Review Article

# Revisiting HIV Latency: Molecular Mechanisms, Therapeutic Barriers, and Emerging Opportunities for Cure

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## Abstract

Viral latency remains one of the major barriers to the prevention and treatment of Human Immunodeficiency Virus (HIV) infection. Despite effective antiretroviral therapy (ART), HIV persists in latent cellular reservoirs, necessitating lifelong treatment and preventing complete viral eradication. This review comprehensively explores the molecular mechanisms underlying HIV latency, therapeutic barriers, and emerging opportunities toward a functional or sterilizing cure. HIV latency is regulated through complex interactions involving integration site heterogeneity, transcriptional repression, chromatin remodeling, and epigenetic modifications that collectively maintain viral dormancy. Resting CD4+ T cells serve as the principal latent reservoir; however, persistence also occurs within lymphoid tissues, gut-associated lymphoid tissues, and the central nervous system, creating sanctuary sites resistant to immune surveillance and pharmacological intervention. Current cure strategies include the "shock and kill" approach using latency-reversing agents such as histone deacetylase inhibitors, bromodomain inhibitors, and protein kinase C agonists, as well as the "block and lock" strategy employing Tat inhibitors and epigenetic silencing agents to achieve durable viral suppression. Immunotherapeutic approaches, including immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy, and broadly neutralizing antibodies, have demonstrated promising potential but remain limited by incomplete reservoir clearance, toxicity, and viral escape. Clinical translation is further complicated by difficulties in reservoir quantification, ethical concerns, and implementation challenges in resource-limited settings. Emerging technologies, particularly artificial intelligence-assisted drug discovery and personalized therapeutic modeling, provide new opportunities for optimizing HIV cure strategies. Future progress will require interdisciplinary collaboration, equitable healthcare access, and innovative interventions targeting both viral persistence and host immune dynamics.

## 1. Introduction

Human immunodeficiency virus (HIV) remains a most challenging public health issues since more than 40 years. The statistical data retrieved from UNAIDS reported that approximately 39 million people are HIV infected worldwide, with an incidence rate of 1.3 million new cases annually and 630,000 deaths were recorded in 2022. Despite extraordinary process in prevention approaches, investigative competences, and the extensive accessibility of antiviral therapy (ART), in the middle- and low-income countries like sub-Saharan Africa, still the HIV continues to enact an inconsistent burden, and nearly two-thirds of all global cases are concentrated **(Bloom *et al.* 2017)**. This insistent epidemic highly affects the health system disparities, and socioeconomic conditions, in addition it significantly enduring scientific challenge to prevent this critical virus once infected has occurred. Recent antiviral therapy plays a crucial role in the treatment of infections, and transformed HIV infection from fatal disease into manageable chronic condition, but still, it is not curative. Lifelong treatment remains necessary to suppress viral replication and prevent disease progression **(Quinn 2008)**. The biological reason for this lack of a cure lies in the phenomenon of HIV latency, a state in which integrated viral genomes, or proviruses, persist silently within long-lived cells despite effective ART. These hidden reservoirs represent the chief obstacle to virus eradication and are the root cause of viral rebound seen almost universally when treatment is interrupted. Latency therefore represents one of the enduring frontiers in HIV research, requiring novel therapeutic strategies aimed at eliminating or permanently silencing these reservoirs to achieve the much-coveted goal of a functional or sterilizing cure **(Castro-Gonzalez *et al.* 2018)**.

HIV latency is broadly defined as a reversible, transcriptionally silent state of the virus within infected host cells. The best-characterized reservoir is the pool of resting memory CD4+ T cells, which harbor the integrated but transcriptionally inactive virus capable of reigniting systemic infection - when activated. In addition to T cells, HIV DNA can also persist in macrophages and other tissue-resident immune cells, further complicating the reservoir landscape. Importantly, the latent pool is established very early after infection, often within days, and persists for decades despite effective viral suppression by ART **(Siliciano and Greene 2011)**. Viral latency highly influence the clinical consequences, first, the latent reservoir significantly reduces the capability of the current viral therapy and become an obstacle for achieving viral eradication, second, the persistence of infected cells highly influenced the immune system, and it dysregulates the immune system and leads to chronic inflammation, which were highly associated with elevated risk of comorbidities including neurocognitive disorders, cardiovascular diseases and accelerating aging. Third, the predictability of viral rebound highly interrupts the treatment and makes structured treatment interruption trials highly risk. The infected people living with HIV, may leads continues the burden of both psychological and financial aspect also it significantly increased the risk of drug-relevant toxicities and incomplete access to treatment in resource-limited settings. Further, the latent reservoir is playing a crucial role in virological curiosity and also represent as core driver of the global health

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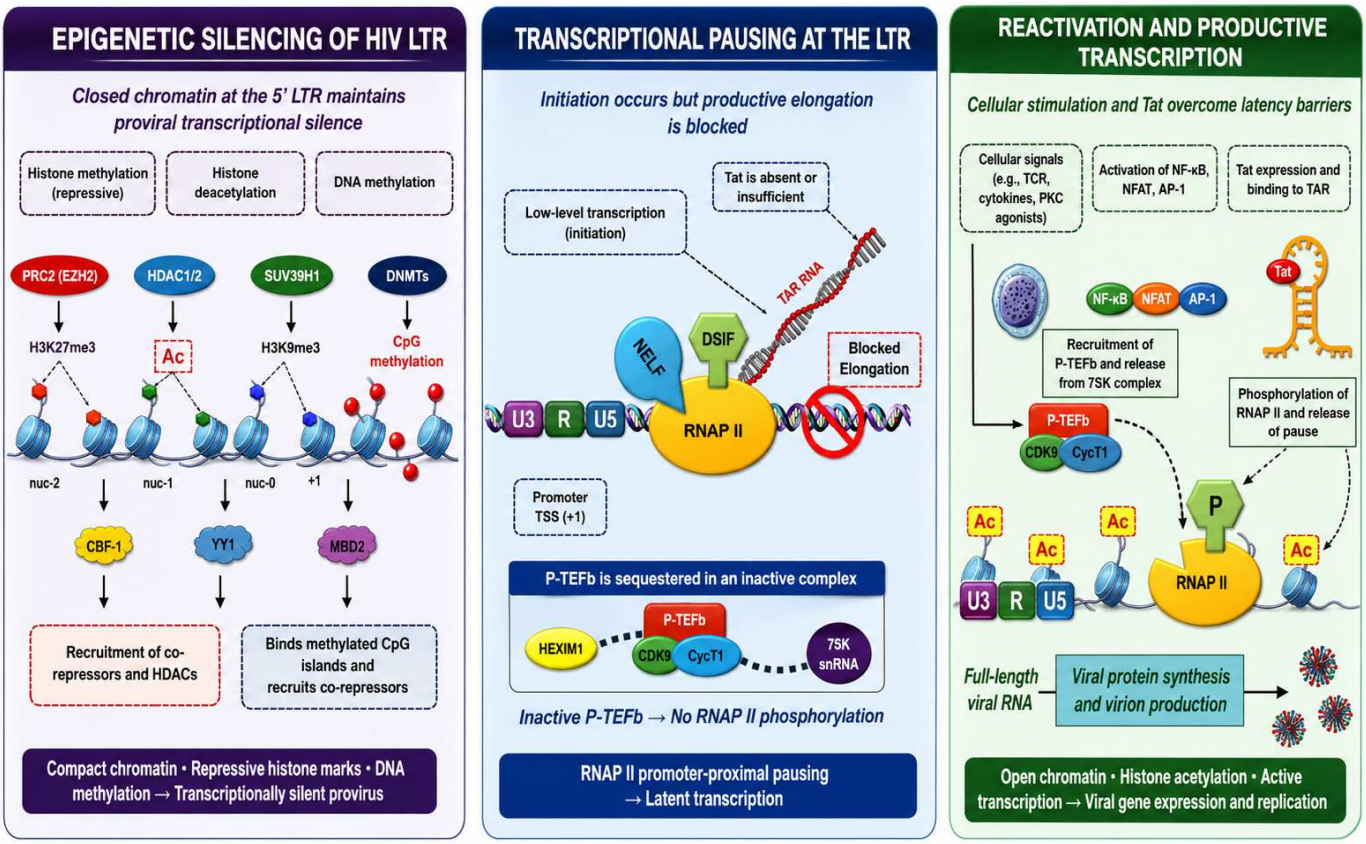


**Figure 1.** Cellular and anatomical HIV reservoirs

challenges of HIV, closing the gap between viral prevention and complete eradication **(Siliciano and Siliciano 2000)**.

