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Mapping and characterizing persistent HIV reservoirs in early-treated individuals: Implications for cure-focused interventions

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ABSTRACT

Despite the transformative impact of antiretroviral therapy (ART), HIV persists in long-lived cellular and anatomical reservoirs that reignite viral replication when treatment is interrupted. Eliminating or durably suppressing these reservoirs remains the central challenge to achieving a cure. Individuals who initiate ART during acute or early infection provide a particularly informative model, as early intervention is generally associated with reduced reservoir size, limited viral diversification, preservation of immune function, and lower levels of inflammation. These features create a valuable biological window for interrogating the earliest events of reservoir seeding and persistence. Recent advances in reservoir mapping including high-sensitivity molecular assays, full-length proviral sequencing, single-cell multi-omics, and spatial imaging have enabled increasingly refined characterization of reservoir composition, cellular identity, clonal dynamics, and tissue distribution. Studies in early-treated cohorts have identified features such as simplified clonal architecture, higher relative inducibility of intact proviruses, and, in some individuals, an increased likelihood of post-treatment control. These insights are informing the development of cure-focused interventions ranging from latency reversal and immune-based strategies to gene-editing approaches and targeted drug delivery. Nonetheless, important challenges remain, including incomplete tissue sampling, assay sensitivity limitations, and uncertainty regarding which cellular and anatomical reservoirs most critically drive viral rebound. Integrative approaches combining multi-omics profiling, predictive biomarkers, and personalized therapeutic strategies will be essential for advancing toward durable ART-free remission.

Keywords: HIV reservoirs, early antiretroviral therapy, acute infection, viral latency, post-treatment control

INTRODUCTION

Four decades into the HIV pandemic, substantial progress in antiretroviral therapy (ART) has transformed infection from a rapidly fatal disease into a manageable chronic condition. Despite this success, the global burden of HIV remains profound, with millions of individuals requiring lifelong therapy and facing ongoing challenges related to treatment access, adherence, drug resistance, and chronic immune activation. ART effectively suppresses plasma viremia but does not eradicate the virus; cessation of therapy almost invariably results in rapid viral rebound. This persistent need for continuous treatment underscores the limitations of current strategies and highlights the pressing need for curative approaches [1].

Operational Definitions

In this review, timing of ART initiation is central to interpretation. We define *acute HIV infection* as the earliest phase of infection corresponding to Fiebig stages I-II, characterized by detectable HIV RNA and/or p24 antigen in the absence of HIV-specific antibodies. *Early HIV infection* refers to Fiebig stages I-V, encompassing the period from initial RNA positivity through evolving seroconversion, typically within the first days to weeks following exposure. The term *very early treatment* is used to describe ART initiation during Fiebig stages I-III, often before or near peak viremia. *Primary infection* is used synonymously with early infection unless otherwise specified. Individuals who initiate ART after full seroconversion (Fiebig VI) are not classified as early-treated in this review and are discussed separately where relevant, as reservoir size, clonal complexity, and post-treatment outcomes differ substantially by timing of ART initiation.

Central to the difficulty of achieving a cure is the presence of long-lived HIV reservoirs. These reservoirs consist of cells and tissues harboring replication-competent virus in a state of reversible latency. They are anatomically widespread most prominently within lymphoid tissues, the gastrointestinal tract, and the central nervous system (CNS) and involve multiple cellular compartments, including various subsets of $CD4^+$ T cells and, potentially, myeloid cells. At the molecular level, reservoir persistence is maintained through integrated proviral DNA that can remain transcriptionally silent yet capable of producing infectious virus upon cellular activation. The stability and heterogeneity of these reservoirs represent major biological obstacles to viral eradication [2].

Individuals who initiate ART during acute or early infection provide a uniquely informative context for studying reservoir biology. Early treatment sometimes within days or weeks of transmission, as defined by the Fiebig staging system limits the extent of viral dissemination, reduces genetic diversification of the virus, and restricts the establishment of long-lived proviral populations. These individuals often demonstrate markedly smaller and less complex reservoirs compared with those who begin therapy during chronic infection. As a result, early-treated cohorts have become invaluable for deciphering the mechanisms of reservoir seeding, persistence, and potential controllability[3].

Early initiation of ART limits the temporal window for viral dissemination and reservoir seeding, making early-treated individuals a valuable model for investigating HIV persistence and informing cure-oriented strategies. Rather than eliminating infection, early ART modifies the biological landscape in which reservoirs form, persist, and respond to intervention. This review synthesizes current evidence on the mechanisms of reservoir establishment, the technologies used to characterize persistence, and the implications of early treatment timing for HIV cure research [4].

Study design and scope

This manuscript is a narrative review synthesizing experimental, clinical, and translational literature on HIV reservoir biology in individuals who initiate ART during acute or early infection. The review integrates findings from virologic, immunologic, and technological studies to examine how early treatment timing shapes reservoir establishment, composition, anatomical distribution, and implications for cure-oriented interventions. Emphasis is placed on studies using advanced reservoir assays, tissue-based analyses, and cohorts treated during defined early infection stages.

BIOLOGY OF HIV RESERVOIR FORMATION IN EARLY INFECTION

Understanding how HIV reservoirs form during early infection provides essential context for interpreting measurements of persistence under suppressive therapy.

Kinetics of Viral Seeding During Acute Infection

The earliest stages of HIV infection are characterized by rapid and widespread dissemination of virus across multiple anatomical compartments. During the eclipse and early Fiebig stages, HIV establishes productive infection within mucosal tissues and draining lymph nodes before systemic viremia becomes detectable. Experimental and clinical studies indicate that reservoir seeding begins within days of exposure, well before peak viremia, and that a small number of initially infected cells can give rise to long-lived proviral lineages. By the time plasma viral load reaches its apex typically within two to four weeks irreversible establishment of the latent reservoir has already occurred. This narrow temporal window represents a major biological constraint on cure strategies, as even minimal early viral replication is sufficient to create a stable population of infected cells capable of long-term persistence.

