Viral and immune predictors of HIV posttreatment control

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Purpose of review
This review focuses on the viral and immune factors influencing HIV posttreatment control (PTC), a rare condition where individuals maintain viral suppression after discontinuing antiretroviral therapy (ART).

Recent findings
Studies demonstrate that early ART initiation leads to smaller HIV reservoirs and delayed viral rebound in PTCs. Virologically, PTCs harbor smaller HIV reservoirs and show lower levels of reservoir transcriptional activity compared with posttreatment noncontrollers. Immunologically, PTCs exhibit distinct T-cell dynamics, with reduced CD4+ and CD8+ T-cell activation and exhaustion, enhanced natural killer (NK) cell activity, and enhanced proliferative responses of HIV-specific CD8+ T cells post-ART interruption. Additionally, humoral immunity, particularly the development of autologous neutralizing antibodies (aNAbs), plays a role in viral control, though broadly neutralizing antibodies (bnAbs) are rare.

Summary
The mechanisms behind posttreatment control are multifactorial, involving virological and immunological factors. Early ART initiation, a smaller and less transcriptionally active HIV reservoir, and immune responses including proliferative T-cell activity and NK cell function are key contributors to achieving ART-free HIV remission.

Keywords
early antiretroviral therapy, HIV posttreatment controllers, HIV reservoir, HIV T-cell responses, viral rebound

INTRODUCTION

Despite ART's effectiveness in suppressing viral replication, a cure remains elusive due to the persistence of the HIV-1 reservoir [1,2], where replication-competent proviruses persist in CD4+ T cells [3▪]. There are multiple cases of HIV cure achieved via allogeneic hematopoietic stem cell transplantation or cord blood stem cell transplantation [4–7], but stem cell transplantation involves a high risk of morbidity and mortality, and is not a practical approach for the vast majority of people with HIV.

After an analytic treatment interruption (ATI), viral rebound typically occurs within a few weeks [8,9], but the exact timing can vary widely among individuals, from a rapid rebound within days to the maintenance of viral suppression for years. HIV posttreatment controllers (PTCs) are a rare subset of individuals with HIV who can maintain viral suppression or low-level viremia after discontinuing antiretroviral therapy (ART) [10▪▪]. Although definitions of posttreatment control can vary across studies, they represent evidence that sustained ART-free HIV control is a realistic possibility [11,12]. The genetic traits of spontaneous controllers ('elite controllers'), such as protective HLA alleles B27 and B57 [13–15], do not appear to be enriched in PTCs [11,16,17▪▪]. Understanding the mechanisms behind posttreatment control is vital for developing strategies to achieve ART-free remission.

THE ROLE OF EARLY ANTIRETROVIRAL THERAPY INITIATION

Starting ART in the acute phase of infection has been linked to numerous beneficial outcomes, such as a smaller HIV-1 reservoir, reduced inflammation, and preserved immune function [18]. Although some

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KEY POINTS

- Posttreatment control (PTC) in HIV is influenced by virological and immune factors, with early ART initiation reducing the viral reservoir size and activity.
- PTCs have smaller and less active HIV reservoirs compared with noncontrollers, including lower HIV DNA levels and fewer intact proviruses.
- Immune responses in PTCs, including enhanced HIV-specific CD8+ T-cell proliferation, stronger CD4+ T-cell responses, and higher NK cell activity, contribute to viral suppression post-ART interruption.
- Autologous neutralizing antibodies (aNAbs) play a role in PTC, though broadly neutralizing antibodies (bnAbs) are less commonly observed.
- Although early ART improves chances of PTC, starting ART at the earliest stage of acquisition may reduce the development of a fully mature immune response.

individuals treated during chronic infection can become PTCs, the majority of those identified in various studies began ART during early HIV infection [11]. A direct comparison of the impact of early ART was performed in the CHAMP study, the largest investigation of PTCs to date [12,19–31]. PTCs were more frequently found in early-treated individuals (13%) compared with those treated during chronic infection (4%), highlighting the impact that early ART initiation has on increasing the likelihood of posttreatment control [12].

