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REVIEW

The selected few: Mechanisms of HIV-1 reservoir persistence

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Combination antiretroviral therapy durably suppresses HIV-1 replication yet leaves untouched a small, highly specialized population of infected cells that sustains lifelong viral persistence and remains the principal obstacle to cure. In this review, we synthesize emerging insights into viral and host mechanisms that maintain this extremely durable cellular reservoir, with emphasis on proviral transcriptional regulation, interactions between immune effectors and infected cells, cell-intrinsic programs governing survival and proliferation, and microenvironmental cues that confer competitive fitness and long-term persistence to infected clones. We argue that viral reservoir cells are considerably more visible, and therefore more vulnerable, to host immune responses than the traditional latency-centered model of HIV-1 persistence has assumed and propose that a deeper mechanistic understanding of these immunological vulnerabilities, rather than latency reversal alone, provides the most rational foundation for designing combination strategies aimed at destabilizing infected cells and achieving durable virological remission or cure.

Introduction

Combination antiretroviral therapy (ART), developed, refined, and optimized over the past several decades, represents one of the most consequential advances in modern medicine and stands as a paradigmatic example of a pharmacologic intervention capable of completely transforming the natural history of a disease. By simultaneously but independently targeting multiple steps in the viral replication cycle, ART achieves durable suppression of viral replication; however, it lacks direct pharmacologic activity against infected cells, some of which persist indefinitely as a long-lasting reservoir of infected cells. Therefore, ART is not a curative intervention, and lifelong antiviral suppression treatment represents the only available therapeutic modality for the >40 million people living with HIV-1 (PLH) today. Cells persisting during ART, frequently referred to as "viral reservoir cells," harbor chromosomally integrated viral DNA but differ profoundly from those sustaining active viral replication in untreated infection and likely represent a highly specialized population of lymphocytes uniquely adapted to survive indefinitely in the immune environment shaped by sustained ART: these cells are exceptionally long-lived, largely due to their residence within long-lived resting memory CD4$^+$ T cell subsets; they typically produce very limited and structurally immature viral transcripts—a condition broadly referred to as viral latency; they exhibit resistance to immune-mediated clearance, and they retain the capacity to proliferate, thereby amplifying and replenishing the pool of infected cells through physiological mechanisms of T cell homeostasis, which frequently leads to large clones of infected cells sharing identical proviral integration sites and proviral sequences. Viral reservoir cells can be detected in both peripheral blood and lymphoid tissues, but due to their exceedingly low frequency, characterizing these cells poses unique experimental challenges; moreover, only a small subset of infected cells harbor genome-intact, replication-competent viral DNA, raising additional analytic difficulties, as described in detail in prior overviews (Abdel-Mohsen et al., 2020). Of note, despite intense research efforts in preclinical and clinical settings, most immunological and pharmacologic approaches to target viral reservoir cells have failed so far, reflecting the extraordinary resilience and persistence of these cells. Nevertheless, recent progress in understanding their biological properties and immunological vulnerabilities can provide critical information for developing clinical interventions aimed at curing HIV-1 infection. In this review, we synthesize recent advances in understanding the virological and immunological mechanisms underlying HIV-1 persistence and latency, evaluate progress in the experimental and functional interrogation of reservoir cells in blood and tissues, and highlight emerging directions that may inform the development of targeted strategies to eradicate this highly specialized cellular reservoir. Specifically, we focus on the role of

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viral latency in HIV-1 persistence, on interactions between immune cells and HIV-1 reservoir cells, and on tissue localization and spatial positioning of infected cells during long-term ART.

The role of viral latency in HIV-1 persistence

Upon initiation of ART, plasma viral load declines rapidly to undetectable levels, typically within weeks, likely reflecting the clearance of cells harboring actively replicating viruses. In contrast, levels of cell-associated HIV-1 DNA decrease far more modestly, with most of this reduction occurring during the initial phase of treatment (White et al., 2022). Thereafter, levels of genome-intact proviral DNA reach a steady-state plateau or decline only very slowly, with an estimated half-life of ∼44 mo, reflecting the long-term survival of infected cells despite ART (Falcinelli et al., 2020; Peluso et al., 2020). Persistence of these viral reservoir cells during ART has most commonly been attributed to specific alterations in the viral gene expression profile. In comparison with infected cells circulating during untreated infection, viral reservoir cells encountered during ART display markedly reduced levels of viral transcription and a distorted pattern of viral transcripts, consistent with selective blocks at the levels of proviral transcriptional elongation, polyadenylation, and splicing, and with additional posttranscriptional restrictions at the stage of viral mRNA nuclear export and protein translation (Dorman et al., 2025; Ferreira et al., 2026; Yukl et al., 2018); this typically leads to the selective production of small, incomplete, and abortive viral transcripts. This altered transcriptional state is broadly referred to as "viral latency"; however, despite this terminology, cell-associated viral transcripts remain detectable in the vast majority of individuals during ART (Coco et al., 2025), and full viral replication cycles rapidly recur once suppressive ART is interrupted, arguing against a sustained suppression of viral transcription typically encountered during latent infection with, e.g., herpesviruses. Correspondingly, recent studies in infected cell clones isolated from study participants on suppressive ART suggest that even when viral RNA is not detectable in individual infected cells at a given time point, proviral transcriptional silence appears neither fixed nor stable (Ferreira et al., 2026). Instead, HIV-1 transcription seems dynamically regulated, with temporal fluctuations likely driven by oscillatory transcriptional control mechanisms, as described in Fig. 1. As a result, single time point measurements may underestimate the true extent of viral transcriptional activity. While some of these fluctuations may reflect stochastic noise, regulated changes associated with the cellular replicative cycle or activation state likely also contribute and warrant further investigation. Nevertheless, it is clear that reduced levels of viral transcription in viral reservoir cells decrease the immunological visibility of reservoir cells, and contribute to their ability to persist long term.

The latent transcriptional profile of HIV-1–infected cells emerges rapidly following ART initiation and has been explained by two nonmutually exclusive conceptual frameworks. The first posits that viral latency is largely a consequence of physiological memory $CD4^+$ T cell differentiation. In this model, $CD4^+$ T cells become infected during an activated state, presumably at the time of antigen encounter, and subsequently transition into a resting memory state as part of normal CD4 T cell ontogeny (Chomont et al., 2009; Finzi et al., 1999). In this resting state, cells are no longer permissive to efficient viral transcription due to cell-intrinsic transcriptional programs, including reduced availability of key transcription factors such as NF-κB that are critical for induction and activation of proviral gene expression (Siliciano and Greene, 2011). This initial restriction may trigger a cascade of reinforcing defects, including impaired Tat-mediated transactivation, inefficient RNA processing, and reduced protein translation (Dorman et al., 2025; Matkovic et al., 2022; Yukl et al., 2018). In support of this model, in vitro tissue culture assays (so called "viral outgrowth assays") have shown that viral latency can be effectively reversed following CD4 T cell activation with T cell receptor ligands or protein kinase C agonists. Notably, within this framework, latency is interpreted primarily as a passive consequence of memory T cell differentiation, and this interpretation implies that viral latency can readily occur in the absence of ART, although cells with active viral replication cycles dominate off therapy.