### 1.2. Scope of the review

The understanding of these formidable barriers, clinical impact, research into the mechanisms and inventing potential approaches for targeting latency has become a key area in the scientific community. This current review aims to emphasize the current knowledge of HIV latency in global health context, and to highlighting the clinical dimensions and implications for the cure research. Here we first outlined both molecular and cellular mechanisms that establish and maintain latency, with understanding the canonical reservoirs including memory $CD4^+$ T cells and its emergence evidence of persistence in tissue compartments. We will then discuss the methodological advances used to detect, quantify, and characterize latent infection, including recent high-resolution single-cell and genomic approaches. The review further explores the therapeutic strategies currently under investigation to counteract latency, ranging from the widely studied "shock-and-kill" approaches to more recent "block-and-lock" paradigms aimed at durable silencing. We will discuss how gene-editing technologies, immune-based interventions, and therapeutic vaccines may be leveraged in the pursuit of functional cures **(Contreras *et al.* 2006)**. Throughout, we will situate these discussions within the broader public health framework, assessing the feasibility of experimental strategies in diverse healthcare settings and the policy considerations needed for future cure rollout. Finally, this review underscores the essential interplay between basic virology, translational medicine, and global equity in the pursuit of an HIV cure. Hence, addressing this latency of HIV is required to overcome the scientific imperative and moral necessity as conventional and curative solution remain the ultimate pathway to ending the pandemic. The understanding of other disciplines and their incorporation is important hence, it offers the comprehensive framework for study the molecular mechanisms HIV latency and advancing toward complete eradication approach that durable, equitable and globally accessible.

## 2. Clinical Aspects of HIV Latency

The HIV latency highly influences the clinical implications, it significantly shaping the fundamental course and management of infection. Latency describes, the dormant state of virus, that integrated with host genomes and evades the host immune system surveillance and antiretroviral therapy (ART), and enduring in reservoirs that counterattack abolition and pose risk of viral rebound if treatment is intermittent **(Schlenter *et al.* 1989)**.

### 2.1. HIV Latency in the Clinical Context

The HIV latent reservoir is chiefly comprising of memory CD4+ T cells and have other types of macrophages, dendritic cells and microglia. These reservoirs are established quickly after infection and are maintained throughout the patient's life, even when ART suppresses plasma viremia to undetectable levels, indicating that reservoir cells remain a source of potential viral reactivation and disease progression. The latent reservoir is defined as the population of cells and tissues where replication-competent HIV persists in a silent state **(Figure 1) (Chen *et al.* 2022)**. Blood, while frequently sampled in clinical research, contains only a minority of the total reservoir. Major anatomical reservoirs include lymphoid tissues (lymph nodes, spleen), gut-associated lymphoid tissue (GALT), reproductive tracts, and the central nervous system (CNS). Autopsy studies have detected proviral DNA in nearly all tissues, including the liver, genital tract, and brain, sometimes in so-called sanctuary sites shielded from optimal ART penetration. Research demonstrates significant differences between reservoirs found in the peripheral blood and those in tissue compartments. Lymph nodes and the gut are particularly enriched with latently infected cells, with the gut estimated to harbor over 98% of the total body reservoir in some non-human primate models **(Banga and Perreau 2024)**. These tissue-based reservoirs

challenge eradication efforts due to difficult sampling, suboptimal drug penetration, and unique local immune milieus. During suppressive ART, residual replication may occur in anatomical sites with poor drug diffusion, contributing to reservoir maintenance. Despite successful plasma viral suppression, interruption of ART almost invariably leads to rapid viral rebound, highlighting the clinical significance of latent reservoirs. This rebound can originate from different tissues and is not associated with ongoing replication in most individuals under ART but rather from the activation of latently infected cells **(Figure 1) (Saksena *et al.* 2010)**.

### 2.2. Clinical Measurement of Latency and Reservoirs

Monitoring HIV latency relies on several complementary methods. The viral outgrowth assay (VOA) is considered the gold standard, quantifying the frequency of cells carrying replication-competent virus, but is labor-intensive and only detects a minimal fraction of the reservoir. PCR-based assays, including quantitative PCR (qPCR) and digital droplet PCR, detect HIV DNA and RNA but cannot distinguish between defective and replication-competent proviruses, often overestimating reservoir size due to the presence of defective genomes **(Massanella *et al.* 2018)**. Emerging next-generation sequencing approaches offer deeper characterization, facilitating identification of viral integration sites and clonal expansion patterns. Biomarkers for latent HIV detection remain under investigation, with no single marker clearly defining the entire reservoir. Current assays suffer from limitations in sensitivity, specificity, and practicality. Most reservoir assays sample peripheral blood, leaving tissue reservoirs underrepresented. In addition, most methods cannot reliably quantify or distinguish inducible, replication-competent proviruses from defective ones, which vastly outnumber intact genomes **(Moar *et al.* 2023)**.

### 2.3. Clinical Barriers to HIV Cure

Eradication of HIV remains hampered by several clinical obstacles. The stick on the ART can be significantly influence by several factors including treatment fatigue, adverse events, and pill burden; hence, it indirectly encourages the viral rebound and resistance. The genetic diversity of HIV and its high incidence of mutation confer drug resistance and lead failure in prevention and cure strategies. After infection, owing to the chronic inflammation leads persistent immune dysfunction which increases the risk of comorbidities including hepatitis C, Tuberculosis and complicating the management and outcomes **(Marsden and Zack 2009)**. The socio-economic disparities like poor access to care, global health inequities and stigma significantly limit the impact of current antiviral therapies especially in resource-limited settings.

## 3. Mechanistic Studies of HIV Latency

The complexity of HIV latency highly influenced by both cellular and molecular mechanisms that regulates the transition of active viral replication to transcriptional silencing. Understanding the molecular mechanism of these intricate processes offers a critical insight into the basic complications in preventing and HIV eradication and informs the therapeutic approaches that effectively targeting the latent reservoirs **(Mbonye and Karn 2014)**.

### 3.1. Cellular and Molecular Mechanisms of Latency

HIV integration shows favoured interactions to actively transcribed genes, with over 90% of the latent proviruses incorporated within the transcriptionally active genes of host organism. Though, the chromatin environment at integration sites plays a critical role in regulating the viral fate. This integration site remarkably associated with latency and shoes distinct chromatin signatures compared to productive infections. Histone methylation sites H3K27me3 and H3K9me3 were enriched with repressive histone mark integrate with non-reactivatable latent infections and are more often found in lamin-associated domains at nuclear periphery. This spatial arrangement within the heterochromatic region responsible for transcriptional silencing by generating a restrictive local environment that obstructs viral gene expression **(Weissman *et al.* 2026)**. The development of HIV latency regulates the recruitment of transcriptional repressors to the viral long terminal repeat (LTR). CBF-1 acts as a key silencing factor that significantly interacts with specific sequences in the HIV LTR and recruit's histone deacetylase (HDAC)-containing corepressor complexes. This complex recruitment regulates the repressive cascade events, such as histone deacetylation followed by methylation via Su39H1 and subsequent binding of heterochromatin protein including HP1α and HP1γ. Similarly, the transcription factor YY1 regulating latency via recruiting HDAC1 to the provirus and developing a repression cascade in chromatin state. This activation state of host cells significantly influences the transcriptional fate, while in resting state CD4+ T cells, the absence of essential transcription factors like NF-κB and NFAT generates the conducive cellular environment to development of latency. In cellular activation state, the presence of positive transcription elongation factor b (P-TEFb), also plays a crucial role in HIV transcription. In resting cells, P-TEFb is requisitioned in an inactive complex with HEXIM and 7SK RNA, further restricting viral transcription **(Tyagi and Karn 2007)**.

### 3.2. Epigenetic Regulation of Latency

The regulation of epigenetic mechanisms represents a fundamental contribution to governing HIV latency, with modifications of histone molecules serving as primary regulators of proviral transcriptional accessibility. The major epigenetic restriction significantly involved in histone methylation especially H3K27 and H3K9 methylation, which is highly essential to maintaining latency of HIV across the several cell types including both primary and transformed T cells, macrophages, and microglial cells. For instance, H3K27 methylation is significantly regulated by polycomb repressive complex 2 (PRC2) with its catalytic subunit EZH2, while H3K9 methylation which derives the multiple methyltransferases such as GLP, SETDB1/2, G9a and SUV39H1/2 **(Shin *et al.* 2026)**. Conversely, histone acetylation marks such as H3K9ac and H3K14ac are associated with transcriptionally active proviruses and are depleted in latent infections. DNA methylation contributes to HIV latency through cytosine methylation at CpG islands flanking the HIV transcription start site. Methyl-CpG binding domain protein 2 (MBD2) recognizes these methylated sites and recruits HDAC2, establishing a repressive chromatin environment. The HIV LTR exhibits a precisely organized nucleosomal structure featuring two positioned nucleosomes (nuc-0 and nuc-1) connected by a nuclease-hypersensitive enhancer region. Nucleosome 1, positioned immediately downstream of the transcription start site, acts as a particularly strong barrier to transcription initiation and must be disrupted during reactivation. Non-coding RNAs play increasingly recognized roles in HIV latency regulation. Long non-coding RNAs (lncRNAs) such as MALAT1 contribute to latency by binding to PRC2 complex and sequestering it from HIV chromatin. The NRON lncRNA maintains latency through dual mechanisms: modulating NFAT activity and promoting Tat protein degradation via the ubiquitin/proteasome system. ATP-dependent chromatin remodeling complexes, particularly the SWI/SNF (BAF) complex, regulate nucleosome positioning at the HIV LTR. These complexes can either endorse latency by establishing repressive nucleosome arrangements or facilitate reactivation by displacing inhibitory nucleosomes **(Figure 2) (Kauder *et al.* 2009)**.