Tissue tropism during acute infection further shapes the nature of the reservoir. HIV preferentially targets activated $CD4^+$ T cells located in lymphoid tissues, particularly the gut-associated lymphoid tissue (GALT), where high cellular density and a permissive immunological environment enable extensive infection. Early trafficking of the virus to the CNS, spleen, and genital tissues has also been documented. The rapid involvement of these diverse anatomical sites contributes to the complex and compartmentalized structure of the reservoir that later persists despite otherwise effective systemic viral suppression [5].

Impact of Very Early ART Initiation

Initiating ART during the earliest phases of infection sometimes before peak viremia is reached has a profound effect on reservoir size and composition. When therapy is started within days of transmission, the cumulative number of infected cells is markedly reduced, and viral diversification is limited, resulting in a reservoir that is less genetically complex and potentially more amenable to targeted interventions. Early ART also blunts immune activation and attenuates the inflammatory milieu that otherwise promotes widespread viral dissemination and long-term establishment of infected cell populations [6].

Comparative analyses demonstrate stark differences between individuals treated during acute versus chronic infection. Those initiating ART early exhibit dramatically lower levels of integrated proviral DNA, reduced frequency of intact proviruses, and diminished clonality of infected cell populations. In contrast, late-treated individuals harbor larger and more heterogenous reservoirs shaped by ongoing rounds of replication, immune pressure, and cellular turnover. Importantly, early treatment does not prevent reservoir formation entirely, but it significantly constrains the breadth and persistence of the proviral landscape, offering a biological foundation for efforts aimed at achieving durable post-treatment viral remission [7].

Mechanisms of Persistence Despite Early ART

Despite the substantial benefits of early ART initiation, several mechanisms enable the survival and long-term persistence of infected cells. A major contributor is the clonal expansion of $CD4^+$ T cells harboring integrated proviruses. Once viral replication is suppressed, these cells can proliferate in response to antigenic stimulation, cytokine signaling, or homeostatic cues, thereby amplifying specific proviral clones without reactivating viral gene expression. Over time, such clonal lineages can dominate the reservoir, even when the overall burden of infected cells remains low [8].

Integration site biology also plays a pivotal role in persistence. HIV shows a preference for integrating within transcriptionally active regions of the host genome, including genes involved in cell growth and survival. Integration into

certain genomic loci may confer a proliferative advantage or support long-term cellular survival, thereby promoting maintenance of the reservoir independent of ongoing viral replication. Some integration events occur in genes associated with clonal expansion, further reinforcing the stability and expansion of infected cell populations.

Additionally, homeostatic proliferation contributes to reservoir longevity. Memory $CD4^+$ T cells, particularly central memory and stem-cell-like subsets, undergo natural cycles of renewal that allow integrated proviruses to persist for years or even decades. These cells exhibit intrinsic longevity, resistance to apoptosis, and the ability to self-renew, making them particularly resilient components of the reservoir even in individuals who begin ART at the earliest stages of infection [9, 10].

Together, these processes explain why early ART initiation, although beneficial, is insufficient to eradicate the reservoir. Understanding these mechanisms is essential for designing cure-oriented interventions capable of targeting the cellular processes that sustain viral persistence. These mechanisms define how early ART constrains reservoir establishment at a biological level. The resulting virologic and immunological characteristics observed in early-treated individuals are synthesized later.

CURRENT APPROACHES TO MAPPING HIV RESERVOIRS

Defining reservoir biology has been enabled by rapid advances in quantitative, qualitative, and spatially resolved measurement technologies.

A comprehensive understanding of HIV reservoir biology relies on a diverse set of methodologies capable of quantifying, characterizing, and spatially localizing infected cells. No single assay fully captures the complexity of latent infection; rather, insights arise from integrating quantitative, qualitative, and imaging-based approaches. Advancements in molecular and cellular technologies have significantly improved the precision with which reservoirs can be studied, particularly in individuals who initiate ART during early infection [11].

Quantitative Assays

Total HIV DNA

Measurement of total HIV DNA remains one of the most widely used proxies for reservoir size. This approach quantifies both intact and defective proviruses and thus provides an estimate of the total burden of infected cells. Although it lacks specificity for replication-competent virus, total HIV DNA offers utility in cohort comparisons, longitudinal studies, and evaluation of early ART effects [12].

Integrated versus unintegrated DNA

Techniques that distinguish integrated proviral DNA from unintegrated forms, such as 2-LTR circles, allow more refined assessment of reservoir stability. Integrated proviruses represent the long-lived reservoir, whereas unintegrated forms generally reflect recent or abortive infection. The ratio of these species can shed light on ongoing viral dynamics and the degree of suppression achieved with early therapy [13].

Cell-associated RNA

Quantification of cell-associated HIV RNA provides insight into transcriptional activity within latently infected cells. Although not every transcriptionally active cell produces replication-competent virus, these assays help identify proviruses capable of partial reactivation. They also inform evaluations of latency-reversing agents (LRA) and naturally occurring fluctuations in reservoir transcription [12].

Quantitative viral outgrowth assays

Quantitative viral outgrowth assays (QVOA) remains the benchmark for measuring the frequency of cells harboring replication-competent HIV. By inducing viral replication ex vivo, QVOA enumerates infectious units per million $CD4^+$ T cells. Its strengths lie in its specificity for functional virus; however, it underestimates the true reservoir size because not all intact proviruses reactivate under experimental conditions. QVOA also requires large cell inputs and is labor-intensive, limiting its scalability for clinical trials [14].

Qualitative and Precision Assays

Intact proviral DNA assay (IPDA) represents a major advance in distinguishing intact from defective proviruses. By targeting conserved regions commonly deleted or mutated in defective genomes, this assay offers a more accurate approximation of the size of the genetically intact reservoir. It is particularly useful for early-treated cohorts, in whom intact genomes are proportionally enriched [15].

Full-length proviral sequencing

Sequencing approaches that generate near full-length proviral genomes allow detailed classification of proviruses into intact, hypermutated, deleted, or otherwise defective categories. These methods provide unparalleled resolution of reservoir composition, viral evolution, and clonal structures. They also support mapping of integration sites when paired with host-genome sequencing [16].