An alternative, more recent perspective emphasizes the role of selective pressures operating shortly after ART initiation. According to this model, ART imposes a bottleneck that favors the survival of infected cells exhibiting low-level or latent viral expression, as these cells are less susceptible to immune recognition and subsequent immune-mediated clearance. In this view, latency is not merely a passive byproduct of T cell biology but reflects an adaptive outcome shaped by host immune selection under ART. This interpretation is consistent with the absence of evolutionarily conserved viral mechanisms specifically designed to induce viral latency and implies that in the absence of ART, such a state of latent infection would not be stably maintained. Strong experimental support for this selection-based model comes from analyses of viral integration sites in long-lived, genome-intact proviruses (Einkauf et al., 2022; Huang et al., 2021; Lian et al., 2023). These studies demonstrate preferential persistence of proviruses integrated in genomic regions that are relatively unfavorable for transcription, including gene deserts, centromeric satellite DNA, zinc finger gene clusters, and other heterochromatin domains, which are remarkably uncommon sites of viral integration during untreated infection (Schroder et al., 2002). These experimental findings are consistent with differential survival of infected cells according to levels of viral antigen expression and can potentially be explained by selection processes during long-term ART that favor preferential persistence of proviruses integrated in chromosomal regions repressing proviral transcriptional activity and protecting against host immune recognition, as shown in Fig. 2. However, other factors, such as cell demise resulting from viral cytopathic effects or integration site–specific changes in cell proliferation and survival (Liu et al., 2020), may also be involved in these selection processes. Of note, genome-intact proviruses, although representing only a small fraction of total proviral DNA, seem more vulnerable to this selection, arguably because they retain all viral segments relevant for HIV-1 immune recognition. In contrast, defective proviruses frequently persist and clonally expand even when integrated into transcriptionally

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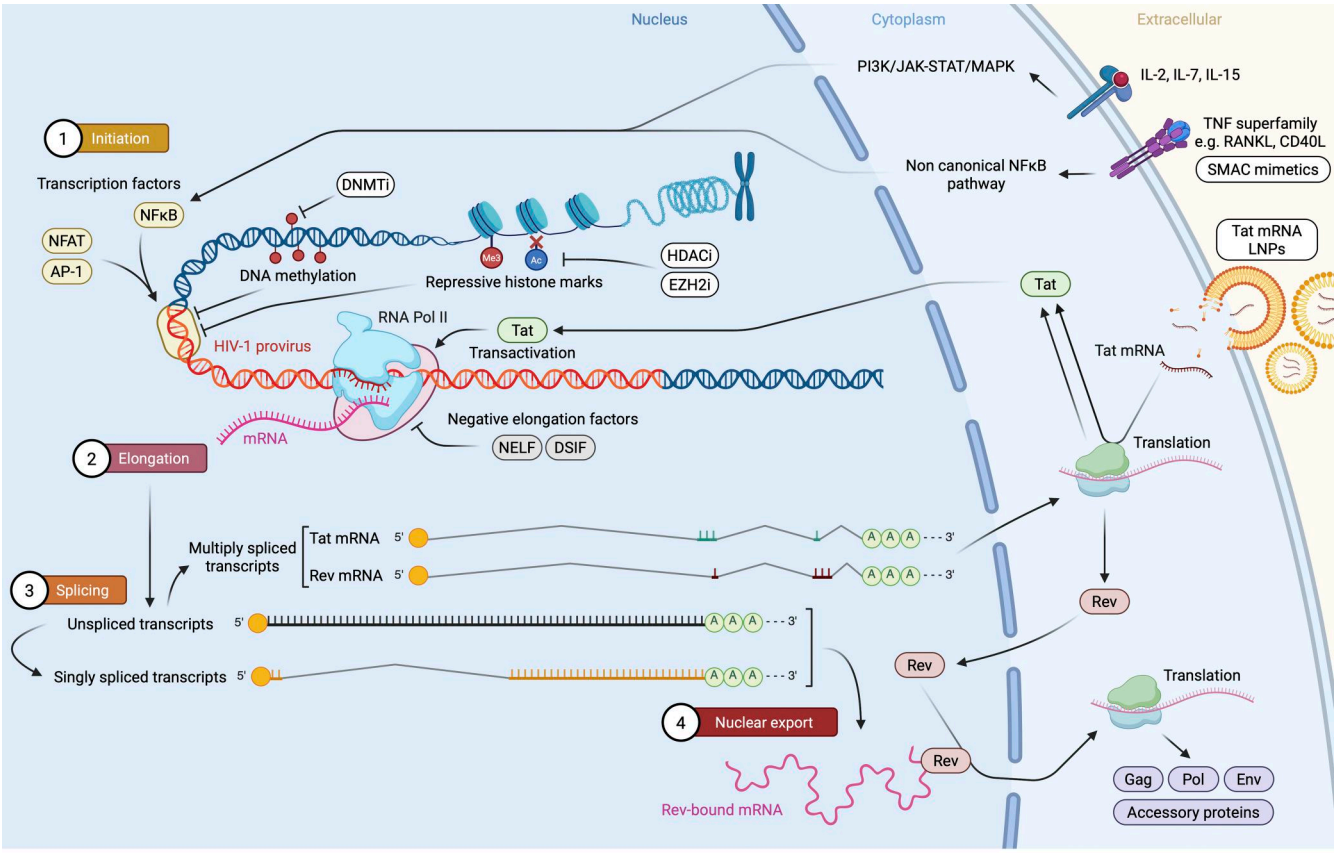

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Figure 1. **Molecular mechanisms regulating proviral transcription.** The image depicts a schematic representation of checkpoint pathways involved in transcriptional control of HIV-1. 1: The initiation of transcription is modulated by binding of host transcription factors to the proviral promoter region and the presence of epigenetic modifications such as DNA methylation and histone marks. 2: Initial transcription results in short and abortive transcripts under the influence of negative elongation factors. Transactivation by the accessory protein Tat is essential to produce full-length transcripts. 3 and 4: While unspliced and singly spliced transcripts are necessary for viral protein production and genome packaging in new virions, these transcripts cannot leave the nucleus without the accessory protein Rev. Multiply spliced transcripts coding for Tat and Rev can enter the cytoplasm and are translated first, feeding forward into the transcriptional loop. Investigational pharmacologic interventions modulating HIV proviral transcription are shown in white labels. DNMTi, DNA methyltransferase inhibitor; EZH2i, enhancer of zeste homolog 2 inhibitor; HDACi, histone deacetylase inhibitor; LNPs, lipid nanoparticles; SMAC, second mitochondrial activator of caspase.

active genic regions, and in some cases can produce high levels of viral RNA that are not suppressed by ART (Omondi et al., 2026; White et al., 2023). This suggests that such defective genomes may lack critical elements required for effective immune recognition, allowing them to evade clearance despite ongoing transcription. Interestingly, the extent to which intact proviruses accumulate in heterochromatic regions varies across individuals, likely reflecting differences in immune selection pressure. In general, selection of intact proviruses in heterochromatin regions appears most pronounced in individuals capable of maintaining viral suppression in the absence of ART (so-called "elite controllers"), presumably reflecting particularly effective antiviral immune activity (Jiang et al., 2020); indeed, intact proviruses in some elite controllers are almost exclusively located in dense heterochromatin regions, where they may be "blocked and locked" and poorly responsive to viral reactivation signals. The precise immune mechanisms responsible for driving this selective process remain incompletely defined and represent an important area for ongoing investigation.

