Lessons learned from HIV antiretroviral treatment interruption trials

Ying Wen[a,b], *Katharine J. Bar*[c], *and Jonathan Z. Li*[a]

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

[a]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, [b]The First Affiliated Hospital, China Medical University, Shenyang, Liaoning, China and [c]University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence to Jonathan Z. Li, MD, Brigham and Women's Hospital, 65 Landsdowne St, Rm 421, Cambridge, MA 02139, USA.
E-mail: jli@bwh.harvard.edu

Curr Opin HIV AIDS 2018, 13:000–000
DOI:10.1097/COH.0000000000000484

KEY POINTS

- HIV treatment interruption trials have been a vital tool in the evaluation of the efficacy of therapeutic vaccines, LRAs, broadly neutralizing antibodies, and other interventions for HIV remission that appear promising in preclinical or early-phase clinical studies.
- 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.
- There is ongoing debate over the design of HIV treatment interruption trials, including the viral load criteria for ART reinitiation, which must balance the participant risks associated with prolonged viremia with missing immune-mediated viral control that can occur after initial HIV rebound.
- Several HIV reservoir predictors of HIV-rebound timing have been reported; the identification of such biomarkers could be used as surrogate endpoints in preclinical and early phase studies to accelerate the evaluation of HIV remission strategies.
- Treatment interruption trials have been instrumental in the identification of HIV posttreatment controllers, but the mechanisms behind their ability to maintain HIV remission is largely unknown.

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.

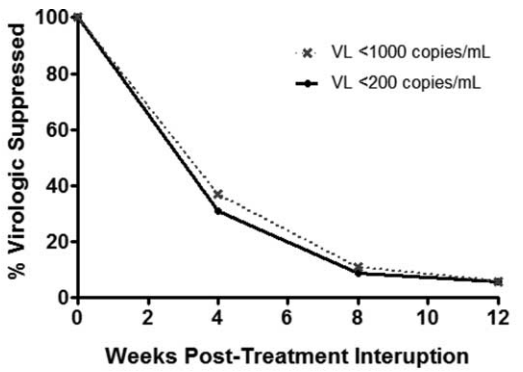

FIGURE 1. Cumulative percentage of participants who maintained virologic suppression after treatment interruption based on two viral load thresholds: 200 and 1000 HIV-1 RNA copies/ml [1▪▪].

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

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 $\log_{10}$ 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 underexplored.

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 stake-holders, including academia, industry and the community. Finally, the identification of

biomarker predictors of viral rebound kinetics and uncovering the mechanisms behind posttreatment control may accelerate the development of novel therapeutics for sustained HIV remission.

Acknowledgements

None.

Financial support and sponsorship

This work was supported in part by the National Institutes of Health (NIH/NIAID) grants AI125109 (to J.Z.L.) and Harvard University Center for AIDS Research 5P30AI060354–08 (to J.Z.L.).

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.