### 3.3. Transcriptional and Post-transcriptional Controls

RNA polymerase II (RNAP II) plays a critical role in in HIV latency mechanisms that significantly pausing at the HIV LTR. In the latent

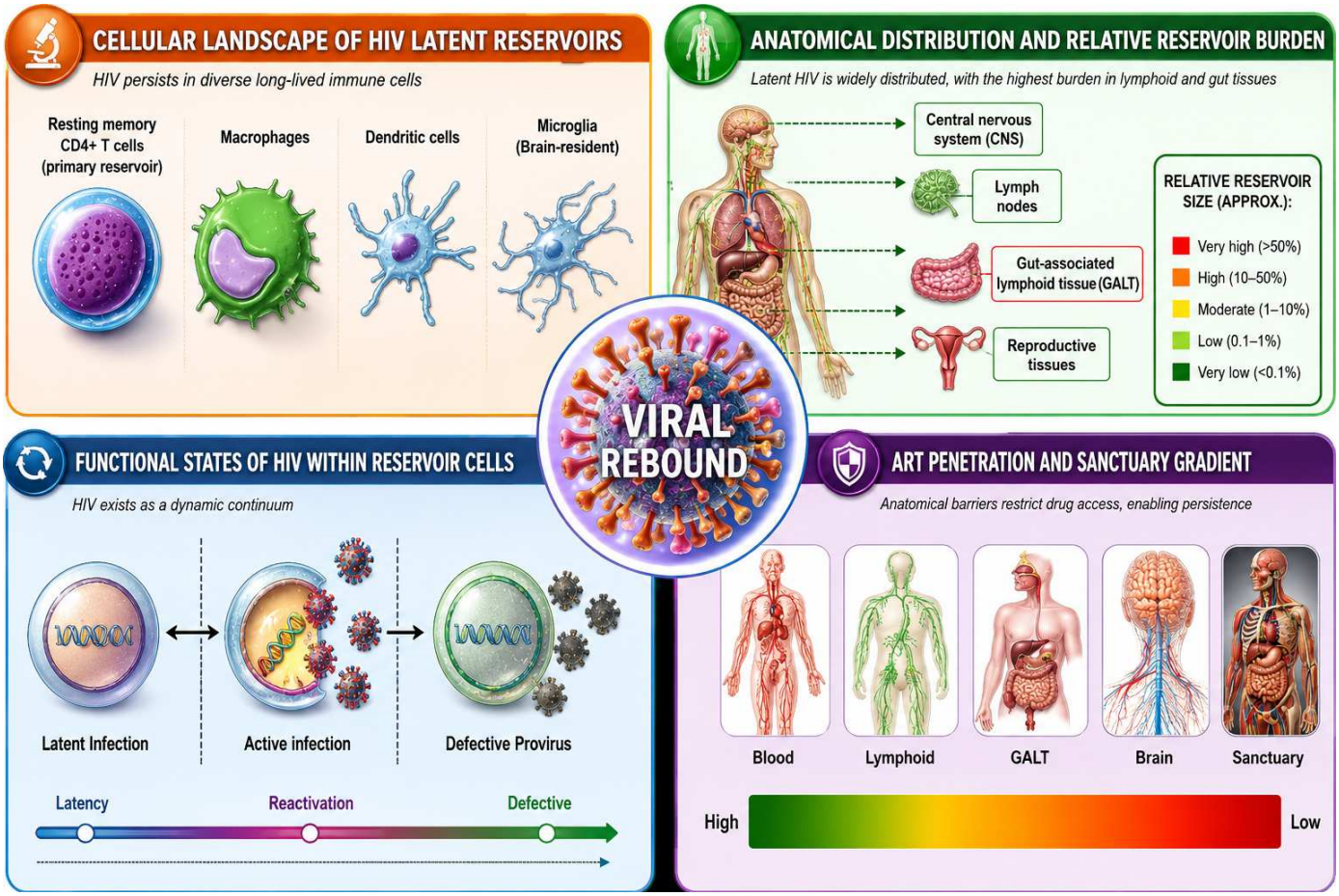


**Figure 2.** Molecular mechanisms of HIV latency and reactivation

infections, transcription initiation may occur, but RNAP II often pause at several position along and downstream of the LTR, which results in incomplete transcription. This pausing mechanism creates production of TAR-gag transcripts that paradoxically regulates latency by developing complexes with repressive factors including PRC2, SIN3A and CUL4B, and creating a negative feedback loop that reinforces transcriptional silencing. MicroRNAs (miRNAs) provide cell-type and tissue-specific regulation of HIV latency. miRNAs of host organisms remarkably target viral transcripts directly or regulates the cellular factor that are essential for viral replication. Number of miRNAs shows differential expression pattern depending on cell type and stage of infection and contributing to the development of maintenance of latency **(Cary *et al.* 2016)**. In addition to miRNAs long-coding RNAs also plays a critical role in regulating mechanism of viral latency via diverse mechanisms, such as transcription factor sequestration, chromatin modification, and protein degradation pathways. Several host signalling pathways also significantly influence the HIV latency status **(Figure 2)**. For instance, NF-κB pathway represents master regulator its activation enhances the viral reactivation via displacement of repressive factors and recruitment of transcriptional activators like p300. Another pathway NFAT also involved in complementary regulation, with IL-7-induced NFAT activation which affects the latency in naïve T cells. P-TEFb availability, effectively controlled by cellular signalling cascades which determines the efficiency of transcriptional elongation and represents a key control mechanism to distinguish the latent from active infection **(Alpuche-Lazcano *et al.* 2024)**.

## 3.4. Protein Regulators of HIV Latency

The complicated directive of HIV latency involves a multifaceted relationship between viral and host proteins that cooperatively regulate the fate of infected cells. Several mechanisms have been involved in the regulation of these protein and function which include transcriptional control, epigenetic modifications, immune restriction, and checkpoint signalling pathways **(Mbonye and Karn 2011)**.

### 3.4.1. Viral Proteins in Latency and Reactivation

#### 3.4.1.1. Tat: Transcriptional Activator

Tat is HIV transactivator protein plays a crucial role in viral transcription as master regulator and represents a critical determinant of latency development versus productive infection. Tat protein remarkably regulates the binding of transactivation response (TAR) element in the budding HIV RNA transcript and recruiting positive transcription elongation factor b (P-TEFb), thereby permitting RNA polymerase II to address pausing and complete efficient transcription. In latent infection, these expression of Tat proteins is critically low or no expression, which creating a self-reinforcing cycle that maintains transcriptional silencing **(Clark *et al.* 2017)**. Recent studies have demonstrated that exogenous Tat delivery can serve as a highly specific latency reversing agent (LRA). A truncated Tat variant (T66) comprising 66 amino acids exhibits comparable transactivation activity to full-length variants while demonstrating minimal off-target effects on host cell transcription, only eight genes were differentially expressed following T66 treatment compared to non-stimulated controls. Importantly, T66 protein induced HIV RNA expression in CD4+ T cells from people with HIV on ART without significantly inducing global cellular activation, contrasting with conventional T cell stimuli like phytohemagglutinin **(Van Gulck *et al.* 2023)**. The HIV-specificity of Tat-based approaches stems from their dependence on the TAR element, which is unique to HIV and absent from host genes.