Other early-treatment studies have also found a relatively high rate of posttreatment control. The CASCADE cohort included participants who initiated treatment within 3 months of HIV acquisition, and found a 5.5% frequency of posttreatment control with a minimum of 24 months of control and 8.2% with a 12-month cutoff [32]. Another study revealed that of PWH who started ART within 6 months of HIV acquisition, 10% achieved PTC and that longer duration on ART was linked to a greater chance of maintaining PTC [33]. On the other hand, a study of eight individuals who initiated ART during the earliest stage of HIV infection (Fiebig 1) and subsequently underwent treatment interruption showed that all participants had rapid viral rebound [34]. These results suggest that ART initiation at the very earliest stages of HIV infection may actually lower the chances of posttreatment control, potentially because of an insufficiently mature antiviral immune response. This concept aligns with a study with Simian immunodeficiency virus (SIV)-infected nonhuman primates (NHP) showing that delaying ART within the first 3 weeks of acquisition leads to reduced postrebound viral levels. However, delaying beyond 3 weeks led to higher viral setpoints because of immune exhaustion or viral escape [35]. Also using NHPs, it has been demonstrated that early ART initiation favors PTC through development of long-term memory CD8+ T cells [36].

Similarly, the ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS, previously AIDS Clinical Trials Group) A5345 prospective treatment interruption study found that early-treated participants had significantly smaller and less transcriptionally active HIV reservoirs compared with those who initiated ART during chronic infection [10▪▪]. Specifically, early-treated participants exhibited lower levels of cell-associated HIV RNA (CA-RNA), total and intact proviral DNA, and infectious units per million resting CD4+ cells by the quantitative viral outgrowth assay. These results provide insight into the reasons that early ART treatment may increase the chances of ART-free HIV control.

VIROLOGICAL CHARACTERISTICS AND PREDICTORS OF POSTTREATMENT CONTROL

Total HIV DNA levels

PTCs consistently exhibit lower total HIV DNA levels compared with noncontrollers. An analysis in the ANRS cohort demonstrated that, among patients receiving early and extended ART, 16% presented sustained virological control [37]. These PTCs shared a common feature of having a very low and stable viral reservoir as reflected by total HIV DNA levels. Similarly, in the ANRS CO6 PRIMO cohort, 8.5% early treated participants (started during the first 3 months of acquisition) suppressed the virus [16]. Compared with noncontrollers, PTCs had higher CD4+ T-cell counts and lower HIV DNA/RNA levels during infection. Importantly, characteristics like subtype, genotypic resistance, tropism, HLA genotype, treatment regimen or treatment duration, were not associated with posttreatment control.

In the VISCONTI study, which included participants from both ANRS cohorts, PTCs exhibited low cell-associated HIV DNA (CA-DNA) in PBMCs and CD4+ T cells. Longitudinal data revealed a further reduction in HIV DNA levels after treatment interruption in some PTCs, suggesting ongoing reservoir control and potential depletion [11]. These findings align with the ANRS SALTO cohort, where participants with HIV DNA levels below 150 copies/10^6 PBMCs at treatment interruption had a higher likelihood of sustained viral control [38]. Further supporting these observations, data from participants in the SPARTAC trial [39] showed that higher HIV DNA levels at ART interruption were associated with

faster viral rebound [40,41]. However, even in patients with ultralow levels of CA-DNA, as studied in the ULTRASTOP study, maintaining long-term ART-free remission is challenging. In this study, individuals with HIV DNA levels less than 50 copies/ml for at least 2 years on ART underwent an ATI. Only 1 out of 10 patients maintained viral control after 48 weeks of ART interruption, underscoring the difficulty of achieving sustained remission, even with small reservoir sizes [42].

Intact reservoir and time to viral rebound

Although total HIV DNA provides an estimate of reservoir size, it does not distinguish between defective and replication-competent proviruses, a factor that may further influence time to viral rebound [43]. A key finding from Sharaf *et al.*'s study on HIV PTCs identified from prior ACTG ATI studies was the distinction between defective and intact proviruses in both PTCs and noncontrollers by near-full length proviral sequencing [44]. PTCs had significantly smaller total, defective and intact proviral reservoirs compared with noncontrollers, a median of about seven-fold smaller. Interestingly, it was a smaller total proviral genome copies that best served as a biomarker of posttreatment control [44]. Using the Intact Proviral DNA Assay (IPDA), intact, defective, and total HIV DNA levels were compared in PTCs and noncontrollers during suppressive ART, and no significant differences were noted in reservoir size between the two groups at the pre-ATI time point [17▪▪]. However, during the ATI, noncontrollers showed significantly more active and larger reservoir, including both intact and defective proviruses.

