Review

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Advancing precision medicine in immune checkpoint blockade for HIV/AIDS: Current strategies and future directions

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SUMMARY: Acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) patients experience significant increase in their survival and decline in the mortality with the advent of antiretroviral therapy (ART). Nonetheless, ART alone still cannot completely cure AIDS/HIV patients. Furthermore, the virus remains latent in resting CD4+T cells for extended periods, posing a continuous threat to AIDS/HIV patients. Immune checkpoint blockades (ICBs), as a promising immunotherapy, inaugurate new pathways for AIDS/HIV cure or remission given their capability to break down the latency limit of HIV, and promote the regeneration and activation of HIV-specific T cells. However, not all AIDS/HIV patients respond to immune checkpoint inhibitors (ICIs), similar to that encountered in cancer patients, accompanied by the risk of severe immune-related adverse events (irAEs) in some cases. Accordingly, the present study was conducted to explore the possibility of personalized medicine tailored to the host discrepancy, with purposes of achieving better treatment outcomes, higher objective response rates, and fewer irAEs. Strategies for ICIs based on individual differences are documented to be conducive to improving therapeutic outcomes for patients. Therefore, this study intended to improving the therapeutic efficacy of ICIs in AIDS/HIV patients within the context of precision immunotherapy, including monotherapy and combination strategies, as well as the application of predictive biomarkers.

Keywords: AIDS/HIV, immune checkpoint blockade, T cell exhaustion, precision immunotherapy, predictive biomarkers

1. Introduction

Acquired immunodeficiency syndrome (AIDS) remains a significant infectious disease. Antiretroviral therapy (ART) is the standard treatment for AIDS/human immunodeficiency virus (HIV) patients, aiding in the restoration of their immune system that has been compromised by the virus (*1*). However, rather than completely eliminating the virus, ART merely suppresses the replication of the virus to levels that are undetectable in the blood. In this way, it can significantly decrease the risk of disease progression and transmission, ultimately, a functional cure of AIDS patients (*2*).

Nevertheless, complete immune reconstitution is not achieved in 10-40 percent of infected individuals (*3*), which may be related to factors such as sustained immune activation, thymic hypoplasia, intestinal flora disruption, and heterogeneity of viral reservoirs (*4*). In recent years, with the rapid development in the field of immunotherapy, immunomodulatory therapies such as immune checkpoint blockades (ICBs) have received widespread attention. These drugs have not only demonstrated significant efficacy in oncology treatment, but have also made important progress in exploring the treatment of chronic infectious diseases such as HIV, hepatitis B, and tuberculosis (*5*). To date, the Food and Drug Administration has approved a total of 25 drugs in 8 classes of ICIs, some of which have entered clinical trials in HIV-infected patients. It is worth noting that the application of ICIs in HIV treatment is becoming increasingly promising as research progresses: a variety of novel monotherapy regimens and combination strategies are currently undergoing phase I and II clinical trials in HIV-infected patients, and the clinical use of such drugs is expected to expand significantly in the future (*6,7*).

Clinical trials of ICIs in patients with HIV have highlighted several critical issues that require the utmost attention of clinicians, investigators, and regulatory agencies (*1*). The main areas of concern are differences in adverse effects after individualized immunotherapy (*3*) effects on CD4+ T-cell dynamics (*4*) characteristics

of viral load fluctuations, and (*5*) heterogeneity in final clinical outcomes. These differences highlight the particular importance of individualized treatment strategies in HIV-infected patients (*8-10*). Current research focuses on exploring biomarkers that can predict the benefit of ICI therapy, overcoming the variability of treatment response by developing precise treatment regimens, and ultimately achieving the goal of converting non-responders into responders. This review systematically summarizes innovative strategies to enhance the effectiveness of ICI therapy within the framework of precision medicine, including but not limited to biomarker screening based on tumor microenvironmental characteristics, treatment timing optimization, and combination therapy regimen design. These research advances not only provide new ideas to improve the clinical management of HIV-infected patients but also represent an important opportunity to achieve breakthroughs in the field of ICI immunotherapy.

2. Immune checkpoint inhibitors and T cell exhaustion in HIV

Immune checkpoints were first discovered and applied for the treatment of cancers (*11*), enabling a dramatic shift in the traditional therapeutic paradigm. Back to the end of the last century, a special immunoglobulin on the surface of CD4+ T cells and CD8+ T cells, was accidentally found by scientists, naming cytotoxic T-lymphocyte antigen 4 (CTLA-4). Another immune checkpoint was fortunately discovered shortly afterwards. When studying the mechanism of programmed cell death in mice, a professor of immunology from Kyoto University in Japan accidentally discovered a key gene involved in programmed cell death, *i.e.*, programmed cell death protein 1 (PD-1). Since then, many new immune checkpoints were observed and involved in studies on underlying mechanisms. Currently, PD-1 monoclonal antibodies (mAbs) are common therapeutic agents clinically. Multiple ICIs, such as Ipilimumab, Nivolumab, and Atezolizumab, when combined with other drugs, have become potent tools in the treatment of various diseases. Subsequently, the clinical application of ICI has been extended to the management of HIV and related coinfections. A large number of clinical drug trials have been carried out for verification, with the achievement of remarkable results in some studies. Validation of the effectiveness and safety of drugs has laid a foundation for the development of immunotherapy-oriented precision treatment strategies (Figure 1).