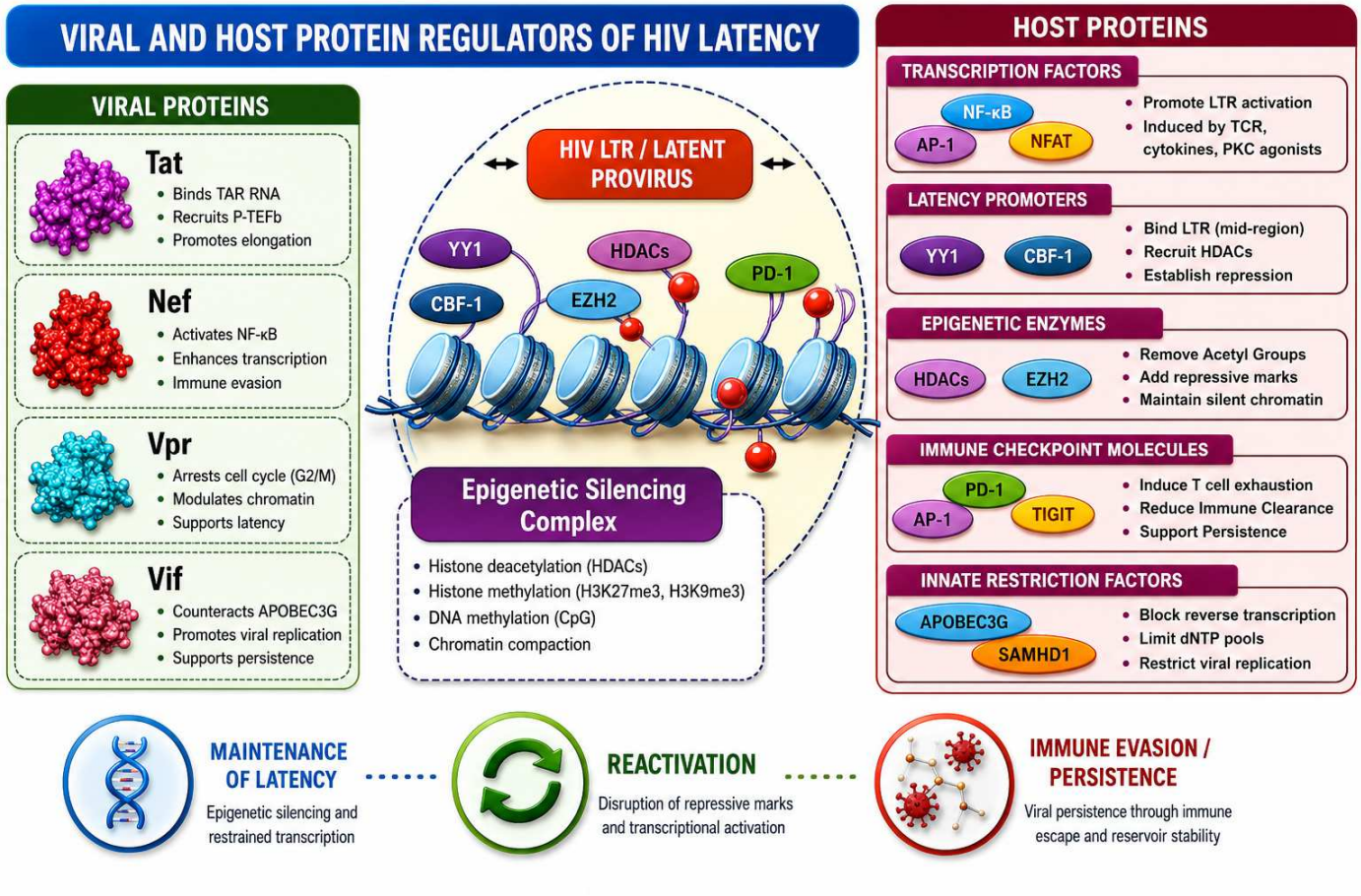


**Figure 3.** Viral and host regulators of HIV latency

### 3.4.1.2. Nef, Vpr, and Vif

HIV accessory proteins contribute indirectly to latency through their effects on host cell physiology and immune evasion. The Nef protein, while not directly regulating viral transcription, modulates host cell surface receptor expression and T cell activation states that can influence latency establishment. Nef downregulates CD4, major histocompatibility complex class I molecules, and various tetraspanin proteins, creating cellular conditions that may favor latency by reducing immune recognition and altering cellular activation states **(Mouzakis *et al.* 2025)**. The viral protein R (Vpr) plays multifaceted roles in viral replication and latency. Beyond its established functions in nuclear import and cell cycle arrest, Vpr exhibits modest transcriptional activity on the HIV long terminal repeat (LTR) through activation of NF-κB, Sp1, and other cellular transcription factors. The transcriptional effects of Vpr appear secondary to its cell cycle arrest function, with increased LTR activity observed in G2/M-arrested cells expressing Vpr. Additionally, Vpr can interact directly with transcription factors including Sp1, the glucocorticoid receptor, and the p300 coactivator, suggesting multiple mechanisms by which it influences viral gene expression **(Bukrinsky and Adzhubei 1999)**.

### 3.4.1.3. Gag-Pol Processing & Viral Maturation Relevance

While Gag-Pol processing primarily occurs during viral particle maturation, the processing events and resulting protein products can influence subsequent infection cycles and latency establishment. Proper Gag-Pol processing is essential for the production of infectious virions, and defects in processing can result in particles with altered infectivity that may be more prone to establishing latent rather than productive infections **(Mattei *et al.* 2014)**.

## 3.4.2. Host Proteins & Pathways in Latency Control

### 3.4.2.1. Transcription Factors

Multiple host transcription factors function as key regulators of HIV latency through their binding to specific sites within the HIV LTR. NF-κB serves as a master regulator, with its activation promoting viral reactivation through displacement of repressive factors and recruitment of transcriptional activators. The NF-κB pathway enables formation of transcriptionally active complexes when combined with AP-1, as AP-1 alone cannot activate HIV transcription in the absence of NF-κB binding. The nuclear factor of activated T cells (NFAT) provides complementary but sometimes opposing regulation to NF-κB, with studies showing that NFAT can inhibit HIV transcription by competing with NF-κB for overlapping binding sites. Activator protein 1 (AP-1) functions synergistically with NF-κB to enhance HIV transcriptional elongation, with the two factors forming functional transcription complexes mediated through physical interactions between the bZIP domain of AP-1 and the Rel-homology domain of NF-κB **(Gibaut *et al.* 2023)**. Repressive transcription factors play equally important roles in maintaining latency. YY1 (Yin Yang 1) contributes to latency by recruiting HDAC-1 to the provirus, establishing a repressive chromatin state. CBF-1 (C-promoter binding factor 1) emerges as a particularly potent silencing factor, binding to NF-κB elements in the HIV LTR and recruiting HDAC-containing corepressor complexes that initiate chromatin condensation and transcriptional silencing.

### 3.4.2.2. Epigenetic Enzymes

Histone deacetylases (HDACs) represent critical regulators of HIV latency through their ability to remove activating acetyl marks from histones. HDAC1/2 and HDAC3 play essential but mechanistically distinct roles in initiating viral latency, with combined inhibition of both

required to reverse established latency. Treatment with HDAC inhibitors not only prevents HIV proviruses from entering latency but also induces lasting epigenetic reprogramming that maintains viral expression even after inhibitor removal. Histone methyltransferases (HMTs) contribute to latency through deposition of repressive methylation marks.

The polycomb repressive complex 2 (PRC2) with its catalytic subunit EZH2 trimethylates histone H3 at lysine 27 (H3K27me3), making proviruses less likely to reactivate. SUV39H1 promotes heterochromatin formation by trimethylating H3K9, while SMYD2 monomethylates H4K20 and recruit's chromatin compaction factors **(Peterson *et al.* 2023)**. BET (bromodomain and extra-terminal) proteins serve as critical readers of histone acetylation marks and can be targeted to modulate HIV latency. These proteins recognize acetylated lysine residues and facilitate transcriptional activation, making BET inhibitors valuable tools in latency reversal strategies when used in combination with other approaches. DNA methyltransferases (DNMTs) contribute to HIV silencing through cytosine methylation at CpG islands flanking the HIV transcription start site, with methyl-CpG binding proteins subsequently recruiting HDACs to establish repressive chromatin environments **(Singh and Sartor 2020)**.

### 3.4.2.3. Restriction Factors

Host restriction factors provide intrinsic antiviral defenses that can influence HIV latency establishment and maintenance. SAMHD1 restricts HIV replication by depleting cellular dNTP pools required for reverse transcription, particularly in myeloid cells and resting CD4+ T cells. By limiting successful infection, SAMHD1 indirectly influences the balance between productive infection and latency establishment. APOBEC3G introduces cytidine-to-uridine mutations in viral DNA during reverse transcription, potentially creating defective proviruses that contribute to the latent reservoir through their inability to produce infectious virus. TRIM5α recognizes incoming viral capsids and promotes their premature uncoating while simultaneously activating innate immune signaling pathways through its E3 ubiquitin ligase activity **(Amie *et al.* 2013)**. These restriction factors also participate in shaping antiviral immunity by connecting intrinsic cellular defenses with innate and adaptive immune responses, potentially influencing the long-term dynamics of latent reservoir maintenance **(Figure 3)**.

