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Immune Checkpoint Inhibitors and HIV Reservoir Persistence: Therapeutic Implications and Challenges

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ABSTRACT

Human immunodeficiency virus (HIV) persisted in latent reservoirs despite effective antiretroviral therapy (ART), presenting the primary barrier to achieving a functional cure. Immune checkpoint inhibitors (ICIs), originally developed for cancer immunotherapy, have emerged as promising agents for reversing HIV latency by modulating T-cell exhaustion pathways. This narrative review critically synthesized current evidence on the therapeutic potential and challenges of ICIs in targeting HIV reservoirs. A comprehensive literature search was conducted across PubMed, Embase, and Web of Science databases (2015–2024) using keywords related to immune checkpoint inhibitors, HIV latency, viral reservoirs, and T-cell exhaustion. Principal findings indicated that programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade can enhance HIV-specific immune responses and induce viral reactivation in vitro and in animal models. However, clinical trials in people living with HIV (PLWH) have demonstrated modest effects on reservoir reduction, with significant inter-individual variability and potential immune-related adverse events. Combination approaches integrating ICIs with latency-reversing agents and therapeutic vaccines showed promise but required optimization. The review concludes that while ICIs represent a rational therapeutic strategy for HIV reservoir elimination, substantial challenges remain in achieving clinically meaningful reservoir depletion. Enhanced understanding of checkpoint molecule dynamics, personalized treatment algorithms, and novel combination regimens are essential for translating this approach into effective cure strategies.

Keywords: Immune checkpoint inhibitors, HIV latency, Viral reservoir, T-cell exhaustion, Functional cure

INTRODUCTION

The advent of combination antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection from a terminal illness into a manageable chronic condition, with life expectancy approaching that of the general population [1–3]. Despite this remarkable success, ART cannot eradicate HIV due to the establishment of latent viral reservoirs in long-lived memory $CD4^+$ T cells and other cellular compartments. Current estimates suggest that approximately 38 million people globally are living with HIV, with 29 million receiving ART as of 2023 [4, 5]. However, treatment interruption invariably leads to rapid viral rebound, typically within 2–4 weeks, necessitating lifelong therapy with attendant concerns regarding adherence, cost, toxicity, and persistent immune activation. The latent reservoir, characterized by integrated but transcriptionally silent proviral DNA, represents the primary obstacle to achieving either a sterilizing or functional cure. Emerging evidence indicates that chronic HIV infection induces progressive T-cell exhaustion mediated by sustained upregulation of inhibitory checkpoint molecules, particularly programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene 3 (LAG-3) [6]. These checkpoint pathways, while serving physiological roles in preventing autoimmunity, become dysregulated during chronic viral infections and contribute to impaired HIV-specific immune responses and maintenance of latency. The success of immune checkpoint inhibitors (ICIs) in oncology has prompted investigation of their potential to reverse HIV latency and reinvigorate exhausted immune responses. This review critically examines the molecular mechanisms underlying checkpoint-mediated T-cell exhaustion in HIV infection, evaluates the therapeutic potential and limitations of ICIs for targeting viral reservoirs, and identifies key challenges and future directions for developing ICI-based HIV cure strategies.

METHODS

A comprehensive narrative review was conducted following systematic literature identification. PubMed/MEDLINE, Embase, and Web of Science databases were searched for English-language articles published between January 2015 and December 2024. Search terms included combinations of "immune checkpoint inhibitors," "programmed death 1," "PD-1," "CTLA-4," "TIM-3," "LAG-3," "HIV," "latency," "viral reservoir," "T-cell exhaustion," "latency reversal," and "functional cure." Inclusion criteria prioritized peer-reviewed original research articles, clinical trials, systematic reviews, and meta-analyses examining checkpoint molecule expression in HIV infection, mechanistic studies of ICI effects on viral latency, and clinical outcomes of ICI administration in people living with HIV. Exclusion criteria included case reports without mechanistic insights, non-English publications, and studies lacking clear methodological descriptions. Reference lists of included articles were manually searched to identify additional relevant studies. Evidence was synthesized narratively with critical appraisal of study quality, sample sizes, methodological rigor, and clinical relevance. Where applicable, data from clinical trials were tabulated to facilitate comparison of outcomes across studies.