In the prospective ACTG A5345 trial [10▪▪], early-treated participants generally experienced delayed viral rebound compared with those treated during chronic infection. Early-treated individuals had smaller reservoirs with fewer intact proviruses, whereas higher levels of intact proviral DNA in chronic-treated individuals strongly predicted faster viral rebound [10▪▪].

Reservoir activity

In several studies, levels of CA-RNA before ATI have predicted the timing of viral rebound after treatment interruption [8,45]. In an analysis of ACTG ATI studies, PTCs were found to have numerically lower CA-RNA levels than noncontrollers before ATI and significantly lower CA-RNA during ATI, indicating reduced viral transcription [17▪▪]. This suggests that PTCs not only have smaller and more defective reservoirs but also exhibit less viral gene expression from infected cells. To pinpoint which steps in RNA transcription are distinct between PTCs and noncontrollers, HIV-1 RNA products from HIV-1 transcription initiation, elongation, and splicing were analyzed, finding that PTCs had lower levels of HIV-1 transcription initiation before ATI [46▪]. During early and late ATI, PTCs had significantly lower proportion of HIV-1 RNA products that finished completion. These data highlight potentially areas of transcriptional block or potentially immune-based clearance of cells with completed RNA transcripts.

In the A5345 study, higher levels of CA-RNA were modestly associated with more rapid HIV rebound, but this association was not statistically significant across all participants [10▪▪]. In early-treated individuals, lower level residual viremia by the integrase single-copy assay (iSCA) was significantly associated with delayed viral rebound. This relationship was also reported in a study of prior ACTG studies [8].

Proviral integration site

HIV integration is not random, and the specific chromosomal location may affect the survival and proliferation of HIV-infected cells [47,48]. The chromosomal environment surrounding the integration site can also impact HIV transcriptional activity [49]. A preliminary report of a few PTCs suggests that the majority of intact proviruses in PTCs are located in nongenic, centromeric, or *ZNF* gene regions associated with deep latency and that the integration site profile could help identify potential PTCs in future studies [50]. These results deserve additional exploration in a larger number of participants.

HIV-SPECIFIC T-CELL RESPONSES

One of the studies with early-treated participants, and a study of early and chronic-treated individuals, both reported that PTCs had lower CD8+ T-cell activation during ART and after ATI compared with noncontrollers [16,17▪▪]. Unlike spontaneous HIV controllers (HICs), PTCs did not frequently carry protective HLA alleles [51]. Instead, they often carried risk alleles like HLA-B07 and HLA-B35, which are associated with faster disease progression [52], supported by other studies [17▪▪].

T-cell effector function in posttreatment controllers

In the VISCONTI study, PTCs exhibited weaker HIV-specific CD8+ T-cell responses to optimal peptides compared with HICs and viremic patients (VIRs) [11]. Specifically, the frequency of HIV-specific CD8+ T cells producing IFN-γ was low, comparable

to individuals on ART, and significantly lower than in HICs and VIRs [11]. Additionally, the capacity of PTCs' CD8+ T cells to suppress HIV infection *ex vivo* was poor, comparable to treated patients and viremic individuals, and much weaker than in HICs. In another study of individuals with early ART initiation, the polyfunctionality of both CD8+ and CD4+ T cells in PTCs was comparable to individuals who continued ART and long-term nonprogressors [53]. Other studies have also reported that HIV-specific CD8+ T-cell effector function does not correlate with HIV-1 reservoir size or posttreatment control [17▪▪].

Interestingly, there is some evidence that stronger HIV-specific CD4+ T-cell responses were associated with lower viral load set point after treatment interruption [27]. Leveraging samples from the CHAMP study, we observed negative correlations between CD4+ T-cell IFN-γ and IL-2 responses to Gag peptides and CA-RNA levels both pre-ATI and early ATI, as well as early rebound viral load [17▪▪] showing that PTCs had higher levels of Gag-specific CD4+ IFN-γ and IL-2-secreting T cells, associated with smaller HIV reservoirs and lower rebound viral load during early ATI [17▪▪].

CD8 T-cell proliferative capacity in posttreatment controllers

Despite relatively weak direct ex-vivo CD8+ effector responses in the VISCONTI and other studies, a recent study reported that CD8+ T cells from PTCs displayed significantly greater proliferative capacity in response to HIV epitopes after ART cessation compared with noncontrollers [54▪]. Two other studies have reached similar conclusions. In one trial, participants received a DNA/MVA vaccine, two broadly neutralizing antibodies (bNAbs), and a toll-like receptor-9 (TLR-9) agonist, followed by ATI [55]. Those able to control viral rebound exhibited a significant increase in proliferating HIV-specific CD8+ T cells, with this early proliferative response associated with lower viral load set points [55]. A second study involving four chronic-treated PTCs found no significant differences in the breadth and magnitude of HIV-specific T-cell responses [37], but PTCs demonstrated higher proliferative responses to Gag and Pol peptides, suggesting that these responses may contribute to viral control [37].