Single-cell multi-omics (scRNA-seq, ATAC-seq, and TCR-seq)

Single-cell technologies have opened a new frontier in reservoir research. scRNA-seq identifies transcriptional programs associated with infected or reactivated cells; ATAC-seq reveals the chromatin landscape surrounding integration sites; and paired TCR sequencing defines clonal relationships within infected T cell subsets. Multi-omic platforms integrate these datasets to link proviral identity, cellular phenotype, and clonal expansion in unprecedented detail [17].

Spatial transcriptomics

Spatially resolved transcriptomics enables localization of HIV transcripts within intact tissue architecture. This approach provides insight into microenvironmental influences on latency, such as follicular dendritic cell networks, cytokine gradients, and cellular interactions within lymphoid structures. Spatial methods are particularly valuable for studying reservoirs in tissues that differ immunologically from blood [18].

Imaging and Anatomical Reservoir Mapping

Positron emission tomography imaging using radiolabeled antibodies or viral antigens

Positron emission tomography (PET) has emerged as a powerful, noninvasive tool to visualize HIV reservoirs in vivo. Radiolabeled antibodies targeting immune markers or viral components allow detection of metabolically active or antigen-expressing cells within deep tissues. These approaches are especially informative for quantifying residual inflammation and for identifying tissue sites that are inaccessible to biopsy [19].

Lymphoid, CNS, and gastrointestinal reservoirs

Imaging studies confirm that the majority of persistent HIV resides in lymphoid structures, including lymph nodes and GALT. PET imaging and related modalities have also highlighted reservoir persistence in immune-privileged compartments such as the CNS, where drug penetration is variable and myeloid cells may contribute to long-term viral maintenance. Characterizing reservoirs across these anatomical sites is essential for designing systemic cure strategies [20].

Emerging in Vivo Tools

Barcoded viral tracing

Barcoded viral libraries allow researchers to track individual viral lineages as they disseminate and persist within the host. This method provides insight into the number of founder variants establishing the reservoir, clonal expansion patterns, and tissue-specific dynamics of persistence. Early-infection cohorts are particularly informative for these lineage-tracing studies [21].

CRISPR-based lineage tracking

CRISPR-enabled genetic recording systems offer an alternative means of marking infected cells and tracking their progeny over time. These tools can be engineered to insert lineage-specific signatures upon infection, thereby allowing precise reconstruction of the developmental trajectories and proliferation dynamics of reservoir cells [22].

In situ hybridization (RNAscope and related methods)

Advanced in situ hybridization techniques detect viral RNA or DNA within fixed tissue sections at single-cell resolution. These methods preserve spatial context, enabling researchers to characterize the anatomical niches occupied by infected cells, identify supportive cellular interactions, and investigate microenvironmental factors that promote latency [23].

TISSUE AND CELLULAR NICHES OF PERSISTENT RESERVOIRS IN EARLY-TREATED INDIVIDUALS

Even when ART is initiated during acute HIV infection, a diverse array of cellular and anatomical niches can harbor long-lived proviral genomes. The characteristics of these reservoirs differ across cell types and tissues, reflecting distinct microenvironmental conditions, immune interactions, and proliferative dynamics. Mapping these niches in early-treated individuals provides crucial insight into the biological constraints that limit the possibility of complete viral eradication [24].

$CD4^+$ T Cell Subsets

Central memory, transitional memory, and stem-cell memory T cells

Memory $CD4^+$ T cell subsets represent the dominant reservoir across infection stages, including in individuals treated very early. Central memory T cells (TCM), characterized by their longevity, robust proliferative capacity, and ability to home to lymphoid tissues, remain a major source of persistent proviral DNA. Transitional memory T cells (TTM) contribute to the reservoir through intermediate longevity and heightened susceptibility to infection during acute immune activation. Stem-cell memory T cells (TSCM), despite representing a small fraction of circulating $CD4^+$ T cells, are particularly potent reservoirs due to their self-renewal properties and capacity to differentiate into multiple T cell lineages. Their exceptional longevity means that intact proviruses integrated within these cells can persist for decades, even in early-treated individuals with otherwise limited reservoir size [9].

Follicular helper T cells as a sanctuary site

Follicular helper T cells (TFH) cells, residing within B cell follicles in secondary lymphoid tissues, constitute a specialized and highly permissive niche for HIV persistence. Their location within germinal centers, which $CD8^+$ T cells poorly infiltrate, provides a degree of immune protection that allows infected TFH cells to persist despite robust systemic viral suppression. Early ART reduces but does not eliminate TFH infection, and studies consistently show that lymph node follicles harbor some of the highest concentrations of replication-competent virus in early-treated individuals. The unique immunological environment of germinal centers including abundant IL-21 signaling and ongoing B cell interactions may further support survival and proliferation of TFH-associated proviruses [9].

Myeloid Lineage Reservoirs

Macrophage and microglial reservoirs

Cells of the myeloid lineage have long been proposed as contributors to HIV persistence, particularly in tissue compartments where macrophages are abundant. Tissue-resident macrophages can survive far longer than circulating monocytes and may persist in a semi-activated state conducive to maintaining latent infection. In the CNS, microglia and perivascular macrophages are among the earliest cellular targets upon viral entry and may sustain infection under conditions where ART penetration varies [25].

Controversies: True persistence vs. uptake of infected cells

Despite circumstantial evidence, the existence of a stable and replication-competent myeloid reservoir remains a topic of debate. Some studies suggest that detected viral nucleic acids in macrophages derive from phagocytosis or uptake of infected T cells rather than genuine infection. Distinguishing true persistence from passive acquisition is technically challenging, particularly in tissues with limited sampling accessibility. Early-treated individuals offer a useful model for addressing this question, as the reduced burden of infected T cells makes it easier to evaluate whether macrophage-associated viral material reflects authentic infection. However, definitive evidence remains unresolved, underscoring the need

for more refined lineage-specific and integration-site analyses [26].