MOLECULAR MECHANISMS OF IMMUNE CHECKPOINT PATHWAYS IN HIV INFECTION

Checkpoint Molecule Expression and T-Cell Exhaustion

Chronic HIV infection induces a progressive state of T-cell dysfunction characterized by hierarchical loss of effector functions, reduced proliferative capacity, altered metabolism, and distinct transcriptional and epigenetic signatures [7]. This exhaustion phenotype is mediated primarily through sustained expression of multiple inhibitory checkpoint receptors on HIV-specific CD8+ T cells. Under physiological conditions, checkpoint molecules such as PD-1 and CTLA-4 serve critical regulatory functions to maintain immune homeostasis and prevent excessive inflammation or autoimmunity [8]. However, persistent antigen stimulation during chronic HIV infection leads to aberrant checkpoint upregulation, converting these molecules from transient regulators into constitutive inhibitors of T-cell function.

PD-1, encoded by the PDCD1 gene, is the most extensively studied checkpoint molecule in HIV pathogenesis. Upon binding to its ligands PD-L1 and PD-L2, PD-1 delivers inhibitory signals through immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that recruit phosphatases such as SHP-2, which dephosphorylate key signaling intermediates in the T-cell receptor (TCR) pathway, including ZAP70 and PI3K [9]. This results in diminished activation of downstream pathways including Ras-MEK-ERK and Akt-mTOR, ultimately suppressing T-cell activation, proliferation, cytokine production, and cytotoxic function. Studies in untreated HIV-infected individuals consistently demonstrate elevated PD-1 expression on HIV-specific $CD8^+$ T cells compared to cytomegalovirus (CMV)-specific cells, with expression levels correlating inversely with viral control and directly with disease progression markers. Importantly, PD-1 expression persists on HIV-specific T cells even after years of suppressive ART, suggesting durable imprinting of the exhaustion phenotype.

CTLA-4, constitutively expressed in regulatory T cells (Tregs) and upregulated on activated conventional T cells, competes with the costimulatory molecule CD28 for binding to CD80/CD86 ligands on antigen-presenting cells [10, 11]. CTLA-4 exhibits higher affinity for these ligands than CD28 and delivers inhibitory signals while also mediating trans-endocytosis of CD80/CD86, thereby reducing costimulatory signals available to neighboring T cells. Research has demonstrated elevated CTLA-4 expression on both $CD4^+$ and $CD8^+$ T cells during chronic HIV infection, contributing to impaired T-cell responses. Additionally, HIV infection expands and functionally enhances Tregs expressing high CTLA-4 levels, which may suppress anti-HIV immunity and contribute to reservoir maintenance.

Beyond PD-1 and CTLA-4, several additional checkpoint molecules are implicated in HIV-associated T-cell dysfunction. TIM-3, upon engagement with galectin-9 or other ligands, induces T-cell tolerance and apoptosis through intracellular signaling cascades. LAG-3 binds major histocompatibility complex (MHC) class II with higher affinity than CD4, interfering with TCR signaling and contributing to exhaustion. T-cell immunoreceptor with Ig and ITIM domains (TIGIT) interacts with CD155 and CD112 to inhibit T-cell activation and natural killer cell function [12]. Importantly, co-expression of multiple checkpoint molecules defines severe exhaustion, with cells expressing three or more inhibitory receptors exhibiting profound functional impairment and association with larger HIV reservoirs.

Checkpoint Pathways and HIV Latency Establishment

Accumulating evidence suggests that checkpoint molecule signaling directly contributes to establishing and maintaining HIV latency. The quiescent metabolic state induced by checkpoint engagement favors transcriptional silencing of integrated provirus. PD-1 signaling suppresses mTOR activity and glycolysis while promoting oxidative phosphorylation and fatty acid oxidation, metabolic characteristics associated with memory T-cell differentiation and HIV latency [13, 14]. Furthermore, checkpoint-mediated inhibition of NF-κB and NFAT, transcription factors essential for HIV long terminal repeat (LTR) activation, directly suppresses viral transcription. Recent studies have identified PD-1 and $CD4^+$ T cells as enriched for intact, replication-competent proviruses compared to PD-1- cells, establishing a direct link between checkpoint expression and reservoir maintenance.