### 3.4.2.4. Checkpoint Proteins

Immune checkpoint molecules including PD-1, CTLA-4, TIGIT, and LAG-3 play crucial roles in defining and maintaining the latent HIV reservoir. Latent infection is significantly enriched in CD4+ T cells expressing these checkpoint molecules, with cells co-expressing multiple checkpoints showing the highest levels of HIV DNA integration.

PD-1 has been demonstrated to have functional roles in latency establishment, maintenance, and reversal. PD-1 engagement can inhibit HIV latency establishment in resting CD4+ T cells, while simultaneously blocking viral production at the transcriptional level by inhibiting T cell receptor-induced HIV reactivation. Conversely, PD-1 blockade with monoclonal antibodies enhances HIV production without increasing T cell activation when combined with other latency reversing agents. The checkpoint molecules CTLA-4, TIGIT, and LAG-3 show similar enrichment patterns in latently infected cells, with memory CD4+ T cells expressing any combination of PD-1, TIGIT, or LAG-3 contributing up to 98% of the total pool of inducible HIV genomes during antiretroviral therapy **(Fromentin *et al.* 2016)**.

This enrichment reflects the synergistic mechanisms by which these receptors dampen T cell functions and create cellular conditions favourable for latency maintenance. These checkpoint proteins thus serve dual roles: they mark latently infected cells and actively contribute to maintaining the transcriptionally silent state through their inhibitory effects on T cell activation pathways. Understanding these mechanisms provides important targets for combination approaches that seek to reverse latency while simultaneously enhancing immune clearance of reactivated cells **(Figure 3)**.

## 4. Therapeutic Opportunities and Cure Strategies

The pursuit of an HIV cure has intensified with innovative therapeutic approaches targeting viral latency through diverse mechanisms. Current strategies encompass latency reversal ("shock and kill"), latency promotion ("block and lock"), and immunological interventions that collectively aim to eliminate or permanently silence the latent reservoir.

### 4.1. Latency-Reversing Agents (LRAs)

Histone deacetylase (HDAC) inhibitors represent the most clinically advanced class of LRAs, functioning by removing repressive acetyl marks from histones to reactivate transcriptionally silent proviruses. Vorinostat (SAHA), panobinostat, and romidepsin have demonstrated the ability to increase HIV RNA expression in resting CD4+ T cells from ART-suppressed patients, with vorinostat showing a mean 4.8-fold increase in unspliced HIV-1 gag RNA expression in clinical trials. However, these agents exhibit limited single-agent activity, typically achieving only 4% of maximum T cell activation levels **(Shirakawa *et al.* 2013)**. Protein kinase C (PKC) agonists activate transcription factors NF-κB and AP-1, representing a mechanistically distinct approach to latency reversal.

Bryostatin-1 emerged as the only single LRA to significantly induce intracellular HIV-1 mRNA production ex vivo in initial studies, though clinical trials showed the drug was safe but required higher dosages to demonstrate measurable PKC activity or HIV transcriptional effects. Ingenol 3,20-dibenzoate has demonstrated more significant reactivation effects in recent studies. Bromodomain and extra-terminal (BET) inhibitors, exemplified by JQ1, function by competing with the viral Tat protein for P-TEFb binding, thereby releasing transcriptional elongation factors from inhibitory complexes. BET inhibitors show particular promise in combination approaches, achieving robust latency reversal when paired with PKC agonists. Recent clinical trials have demonstrated that combination LRA approaches achieve superior efficacy compared to single agents. PKC agonists combined with HDAC inhibitors or BET inhibitors show dramatic viral transcription induction with formal drug synergy as demonstrated by Bliss independence modeling. These combinations approach levels of viral reactivation seen with maximal T cell activation, representing substantial progress toward clinically meaningful latency reversal.

Clinical trials combining therapeutic vaccines with LRAs have yielded mixed results. The Vacc-4x peptide-based HIV vaccine combined with romidepsin showed moderate decreases in latently infected CD4+ T cell frequencies but failed to delay viral rebound during analytical treatment interruption. Ongoing studies are investigating combinations of panobinostat with pegylated interferon-α2a based on post hoc observations of enhanced effects **(Jiang and Dandekar 2015)**. Despite promising preclinical results, LRAs face significant clinical limitations. HDAC inhibitors impair HIV-specific cytotoxic T lymphocyte responses, potentially undermining the "kill" component of shock-and-kill strategies by reducing immune-mediated clearance of reactivated cells. Single-agent LRAs typically achieve only modest reactivation levels, with most studies showing no measurable depletion of the latent reservoir despite detectable increases in viral RNA expression. Safety concerns include off-target effects on host gene expression, with older generation LRAs like valproic acid showing no consistent reservoir depletion after 16-32 weeks of treatment. The multifactorial nature of HIV latency suggests that no single drug may effectively reverse all blocks to proviral gene expression, necessitating complex combination regimens with associated toxicity concerns **(Salahong *et al.* 2021)**.

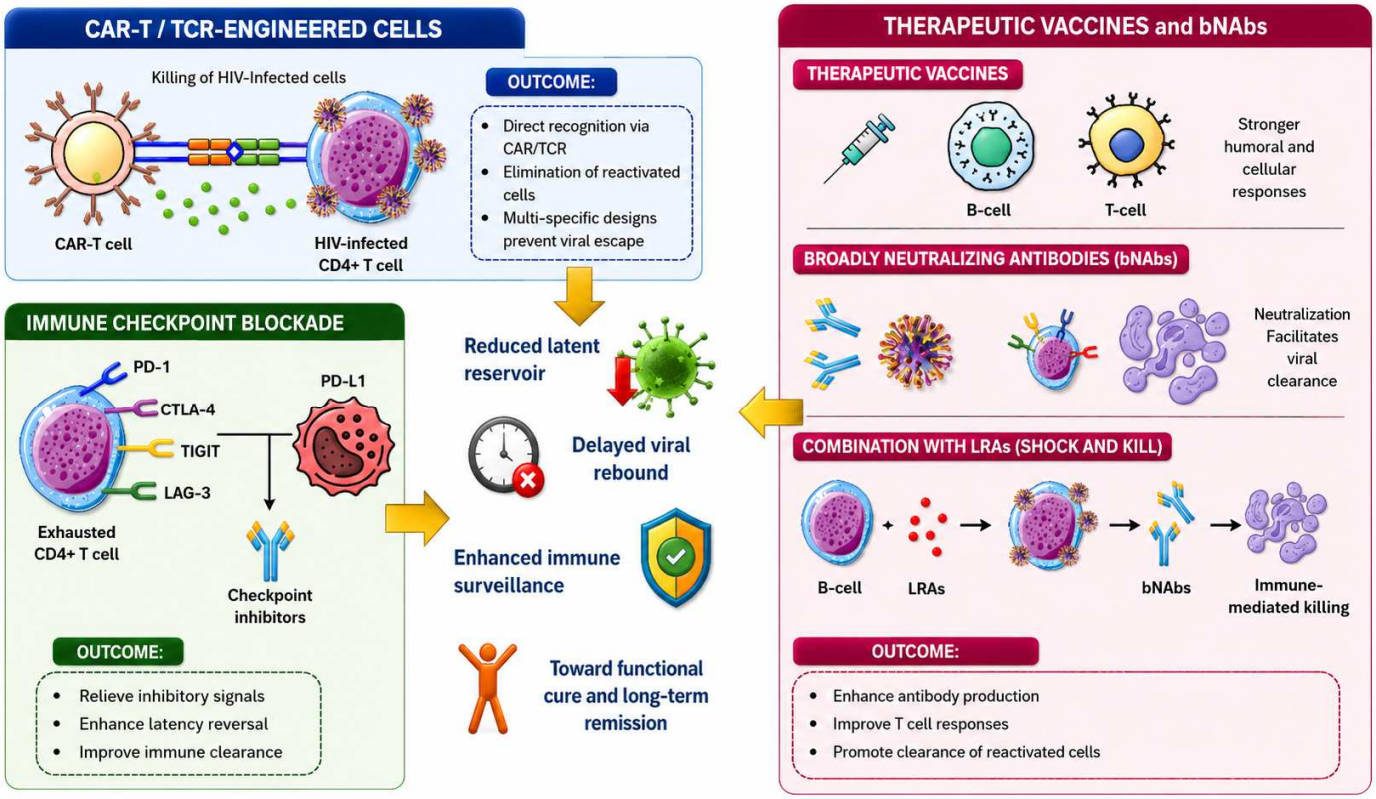


**Figure 4.** Immunological strategies for HIV latency reversal and immune clearance

## 4.2. Latency-Promoting Agents (LPAs)

### 4.2.1. Epigenetic Silencing Agents & "Block and Lock"

The "block and lock" approach aims to permanently silence latent reservoirs using latency-promoting agents that induce "super latency" or "deep latency" states through repressive epigenetic modifications. This strategy mimics natural viral silencing observed in human endogenous retroviruses, which comprise ~8% of the human genome and remain epigenetically silenced. RNA-based therapeutics targeting specific sequences within the HIV genome represent a promising epigenetic silencing approach. The siPromA system, targeting the HIV promoter region, was among the first block-and-lock therapeutics identified, demonstrating the feasibility of sequence-specific transcriptional gene silencing (**Ahlenstiel *et al.* 2020**). Advanced approaches combine multiple RNA therapeutics targeting different viral genome sites to address HIV-1 sequence diversity.