2. Hutter G, Nowak D, Mossner M, *et al.* Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009; 360:692–698.
3. Shiver JW, Fu TM, Chen L, *et al.* Replication-incompetent adenoviral vaccine vector elicits effective antiimmunodeficiency-virus immunity. Nature 2002; 415:331–335.
4. Santra S, Schmitz JE, Kuroda MJ, *et al.* Recombinant canarypox vaccine-elicited CTL specific for dominant and subdominant simian immunodeficiency virus epitopes in rhesus monkeys. J Immunol 2002; 168:1847–1853.
5. Luckay A, Sidhu MK, Kjeken R, *et al.* Effect of plasmid DNA vaccine design and in vivo electroporation on the resulting vaccine-specific immune responses in rhesus macaques. J Virol 2007; 81:5257–5269.
6. Schooley RT, Spritzler J, Wang H, *et al.,* AIDS Clinical Trials Group 5197 Study Team. AIDS clinical trials group 5197: a placebo-controlled trial of immunization of HIV-1-infected persons with a replication-deficient adenovirus type 5 vaccine expressing the HIV-1 core protein. J Infect Dis 2010; 202:705–716.
7. Rosenberg ES, Graham BS, Chan ES, *et al.,* AIDS Clinical Trials Group A5187 Team. Safety and immunogenicity of therapeutic DNA vaccination in individuals treated with antiretroviral therapy during acute/early HIV-1 infection. PLoS One 2010; 5:e10555.
8. Angel JB, Routy JP, Tremblay C, *et al.* A randomized controlled trial of HIV therapeutic vaccination using ALVAC with or without Remune. AIDS 2011; 25:731–739.
9. Goldstein G, Damiano E, Donikyan M, *et al.* HIV-1 Tat B-cell epitope vaccination was ineffectual in preventing viral rebound after ART cessation: HIV rebound with current ART appears to be due to infection with new endogenous founder virus and not to resurgence of preexisting Tat-dependent viremia. Hum Vaccin Immunother 2012; 8:1425–1430.
10. Garcia F, Climent N, Guardo AC, *et al.* A dendritic cell-based vaccine elicits T cell responses associated with control of HIV-1 replication. Sci Transl Med 2013; 5:; 166ra2.
11. Lévy Y, Thiébaut R, Montes M, *et al.* Dendritic cell-based therapeutic vaccine elicits polyfunctional HIV-specific T-cell immunity associated with control of viral load. Eur J Immunol 2014; 44:2802–2810.
12. Pollard RB, Rockstroh JK, Pantaleo G, *et al.* Safety and efficacy of the peptide-based therapeutic vaccine for HIV-1, Vacc-4x: a phase 2 randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2014; 14:291–300.
13. Jacobson JM, Routy JP, Welles S, *et al.* Dendritic cell immunotherapy for HIV-1 infection using autologous HIV-1 RNA: a randomized, double-blind, placebo-controlled clinical trial. J Acquir Immune Defic Syndr 2016; 72:31–38.
14. Thompson M, Heath SL, Sweeton B, *et al.* DNA/MVA vaccination of HIV-1 infected participants with viral suppression on antiretroviral therapy, followed by treatment interruption: elicitation of immune responses without control of re-emergent virus. PLoS One 2016; 11:e0163164.
15. Sneller MC, Justement JS, Gittens KR, *et al.* A randomized controlled safety/ ■ efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection. Sci Transl Med 2017; 9:; pii: eaan8848.