The anatomical distribution of checkpoint molecule-expressing cells also has implications for reservoir persistence. PD-1+ $CD4^+$ T cells preferentially reside in lymphoid tissues, which serve as major anatomical reservoirs for HIV. These cells exhibit reduced susceptibility to HIV-specific $CD8^+$ T-cell-mediated killing, potentially due to checkpoint-mediated immune suppression within the tissue microenvironment. Additionally, follicular helper T cells (Tfh), which represent a significant reservoir compartment, constitutively express high levels of PD-1 and reside in B-cell follicles with limited $CD8^+$ T-cell access, creating an immune-privileged sanctuary for viral persistence.

Biochemical Crosstalk and Combinatorial Inhibition

The checkpoint molecule network exhibits substantial biochemical crosstalk and functional redundancy, complicating single-agent blockade strategies. Co-expression patterns suggest coordinated regulation, with transcription factors such as TOX, NFAT, and BATF implicated in driving the exhaustion program [15]. Epigenetic modifications, including DNA methylation and histone modifications at checkpoint gene loci, stabilize the exhausted state and contribute to its irreversibility. These epigenetic changes parallel modifications at the HIV LTR that maintain latency, suggesting shared regulatory mechanisms. Understanding these interconnected pathways is essential for designing effective combination ICI strategies and identifying biomarkers of treatment response.

PRECLINICAL EVIDENCE FOR IMMUNE CHECKPOINT BLOCKADE IN HIV

In Vitro Studies of Latency Reversal

Multiple in vitro studies have evaluated ICI effects on HIV-infected cell lines and primary cells from ART-suppressed individuals. PD-1 blockade using monoclonal antibodies or PD-L1 inhibition has demonstrated the capacity to enhance HIV-specific $CD8^+$ T-cell proliferation, cytokine production (IFN-γ, TNF-α, IL-2), and cytotoxic degranulation [16]. In latently infected cell line models, PD-1 blockade alone induces modest viral reactivation, with significantly enhanced effects when combined with other latency-reversing agents (LRAs) such as histone deacetylase inhibitors (HDACis) or protein kinase C agonists. These studies suggest that checkpoint blockade may act synergistically with transcriptional activators to overcome latency.

Studies using $CD4^+$ T cells from ART-suppressed PLWH have yielded variable results. Some investigations report increased cell-associated HIV RNA following PD-1 blockade, indicating transcriptional reactivation, while others observe minimal effects [17]. This heterogeneity likely reflects inter-individual variability in reservoir composition, checkpoint expression levels, and residual immune function. Importantly, ex vivo studies combining PD-1 blockade with therapeutic vaccination antigens or toll-like receptor agonists demonstrate enhanced HIV-specific T-cell responses, supporting combination approaches.

CTLA-4 blockade has received less attention in HIV latency research but shows promise in enhancing T-cell activation and proliferation. Studies in primary cells demonstrate that CTLA-4 inhibition increases $CD4^+$ and $CD8^+$ T-cell responses to HIV antigens, with some evidence of viral reactivation [18, 19]. However, CTLA-4 blockade carries greater risk of immune-related adverse events due to its broader effects on T-cell activation, necessitating careful evaluation in clinical settings.

Animal Model Studies

Nonhuman primate (NHP) models, particularly simian immunodeficiency virus (SIV)-infected rhesus macaques on suppressive ART, have provided valuable insights into ICI therapeutic potential. Administration of anti-PD-1 antibodies to ART-suppressed, SIV-infected macaques resulted in enhanced SIV-specific T-cell responses, increased plasma viral RNA levels, suggesting reactivation from latency, and modest reductions in cell-associated SIV DNA in some but not all treated animals [20]. Importantly, PD-1 blockade was generally well tolerated without severe immune-related toxicities, although transient increases in inflammatory markers were observed.

Studies combining PD-1 blockade with therapeutic SIV vaccines in NHPs have demonstrated enhanced vaccine-induced immune responses and, in some cases, prolonged post-treatment viral control following analytical treatment interruption (ATI) [21]. These findings support the concept that checkpoint inhibition may synergize with immune-based interventions to enhance reservoir clearance and immune-mediated viral control. However, significant variability in treatment outcomes across individual animals highlights challenges in predicting response and the need for biomarkers of treatment efficacy.

Humanized mouse models infected with HIV have similarly been employed to evaluate ICI effects. These studies generally confirm enhancement of HIV-specific immune responses and variable effects on viral reservoir size. However, limitations in recapitulating human immune system complexity and reservoir dynamics temper the translational relevance of these findings.