The study indicating that early ART initiation in NHPs promoted the expansion of memory CD8+ T cells also highlights that these cells express TCF1, a transcription factor in stem-like cells that have enhanced proliferative and suppressive capacities [36]. A second study further confirmed the critical role of TCF1+ CD8+ T cells in controlling viral replication in NHP, noting their effector functions in viral suppression [56].

HUMORAL IMMUNITY IN POSTTREATMENT CONTROLLERS

Autologous neutralizing antibodies

In early-treated participants, autologous neutralizing antibodies (aNAbs) begin developing during acute infection and mature during suppressive ART, enhancing B-cell responses potentially through residual viral antigen exposure [57▪▪]. aNAbs exert selective pressure on rebounding HIV-1 variants post-ATI, which often exhibit resistance to neutralization by contemporaneous plasma [57▪▪]. Interestingly, more robust post-ATI aNAb responses against pre-ART virus were associated with lower post-ATI viral loads, emphasizing the potential of aNAbs to control viral rebound [57▪▪]. In addition, a study analyzing two PTCs with sustained viral suppression after ATI reported two distinct mechanisms of viral control [58], including one participant with strong aNAb responses. In that study, one individual maintained long-term viral control with strong polyfunctional HIV-specific CD8+ T-cell activity. In contrast, another participant had weaker HIV-specific CD8+ T-cell activity, but their long-term viral suppression appeared to be mediated at least partially through potent autologous IgG-mediated neutralization of the virus, maintaining suppression for over 1400 days [58].

Findings from the VISCONTI group reported that PTCs with intermittent viral exposure were more likely to develop robust functional antibody responses [59], exhibiting higher levels of Env-specific memory B cells and cross-neutralizing antibodies. This suggests that brief viral exposures can trigger coordinated antibody responses that contribute to controlling HIV-1 infection without continuous ART [59]. One participant developed anti-V1/V3-glycan bnAbs with a potent bnAb variant showing a broad neutralization efficacy and exhibiting strong antibody-dependent cellular cytotoxicity [60]. Although this bnAb did not neutralize the contemporaneous virus, autologous neutralization was achieved, suggesting that polyclonal responses may sustain remission. Notably, an ACTG PTC study showed no evidence of bnAbs among PTCs [57▪▪].

INNATE IMMUNITY IN POSTTREATMENT CONTROLLERS

An ACTG PTC study reported higher levels of activation markers in NK cells before and during early ATI [17▪▪]. These increased activation levels were

correlated with lower CA-RNA and reduced viral load rebound. Another ACTG study demonstrated that higher NK cell activation was associated with lower levels of defective proviral genomes [44]. In addition, PTCs had a higher percentage of activated NK cells compared with noncontrollers, indicating a more vigorous innate immune response. This suggests that NK cells not only reduce the overall proviral burden but also play an essential role in controlling HIV replication without continuous ART [61]. Early ART initiation, an intervention that increases the chances of ART-free control, preserves NK cell function and limits the expansion of dysfunctional NK cell subsets [62], as NK cell activation has also been cited as relevant in the achievement of posttreatment control [17▪▪]. They also indicated that NK cells in early-treated individuals had lower activation levels and were associated with smaller HIV reservoirs.

Furthermore, soluble inflammatory markers such as IP10, sCD163, IFN-γ, and IL10 were higher in noncontrollers during ATI compared with PTCs [17▪▪]. Another example of robust innate immune response involves a PTC treated with cyclosporine, IL-2, granulocyte macrophage colony-stimulating factor, and pegylated interferon alfa, who maintained undetectable viral loads after ATI [63▪]. This individual showed continuous HIV DNA decline, accompanied by expanding populations of memory-like NK cells and cytotoxic gamma-delta CD8+ T-cell populations. Genetic analysis suggested that favorable KIR alleles and the HLA-E01:03 genotype may have supported this NK cell antiviral activity [63▪].