### 4.2.2. Tat Inhibitors

Didehydro-cortistatin A (dCA) represents the most clinically advanced block-and-lock agent, functioning as a potent Tat inhibitor that blocks HIV transcription and reactivation. In humanized mouse models, dCA treatment for four weeks prior to treatment interruption delayed viral rebound from 10 days in controls to 19 days in treated animals, with enhanced nucleosomal occupancy at the LTR Nuc-1 region explaining its long-term effects. Recent mechanistic studies reveal that dCA promotes tight nucleosome-DNA association by increasing deacetylated histone 3 occupancy and enhancing recruitment of the repressive BAF chromatin remodeling complex while inhibiting the activating PBAF complex (**Mousseau *et al.* 2015**). This creates a durable repressive epigenetic landscape that resists reactivation even upon LRA stimulation.

## 4.3. Long-term Suppression Approaches

Combination block-and-lock strategies show enhanced efficacy over single agents. LEDGINs (lens epithelium-derived growth factor inhibitors) retarget HIV integration away from transcriptionally active chromatin regions, inducing deep latency that persists after drug removal. When combined with BRD4 modulator ZL0580, LEDGINs demonstrate additive effects in blocking HIV transcription through dual mechanisms: retargeting integration to silent chromatin and blocking enhancer activity. The block-and-lock approach offers potential advantages including elimination of daily ART requirements if permanent viral silencing is achieved and reduced risk of viral rebound compared to shock-and-kill strategies. However, challenges include ensuring complete and durable silencing across genetically diverse viral populations and developing agents with sufficient specificity to avoid off-target host gene effects (**Pellaers *et al.* 2024**).

## 4.4. Immunological Approaches and Novel Strategies

### 4.4.1. Immune Checkpoint Blockade

Immune checkpoint molecules including PD-1, CTLA-4, TIGIT, and LAG-3 are enriched on latently infected CD4+ T cells, with cells expressing multiple checkpoints showing the highest HIV DNA levels. PD-1 blockade enhances HIV production when combined with other LRAs without increasing global T cell activation, representing a promising combination approach. Clinical trials investigating checkpoint inhibitor combinations have shown promise, with studies demonstrating that immune checkpoint blockade can enhance latency reversal and potentially improve immune clearance of reactivated cells (**Van der Sluis *et al.* 2020**). However, safety concerns regarding immune-related adverse events require careful monitoring in HIV-positive populations.

### 4.4.2. CAR-T and TCR-Engineered Cells

Chimeric antigen receptor T (CAR-T) cell therapy has been adapted for HIV cure strategies, with broadly neutralizing antibody-based CARs showing particular promise. Unlike CD4-based CAR constructs that render cells susceptible to HIV infection, bNAb-based CARs avoid this vulnerability while maintaining potent anti-HIV activity. Recent clinical trials demonstrate that bNAb-based CAR-T cells can eliminate HIV-

reactivated infected CD4+ T lymphocytes and show delayed viral rebound during analytical treatment interruption. However, viral escape through spontaneous mutations remains a limitation, with resistant variants emerging that evade CAR-T cell recognition **(Han *et al.* 2026)**. Multi-specific CAR designs targeting multiple HIV envelope epitopes show improved efficacy, with up to 99% reduction in cellular HIV infection in vitro and >97% reduction in vivo **(Figure 4)**.

### 4.4.3. Therapeutic Vaccines & Neutralizing Antibodies

Broadly neutralizing antibodies represent a dual-function therapeutic approach, providing both viral neutralization and immune-mediated clearance of infected cells through Fc effector functions. Recent clinical trials of triple bNAb combinations show enhanced potency, with 83% of participants maintaining virologic suppression for at least 28 weeks and 42% showing suppression for 38-44 weeks despite declining antibody levels. The combination of bNAbs with LRAs shows particular promise in "shock and kill" strategies, with bNAbs engaging the host immune system to clear cells expressing HIV envelope proteins following latency reversal. Engineering approaches including LS mutations to extend antibody half-life and Fc modifications to enhance effector functions are advancing the therapeutic potential of these agents **(Thavarajah *et al.* 2024)**. Therapeutic vaccines combined with bNAbs are being investigated in clinical trials including the HIVCAR trial and ACTG A5386 study, which evaluate combination immunotherapies incorporating vaccines, bNAbs, and cytokines like IL-15 superagonists. These approaches aim to enhance both innate and adaptive immune responses against the latent reservoir **(Figure 4)**.

## 4.5. AI/ML-Driven Drug Discovery for Latency Modulation

Artificial intelligence and machine learning approaches are revolutionizing HIV cure research through accelerated drug discovery and optimization. Long short-term memory (LSTM) variational autoencoder architectures enable generation of novel HIV therapeutic candidates with properties optimized for latency modulation, significantly streamlining the drug discovery process and reducing development timelines. AI-enabled virtual screening applications rapidly determines the large quantity of chemical libraries to identify potential and effective LRA and LPA candidates, with deep learning models which predicts the drug-target interactions and resistance profiles. For instance, Generative adversarial networks (GANs) and reinforcement learning algorithms significantly regulates design of compounds specifically tailored to HIV targets, with improved binding affinity predictions and adherence to drug-likeness criteria. Machine learning models optimize combination therapy approached by envisaging synergistic drug interactions and predicting optimal dosing regimens for LRA combination **(Jin and Zhang 2025)**. These AI-enabled technologies hold promising effort for addressing the complex nature of HIV latency by simultaneously focusing multiple regulatory pathways while reducing the toxicity via predictive modelling of off-target effects.

## 5. Future Directions and Perspectives

The continues research in the scientific discovery to clinical implementations demonstrates the ultimate test of HIV cure research viability. The deep understanding of mechanisms HIV viral latency, the challenges of translating these discoveries into worldwide accessible therapeutic interventions demand comprehensive strategies to overcome the scientific, ethical and equity considerations.

## 5.1. Integrating Insights with Clinical Translation

### 5.1.1. Bench-to-Bedside Challenges

The key challenge in the cure research of HIV latency is translation of laboratory inventions to clinical applications. Owing to the complex multifactorial nature of HIV latency the translation process faces significant obstacles across multiple domines, and it is demanding sophisticated combinations of other disciplines, but that are difficult to standardize and implement safely. Current mechanistic study demonstrates that no single intervention can address the key regulatory pathways that are effectively involved in viral persistence, and requiring combination of latency-reactivating factors, potential gene-editing techniques and immune modulators. Animal model is very crucial and essential techniques for safety evaluation, though it may not reflect human reservoir dynamics, or immune response, and tissue distribution patterns. Owing the heterogeneity of the latent reservoirs significantly influenced by several factors including, viral clade, duration of infection, immune status, host genetics, and also complicates the translation of mechanistic discoveries into globally accessible interventions. Hence, the clinical trial design present additional challenges, especially regarding analytical treatment interruptions (ATIs), which are highly required to access the efficacy of cure research, but it also exhibits risk of viral rebound and transmission **(Richman 2011)**. The field necessitates improved coordination of HIV reservoir assessment methods, consistent biomarkers, and vibrant benchmarks defining remission success. Current reservoir measurement techniques often disagree, making it difficult to assess intervention efficacy and compare results across studies. The risk-benefit profile of cure interventions remains challenging, as most experimental approaches involve significant health risks with modest direct benefit to participants. Many interventions require immunosuppression or immune activation that could increase susceptibility to opportunistic infections or malignancies. The long-term consequences of interventions like gene editing remain unknown, requiring extended follow-up periods that complicate study design and participant retention **(Rouzioux and Richman 2013)**.