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

16. Skiest DJ, Su Z, Havlir DV, *et al.,* AIDS Clinical Trials Group 5170 Study Team, Interruption of antiretroviral treatment in HIV-infected patients with preserved immune function is associated with a low rate of clinical progression: a prospective study by AIDS Clinical Trials Group 5170. J Infect Dis 2007; 195:1426–1436.
17. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. El-Sadr WM, Lundgren J, *et al.* CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006; 355:2283–2296.
18. Marchou B, Tangre P, Charreau I, *et al.,* ANRS 106 Study team. Intermittent antiretroviral therapy in patients with controlled HIV infection. AIDS 2007; 21:457–466.
19. Tebas P, Stein D, Tang WW, *et al.* Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med 2014; 370:901–910.
20. Li JZ, Heisey A, Ahmed H, *et al.,* ACTG A5197 Study Team. Relationship of HIV reservoir characteristics with immune status and viral rebound kinetics in an HIV therapeutic vaccine study. AIDS 2014; 28:2649–2657.
21. Macatangay BJ, Riddler SA, Wheeler ND, *et al.* Therapeutic vaccination with dendritic cells loaded with autologous HIV type 1-infected apoptotic cells. J Infect Dis 2016; 213:1400–1409.
22. Loret EP, Darque A, Jouve E, *et al.* Intradermal injection of a Tat Oyi-based therapeutic HIV vaccine reduces of 1.5 log copies/mL the HIV RNA rebound median and no HIV DNA rebound following cART interruption in a phase I/II randomized controlled clinical trial. Retrovirology 2016; 13:21.
23. Tung FY, Tung JK, Pallikkuth S, *et al.* A therapeutic HIV-1 vaccine enhances anti-HIV-1 immune responses in patients under highly active antiretroviral therapy. Vaccine 2016; 34:2225–2232.
24. Li JZ, Smith DM, Mellors JW. The need for treatment interruption studies and biomarker identification in the search for an HIV cure. AIDS 2015; 29:1429–1432.
25. Henrich TJ, Hanhauser E, Marty FM, *et al.* Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. Ann Intern Med 2014; 161:319–327.
26. Scheid JF, Horwitz JA, Bar-On Y, *et al.* HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. Nature 2016; 535:556–560.
27. Bar KJ, Sneller MC, Harrison LJ, *et al.* Effect of HIV antibody VRC01 on viral rebound after treatment interruption. N Engl J Med 2016; 375: 2037–2050.
28. Rasmussen TA, Tolstrup M, Brinkmann CR, *et al.* Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. Lancet HIV 2014; 1:e13–e21.
29. Gay CL, DeBenedette MA, Tcherepanova IY, *et al.* Immunogenicity of AGS-004 dendritic cell therapy in patients treated during acute HIV infection. AIDS Res Hum Retroviruses 2018; 34:111–122.
30. Mothe B, Climent N, Plana M, *et al.,* RISVAC-03 Study Group. Safety and immunogenicity of a modified vaccinia Ankara-based HIV-1 vaccine (MVA-B) in HIV-1-infected patients alone or in combination with a drug to reactivate latent HIV-1. J Antimicrob Chemother 2015; 70:1833–1842.
31. Leth S, Schleimann MH, Nissen SK, *et al.* Combined effect of Vacc-4x, recombinant human granulocyte macrophage colony-stimulating factor vaccination, and romidepsin on the HIV-1 reservoir (REDUC): a single-arm, phase 1B/2A trial. Lancet HIV 2016; 3:e463–e472.
32. Montserrat M, Plana M, Guardo AC, *et al.* Impact of long-term antiretroviral therapy interruption and resumption on viral reservoir in HIV-1 infected patients. AIDS 2017; 31:1895–1897.
33. Tubiana R, Ghosn J, De-Sa M, *et al.* Warning: antiretroviral treatment interruption could lead to an increased risk of HIV transmission. AIDS 2002; 16:1083–1084.
34. Macatangay BJ, Yang M, Sun X, *et al.,* A5217 Team. Brief report: changes in levels of inflammation after antiretroviral treatment during early HIV infection in AIDS Clinical Trials Group Study A5217. J Acquir Immune Defic Syndr 2017; 75:137–141.
35. van den Ham HJ, Cooper JD, Tomasik J, *et al.,* DC-TRN trial investigators. Dendritic cell immunotherapy followed by cART interruption during HIV-1 infection induces plasma protein markers of cellular immunity and neutrophil recruitment. PLoS One 2018; 13:e0192278.
36. Colven R, Harrington RD, Spach DH, *et al.* Retroviral rebound syndrome after cessation of suppressive antiretroviral therapy in three patients with chronic HIV infection. Ann Intern Med 2000; 133:430–434.
37. Gianella S, Kosakovsky Pond SL, Oliveira MF, *et al.* Compartmentalized HIV rebound in the central nervous system after interruption of antiretroviral therapy. Virus Evol 2016; 2:vew020.

38. Routy JP, Boulassel MR, Nicolette CA, Jacobson JM. Assessing risk of a short-term antiretroviral therapy discontinuation as a read-out of viral control in immune-based therapy. J Med Virol 2012; 84: 885–889.

39. Rothenberger MK, Keele BF, Wietgrefe SW, *et al.* Large number of rebounding/founder HIV variants emerge from multifocal infection in lymphatic tissues after treatment interruption. Proc Natl Acad Sci U S A 2015; 112:E1126–E1134.

40. Calin R, Hamimi C, Lambert-Niclot S, *et al.,* ULTRASTOP Study Group. Treatment interruption in chronically HIV-infected patients with an ultralow HIV reservoir. AIDS 2016; 30:761–769.

41. ■■ Clarridge KE, Blazkova J, Einkauf K, *et al.* Effect of analytical treatment interruption and reinitiation of antiretroviral therapy on HIV reservoirs and immunologic parameters in infected individuals. PLoS Pathog 2018; 14:e1006792.

This study reported that short-term treatment interruption does not lead to irreversible expansion of the HIV reservoir.

42. Salantes DB, Yu Z, Mampe F, *et al.* HIV-1 latent reservoir size and diversity are stable following brief treatment interruption. J Clin Invest. in press

43. Strongin Z, Sharaf R, VanBelzen DJ, *et al.* Effect of short-term ART interruption on levels of integrated HIV DNA. J Virol 2018; pii: JVI.00285-18. doi: 10.1128/JVI.00285-18. [Epub ahead of print]

44. Henrich TJ, Hu Z, Li JZ, *et al.* Long-term reduction in peripheral blood HIV type 1 reservoirs following reduced-intensity conditioning allogeneic stem cell transplantation. J Infect Dis 2013; 207:1694–1702.