How the characteristic viral expression profile of latently infected cells is maintained during ART has been dissected in considerable detail, both to clarify the regulatory circuitry underlying this state and to identify pharmacologic or immunologic targets that might be exploited to increase the vulnerability and reduce the persistence of infected cells (Fig. 1). Much of this work has focused on host transcriptional factors that constrain or permit HIV-1 gene expression, and on clinical attempts to manipulate these pathways as part of "latency reversal" strategies, designed to induce transcription and increase exposure of infected cells to host immune recognition. A major line of investigation in this context has centered on transcription factors that promote HIV-1 transcription, particularly NF-κB, NFAT, and AP-1, which bind to cis-regulatory elements in the viral long terminal repeat (LTR) and can potently induce viral gene expression upon cellular activation. In parallel, multiple transcriptional repressors and negative elongation factors have been implicated in maintaining low-level or silent proviral transcription, highlighting a complex

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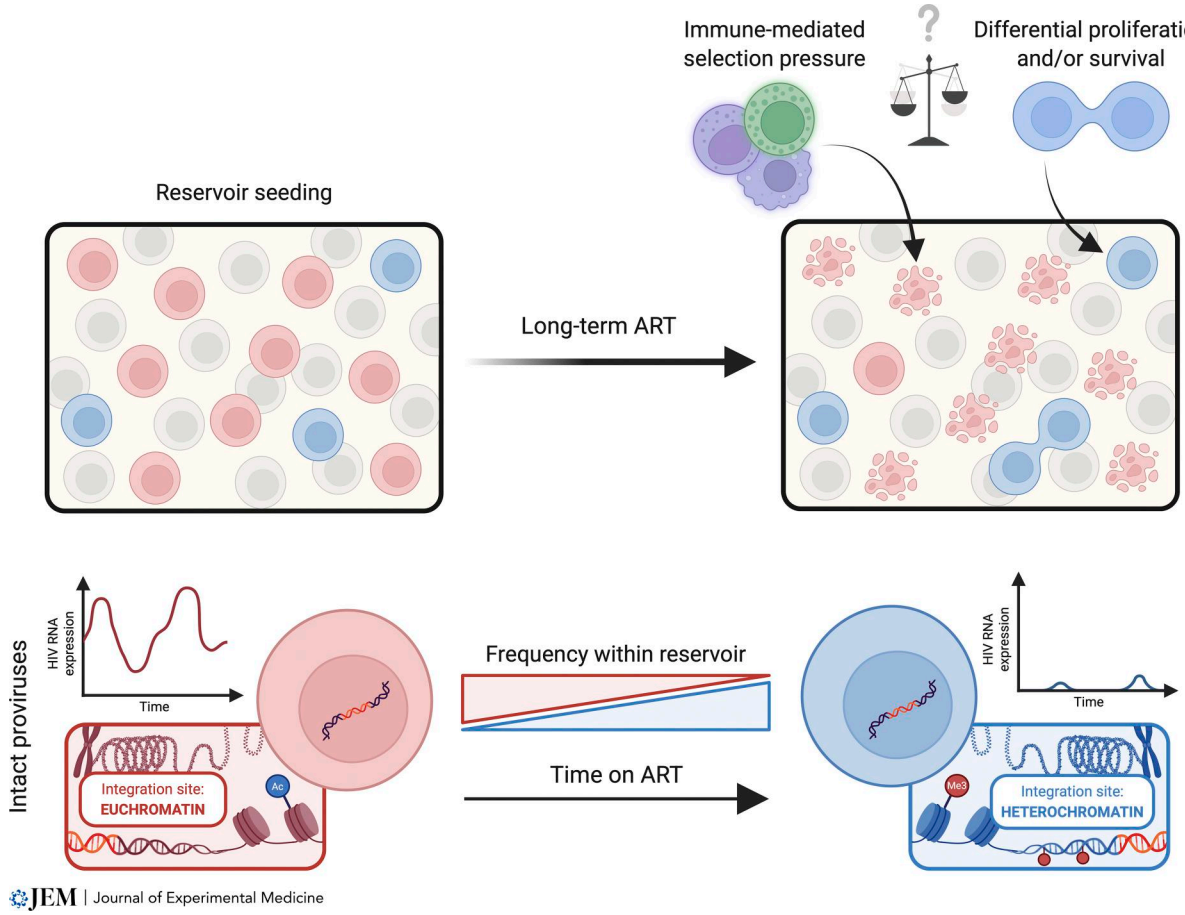

Figure 2. **Proposed model of longitudinal selection and persistence of intact proviruses integrated into repressive genomic regions.** During long-term ART, genome-intact proviruses integrated in repressive heterochromatin regions tend to accumulate, while intact proviruses integrated in accessible chromatin are selected against. Host immune responses that preferentially eliminate intact proviruses integrated in permissive chromatin regions supporting residual proviral transcription represent one possible driver of this process. Of note, this effect is not observed for cells harboring defective proviruses, which appear to evade immune recognition despite sometimes high levels of RNA expression, presumably because they lack proviral sequences relevant for immune recognition. ART, antiretroviral therapy.

balance of activating and inhibitory inputs at the HIV-1 promoter (D'Orso, 2025).

Epigenetic regulation at or near the proviral integration site has emerged as an equally important determinant of HIV-1 transcriptional competence. Repressive chromatin states at the proviral 5′ LTR region, including histone deacetylation, H3K27 and H3K9 methylation, and DNA methylation, have all been associated with transcriptional silencing, providing a rationale for targeting chromatin modifiers to reverse latency (Verdikt et al., 2021). Similarly, the human silencing hub complex, a nuclear repressor that can bind to integrated proviral DNA, can reduce proviral gene expression through the deposition or maintenance of repressive chromatin modifications, in particular H3K9me3 (Matkovic et al., 2022; Yurkovetskiy et al., 2018). These insights have motivated preclinical and clinical testing of chromatin-modifying agents, such as histone deacetylase inhibitors, EZH2 inhibitors, and DNA methyltransferase inhibitors, which can induce measurable increases in cell-associated HIV-1 RNA (Bouchat et al., 2016; Sedohara et al., 2025; Sogaard et al., 2015) and, in some studies, modestly accelerate selection of proviruses integrated in repressive chromatin (Armani-Tourret et al., 2024). However, despite clear evidence of on-target induction of viral transcription in vivo, these interventions have so far failed to produce a durable or clinically meaningful reduction in the size of the HIV-1 reservoir. Common γ-chain cytokines, including IL-7, IL-15, and IL-2, have also been explored as latency-reversing agents based on in vitro data demonstrating that they can drive T cell activation and enhance proviral transcription (Freeman et al., 2025; Rhein et al., 2025). Early clinical trials, however, have shown at best transient increases in plasma viremia or cell-associated RNA without consistent or sustained depletion of reservoir cells, and have raised concerns that cytokine-driven proliferation might paradoxically expand latently infected clones.

Recent efforts have turned to more targeted approaches to boost viral transcription, including the delivery of mRNA-encoded Tat in lipid nanoparticles (Tat-LNPs) to selectively enhance transcription from integrated proviruses while minimizing off-target effects in uninfected cells. Preclinical data from in vitro models support the ability of exogenous Tat to effectively reverse latency, to a larger magnitude than maximal

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mitogenic stimulation with PMA/ionomycin (Cevaal et al., 2025; Pardons et al., 2023). Interestingly, this targeted reactivation induced minimal alterations in the expression of host genes of infected cells, highlighting the limited cellular toxicity and immune activation of this approach. Furthermore, the synergistic potential of Tat-LNPs with other latency-reversing agents was recently reported (Raines et al., 2024), and may be particularly pronounced when Tat mRNA is administered with novel lipid formulations specifically engineered to improve mRNA delivery to hard-to-transfect resting CD4 T cells. Lipid nanoparticles could also deliver CRISPR activation components as larger, more complex, and potentially HIV-1 RNA-specific therapeutics to enhance proviral transcription (Cevaal et al., 2025; Fisher et al., 2025). Nevertheless, these strategies remain at an early stage and await rigorous evaluation in animal models and human studies.

Collectively, more than a decade of clinical and preclinical work aimed at pharmacologically inducing HIV-1 transcription has not yielded major advances in the durable elimination of infected cells. These observations raise important conceptual questions about the extent to which transcriptional latency alone accounts for long-term HIV-1 persistence and suggest that enhancing viral gene expression by itself is unlikely to be sufficient to destabilize the reservoir. A deeper understanding of the physiological behavior of reservoir cells, including their survival pathways, tissue localization, clonal dynamics, and interactions with adaptive and innate immune responses, will likely be required to design more effective viral elimination strategies.