### 5.1.2. Personalized Medicine Approaches

The future of HIV cure research lies increasingly in precision medicine strategies that tailor interventions to individual characteristics. Pharmacogenomic approaches already demonstrate promise in optimizing antiretroviral therapy, with genetic polymorphisms in drug-metabolizing enzymes and transporters significantly affecting drug exposure and treatment outcomes. For example, individuals with specific MDR1 polymorphisms show significantly reduced treatment failure rates with lopinavir/ritonavir combinations, suggesting that prospective genetic testing could guide therapy selection. Therapeutic drug monitoring (TDM) represents an underutilized tool in personalized HIV care that could be expanded to cure research applications. While currently not part of standard care due to cost-effectiveness concerns, TDM shows particular value in high-risk populations including pregnant women, treatment non-responders, and those with suspected drug interactions **(Yu *et al.* 2021)**. Advanced prediction algorithms integrating pharmacokinetic, pharmacodynamic, and genetic data could enable "just-in-time" identification of patients who would benefit from specific interventions. Host genetic factors influencing immune responses, viral control, and treatment outcomes offer additional personalization opportunities. HLA-B*5701 screening for abacavir hypersensitivity represents the most established example of HIV pharmacogenomics in clinical practice. Future approaches may incorporate genetic markers predicting immune checkpoint expression patterns, latency reversal responsiveness, or susceptibility to specific cure interventions. The integration of comprehensive biomarker panels, including viral reservoir characteristics, immune activation markers, and host genetic profiles, could enable stratification of patients into subgroups most likely to benefit from specific cure strategies. Machine learning approaches show promise in analysing complex, multi-dimensional datasets to identify predictive patterns and optimize treatment algorithms **(Meissen *et al.* 2022)**. Reservoir

heterogeneity across anatomical sites and cell types necessitates personalized approaches based on individual reservoir characteristics. The recent techniques, like single cell sequencing and advanced imaging methods may eventually enable and helping to study the individual latent reservoir, which give ideas for selection of targeted interventions. This precision approach can significantly reduce the toxicity by avoiding the interventions unlikely to benefit individual person, while increasing the effectiveness via tailored combinations approaches **(Mbhele *et al.* 2025)**.

## 5.2. Global Health and Ethical Considerations

### 5.2.1. Equitable Access to Cure Strategies

The HIV burden excessively affects the low- and middle-income countries globally, where the nearly 70% people has infected with HIV, yet the most cure research requires in high-income settings with comparatively low HIV prevalence. This topographical divergence positions important queries about the relevance and pertinency of cure plans developed primarily in resource-rich environments to global population most affected by HIV. Geographic regions significantly influence the genetic diversity of the HIV, the non-B subtypes predominantly reported in sub-Saharan Africa and Asia. Several cure applications including particularly those involving widely neutralizing antibodies and therapeutic vaccines, may shows sub-type specific efficacy patterns than required evaluation across diverse viral clades **(Lu *et al.* 2025)**. Gene therapy applications with sophisticated immunomodulatory innovation, and integrating complex regimens demands specialized laboratory techniques, well-trained manual power, and robust supply chain that may represent a unavailable in resource-limited settings. The concept of "scalability" must be combined into cure research from its beginning, assessing whether intrusions can persuasively be applied in diverse healthcare systems with varying capacity. Economic deliberations signify possibly the most important barrier to impartial access. The high initial costs of innovative therapeutics, as demonstrated by hepatitis C cure evaluating, could reduce HIV cure interferences unreachable to those who need them most. Early incorporation of cost-effectiveness analyses, manufacturing reflections, and access development into cure research could avert the development of intrusions that benefit only wealthy populations. The principle of global health equity demands that HIV cure research clearly address employment in resource-limited settings rather than treating this as an afterthought. This comprises developing "cure strategies in a box" that diminish infrastructure supplies, exploring lower-cost manufacturing methods, and attractive LMIC researchers and communities through the research process **(Linas *et al.* 2014)**. The HIV Cure Africa Acceleration Partnership signifies a vital step toward broader global engagement in cure research.

### 5.2.2. Ethical Dimensions of Clinical Trials

HIV inconsistently affects the marginalized populations most specifically sex workers, and people who inject the drugs, homosexual contacts, transgender individuals, ethnic and racial minorities and people exposing with poverty. These populations face several challenges in healthcare and research participation such as systemic exclusion, discrimination, criminalization and stigma from medical care. The historical manipulation of vulnerable populations in clinical research requires particular attention to ethical safeguards in HIV cure research. Owing to the high-risk and low benefit profile cure innovation approaches raises number of concerns about the potential for unethical exploitation of individuals desperate for therapeutic alternatives. Robust informed agreement procedures must clearly differentiate between potential benefits to society versus direct benefits to distinct participants, recognise the experimental nature interferences and indefinite predictions for personal benefit **(Mayer and Allan-Blitz 2019)**. Community engagement signifies both an ethical imperious and an applied requirement for successful cure research. In 1983, HIV activists developed Denver Principles for meaningful involvement of people living with HIV in all aspects of research affecting them. The active stakeholder appointment should start primary in research planning and endure via study contact and result distribution. A careful ethical consideration is highly recommended for conducting cure research in criminalized populations also represents as key challenges in this process. People who inject drugs may faces legal risk from research participation, whereas the sex workers may address the increase stigmatization. Hence the predictive measures should be incorporating in the research protocols, specialized venue-based recruitment approaches, certificates of confidentiality, and culturally competent research staff are key predictive measures which should be integrated into the research protocols **(Dube *et al.* 2023)**. Gender equity is another key challenge in cure research, with most early trials predominantly enrolling men. The exclusion of pregnant women from cure research program also creates the additional inequities, and this populations signifies a remarkable proportion of women living with HIV globally. Age-related consideration also an important ethical complexity, because pediatric require specialized techniques and acknowledging difference in immune systems and distinct ethical frameworks for assent and consent. Aged peoples may face significant obstacles and increased risk from immunomodulatory innovations due to age-relevant immune systems dysfunction and comorbidities **(Shankar *et al.* 2025)**. The possible for HIV cure research to aggravate current health disparities strains proactive care to equity throughout the research continuum. In early phase research ensures that key barriers to participation among the marginalized population, and establishment of innovative strategies that prioritize equitable access. Long-tern follow-up needs in cure research and rise number of quires about ongoing obligations to participants especially those from vulnerable populations who may have very limited access to get standard medical care. Incorporating the social science research with biomedical cure applications is requires for understanding the community perspective, to address the misconception and establishing culturally appropriate employment strategies. A proof-of-concept to larger efficacy trials increases the ethical stakes, hence this area should maintain the commitment to ethical principles while advancing toward innovation that could transform HIV from chronic condition which needs lifelong treatment into curable conditions. This necessitates ongoing conversation between researchers, communities, ethicists, and policymakers to safeguard that the detection of scientific advancement remains stranded in respect for human dignity and social justice **(Bouabida *et al.* 2023)**.

## 6. Research Gaps in HIV Latency and Cure

Over the decades of intensive research in HIV cure strategies, still, a significant knowledge gaps continue that remarkably limits the progress towards the cure approaches. These research gap extends the understanding of fundamental mechanisms, methodological limitations and translational challenges, and execution barriers that collectively obstruct the establishment of potential curative interventions.

## 6.1. Mechanistic Understanding Limitations

The poor understanding of HIV latency establishment and maintenance mechanisms represents a fundamental research gap. Several regulatory pathways have been studied, still, the precise molecular events that determine the infected cell enters productive replication or latency is poorly understood. The heterogeneity of latency mechanisms noticed in different types of cells, anatomical sites, and viral subtypes generates the complexity that current models cannot fully capture. The role of epigenetic regulation in HIV latency remains incompletely understood, particularly regarding the interplay between different chromatin modifications and their temporal dynamics during latency establishment

and reversal. Critical gaps exist in understanding how integration site selection influences long-term latency stability and whether specific chromatin environments predispose proviruses to permanent silencing versus reactivation potential. Cellular reservoir heterogeneity presents another major knowledge gap. Beyond the well-characterized resting memory CD4+ T cells, the contribution of other cell types including tissue-resident macrophages, microglia, and newly identified stem-like memory T cells to the total reservoir remains poorly quantified **(Marsden and Zack 2010)**. The central nervous system reservoir represents a particularly significant gap, as limited access to brain and spinal tissues in living individuals restricts our understanding of viral dynamics within these anatomically privileged sites.