Anatomical Compartments

Lymph nodes

Lymphoid tissues are among the earliest and most heavily seeded sites during acute infection. Even with rapid ART initiation, lymph nodes retain substantial numbers of infected TCM and TFH cells, as well as clonally expanded proviral populations. The dense cellular architecture, limited cytotoxic T lymphocyte access to germinal centers, and persistent immune activation contribute to ongoing reservoir stability [27].

GALT

The gastrointestinal tract is a major reservoir due to its vast $CD4^+$ T cell density and early depletion during acute infection. Although early ART reduces viral dissemination in GALT, the tissue's large immunological surface area and slower immune restoration compared with blood allow proviral genomes to endure. Residual inflammation and microbial translocation may further sustain local reservoir maintenance [5].

CNS

Limited drug penetration, immune privilege, and long-lived microglial populations make the CNS a potential reservoir even in early-treated individuals. While ART reduces viral RNA in the cerebrospinal fluid, low-level infection can persist within microglia and perivascular macrophages. CNS reservoirs pose unique challenges, both for sampling and for designing cure strategies that effectively target this compartment [28].

Genital tract

The genital mucosa can harbor persistent proviral DNA, although reservoir magnitude varies between men and women and across tissues such as the cervix, vagina, and seminal tract. Early ART reduces viral shedding and tissue viral burden yet localized immune activation and compartmentalized viral evolution can contribute to reservoir maintenance [29].

Bone marrow

Bone marrow contains long-lived hematopoietic and stromal cells capable of harboring integrated HIV. Although the contribution of this compartment to systemic persistence remains less well-characterized, studies suggest that progenitor cells and resident memory T cells in the marrow can support long-term proviral survival [30].

Implications of sanctuary site pharmacology

Anatomical sanctuary sites frequently display suboptimal ART penetration, creating microenvironments where low-level viral transcription or cell survival may persist despite systemic suppression. Differences in drug distribution across lymphoid tissues, CNS compartments, and mucosal sites shape reservoir maintenance and may influence the efficacy of cure interventions. Understanding pharmacological gradients within these tissues is therefore essential for designing therapies that can reach and eliminate hidden proviral populations.

DISTINCTIVE FEATURES OF RESERVOIRS IN EARLY-TREATED INDIVIDUALS

Building on the mechanistic framework outlined before, this section focuses on the distinctive virologic, immunologic, and clonal features observed in individuals who initiate ART during acute or early HIV infection

Initiation of ART during acute HIV infection profoundly influences the size, composition, and functional properties of the viral reservoir. Compared with individuals who begin therapy during chronic infection, early-treated individuals harbor reservoirs that are smaller, less genetically heterogeneous, and often more immunologically favorable for cure-focused interventions. These distinctive features provide critical insights into the biological mechanisms that support durable viral remission and highlight why early therapy represents a unique model for understanding reservoir persistence [31].

Smaller Reservoir Size and Lower Genetic Diversity

One of the most consistent findings across early-treatment cohorts is the markedly reduced size of the latent reservoir. Early ART limits the duration of uncontrolled viral replication, sharply restricting the number of infected cells that become long-lived memory populations. As a result, total and integrated HIV DNA levels are substantially lower than in chronically treated individuals. In parallel, the genetic diversity of the reservoir is diminished because fewer viral variants are able to disseminate and establish proviral lineages before suppression is achieved. This reduction in genetic complexity has important implications: smaller, less diverse reservoirs are theoretically more amenable to targeted immune-based or molecular eradication strategies [32].

Reduced Immune Exhaustion Signatures

Early suppression of viremia mitigates the prolonged immune activation that characterizes untreated HIV infection. Consequently, $CD4^+$ and $CD8^+$ T cells from early-treated individuals display lower levels of exhaustion markers such as PD-1, TIGIT, and LAG-3. These immunological differences may influence reservoir persistence in several ways. First, reduced immune exhaustion may preserve antiviral $CD8^+$ T cell function, enhancing the capacity for immune surveillance of reactivating cells. Second, lower levels of immune activation reduce the likelihood that newly infected cells form stable reservoirs. Finally, diminished chronic inflammation supports the survival of less differentiated memory T cell subsets, altering the overall reservoir landscape [33]. Together, these immunological features may contribute to a more dynamic and potentially more controllable reservoir in early-treated individuals.

Distinct Clonal Architecture

The clonal composition of the reservoir differs substantially between early- and late-treated individuals. Although clonal expansion is a universal feature of HIV persistence, the timing of ART influences the degree and nature of this proliferation. Early ART limits initial seeding events, which means that a relatively small number of founder viruses may dominate the reservoir. Over time, these early-established infected cells can undergo homeostatic or antigen-driven proliferation, giving

rise to expanded clones that represent a large proportion of the total reservoir despite their limited overall size.

Importantly, early-treated individuals tend to harbor fewer large, highly expanded clones compared with those treated during chronic infection. The relative simplicity of this clonal architecture facilitates integrative analyses of proviral fate, integration sites, and proliferative dynamics. This simplified landscape also provides a more tractable model for studying how specific clones persist or decline over time [34].

Higher Prevalence of Intact Proviruses

A paradoxical feature of early-treated individuals is that, while their overall reservoir is smaller, a higher proportion of proviruses are genetically intact. In chronic infection, ongoing rounds of replication, immune pressure, and intrinsic cellular processes generate a large burden of defective genomes. In contrast, early suppression prevents the generation and accumulation of these defective proviruses, resulting in a reservoir enriched for intact genomes with replication potential.

This enrichment underscores a key challenge: even small reservoirs may represent a meaningful barrier to cure if they contain a high frequency of functional proviruses capable of reactivation. At the same time, the reduced complexity of the reservoir may make these intact genomes easier to target through latency reversal, immune-based strategies, or gene-editing approaches [34].