CLINICAL EVIDENCE AND THERAPEUTIC OUTCOMES

Case Reports and Observational Studies in Cancer Patients

Initial clinical insights into ICI effects on HIV came from case reports of PLWH receiving ICIs for cancer treatment. Several reports described PLWH with various malignancies treated with anti-PD-1 (pembrolizumab, nivolumab) or anti-CTLA-4 (ipilimumab) antibodies while maintaining ART [22]. These cases generally reported acceptable safety profiles without unexpected toxicities or opportunistic infections, though immune-related adverse events

(irAEs) characteristic of ICI therapy occurred at similar rates to HIV-negative populations. Regarding virological outcomes, most reports documented continued viral suppression on ART, with some cases noting transient increases in plasma HIV RNA ("viral blips") or increases in cell-associated HIV RNA suggesting latency disruption. However, these observations were inconsistent and occurred in the context of ongoing ART, limiting conclusions about reservoir reduction.

Systematic analyses of HIV-infected cancer patients receiving ICIs have been published, encompassing larger cohorts. One retrospective study of 73 PLWH treated with ICIs for various cancers found that ICIs were generally safe and effective for cancer treatment, with oncological response rates comparable to HIV-negative patients [23]. Virological outcomes showed that most patients maintained HIV suppression, though approximately 15% experienced viral blips. Immunological parameters, including CD4+ T-cell counts, remained stable or improved in most patients, contrasting initial concerns about potential CD4+ depletion [24, 25]. These data support the safety of ICIs in PLWH but provide limited evidence for therapeutic effects on HIV reservoirs due to continued ART use and absence of systematic reservoir assessments.

Analytical Treatment Interruption Studies

The ultimate test of cure strategies is analytical treatment interruption (ATI), wherein ART is temporarily suspended under close monitoring to assess viral rebound kinetics [26]. To date, no ICI-based intervention has achieved sustained virological remission during ATI in a substantial proportion of participants [27]. Most individuals experience rapid viral rebound (median 2–4 weeks), similar to control populations, indicating insufficient reservoir elimination or immune control. However, a small number of treated individuals have shown delayed rebound or lower post-rebound viral loads, suggesting partial treatment effects. These variable outcomes underscore the need for biomarkers to predict treatment response and guide personalized therapeutic strategies.

Safety and Tolerability Considerations

Safety is a paramount consideration for ICI use in PLWH, particularly given the immune dysregulation inherent to HIV infection [28]. ICIs are associated with immune-related adverse events (irAEs) resulting from loss of immune tolerance, including dermatologic reactions, colitis, hepatitis, endocrinopathies, and rarely severe neurological or cardiac events [29, 30]. In PLWH, concerns exist regarding potential exacerbation of immune activation, opportunistic infections, or autoimmune complications [31].

Clinical experience thus far indicates that ICIs are generally well tolerated in ART-suppressed PLWH, with irAE profiles broadly similar to HIV-negative populations [32]. Rates of Grade 3 or higher adverse events are comparable, and no consistent increase in opportunistic infections has been observed. However, sample sizes remain limited, and longer-term safety data are needed. Importantly, CD4+ T-cell counts typically remain stable or increase during ICI treatment, allaying concerns about immune depletion. Careful patient selection, excluding individuals with pre-existing autoimmune conditions or inadequate immune reconstitution, and close monitoring for irAEs are essential components of safe ICI administration in PLWH.

CHALLENGES AND LIMITATIONS OF CURRENT APPROACHES

Insufficient Reservoir Reduction

The most significant limitation of ICI monotherapy is the failure to achieve clinically meaningful HIV reservoir reduction in most individuals [33]. While enhanced immune responses and viral transcriptional reactivation have been documented, these effects have not translated into substantial decreases in the latent reservoir size. Multiple factors contribute to this limitation. First, latency reversal alone is insufficient without effective clearance mechanisms. Even if ICIs induce viral reactivation, reservoir-harboring cells may not be efficiently eliminated by host immune responses or undergo productive viral replication leading to cytopathic death. Second, the HIV reservoir is highly heterogeneous, comprising diverse cellular subsets, anatomical locations, and proviral integration sites, each potentially exhibiting different susceptibility to ICI-mediated reactivation and clearance. Third, many proviruses within the reservoir are defective and incapable of producing infectious virus, yet persist as integrated DNA detected by standard reservoir assays, complicating interpretation of treatment effects.