### 6.2. Methodological and Technical Gaps

Current reservoir quantification methods suffer from fundamental limitations that impede accurate assessment of curative interventions. The quantitative viral outgrowth assay (QVOA), considered the gold standard for measuring replication-competent virus, significantly underestimates reservoir size and requires substantial cell numbers and resources. Newer intact proviral DNA assays show promise but remain clade-dependent and cannot distinguish between replication-competent and defective genomes. A critical gap exists in developing biomarkers that can predict viral rebound without requiring treatment interruption. Current approaches rely on analytical treatment interruptions that pose risks to participants and their partners, limiting the scope and safety of cure research. The field urgently needs non-invasive biomarkers that correlate with rebound potential and can guide therapeutic decision-making. Tissue sampling confines characterise another key methodological gap. Most reservoir studies rely on peripheral blood samples, which contain only a small fraction of the total body reservoir **(Lungu *et al.* 2021)**. Retrieving tissue reservoirs needs invasive measures that are regularly impractical in clinical settings, generating a substantial sampling bias in our empathetic of reservoir distribution and dynamics.

### 6.3. Translational and Clinical Research Gaps

The transformation of mechanistic understanding into potential interventions faces still a remarkable obstacle in clinical research. To predict the accurate human response against species specific impact in immune systems, reservoir characteristics and tissue distribution, preclinical models play a crucial role and are significantly essential for initial screening. Hence, the lack of validated animal models that truly review the HIV latency dynamics limits the predictive value of preclinical studies. Another remarkable research gap is clinical trial design in HIV cure research; the standard endpoint measurements are highly essential treatment interruptions that carry ethical and safety concerns especially in vulnerable populations. The field lacks consensus on optimal trial designs, participant selection criteria, and safety monitoring protocols for early-phase cure studies. Single-agent approaches have consistently failed to achieve meaningful reservoir depletion, suggesting that combination strategies are necessary. However, rational combination design is hampered by incomplete understanding of drug interactions, optimal dosing sequences, and synergistic mechanisms **(Ma *et al.* 2025)**. The complexity of multi-drug regimens creates challenges in identifying the active components and optimizing treatment protocols.

### 6.4. Global Health and Implementation Gaps

A major research gap exists in the applicability of cure strategies developed primarily in high-income countries to global populations most affected by HIV. Most cure research has been conducted in resource-rich settings with predominantly subtype B virus, while the global epidemic is dominated by non-B subtypes with potentially different reservoir characteristics. This geographic and viral diversity gap raises questions about the universal applicability of current cure approaches. The interaction between common coinfections in resource-limited settings, including tuberculosis, malaria, and helminthic infections, and HIV cure strategies remains poorly understood. These coinfections may affect immune activation states, reservoir sizes, and responses to latency-reversing interventions in ways that could compromise cure efficacy. Chronic immune activation from persistent coinfections may create inflammatory environments that influence reservoir establishment and maintenance differently than in controlled clinical trial populations. In low and middle-income countries, development of well infrastructure shows several limitations that also create remarkable barriers to implementation of well-established cure strategies. The lack of well-established and sophisticated laboratory, reliable supply chain, trained personnel, are highly required for interventions limits global access to experimental cure strategies **(Rossouw *et al.* 2017)**. The insufficient research capacity building and technological transfer also must me address to overcome the implementation gaps.

### 6.5. Ethical and Social Research Gaps

In HIV cure research, community engagement remains inadequate, especially among the marginalized population most affected by HIV. The research gaps in understanding the community perception regarding cure research, preferred intervention features, and acceptable risk levels. The gap between the researcher main concern and community needs may leads the unacceptable and inaccessibility of cure strategies practically though it was technically successful. Hence, there is high demand for long-term follow-up in cure research to create ethical obligations that are poorly understood **(Sanchez *et al.* 2025)**. Participants in cure studies require decades of monitoring to assess intervention durability and detect late adverse effects, yet frameworks for ongoing care and support are inadequately developed. The potential for cure interventions to affect future health in unpredictable ways raises questions about intergenerational consent and family counselling needs.

### 6.6. Future Research Priorities

Addressing these research gaps requires coordinated efforts across multiple domains. Priority areas include developing more sophisticated in vitro and in vivo models that better recapitulate human reservoir dynamics, advancing reservoir quantification technologies that can assess tissue compartments non-invasively, and establishing international consortia to standardize methodologies and enable comparative analyses. The integration of artificial intelligence and machine learning approaches represents a promising avenue for addressing some research gaps by analysing complex datasets, predicting drug interactions, and identifying novel therapeutic targets. However, these computational approaches require high-quality datasets that may not exist for many key research questions. Ultimately, there is need for sustained investment in fundamental scientific research, community engagement initiatives and development of clinical infrastructure, to closing these research gaps **(Kang *et al.* 2025)**. In addition, interdisciplinary approaches also need to address the complexity of HIV latency, the integration other crucial areas like immunology, virology, pharmacology and social science may help to develop curative interventions that scientifically sound and also easily accessible and acceptable world-wide.

## 7. Conclusion

In modern medicine, HIV latency is one of the remarkable formidable challenges and exemplifying a complex interplay of viral determination mechanisms that have evolved to evade both immune systems surveillance and therapeutic intervention. The present comprehensive review demonstrates the complex nature of HIV latency, revealing a phenomenon that ranges far beyond simple transcriptional silencing to

encompass sophisticated regulatory mechanisms covering epigenetic modifications, cellular activation states, host-pathogen interactions and anatomical sanctuary sites. The understanding of HIV latency mechanisms demonstrates their heterogeneity owing to the presence of various cell types, and tissue compartments, and viral subtypes. The complex nature of chromatin remodelling, and transcription factors, epigenetic enzymes produce multiple layers of regulation that cooperatively maintain the viral dormancy while preserving the potential of reactivation. This complexity illustrates the single-agent approach to reversal of latency have reliably failed and underlines the need for combination strategies which targeting multiple pathways simultaneously. The clinical implications of HIV latency continue virological considerations to incorporate thoughtful impacts on patient quality of life, healthcare system, and global health worldwide. Though, the significant advances in antiretroviral therapy that exhibits ability to transformed HIV from a fatal disease to manageable chronic condition, the persistence of latent reservoirs requires prolong treatment, in addition, psychological, financial and toxicological burdens also interconnected. The inconsistent impact on marginalized populations and those have limited resource settings highlights the immediate action must be needed for curative interventions that address both scientific and equity challenges. Current therapeutic methods, such as "shock and kill" and "block and lock" strategies shows promise, but it also exhibits remarkable obstacles such as partial reactivation, off-target toxicity and implementation complexity. The integration of modern approaches such as gene editing, artificial intelligence and cellular immunotherapy provides new opportunities for overcome these challenges, yet the conventional research gaps persist in our understanding of reservoir dynamics, optimal combination strategies, and long-term intervention durability. The path progression required extraordinary collaboration with other disciplines, and sectors guided by principles of scientific rigor and social justice. Success will be quantified not only by achieving viral eradication in select individuals but by establishing interventions, that are more effective, affordable, safe and accessible to all HIV infected people globally. The ultimate aim is to transforming HIV from chronic conditions requiring prolong treatment into curable conditions, which demands sustained commitment into both scientific innovation and global health equity. The teachings learned from HIV latency research will indubitably inform techniques to other persistent viral infections and contributes to our broader understanding of host-pathogen interaction in chronic conditions.

## 8. Disclosure Statements

### 8.1. Author Contribution

**FA:** literature collection, data curation, visualization, writing—original draft preparation, **FAF:** Literature survey, validation of scientific content, writing—review and editing. **AAA:** Investigation, data interpretation, and manuscript review. **RMI:** validation, review and editing, and critical intellectual input. **MME:** scientific validation, and manuscript revision. **PM:** Data analysis, visualization, writing—review and editing. **RV:** Overall supervision, conceptual framework development, project coordination, critical review, and final approval of the manuscript. All authors have read and approved the final version of the manuscript and agreed to the published version of the article. **RV:** served as the corresponding author and was responsible for overall coordination of the study and manuscript.

### 8.2. Declaration of Generative AI

The authors used generative artificial intelligence tools solely for language editing and grammatical correction. The AI tools did not contribute to the study design, data collection, analysis, interpretation, or generation of scientific content. All content has been reviewed and approved by the authors, who take full responsibility for the integrity and accuracy of the work.

### 8.3. Ethics approval (for clinical/animal studies)

Ethical approval was not required for this study because it is a review article based exclusively on previously published literature and does not involve human participants, human-derived samples, animals, or experimental interventions.

### 8.4. Informed Consent Statement

Not applicable. This study did not involve human participants, human-derived samples, or clinical data; therefore, informed consent was not required.

### 8.5. Data Availability Statement

No new data were generated or analyzed in this study. All information discussed in this review was obtained from publicly available published literature and cited appropriately within the manuscript.

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The authors declare that they have no known financial, personal, academic, or other relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript. All authors confirm that there are no competing interests to declare.

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### 8.10. Supplementary Information

No supplementary information or additional files are associated with this manuscript.

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