Enhanced Potential For Post-Treatment Control

Perhaps the most clinically significant feature of early-treated individuals is their increased likelihood of achieving post-treatment viral control. Several cohorts including those treated in very early Fiebig stages have demonstrated delayed or absent viral rebound following structured treatment interruption. Multiple factors likely contribute to this phenomenon, including preserved antiviral immunity, limited reservoir diversity, reduced immune exhaustion, and the restricted anatomical and cellular distribution of infected cells.

Although complete functional cure remains rare, early therapy clearly shifts the immunologic and virologic landscape toward one that is more favorable for long-term control. Understanding the mechanisms that enable post-treatment remission in these individuals may guide the development of therapeutic interventions that replicate such conditions in those treated during chronic infection [16].

HOST AND IMMUNE FACTORS SHAPING RESERVOIRS WITH EARLY ART

The interaction between the host immune system and HIV profoundly influences the establishment, composition, and persistence of latent reservoirs, even when ART is initiated during acute infection. Early ART alters but does not eliminate the innate and adaptive immune processes that shape reservoir dynamics. Understanding these immunologic determinants is essential for identifying individuals most likely to achieve durable remission and for designing cure strategies that harness or augment host immunity [6].

Innate Immune Responses

Type I interferon dynamics

Type I interferons (IFNs) are rapidly induced upon HIV exposure and play a dual role in shaping reservoir formation. On one hand, IFN signaling can restrict viral replication early by inducing antiviral effector pathways and limiting dissemination. On the other hand, sustained IFN activation contributes to immune dysfunction, persistent inflammation, and the expansion of target cells susceptible to infection. Early ART initiation tempers prolonged IFN-driven inflammation while preserving its early protective effects. This altered IFN landscape may contribute to the smaller, less diversified reservoirs observed in individuals treated within days or weeks of infection [35].

Natural killer cells

Natural killer (NK) cells exert important antiviral activity during acute infection and continue to influence reservoir maintenance under ART. Early treatment preserves NK cell cytotoxic potential and supports the maintenance of subsets with stronger antiviral phenotypes, including those expressing NKG2C, CD57, or adaptive-like signatures. Preserved NK cell function may enhance immune surveillance and clearance of cells that sporadically express viral antigens, thereby influencing reservoir stability. Variability in NK cell education and receptor-ligand interactions may partly explain differences in reservoir size among early-treated individuals [36].

Adaptive Immune Responses

CD8$^+$ T cell fitness and breadth

CD8$^+$ T cell responses play a central role in controlling HIV replication. Early suppression limits chronic antigen exposure and prevents the progressive exhaustion of CD8$^+$ T cells. As a result, early-treated individuals often exhibit more polyfunctional, proliferative, and metabolically fit CD8$^+$ T cell populations. These preserved responses may exert selective pressure on infected cells, shaping reservoir composition by eliminating more immunogenic proviral lineages and favoring the persistence of less visible or transcriptionally silent clones. The breadth and specificity of CD8$^+$ T cell responses, influenced by both infection timing and host genetics, correlate with improved post-treatment control in some cohorts [37].

HIV-specific antibody responses

Early ART curtails the development of fully matured antibody responses, yet durable low-level HIV-specific antibodies often persist. While such antibodies have limited capacity to eliminate deeply latent reservoirs, they may contribute to immune surveillance of transiently reactivated virus. In individuals receiving broadly neutralizing antibodies (bNAbs) as part of analytical treatment interruption (ATI) studies, early-treated individuals frequently exhibit enhanced responsiveness, suggesting that preserved B cell function may synergize with therapeutic immunomodulation [11].

Inflammation and Immune Activation

Residual inflammation despite early ART

Even when ART is initiated at the earliest detectable stages, complete normalization of immune activation is rarely achieved. Low-level inflammation persists in blood and tissues, driven by factors such as microbial translocation, incomplete mucosal restoration, and lingering innate immune signaling.

These inflammatory signals can influence reservoir dynamics by promoting survival or proliferation of infected memory T cells [38].

Impact on reservoir persistence

Chronic, low-grade activation contributes to homeostatic T cell turnover, which in turn can propagate proviral clones without reactivating viral transcription. In addition, tissue-specific inflammatory microenvironments such as those in gut mucosa or lymph node follicles may provide survival advantages for infected cells. Understanding how residual immune activation differs between tissue sites in early-treated individuals remains a key research priority, as these subtleties may dictate reservoir stability [39].

Genetic and Epigenetic Influences

HLA alleles and CCR5 variants

Host genetic factors exert strong influence over viral replication dynamics and reservoir characteristics. Protective HLA class I alleles, including HLA-B*57 and HLA-B*27, support more potent $CD8^+$ T cell responses, which may limit reservoir seeding even before ART is initiated. Similarly, CCR5 genetic variants most notably the CCR5-Δ32 mutation alter viral entry and can reduce the frequency of infected cells. Combinations of favorable immunogenetic traits may enrich the subset of early-treated individuals capable of achieving post-treatment control [40].

Integration site chromatin accessibility

Epigenetic features of host chromatin strongly influence the fate of integrated proviruses. HIV preferentially integrates into actively transcribed regions of the genome; however, the degree of chromatin accessibility at integration sites varies across cell subsets and tissue environments. In early-treated individuals, integration events occur within a narrower temporal window, potentially resulting in a more uniform distribution of chromatin states. Integration into genes associated with T cell survival or proliferation can promote persistence through clonal expansion. Conversely, integration into more repressive chromatin regions may render proviruses less inducible, contributing to functional latency that complicates eradication efforts [41].

CURE-FOCUSED INTERVENTIONS INFORMED BY RESERVOIR MAPPING

Advances in reservoir mapping have provided increasingly precise insight into the anatomical, cellular, and molecular features that allow HIV to persist despite early initiation of ART. These discoveries have directly informed the development of cure-focused interventions aimed either at eliminating latently infected cells or at achieving durable ART-free remission. The following section outlines key therapeutic strategies and how reservoir characteristics in early-treated individuals influence their potential efficacy [42].

Block-and-Kill Strategies

LRAs: What works in early-treated individuals?