Interactions between reservoir cells and host immune cells

A long-standing paradigm in HIV-1 research has held that owing to their minimal levels of viral transcription and protein expression, HIV-1 reservoir cells largely evade immune recognition and cannot be effectively engaged by host immune effector cells. Consequently, pharmacologic induction of viral transcription has been widely considered a prerequisite for enabling immune-mediated clearance of these cells. However, accumulating evidence challenges this view, suggesting that components of the immune system can recognize and exert selective pressure on reservoir cells even in the absence of latency-reversing interventions.

One of the most compelling observations supporting this view comes from longitudinal analyses following ART initiation, which demonstrate that cells harboring intact proviruses decline more rapidly than those containing defective genomes (Cho et al., 2022; Gandhi et al., 2021; Garcia-Broncano et al., 2019; Peluso et al., 2020). This pattern is best explained by the preservation of full viral coding potential in intact proviruses, whereas defective proviruses frequently lack regions critical for immune recognition, thereby conferring relative resistance to host immune responses. In parallel, the decay of intact proviruses is accompanied by the preferential persistence of infected cell clones harboring intact proviruses with integration sites in heterochromatic regions (Fig. 2). This distribution is consistent with immune-mediated selection against proviruses integrated into transcriptionally active genomic regions, where higher levels of viral gene expression likely enhance immune visibility. Collectively, these data suggest that host immune cells can at least recognize and engage a subset of infected cells, despite the low levels of viral transcription typically observed in reservoir cells.

The specific immune effectors responsible for recognizing and targeting reservoir cells remain an area of active investigation (Fig. 3). In simian immunodeficiency virus (SIV)–infected nonhuman primates (NHPs), multiple lines of evidence support a role for virus-specific CD8 T cells. For example, recent work identified a TOX^{hi} $TCF1^{+}$ $CD39^{+}$ antigen-specific CD8 T cell population in ART-treated animals that combines polyfunctional effector activity with stemlike, self-renewing properties (Strongin et al., 2024). The frequency of this subset inversely correlated with levels of total and intact SIV DNA, as well as cell-associated RNA, in lymph nodes, the principal site of viral persistence. Notably, these cells exhibited the capacity to traffic to germinal centers, a key anatomical reservoir, motivating efforts to enhance T cell access to these compartments therapeutically (Pampena et al., 2025). Similar findings have been reported in animal models of viral posttreatment control, where lower levels of intact SIV DNA in lymph nodes prior to analytical treatment interruption were associated with enhanced CD8 T cell polyfunctionality, proliferative capacity, and antiviral activity (Charre et al., 2026). Augmentation of virus-specific T cell responses in NHP models of SIV infection has also been shown to prolong viral control after ART interruption (Omange et al., 2026). In contrast, experimental depletion of CD8 T cells in ART-treated NHPs did not measurably influence reservoir size, suggesting that effects of CD8 T cells against viral reservoir cells require additional, currently unidentified host factors (Statzu et al., 2023). Overall, these results from the NHP model highlight important differences compared with human studies. In humans, correlations between HIV-1–specific CD8 T cell responses and reservoir sizes are often positive, suggesting that larger reservoirs may drive expansion of virus-specific T cells without necessarily enabling effective clearance (Dube et al., 2023; Stevenson et al., 2021; Takata et al., 2023; Thomas et al., 2017). Evidence for antiviral immune effects of HIV-1–specific T cells in humans is largely confined to elite controllers and posttreatment controllers, where such responses consistently correlate with durable viral control off-treatment. Specifically in study participants who received prior treatment with broadly neutralizing antibodies (bnAbs), posttreatment control was associated with distinct populations of HIV-1–specific CD8 T cells with a T memory stem cell–like transcriptional program and strong functional abilities to proliferate in response to antigenic stimulation (Crain et al., 2026; Kiani et al., 2026; Peluso et al., 2026). These observations correspond well to prior studies in which strong proliferative activities of HIV-1–specific T cells were identified as distinct immunological characteristics of individuals with spontaneous, drug-free control of HIV-1 replication (Migueles et al., 2002).

Of note, efforts to enhance T cell–mediated targeting of reservoir cells have included strategies to induce virus-specific CD8

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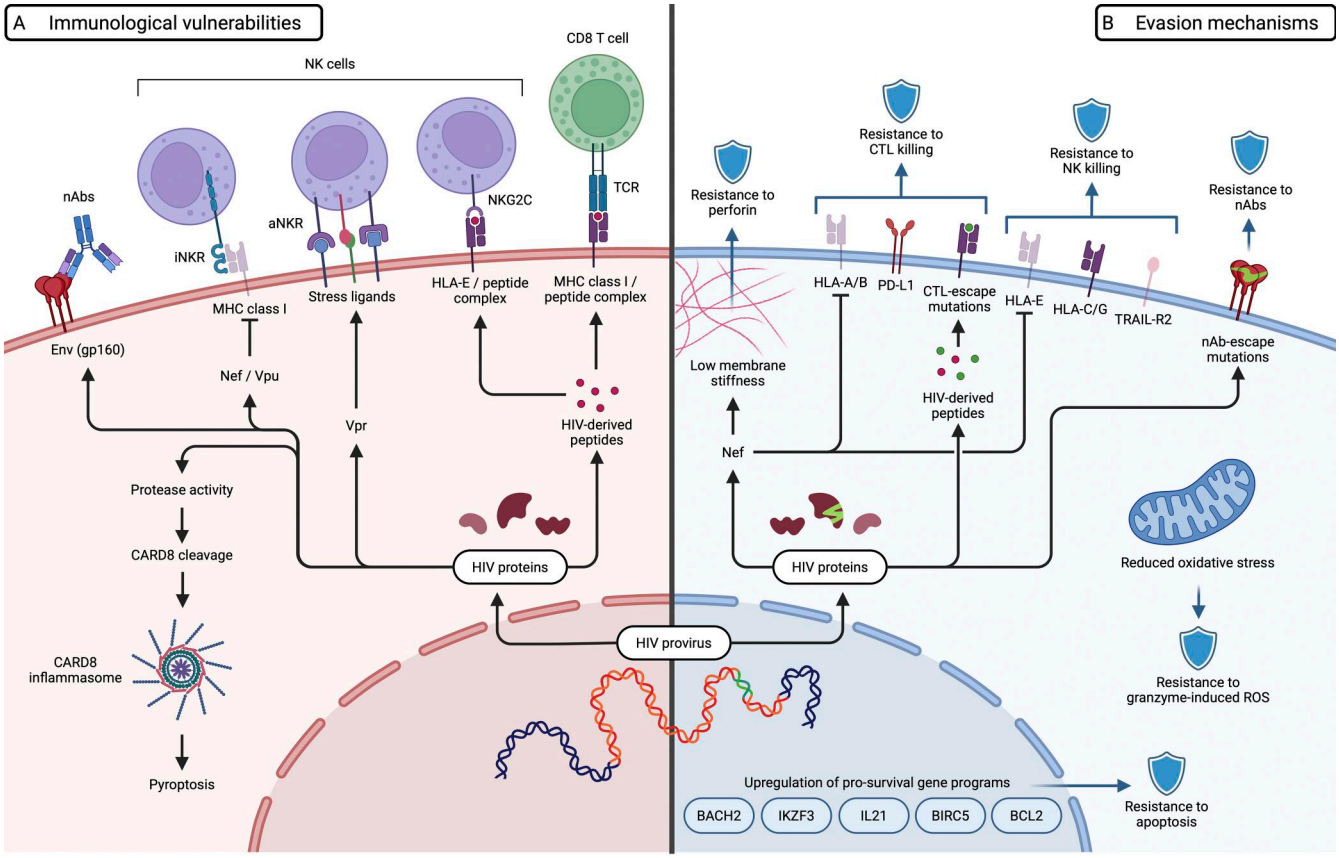