45. Donn Colby NC, Eugene K. HIV RNA rebound postinterruption in persons suppressed in Fiebig I acute HIV. In: Conference on Retroviruses and Opportunistic Infections. 2017, Seattle,WA, USA.

46. Pankau MD, Wamalwa D, Benki-Nugent S, *et al.* Decay of HIV DNA in the reservoir and the impact of short treatment interruption in Kenyan infants. Open Forum Infect Dis 2018; 5:ofx268.

47. Mellors JW, Rinaldo CR Jr, Gupta P, *et al.* Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996; 272: 1167–1170.

48. Katzenstein DA, Hammer SM, Hughes MD, *et al.* The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. AIDS Clinical Trials Group Study 175 Virology Study Team. N Engl J Med 1996; 335:1091–1098.

49. Williams JP, Hurst J, Stohr W, *et al.,* SPARTACTrial Investigators. HIV-1 DNA predicts disease progression and posttreatment virological control. Elife 2014; 3:e03821.

50. Yerly S, Gunthard HF, Fagard C, *et al.* Proviral HIV-DNA predicts viral rebound and viral setpoint after structured treatment interruptions. AIDS 2004; 18:1951–1953.

51. ■ Henrich TJ, Hatano H, Bacon O, *et al.* HIV-1 persistence following extremely early initiation of antiretroviral therapy (ART) during acute HIV-1 infection: an observational study. PLoS Med 2017; 14:e1002417.

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

52. ■ Cummins NW, Rizza S, Litzow MR, *et al.* Extensive virologic and immunologic characterization in an HIV-infected individual following allogeneic stem cell transplant and analytic cessation of antiretroviral therapy: a case study. PLoS Med 2017; 14:e1002461.

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.

53. Park YJ, Etemad B, Ahmed H, *et al.* Impact of HLA class I alleles on timing of HIV rebound after antiretroviral treatment interruption. Pathog Immun 2017; 2:431–445.

54. Huang Y, Pantaleo G, Tapia G, *et al.* Cell-mediated immune predictors of vaccine effect on viral load and CD4 count in a phase 2 therapeutic HIV-1 vaccine clinical trial. EBio Medicine 2017; 24:195–204.

55. Stephenson KE, Neubauer GH, Bricault CA, *et al.* Antibody responses after analytic treatment interruption in human immunodeficiency virus-1-infected individuals on early initiated antiretroviral therapy. Open Forum Infect Dis 2016; 3:ofw100.

56. Hocqueloux L, Prazuck T, Avettand-Fenoel V, *et al.* Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS 2010; 24:1598–1601.

57. Goujard C, Girault I, Rouzioux C, *et al.,* ANRS CO6 PRIMO Study Group. HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy. Antivir Ther 2012; 17:1001–1009.

58. Lodi S, Meyer L, Kelleher AD, *et al.* Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion. Arch Intern Med 2012; 172:1252–1255.

59. Sáez-Cirion A, Bacchus C, Hocqueloux L, *et al.* Posttreatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy. ANRS VISCONTI Study. PLoS Pathog 2013; 9:e1003211.

60. Martin GE, Gossez M, Williams JP, *et al.* Posttreatment control or treated controllers? Viral remission in treated and untreated primary HIV infection. AIDS 2017; 31:477–484.

61. Persaud D, Gay H, Ziemniak C, *et al.* Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med 2013; 369:1828–1835.

62. Frange P, Faye A, Avettand-Fenoel V, *et al.,* ANRS EPF-CO10 Pediatric Cohort and the ANRS EP47 VISCONTI study group. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. Lancet HIV 2016; 3:e49–e54.

63. Maggiolo F, Di Filippo E, Comi L, Callegaro A. Posttreatment controllers after treatment interruption in chronically HIV-infected patients. AIDS 2018; 32:623–628.

64. Golnaz Namazi JF, Evgenia A. THE CHAMP cohort: posttreatment controllers identified from 9 clinical studies. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, MA, USA.

65. Samri A, Bacchus-Souffan C, Hocqueloux L, *et al.* Polyfunctional HIV-specific T cells in post-treatment controllers. AIDS 2016; 30:2299–2302.

66. Henderson GE, Peay HL, Kroon E, *et al.* Ethics of treatment interruption trials in HIV cure research: addressing the conundrum of risk/benefit assessment. J Med Ethics 2018; 44:270–276.