Block-and-kill approaches aim to induce proviral transcription in latently infected cells while simultaneously promoting immune-mediated clearance. Early-treated individuals may be particularly suitable candidates because their reservoirs are smaller, less genetically diverse, and enriched for intact proviruses that are more consistently inducible. Histone deacetylase inhibitors, protein kinase C agonists, and toll-like receptor agonists have shown varying degrees of latency reversal in ex vivo studies. However, their clinical impact remains limited, partly due to incomplete reactivation and insufficient immune clearance. Importantly, early-treated reservoirs often exhibit lower transcriptional repression, raising the possibility that milder or more targeted LRAs may effectively induce reactivation with reduced systemic toxicity [43].

Immune-based clearance mechanisms

For latency reversal to translate into reservoir reduction, robust immune effector mechanisms must eliminate reactivated cells. Early-treated individuals exhibit preserved $CD8^+$ T cell functionality and NK cell activity, making them more capable of clearing antigen-expressing cells than those treated during chronic infection. Enhancing these responses through checkpoint blockade, cytokine stimulation, or adoptive cell therapies may amplify the kill phase. Understanding the cellular distribution and phenotypic features of the reservoir is essential for matching LRAs with appropriate immune effectors [8].

Shock-and-Kill vs. "Lock-and-Block"

Epigenetic silencing approaches

While shock-and-kill attempts to flush out latent virus, lock-and-block strategies seek to permanently suppress proviral transcription. Small molecules that reinforce epigenetic silencing such as inhibitors of bromodomain proteins or modulators of chromatin modifiers can stabilize latency and prevent rebound if ART is interrupted. This approach may be particularly effective in early-treated individuals who already harbor transcriptionally quiescent reservoirs with minimal inflammation [44].

Durability and safety considerations

The feasibility of long-term epigenetic repression hinges on durability and safety. Because lock-and-block does not eliminate infected cells, lifelong suppression may be required to prevent reactivation. Additionally, broad epigenetic modifiers may affect host gene expression, creating potential toxicity concerns. Precise understanding of integration site landscapes, chromatin states, and cellular niches in early-treated individuals is essential for designing tools that silence proviruses without perturbing essential cellular pathways [45].

Immunotherapeutics

Therapeutic vaccines

Therapeutic vaccination aims to enhance HIV-specific immunity, particularly $CD8^+$ T cell responses, to improve recognition and clearance of infected cells. Early-treated individuals may benefit disproportionately because their immune repertoires are less exhausted and more functionally competent. Vaccine platforms under study include viral vectors, mRNA constructs, and mosaic immunogens designed to broaden epitope coverage and compensate for limited reservoir diversity [46].

bNAbs

bNAbs hold promise for both direct antiviral activity and immune modulation. They can neutralize circulating virus, mediate antibody-dependent cellular cytotoxicity, and potentially target reactivated reservoir cells. In early-treated cohorts, bNAbs have demonstrated prolonged suppression during treatment interruption, likely due to preserved immune synergy and the limited diversity of proviral quasispecies. Combinations of bNAbs targeting distinct epitopes appear most effective in delaying or preventing viral rebound [47].

CAR-T and CAR-NK cells

Chimeric antigen receptor (CAR) engineered T cells and NK cells offer a means of redirecting potent cytotoxicity toward HIV-infected cells. Their efficacy depends on stable antigen expression on target cells, which is often sporadic in deeply latent reservoirs. Nonetheless, the smaller and more homogeneous reservoirs in early-treated individuals may present more tractable targets. Refinements such as multi-antigen CARs, armored CAR constructs, and incorporation of latency-sensing elements may improve specificity and durability [48].

Gene-Editing Approaches

CRISPR-mediated excision or inactivation

Gene-editing strategies seek to directly eliminate or incapacitate integrated proviruses. CRISPR-Cas systems can target viral sequences for excision, induce lethal mutations, or disrupt regulatory elements required for transcription. Early-treated individuals, with fewer intact and less diverse proviruses, may be more amenable to targeting with a defined set of CRISPR guides. Challenges remain in delivering editors to all relevant reservoirs and avoiding off-target effects.

CCR5 gene editing

Modifying host factors, particularly CCR5, represents another viable cure pathway. CCR5 disruption prevents new rounds of infection and may allow resistant cells to repopulate the immune system. Early-treated individuals may achieve greater benefit because their reservoirs contain fewer CXCR4-using variants, and the immune environment is less inflamed. Edited hematopoietic stem cells or peripheral T cells are under investigation as potential long-term protective strategies [49].

Stem-Cell Transplantation and Elite Remission

Relevance of early ART to functional cure phenotypes

Stem-cell transplantation has demonstrated that durable HIV remission is achievable, albeit in highly selected clinical contexts. While transplantation itself is not broadly scalable, insights from these rare cures including the role of donor CCR5 deficiency, graft-versus-host immunity, and profound immune reconstitution inform more generalizable strategies. Early ART may mimic some aspects of post-transplant reservoir restriction, such as reduced diversity and limited tissue dissemination, thereby creating conditions more conducive to functional cure. Several early-treated individuals exhibiting post-treatment control share immunological characteristics with elite controllers, suggesting that early intervention can shift host-virus dynamics toward a remission-compatible phenotype [50].

CLINICAL EVIDENCE AND CASE STUDIES OF EARLY-TREATED COHORTS

Clinical studies of individuals who initiated ART during acute or very early infection have provided some of the most compelling insights into the biological and immunological determinants of HIV persistence. These cohorts illustrate how early therapeutic intervention shapes reservoir size, composition, and long-term control outcomes. Although the degree of viral remission varies widely, early-treated populations consistently demonstrate more favorable virologic and immunologic profiles than those treated during chronic infection. The following examples highlight key cohorts that have advanced understanding of early intervention and its implications for cure research [8].