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Figure 3. **Immunological vulnerabilities and immune evasion mechanisms in HIV-1 reservoir cells. (A)** Multiple, partly overlapping effector mechanisms can recognize and target reservoir cells, including virus-specific CTLs, NK cells acting through missing-self recognition, anAbs, and cell-intrinsic innate immune sensing. **(B)** Reservoir cells persist by resisting or evading these responses—for example, through immune escape mutations, engagement of inhibitory NK receptors, resistance to cytotoxic effector molecules, and cell-intrinsic survival programs. aNKR, activating NK receptor; CTL, cytotoxic T lymphocyte; iNKR, inhibitory NK receptor; anAbs, autologous neutralizing antibodies; NK cells, natural killer cells; ROS, reactive oxygen species.

T cells restricted by HLA-E, a nonclassical HLA class Ib molecule with very limited genetic polymorphisms. These efforts are motivated to a large extent by NHP studies demonstrating complete SIV replication arrest in ∼60% of animals that received a cytomegalovirus (CMV)-vectored vaccine designed to induce HLA-E–restricted antiviral T cell responses (Hansen et al., 2013; Hansen et al., 2025). However, HLA-E–restricted HIV-1–specific CD8 T cells are difficult to detect in humans, although recent studies have started to identify specific populations of HLA-E–restricted cytotoxic T cells in elite controllers, specifically against viral epitopes corestricted by HLA-B*57 (Maroney et al., 2026; Sun et al., 2026). Of note, the feasibility of inducing HLA-E–restricted HIV-1–specific CD8 T cell responses through in vitro priming has been demonstrated recently, possibly offering a potential path toward vaccine-mediated induction of such immune responses in vivo (Yang et al., 2021). However, the relative instability of HIV-1–derived peptides complexed with HLA-E raises questions as to whether they could sustain therapeutically relevant levels of antigen presentation (Wallace et al., 2024).

bnAbs have emerged as promising passive immunotherapeutic agents capable of recognizing diverse HIV-1 strains. Clinical trials have demonstrated that bnAbs can delay viral rebound and, in some individuals, contribute to posttreatment control (Fisher et al., 2026; Lee et al., 2026; Peluso et al., 2026). Notably, reductions in reservoir size during bnAb treatment have only been observed in a limited number of studies (Gaebler et al., 2022; Fumagalli et al., 2026; Lee et al., 2026), with additional trials underway to further define these effects. In contrast, autologous neutralizing antibodies, which typically exhibit narrow specificity and are prone to rapid viral escape, may still influence rebound kinetics and contribute to prolonged control in specific individuals—particularly when combined with favorable immunologic conditions and limited proviral diversity (Fisher et al., 2026; Garcia et al., 2026). Therapeutic vaccination strategies aimed at enhancing such autologous antibody responses are currently under investigation.

Cell-intrinsic immune mechanisms also represent a promising avenue for targeting reservoir cells. The CARD8 inflammasome, activated by HIV-1 protease within infected CD4 T cells, can induce pyroptotic cell death and may contribute to CD4 T cell depletion during untreated infection (Wang et al., 2024). This pathway can be therapeutically exploited using "targeted activators of cell kill," which induce premature activation of HIV-1 protease, thereby enhancing CARD8-mediated

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recognition and selective elimination of infected cells after pyroptosis induction (Balibar et al., 2023; Hollander et al., 2025). Clinical evaluation of these agents will be essential to determine their translational potential.

Emerging data also implicate natural killer (NK) cells in the recognition and control of HIV-1 reservoir cells. Multi-omics analyses of reservoir cells from early-treated individuals have revealed phenotypic signatures consistent with NK cell–mediated immune selection, including upregulation of HLA-C and HLA-G, which confer protection from KIR- and LILRB1-expressing NK cells, respectively (Sun et al., 2024). Complementary in vitro studies demonstrate that HIV-1–infected CD4 T cells that survive NK cell killing exhibit increased expression of HLA-A, HLA-B, and HLA-E, enhancing resistance to NK cells while potentially increasing susceptibility to CD8 T cell responses (Grasberger et al., 2026, *Preprint*). These observations suggest a dynamic interplay between NK cells and T cells in shaping reservoir composition, although this remains to be fully elucidated. Of note, a subset of NK cells expressing NKG2C can be activated by pathogen-derived peptides presented on HLA-E, raising the possibility that HIV-1–derived peptides presented via HLA-E may modulate NK cell responses (Hammer et al., 2018; Jost et al., 2023). Additional support for a role of NK cells in restricting HIV-1 reservoir size comes from recent observations in a larger cohort of 104 study persons on long-term (~20 years) ART, in whom frequencies of intact proviruses were inversely associated with KIR2DL1-educated, NKG2C$^+$ "adaptive" NK cells, and were significantly lower in carriers of immunogenetic characteristics favoring effective KIR-dependent NK cell education (Tan et al., 2026). Moreover, associations between NK cell education and posttreatment control of HIV-1 replication were reported in young children (Niesar et al., 2026), in SIV-infected non-human primates (Chapel et al., 2026) and in a unique group of adult posttreatment controllers from the VISCONTI cohort (Essat et al., 2025). Other pathways possibly involved in NK cell–mediated lysis of HIV-1–infected cells have also been described, including the recognition of stress molecules on the cell surface of infected cells through different activating NK receptors, such as NKp30, NKG2D, or DNAM-1 (Matusali et al., 2012; Pi et al., 2025). Beyond NK cells, it is possible that γδ T cells, another key immune effectors involved in the recognition of stressed virally infected cells, could also target the HIV-1 reservoir, specifically when co-expressing surface markers involved in innate immune recognition of HIV-1; investigating such mechanisms remains an important area for future investigations (Mann et al., 2025).

Collectively, these findings point to a complex, multilayered, and bidirectional interaction between the immune system and HIV-1 reservoir cells. Rather than being governed by a single dominant effector mechanism, immune-mediated control of the reservoir likely emerges from the coordinated action of multiple components—including CD8 T cells, NK cells, and cell-intrinsic pathways—whose relative contributions vary across anatomical sites, stages of infection, and host and viral genetic contexts (Fig. 3 A). This integrated perspective may help explain the heterogeneity of outcomes observed across experimental systems and study participant populations, and provide a conceptual framework for the development of combinatorial cure strategies.

Intrinsic mechanisms of reservoir cell survival and persistence

Cells that harbor the viral reservoir during long-term ART are, by definition, survivors. However, infected cells do not merely persist; they can also actively proliferate and expand. Their persistence therefore relies, at least in part, on established mechanisms of T cell homeostasis that sustain infected cell clones. Clonal expansion of infected cells may be driven by at least three distinct, nonmutually exclusive mechanisms. First, proliferation in response to cognate antigen stimulation is likely the predominant driver, with antigens associated with chronic herpesvirus infections, particularly CMV and Epstein-Barr virus, representing an important source of persistent antigenic stimulation (Mendoza et al., 2020; Simonetti et al., 2021). Second, homeostatic proliferation induced by cytokines such as IL-7 and IL-15 may promote the expansion and long-term maintenance of infected cells (Chomont et al., 2009). Third, proviral integration may also contribute to the clonal expansion of infected cell populations through insertional mutagenesis of genes involved in cellular growth, survival, or proliferation (Maldarelli et al., 2014; Wagner et al., 2014). Of note, clonal proliferation of infected cells may be particularly critical for reservoir maintenance because it can permit to outpace antiviral immune surveillance and resist negative host selection factors (Einkauf et al., 2022). Yet, the mechanisms by which reservoir cells acquire this competitive fitness advantage and adopt a possible state of enhanced turnover remain poorly defined (Fig. 3 B).

