trial reported a high frequency of sustained HIV remission in early-treated individuals undergoing ART interruption.

Progress in achieving long-term HIV remission


This study reported that short-term treatment interruption does not lead to irreversible expansion of the HIV reservoir.
45. Donn Colby NC, Eugene K. HIV RNA rebound postinterruption in persons suppressed in Reibig I acute HIV. In: Conference on Retroviruses and Opportunistic Infections. 2017, Seattle, WA, USA.

A report of a patient who initiated ART during extremely early infection and experienced HIV remission for more than 7 months during treatment interruption.

A report of a patient who underwent stem cell transplantation with a significant reduction in the HIV reservoir size and achieved HIV remission for more than 9 months after treatment interruption.