The VISCONTI Cohort

The French VISCONTI cohort remains one of the most well-known examples of long-term post-treatment controllers who initiated ART during primary infection. Individuals in this cohort demonstrated sustained viral remission for years after treatment interruption, despite not displaying the classical immunogenetic features of elite controllers. Their viral reservoirs were small, less diverse, and enriched for defective proviruses, suggesting that early therapy profoundly limited reservoir establishment. Immunologically, VISCONTI participants exhibited preserved $CD4^+$ T cell counts, low levels of immune activation, and functional but not excessively strong HIV-specific responses. Collectively, these findings highlight that early ART can create a host-virus equilibrium that supports durable control, even in the absence of traditional protective genetic factors [51].

Thai Acute Infection Studies

Clinical cohorts in Thailand, particularly those enrolling individuals diagnosed during Fiebig I-III stages, have provided exceptional granularity on the impact of ultra-early therapy. Participants often begin ART within days of infection, enabling researchers to assess reservoir seeding at its earliest stages. These studies consistently show that very early ART dramatically reduces total and intact proviral DNA, limits viral diversification, and preserves robust HIV-specific immunity. Importantly, some participants demonstrated delayed or absent viral rebound during ATI, offering valuable data on predictors of remission. These cohorts have also contributed to high-resolution reservoir mapping through extensive tissue sampling, including gut and lymph node biopsies, thereby illuminating the anatomical distribution of reservoirs under early ART [52].

African Early ART Cohorts

Early-treated cohorts across sub-Saharan Africa, including those within major test-and-treat initiatives, provide essential insights into the global generalizability of early ART outcomes. Many individuals in these settings initiate therapy soon after seroconversion as part of routine public health screening programs. Studies from Uganda, South Africa, Botswana, and Kenya have documented reduced reservoir sizes, lower inflammatory signatures, and preserved T cell function in early-treated individuals. These cohorts are biologically and genetically diverse, offering opportunities to investigate how host genetics, including HLA variability and differing viral subtypes, influence reservoir establishment and remission

potential. Moreover, they help identify cure-relevant biomarkers that are applicable in real-world, resource-limited settings [53].

Pediatric Early-Treated Cases

Early initiation of ART in infants presents a unique clinical context due to the distinct immunological milieu and developmental plasticity of the neonatal immune system. Several pediatric cases have shown prolonged periods of remission after treatment interruption, the most notable being the so-called “Mississippi child,” who maintained viral suppression for more than two years off ART before eventual rebound. Infants who begin ART within hours to days of birth often exhibit extremely small reservoirs, minimal viral diversification, and unusually low levels of immune activation. These characteristics suggest that early-life immune immaturity, combined with rapid ART initiation, may limit reservoir establishment more effectively than in adults. Pediatric cohorts continue to inform how timing, developmental immunology, and anatomical compartmentalization shape long-term outcomes [54, 55].

Insights from ATI Trials

ATI studies provide critical evidence on the functional relevance of reservoir characteristics identified in early-treated individuals. Controlled treatment interruption allows assessment of time to viral rebound, rebound viral kinetics, and immunologic correlates of remission. Across multiple trials, early-treated participants consistently display delayed rebound compared with those treated during chronic infection. Factors associated with extended remission include smaller reservoir size, reduced viral diversity, lower immune exhaustion, and preserved cytotoxic T cell function. ATIs have also shed light on the heterogeneity of early-treated individuals: while some maintain prolonged suppression, others rebound rapidly despite low reservoir measurements, underscoring the multifactorial nature of remission. These trials continue to refine biomarker development and guide selection of participants for interventional cure studies.

KEY KNOWLEDGE GAPS, METHODOLOGICAL CHALLENGES, AND CONTROVERSIES

Despite major advances in characterizing HIV reservoirs, particularly in individuals who commence ART during early infection, substantial gaps and uncertainties remain. These unresolved questions reflect the biological complexity of HIV persistence and the technical constraints of current investigative tools. A clear articulation of these challenges is essential for guiding future research and for setting realistic expectations regarding the feasibility of cure strategies [56].

Are Macrophages True Reservoirs?

One of the most enduring controversies in reservoir research concerns whether macrophages, including tissue-resident macrophages and microglia, constitute genuine long-lived HIV reservoirs. Evidence of viral DNA and RNA within myeloid cells has been repeatedly documented; however, distinguishing true infection from uptake of cellular debris or virions remains technically challenging [57]. Moreover, macrophages can phagocytose infected T cells, leading to false-positive signals in molecular assays. In early-treated individuals whose overall reservoir burden is lower, the difficulty of establishing macrophage infection becomes even more pronounced. Definitive proof of replication-competent virus originating from macrophages is limited, and advances in single-cell genomics, viral integration site mapping, and lineage tracing will be essential to clarify whether these cells play a meaningful role in long-term persistence [8].

How Much Reservoir Exists in Hard-to-Sample Tissues?

A substantial proportion of the HIV reservoir resides in tissues that are difficult or risky to access, such as the CNS, GALT, and deep lymphoid structures. These compartments differ markedly from peripheral blood in immune composition, drug penetration, and microenvironmental factors that influence proviral survival. Even in early-treated individuals, where reservoir seeding is limited, the precise burden of provirus in these tissues remains poorly quantified. CNS reservoirs, for example, may persist within microglia or perivascular macrophages and are rarely sampled directly in living individuals. Similarly, the gut harbors vast numbers of $CD4^+$ T cells, yet tissue sampling often captures only small, localized areas that may not represent the broader reservoir landscape. Without accurate quantification across compartments, it remains difficult to determine the true potential for eradication or functional remission [39].

Limitations of Sampling and Assay Sensitivity

Most reservoir assays rely on peripheral blood, which represents only a small fraction of the body’s infected cells. Even the most sensitive molecular assays struggle to distinguish between intact, inducible proviruses and defective genomes that pose no clinical threat. QVOA, while specific for replication-competent virus, underestimate reservoir size and require large sample volumes that are impractical in many clinical settings. Newer techniques, such as IPDA, full-length sequencing, and single-cell multi-omics, offer improved resolution but remain technically demanding and often limited by sampling depth. The stochastic nature of latency, combined with the rarity of reservoir cells in early-treated individuals, further complicates detection. These limitations make it difficult to measure the true impact of cure interventions or to identify reliable biomarkers predictive of treatment outcomes [12].