Immune Exhaustion Heterogeneity and Irreversibility

T-cell exhaustion in chronic HIV infection is not uniform but exists along a spectrum from moderate to severe dysfunction. Severely exhausted cells, characterized by co-expression of multiple checkpoint molecules and epigenetic fixation of the exhaustion program, may be refractory to single-agent checkpoint blockade. Studies demonstrate that progenitor exhausted cells (expressing intermediate checkpoint levels and retaining proliferative capacity) respond better to ICI treatment than terminally exhausted cells [34]. In chronic HIV infection, particularly in individuals with prolonged infection duration or incomplete immune reconstitution on ART, terminally exhausted cells may predominate, limiting ICI efficacy. Furthermore, epigenetic modifications at checkpoint gene loci and transcription factor binding sites may render the exhaustion phenotype partially irreversible, necessitating epigenetic modifying agents alongside checkpoint blockade.

Anatomical and Cellular Reservoir Barriers

HIV persists in multiple anatomical compartments with variable immune surveillance, including lymphoid tissues, gut-associated lymphoid tissue, central nervous system, and genital tract [35]. Checkpoint inhibitor penetration into these tissues and their effects on reservoir cells within immune-privileged sites remain poorly characterized. Additionally, specific cellular subsets harbor latent HIV, including central memory T cells, transitional memory cells, follicular helper T cells, and potentially macrophages and other myeloid cells. The expression profiles of checkpoint molecules vary across these subsets, and optimal ICI strategies may differ for targeting distinct reservoir components. Tfh cells, a major reservoir in lymphoid tissues, reside in B-cell follicles with limited CD8+ T-cell access, potentially limiting the efficacy of ICI-enhanced CD8+ responses even if viral reactivation occurs.

Biomarker and Predictive Marker Deficiency

A critical gap in current research is the absence of validated biomarkers to predict ICI treatment response or to monitor treatment efficacy in real-time. Baseline checkpoint molecule expression levels, HIV-specific T-cell functional capacity, reservoir size and composition, and host genetic factors likely influence treatment outcomes, but integrated predictive models are lacking [36]. Similarly, dynamic biomarkers during treatment, such as changes in cell-associated RNA, specific cytokine profiles, or T-cell phenotypic shifts, require validation as surrogates for reservoir reduction and clinical benefit. Development of such biomarkers is essential for patient stratification and adaptive trial designs.

Timing and Population Considerations

The optimal timing of ICI intervention in the course of HIV infection remains uncertain. Early ART initiation preserves immune function and limits reservoir establishment, potentially enhancing ICI efficacy [37]. Conversely, individuals with longstanding infection and larger reservoirs face greater challenges. Clinical trials have predominantly enrolled ART-suppressed individuals with chronic infection, but studies in acute or early infection cohorts may yield more favorable outcomes. Additionally, elite controllers and post-treatment controllers who naturally maintain viral suppression without ART represent unique populations where ICI augmentation of pre-existing effective immunity might be particularly beneficial.

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Combination Therapeutic Strategies

Given the limitations of ICI monotherapy, rational combination approaches represent the most promising path forward. The "shock and kill" paradigm envisions combining latency-reversing agents (LRAs) to induce viral reactivation with immune-enhancing strategies to clear reactivated cells. ICIs may serve as the immune-enhancing component, synergizing with LRAs such as histone deacetylase inhibitors (vorinostat, romidepsin, panobinostat), protein kinase C agonists (bryostatin-1), or bromodomain inhibitors [38]. Preclinical studies support synergy between these agent classes, though clinical translation has been limited by modest LRA potency and lack of effective clearance mechanisms.

Therapeutic vaccines designed to prime or boost HIV-specific T-cell responses may synergize with checkpoint blockade [39]. By providing antigenic stimulation concurrent with removal of inhibitory signals, this combination aims to expand functional HIV-specific T-cell populations capable of recognizing and eliminating reservoir cells. Several clinical trials combining ICIs with therapeutic vaccines are ongoing, with preliminary results awaited.

Broadly neutralizing antibodies (bNAbs) represent another complementary approach. bNAbs can neutralize diverse HIV strains, mediate antibody-dependent cellular cytotoxicity (ADCC) against infected cells, and potentially target latently infected cells expressing viral envelope protein upon reactivation. Combining bNAbs with ICIs could enhance both viral neutralization and immune-mediated clearance of reservoir cells. Early-phase clinical trials evaluating this combination are underway.