Recent progress in delineating intracellular pathways and programs that promote the survival of infected cells has been driven by a new generation of single-cell technologies. These approaches permit selective interrogation of rare HIV-1–infected cells embedded within vast excesses of uninfected cells derived from individual study participants. By leveraging the detection of viral RNA and/or DNA reads in high-throughput single-cell RNA sequencing (RNA-seq) and assay for transposase-accessible chromatin using sequencing (ATAC-seq) datasets, such studies can contrast transcriptional and epigenetic features that distinguish infected from uninfected cells. These complex analyses, now implemented by multiple groups (Frouard et al., 2026; Peterson et al., 2026; Wei et al., 2025; Wu et al., 2023), have revealed a number of host genes that are upregulated in infected cells and could potentially be causally involved in viral reservoir cell persistence, although they could also influence cellular permissiveness to viral infection pre-ART. Among others, upregulation of the genes IKZF3, IL-21, and BIRC5 has been observed in infected cells, where their increased expression can augment proliferative capacity, promote survival under cellular stress conditions, or otherwise enhance cellular resilience (Wei et al., 2023). When applied to gut tissues, these assays further identified epigenetic activation of BACH2 in virally infected CD4 T cells, driving a durable, stem cell–like transcriptional program and diverting cells away from terminal differentiation states more prone to activation-induced cell death (Wei et al., 2025).

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Notably, this BACH2-governed survival program has also been documented in reservoir cells from peripheral blood, and experimental deletion of BACH2 in circulating CD4 T cells in a murine model of ART-treated HIV-1 infection reduced viral persistence and limited viral rebound (Gao et al., 2025).

An alternative single-cell strategy—based on high-throughput single-cell multiplex PCRs to identify infected cells through strategic amplification of viral DNA segments—similarly demonstrated upregulation of survival markers, including the IL-7 and IL-21 receptors, on cells harboring intact proviruses (Sun et al., 2023a). These observations further reinforce the concept that selection for cells with favorable, cell-intrinsic survival programs is a fundamental mechanism underpinning reservoir persistence. A particularly compelling example further supporting this hypothesis involves the anti-apoptotic protein BCL-2, which plays a well-established role in sustaining malignant B cell survival in chronic lymphocytic leukemia and is an approved therapeutic target in that setting. Evidence supporting a role for BCL-2 in maintaining HIV-1 persistence emerges from in vitro infection models (Arandjelovic et al., 2023; Ren et al., 2020), from murine models of HIV-1 infection (Chandrasekar et al., 2022), and from NHP studies (Salinas et al., 2026), in which pharmacologic BCL-2 inhibition at the time of ART initiation induced a durable reduction in reservoir size. Human clinical trials exploring pharmacologic effects of BCL-2 inhibition on viral reservoir cell persistence are currently underway.

Beyond upregulating survival and proliferative programs, HIV-1 reservoir cells may be specifically adapted to evade immune-mediated killing. Initial support for this concept came from tissue culture model systems, and it has recently been examined in more depth using "authentic reservoir clones" (ARCs)—HIV-1–infected cell clones directly isolated from study participants via limiting-dilution culture (Ferreira et al., 2026). Functional assays across eight ARCs revealed marked heterogeneity in susceptibility to autologous HIV-specific cytotoxic T lymphocytes (CTLs). One clone with a regulatory T cell phenotype and another clone with a Th1-like phenotype displayed pronounced cell-intrinsic resistance downstream of CTL recognition. A third clone exhibited intermediate levels of resistance, and the rest of them were efficiently eliminated by autologous CTLs. Importantly, this resistance was linked to a state of reduced oxidative stress that could be reversed by treatment with deferoxamine, a Food and Drug Administration–approved iron chelator that increases hypoxic stress. Complementing these findings, decreased cell membrane stiffness—potentially mediated by the viral Nef protein—may lower the susceptibility of infected cells to T cell–mediated cytotoxicity, as perforin can efficiently form lytic pores only when the cytoskeleton provides sufficient mechanical rigidity (Leyre et al., 2025, *Preprint*). This model aligns with earlier observations that mechanically "soft" leukemic T cells can resist perforin-dependent CTL killing (Zhou et al., 2024).

Consistent with these mechanistic insights, single-cell proteogenomic profiling has shown that compared with the overall memory CD4 T cell compartment, reservoir cells harboring intact proviruses frequently express elevated levels of negative immunoregulatory molecules that deliver "do not kill me" signals to CTL and NK cells, suggesting preferential survival of such cells during prolonged ART (Sun et al., 2023a). In line with these observations, in vitro studies demonstrated that reservoir cells surviving repeated rounds of NK cell–mediated attack downregulated the death receptor TRAIL-R2, thereby attenuating activating signals to NK cells and reducing susceptibility to NK cytotoxicity (Grasberger et al., 2026, *Preprint*). Moreover, in NHP models, dual blockade of the immune checkpoint PD-1 and of IL-10 restored CD8 T cell function and delayed SIV rebound, an effect attributed at least in part to epigenetic remodeling of type I interferon–related loci (Ghneim et al., 2026). However, translating such immunomodulatory strategies into human interventions is challenging because of the known toxicity of immune checkpoint inhibitors. In particular, studies of PD-1 blockade in individuals on ART revealed clinically meaningful autoimmune manifestations, which likely preclude the use of these agents in otherwise healthy, virologically suppressed persons (Gay et al., 2024; Ramgopal et al., 2025). Nevertheless, administration of PD-1 antibodies to PLH for concomitant oncologic indications revealed activation of HIV-1–specific T cell responses and antiviral type I interferon signatures (Talla et al., 2026).

Anatomical niches supporting HIV-1 reservoir persistence

Beyond cell-intrinsic barriers to immune-mediated killing, anatomical localization provides an additional layer of protection for HIV-1 reservoir cells by limiting immune surveillance in specific tissue niches illustrated in Fig. 4. The central nervous system (CNS) is a prototypical immune sanctuary, due to the blood–brain barrier that tightly regulates access of immune cells, arguably to limit uncontrolled entry of inflammatory cells and mediators and avoid bystander immune damage to neurons. However, digital droplet–based PCR assays and near–full-length single-genome proviral sequencing have demonstrated the persistence of intact HIV-1 proviruses in brain tissue (Cochrane et al., 2022; Nuhn et al., 2025; Sun et al., 2023b), likely suggesting that virally infected CD4 T cells can, in certain cases, penetrate the CNS, and either find a local tissue environment conducive to their persistence or act as "Trojan horses" to infect long-lived resident cells of the CNS. Such cells include microglia, a long-lived and self-renewing form of CNS macrophages; experimental findings using autopsy material from PLH indeed demonstrated outgrowth of HIV-1 from microglia, with isolation of viral species competent to infect both microglia and CD4 T cells in vitro (Tang et al., 2023). Consistently, application of single-cell sequencing technologies to rapid autopsy brain samples revealed the presence of integrated HIV-1 DNA and HIV-1 transcripts in about 0.5% of microglia (Schlachetzki et al., 2024). Seeding of proviruses in the CNS could also involve HIV-1–infected monocytes that are able to migrate through the blood–brain barrier and differentiate into long-lived perivascular macrophages (Veenhuis et al., 2023). Viral infection of these CNS cells can result in disrupted neuronal homeostasis, potentially driving AIDS-associated neurological complications. Of