Translation Challenges For Cure Interventions

Even as mechanistic insights accumulate, translating reservoir science into effective clinical interventions remains a formidable challenge. Strategies such as latency reversal, immune enhancement, gene editing, or pharmacologic silencing often demonstrate promising activity ex vivo but face barriers in vivo, where tissue penetration, immune accessibility, and off-target effects become critical constraints [58]. Early-treated individuals may be ideal candidates for cure trials due to their smaller and less diverse reservoirs, yet their reservoir characteristics may also complicate intervention design; for example, a higher proportion of intact proviruses increases the potential for rebound if strategies fail to completely suppress or eliminate latent cells. Additionally, ethical considerations surrounding ATI, especially in populations with very low reservoir levels, require careful balancing of scientific benefit and participant safety. Addressing these translational hurdles will require coordinated advances in drug delivery, immune engineering, and reservoir measurement [59].

FUTURE DIRECTIONS

As understanding of HIV reservoir biology continues to deepen, particularly in individuals who initiate ART during early infection, new opportunities emerge for developing more precise and effective cure strategies. The next decade of research will likely be defined by integrative, high-resolution approaches that combine advanced technologies with clinical studies aimed at translating reservoir insights into therapeutic interventions. The following directions highlight some of the most promising avenues [60].

High-Resolution, Multi-Omics Reservoir Atlases

A comprehensive atlas integrating genomic, transcriptomic, epigenomic, proteomic, and spatial data across tissue compartments would significantly advance the field. Such an atlas would identify the full spectrum of reservoir cell states, their anatomical niches, and the microenvironmental signals that sustain persistence. For early-treated individuals whose reservoirs are smaller and less heterogeneous, multi-omics mapping may provide particularly clear insights into the earliest and most durable proviral lineages. These resources would not only refine molecular targets for cure interventions but also illuminate the cellular pathways that govern latency, clonal expansion, and reactivation [61].

Longitudinal Single-Cell Profiling

Single-cell technologies have already transformed reservoir research, but most studies capture snapshots rather than continuous trajectories. Longitudinal single-cell profiling across blood and tissue samples will allow researchers to trace the fate of infected cells over time, identify transitions between latent and transcriptionally active states, and quantify the clonal dynamics that support long-term persistence. Such studies could reveal whether specific cellular phenotypes or integration sites predict expansion or decay of proviral lineages. In early-treated individuals, where the reservoir is more tractable, longitudinal profiling may be especially powerful for uncovering the mechanisms that enable durable remission [62].

Predictors of Post-Treatment Control

A central goal of future research is to identify reliable biomarkers that predict the likelihood and durability of post-treatment viral control [63]. Potential predictors include reservoir size, proportion of intact proviruses, clonal architecture, immune activation levels, T cell functional profiles, and host genetic factors. Integrating these features into predictive models could guide the selection of participants for ATIs or interventional cure trials [64]. For early-treated individuals, who demonstrate a higher probability of remission, predictive biomarkers could help distinguish those who might safely discontinue ART from those requiring continued therapy or adjunctive interventions [65].

Targeted Drug Delivery to Anatomical Sanctuaries

As reservoir mapping reveals the anatomical distribution of persistent provirus, new strategies must be developed to improve drug delivery to sanctuary sites such as lymph nodes, GALT, and the CNS. Nanoparticle-based delivery systems, antibody-drug conjugates, and agents engineered to cross the blood-brain barrier represent promising avenues. Targeted delivery may enhance the efficacy of LRAs, immune modulators, or gene-editing tools by increasing local drug concentrations while minimizing systemic toxicity. Tailoring these delivery platforms to early-treated individuals whose reservoirs may be confined to fewer and more specific sites could significantly improve success of cure interventions [66].

Toward Personalized Cure Strategies

The heterogeneity of reservoir characteristics across individuals underscores the need for personalized approaches to HIV cure [67]. Personalized strategies may involve tailoring therapeutic combinations based on reservoir composition, host genetics, tissue distribution, and immune functionality. Machine learning models integrating clinical, immunologic, and multi-omic data could help identify the most effective intervention combinations for specific patient profiles. For early-treated individuals, personalized strategies may build upon their preserved immune capacity and limited reservoir diversity to design interventions that either eliminate infected cells or support long-term functional remission [68, 69].

CONCLUSION

Over the past decade, advances in reservoir mapping have fundamentally reshaped our understanding of HIV persistence, particularly in individuals who begin ART during acute infection. High-resolution molecular and cellular analyses have revealed that early treatment dramatically restricts the size, diversity, and anatomical spread of the viral reservoir. These insights highlight the complex interplay between viral dynamics, host immunity, and tissue-specific microenvironments that together determine the long-term fate of proviral lineages. By integrating quantitative assays, single-cell technologies, spatial mapping, and clinical observations, researchers now have a more detailed portrait of the reservoir than ever before.

Early-treated individuals have emerged as a crucial cohort for investigating mechanisms of viral remission and informing cure strategies. Their reservoirs are smaller, less genetically complex, and associated with more preserved immune function, all factors that increase the likelihood of durable control. Studies in these populations have illuminated the conditions under which HIV latency is established, how reservoirs persist despite therapy, and which immunologic and virologic markers predict post-treatment outcomes. Moreover, data from early-treated cohorts have provided critical benchmarks for assessing new interventions, from LRAs and immunotherapies to gene-editing technologies and targeted drug delivery systems.

Looking ahead, the path toward achieving long-term ART-free remission will require an integrated approach that couples deep biological insight with innovative therapeutic design. Continued refinement of reservoir measurement techniques, development of predictive biomarkers, and advancement of personalized cure strategies will be essential. Although significant challenges remain, including those related to tissue accessibility, reservoir heterogeneity, and intervention scalability the scientific progress achieved through studies of early-treated individuals offers a compelling roadmap. With sustained effort, multidisciplinary collaboration, and strategic clinical translation, the prospect of durable remission or even a functional cure appears increasingly within reach.

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