Novel ICIs targeting alternative checkpoint molecules (TIM-3, LAG-3, TIGIT) or bispecific antibodies simultaneously blocking multiple pathways warrant investigation. Given the redundancy and crosstalk within checkpoint networks, multi-pathway blockade may overcome limitations of single-agent approaches. Additionally, agonistic antibodies targeting costimulatory molecules (4-1BB, OX40, GITR) may complement inhibitory checkpoint blockade by actively stimulating T-cell function.

Advanced Technologies and Analytical Approaches

Next-generation sequencing technologies enable comprehensive characterization of the HIV reservoir, including intact proviral DNA assays (IPDA) that distinguish replication-competent from defective proviruses, and single-cell RNA sequencing (scRNA-seq) to profile reservoir cell transcriptional states and heterogeneity. These tools can assess ICI effects on intact reservoirs and identify cellular subsets responsive to treatment.

Single-cell multi-omics approaches integrating transcriptomics, surface proteomics, and T-cell receptor sequencing can elucidate mechanisms of ICI response and resistance at unprecedented resolution [40]. Identification of transcriptional signatures or cell surface markers distinguishing ICI-responsive from non-responsive cells could guide patient selection and treatment optimization.

Advanced imaging techniques, including positron emission tomography (PET) with HIV-targeted radiotracers, may enable non-invasive monitoring of reservoir dynamics and anatomical distribution in real-time, overcoming limitations of peripheral blood sampling.

Personalized and Precision Medicine Approaches

Future ICI strategies will likely require personalized approaches based on individual reservoir characteristics, immune profiles, and host genetics [41]. Machine learning algorithms integrating multi-dimensional data (reservoir size/composition, checkpoint expression patterns, HIV-specific T-cell repertoire, HLA genotype, viral genetics) could predict treatment response and optimize individualized combination regimens [42].

Pharmacogenomic considerations may also inform ICI dosing and selection. Genetic polymorphisms affecting checkpoint molecule expression, signaling pathways, or drug metabolism could influence treatment outcomes and toxicity risk, warranting pharmacogenetic screening.

Regulatory and Ethical Considerations

As ICI-based cure strategies advance toward larger clinical trials, regulatory and ethical considerations emerge. The benefit-risk calculus differs fundamentally from cancer treatment, where ICIs address life-threatening malignancies. In PLWH with effective viral suppression on ART, exposing patients to irAE risks requires clear potential for substantial clinical benefit, such as ART-free remission [43]. Careful attention to informed consent, trial design (appropriate control groups, meaningful endpoints), and data safety monitoring is essential. Additionally, equitable access to emerging cure interventions must be prioritized, ensuring that populations disproportionately affected by HIV globally can benefit from therapeutic advances [44].

CONCLUSION

Immune checkpoint inhibitors represent a rational and mechanistically grounded approach to targeting HIV latency and reinvigorating exhausted HIV-specific immune responses. Substantial preclinical and early clinical evidence demonstrates that PD-1 and CTLA-4 blockade can enhance T-cell function and induce viral transcriptional reactivation in some individuals. However, translation of these effects into clinically meaningful reservoir reduction has proven elusive, with current ICI monotherapy failing to achieve substantial or durable decreases in latent HIV reservoirs in most participants. This disconnect reflects fundamental challenges including insufficient clearance of reactivated cells, heterogeneity and potential irreversibility of T-cell exhaustion, anatomical and cellular barriers to reservoir access, and the complexity of the latent reservoir itself. Future progress requires moving beyond single-agent checkpoint blockade toward rationally designed combination strategies integrating latency-reversing agents, therapeutic vaccines, broadly neutralizing antibodies, and possibly novel checkpoint or costimulatory pathway modulators. Advanced technologies enabling precise reservoir quantification, cellular phenotyping, and real-time monitoring will be essential for evaluating these interventions. Personalized treatment approaches guided by predictive biomarkers and individual reservoir/immune characteristics represent the likely path to optimizing ICI efficacy. While challenges are substantial, the foundational understanding of checkpoint biology in HIV infection and encouraging signals from early studies justify continued investigation. With refined strategies and enhanced patient selection, ICIs may ultimately contribute to effective HIV cure regimens, potentially in combination with other modalities, offering hope for ART-free viral remission. Future clinical trials should prioritize rationally designed combination regimens pairing immune checkpoint inhibitors with complementary latency-reversing agents and immune-enhancing interventions, employing advanced reservoir assays and predictive biomarkers to optimize patient selection and treatment monitoring.

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