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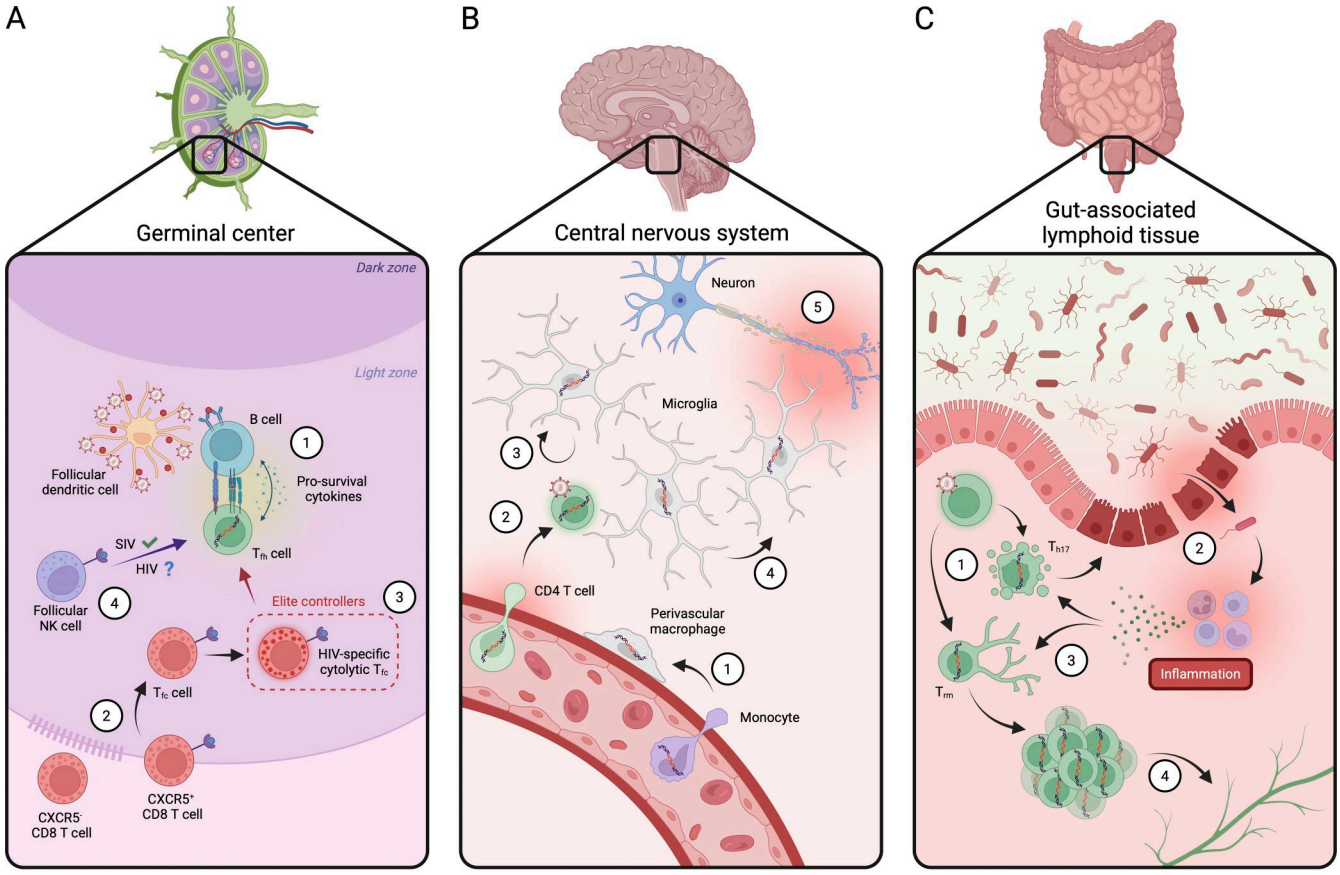

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Figure 4. **Critical anatomical compartments supporting HIV-1 reservoir persistence. (A)** In the lymph nodes, germinal centers are a favorable environment for HIV-1 persistence. 1: Tfh are very permissive to infection and persist long term due to survival signals provided by interacting B cells. 2: Most CD8 T cells are excluded from the germinal center light zone, but a rare fraction of CXCR5$^+$ CD8 T cells can enter and constitute a Tfc population. 3: In elite controllers, this Tfc population has a higher frequency of HIV-specific cells, with an increased cytolytic potential. 4: Follicular NK cells may accumulate in lymph nodes; however, their ability to mediate reservoir clearance has only been demonstrated in NHP models. **(B)** CNS is separated from the peripheral blood compartment by the BBB. 1: However, infected monocytes can cross the BBB and possibly populate the perivascular space, resulting in a long-lived perivascular macrophage reservoir. 2: CD4 T cells can, in some cases, cross the BBB as well and infect microglia, potentially through cell-to-cell transmission. 3: Microglia are long-lived, self-renewing cells, which upon infection can promote long-term persistence of HIV in the CNS. 4: Cell-to-cell transmission can also occur between microglia. 5: Loss of microglial homeostasis resulting from HIV-1 infection has been linked to neuron damage and development of neurological non-AIDS complications such as HIV-associated neurocognitive disorders. **(C)** Gut T helper 17 (Th17) lymphocytes are preferentially depleted, early on during HIV-1 infection. 1: Loss of Th17 homeostasis results in impaired epithelial integrity. Some infected Th17 cells transition to a Trm phenotype. 2: Continuous microbial translocation events lead to sustained local inflammation and drive chronic systemic immune activation, which has been associated with non-AIDS adverse outcomes. 3: Gut bacteria–derived peptides can trigger cognate CD4 responses, further fueling the expansion of some reservoir clones. 4: Gut reservoir cells can be a major source of proviral dissemination, especially to gut-draining lymph nodes, and serve as primary sites for fueling rebound viremia. Tfh, follicular helper T cells; Tfc, follicular cytolytic T cell; BBB, blood–brain barrier; Trm, long-lived resident memory T cell.

note, proviral dynamics between the blood and CNS compartments could be bidirectional, as suggested in an autopsy study inferring reservoir dissemination routes from phylogenetic evolution of viral env sequences (Chaillon et al., 2020). These observations are of relevance for HIV-1 cure strategies since they suggest that viral reservoirs in the CNS could possibly act as a plausible source for viral rebound, although additional experimental studies will be necessary to more definitively investigate this.

The gastrointestinal tract also warrants particular attention as an anatomical location for HIV-1 persistence because the gut contains most of the body's CD4 T cells, and viral reservoir cells are disproportionately enriched in gut-associated lymphoid tissue (Chaillon et al., 2020; Estes et al., 2017). Early in infection, HIV-1–driven depletion of mucosal Th17 cells disrupts the epithelial barrier and promotes chronic local inflammation, which is only partially reversible during ART and is a well-recognized driver of systemic immune activation in PLH (Brenchley et al., 2006; Kim et al., 2013). Within this perturbed milieu, Th17 cells become preferential targets for viral infection and reservoir establishment (Peterson et al., 2026). Under the influence of BACH2, cells can then be redirected into a long-lived, tissue-resident memory phenotype (Wei et al., 2025). In this way, mucosal damage, cell-intrinsic programming, and anatomical localization can converge to sustain viral persistence. Within this already favorable niche, the gut microbiome appears to

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further shape reservoir biology. In an autopsy study spanning multiple gastrointestinal segments, Trunfio et al. found that microbiome diversity correlated positively with reservoir transcriptional activity, measured as multiply spliced Tat/Rev RNA, in the small intestine, but negatively with viral transcription in the colon. No association was seen with total HIV-1 DNA, although intact proviral DNA was not specifically quantified and might have revealed different patterns (Trunfio et al., 2026). Building on this, Espinosa Ortiz et al. reported an enrichment of HIV-1 proviruses in circulating gut bacteria–specific CD4 T cells compared with bulk or CMV-specific CD4 T cells; these bacteria-specific infected cells were heavily clonally expanded, consistent with repeated stimulation by enteric antigens (Espinosa Ortiz et al., 2026, *Abstract*). These findings align with phylogenetic analyses of viral sequences from multiple anatomical sites, which implicate the gut as a major source of viral dissemination to other tissues (Chaillon et al., 2020), and are further supported by in vivo NHP studies with barcoded SIV, showing that gut-resident reservoir cells are a principal source of rebound viremia after treatment interruption (Keele et al., 2026). Together, these data support a model in which gut reservoir cells are expanded and stabilized by antigen-driven clonal proliferation and, in the context of persistent immune activation, assume a disproportionate role in fueling viral rebound.