CONCLUSION

Posttreatment control in HIV is driven by a complex interplay of smaller viral reservoirs, reduced reservoir activity and coordinated immune responses, potentially including enhanced CD8 T-cell proliferation, aNAb, and NK cell activity amongst other features (Fig. 1). Early ART initiation plays a critical role in increasing the likelihood of achieving

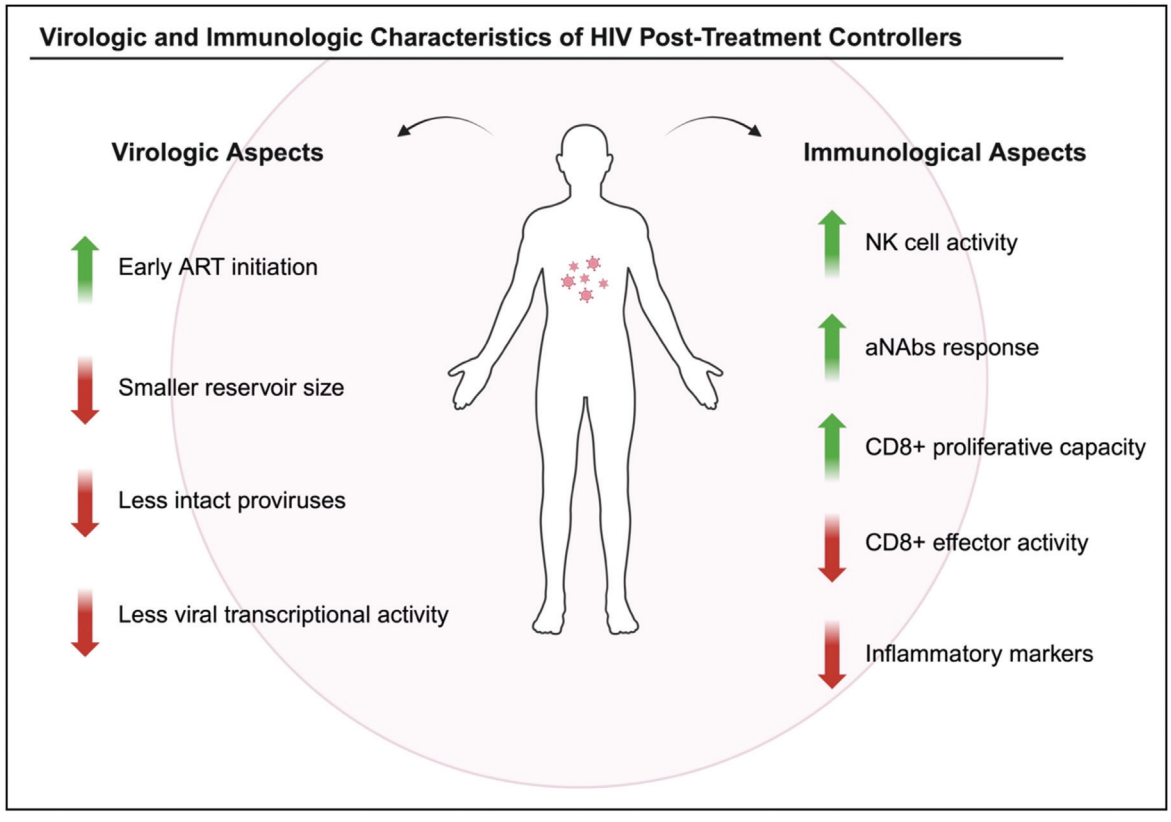

FIGURE 1. Key virological and immunological factors associated with HIV posttreatment controllers, individuals who maintain viral suppression after discontinuing antiretroviral therapy. On the virologic side, posttreatment controllers (PTCs) benefit from early antiretroviral therapy (ART) initiation, which leads to smaller reservoir sizes, fewer intact proviruses, and reduced viral transcriptional activity. Immunologically, PTCs display enhanced natural killer (NK) cell activity, stronger autologous neutralizing antibody (aNAb) responses, and increased CD8+ T-cell proliferative capacity. They also have lower CD8+ T-cell effector activity and reduced inflammatory markers, contributing to effective ART-free HIV control. Created in BioRender. Mesquita, F. (2024). BioRender.com/b28f109.

posttreatment control, likely due to its multifaceted impact on both restricting reservoir size/diversity and preserving host immune function. Understanding these mechanisms for posttreatment control is essential for developing strategies aimed at achieving sustained ART-free remission for more individuals with HIV, ultimately guiding future therapeutic advancements.

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Conflicts of interest

J.Z.L. has consulted for Abbvie and Imunon..

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