Recent work has also refined the long-standing view of lymph node germinal centers as privileged sanctuaries for long-term HIV-1 persistence. Indeed, the main cellular compartment harboring HIV-1 in lymph nodes is follicular helper T cells, which receive potent and sustained survival signals from interacting B cells in the germinal center light zone (Perreau et al., 2013). In addition, this anatomical location retains a relative immune privilege, due to the fact that they can be poorly accessed by cytotoxic T cells. More recent studies, however, indicate a more nuanced role of germinal centers for viral persistence. In particular, in at least a subset of individuals with elite viral control, HIV-1–specific CXCR5^{+} CD8 T cells can infiltrate germinal centers and constrain ongoing viral replication (Collins et al., 2023). Consistently, analyses of paired lymph node and peripheral blood samples from elite controllers further show that lymph nodes can harbor lower frequencies of intact proviruses than blood (Marzi et al., 2025), suggesting that in this context, lymphoid tissues do not invariably function as protected sanctuaries but can also become sites of effective antiviral immune surveillance. Finally, while the accumulation of NK cells in lymph nodes of PLH has long been described, only recently has their involvement in HIV-1 reservoir targeting been suggested. Indeed, in an African green monkey model of SIV infection, NKG2A^{low} NK cells were expanded in lymph nodes and mediated potent HLA-E–restricted SIV-directed cytotoxic responses (Huot et al., 2021). The validity of such findings in humans deserves further studies, with important implications for HIV-1 cure strategies.

Prospects and strategies toward a cure for HIV-1 infection

With >40 million people who live with HIV-1 worldwide and for whom lifelong antiretroviral suppression treatment represents the only available treatment option, it is clear that the development of a safe, effective, and scalable curative therapeutic intervention for HIV-1 infection would have a transformative impact on global health. To date, such a cure has been reported in at least seven individuals with concomitant hematologic malignancies who underwent allogeneic hematopoietic stem cell transplantation (HSCT) using donor cells homozygous for the CCR5Δ32 mutation, thereby conferring resistance to R5-tropic HIV-1. Interestingly, emerging evidence suggests that stem cell transplantation from donors heterozygous for the CCR5Δ32 variant or even homozygous for the wild-type allele may, under certain conditions, also provide clinical benefit (Sáez-Cirión et al., 2024; Chapel et al., 2026; Gaebler et al., 2026). These rare cases challenge our understanding of how HSCT can support a cure of HIV-1 infection and provide a foundational basis for a hypothetical graft-versus-HIV reservoir effect (Gaebler et al., 2025). In addition, the use of cord blood units harboring the CCR5Δ32 mutation may further broaden donor availability, particularly for individuals lacking suitably matched adult donors (Hsu et al., 2023). Nevertheless, these approaches remain limited to highly selected clinical contexts involving severe hematologic diseases and are not readily generalizable as widely applicable therapeutic strategies for the broader population of PLH.

How can insights into the mechanisms of HIV-1 persistence and the dynamics of viral reservoir cells then inform the rational design of curative interventions with broader applicability for PLH? We propose that the most important, and arguably most actionable, finding from recent studies in HIV-1 reservoir cell biology is the discovery of a previously underappreciated degree of immunological vulnerability within the viral reservoir cell pool, challenging earlier models that framed latency and proviral transcriptional silence as the principal barriers to eradication. The identification of these vulnerabilities provides a strong conceptual foundation for therapeutic strategies that actively harness the immune system to target reservoir cells, particularly since accumulating evidence indicates that latently infected cells retain features rendering them susceptible to immune-mediated clearance, even when proviral gene expression is low and/or intermittent. Building on this evolving perspective, a central objective for HIV-1 cure research is to define, at the molecular and cellular level, how reservoir cells can be effectively recognized, targeted, and eliminated by host immune responses.

We anticipate that clinical strategies designed to exploit these immunological vulnerabilities will likely require combinatorial interventions that can synergistically attack multiple weaknesses within the reservoir cell pool, engaging diverse and complementary components of the immune system's armamentarium. For instance, an initial step in such interventions could aim to reduce the frequency of infected reservoir cells through pharmacologic approaches that destabilize the viral reservoir, such as agents that sensitize infected cells to intrinsic death pathways. Alternatively, such strategies could involve immune interventions that engage effector cell populations specifically designed to recognize infected cells with low or intermittent antigen production, including T cell engagers, chimeric antigen receptor (CAR)-T or CAR-NK cell products, or

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other engineered cellular therapies. A subsequent, secondary intervention could then be administered to block rebound viremia and sustain long-term immune surveillance over the small reservoirs of infected cells that survive initial reservoir-reducing strategies. Of note, a quantitative reduction of the viral reservoir is likely to constitute a valuable clinical objective in its own right, independently of any effect on rebound or drug-free immune control. Indeed, emerging evidence links reservoir size to the risk of non-AIDS comorbidities, including cardiovascular disease, carotid atherosclerosis, liver fibrosis, and malignancies, with these associations persisting even after adjustment for age, sex, and nadir CD4 T cell counts (Delporte et al., 2026, *Abstract*). Interventions that reduce viral reservoir burden may therefore address the critical unmet need of reducing the persistent excess morbidity observed in PLH despite effective ART.

Importantly, given the profound diversity of HIV-1 sequences circulating worldwide, and the notable variations in host immunogenetic profiles that impact the evolution of innate and adaptive immune responses, the development of "one-size-fits-all" immune interventions with universal global applicability is unlikely. Rather, we argue that progress in defining actionable immunological targets for curative interventions of HIV-1 will require a deep characterization of the host and viral immunogenetic profile, which would then permit to customize and tailor interventions specifically to the viral and host genetic backgrounds of a given individual. For example, personalized mRNA-based vaccines incorporating autologous viral sequences could be leveraged to direct both innate and adaptive immune responses against participant-specific vulnerabilities within the reservoir, while blocking viral immune escape through viral sequence diversification with ART. Such an approach could be enabled by continued innovation in next-generation sequencing technologies, coupled with anticipated reductions in sequencing costs that will facilitate scalability and broader implementation. To realize this vision, future research efforts could prioritize large-scale, integrative analyses of viral and host genomic data, ideally within globally representative cohorts encompassing diverse regions of the epidemic and with balanced representation of sexes and inclusion of pediatric and adolescent populations across different stages of infection. These studies should be tightly coupled with mechanistic investigations to elucidate how specific immune responses can effectively recognize and eliminate reservoir cells. While the challenges of developing curative interventions for HIV-1 remain enormous, we are optimistic that the human immune system, if appropriately primed and directed, can be effectively engaged to recognize and eliminate the persisting reservoirs of virally infected cells that represent the main barrier to a cure of HIV-1 infection.

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