Intense immune activation may lead to T-cell depletion, CD4+ T-cell expression and CD8+ T-cell expression. Consequently, the viral replication cannot be controlled during HIV infection. CD4+ T cells are T lymphocytes that express T cell receptors that can promote the antibody and CTL response. In the HIV-infected state, CD4+ T cells are depleted, resulting in the loss of their antiviral CTL response and their ability to control viral load. PD-1 expression on HIV-specific T cells is a major marker of T cell exhaustion that may

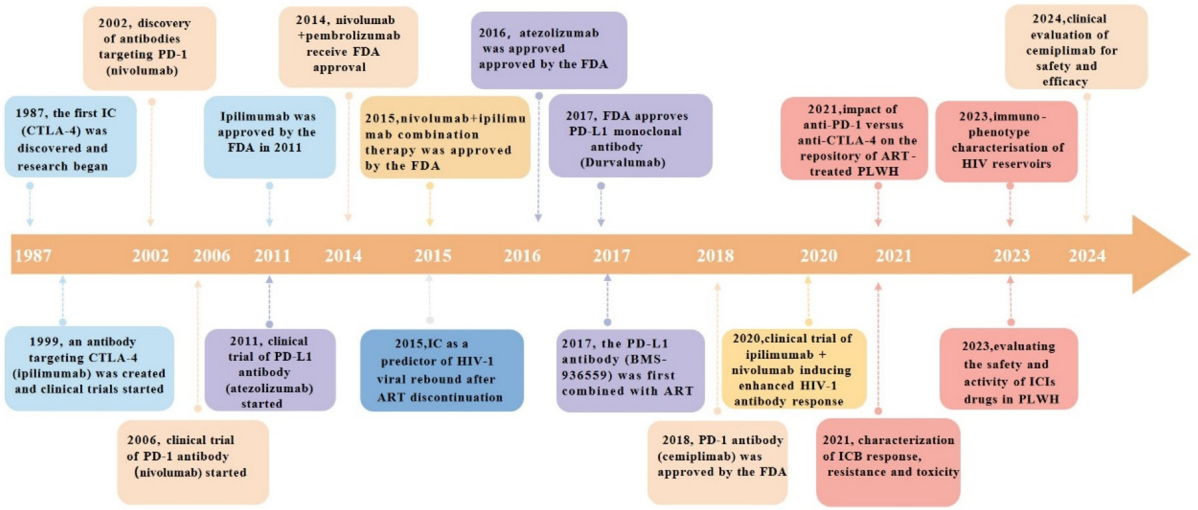

Figure 1. Immune checkpoint discovery and clinical studies of ICB in HIV treatment. Major immune checkpoints and checkpoint inhibitors in HIV therapy. In 1987 CTLA-4 became the first immune checkpoint in history to be discovered, and in 1999 ipilimumab was created and began clinical trials and was approved for marketing by the FDA in 2011 (blue section). In the same year, an antibody targeting PD-L1 (atezolizumab) also began a clinical trial component. 2002, the discovery of the first antibody targeting PD-1 (nivolumab) and subsequent clinical trials, while different antibodies including pembrolizumab and cemiplimab were also developed for clinical therapy (orange part). Since then, PD-L1 antibodies including durvalumab and BMS-936559 were introduced and applied to clinical treatment (purple section). The yellow part of the figure shows the combination strategy of immune checkpoint inhibitors and the application in HIV treatment. The grey part is one of the indicators that IC may be regarded as a predictor of viral rebound after ART treatment interruption. The red part indicates the clinical safety and efficacy assessment of combination therapy with ICIs.IC, immune checkpoint; FDA, US Food and Drug Administration; ICB, immune checkpoint blockade; ICIs, immune checkpoint inhibitors; ART, antiretroviral therapy; PLWH, people living with HIV.

indicate disease progression. PD-1 expression has been confirmed to correlate with reduced CD8+ T cell function, viral load and CD4 T cell counts (*12*).

It is possible for receptor surface drivers to sufficiently activate ligands, and tyrosine phosphorylation at the cytoplasmic ends of cells to activate inhibitory signals mediated by transduction factors, thus preventing the generation of T cell receptor-mediated activation signals (*13*). For example, in immune cells, PD-1 signaling depends mainly on the core factor tyrosine phosphatase SHP-2, which may be recruited to PD-1 after binding to its ligand PD-L1. Further phosphorylation of ITSM can induce the conversion of SHP-2 to an active conformation, reduce the phosphorylation of CD3 and CD28, and thus exert a negative regulation on the signal strength of TCR. However, unlike PD-1, CTLA-4 lacks the ITSM motif bound to SHP-2, suggesting a possible indirect recruitment. In the large immune signaling network, it is critical to uncover the mechanisms of the checkpoint signaling pathways, which may provide potential reference for subsequent development of ICIs. In general, the invasion of pathogens (e.e., bacteria or viruses) may trigger a range of immune responses in the host. During the development of HIV infection, there may be gradual change in the mechanism underlying the involvement of HIV-specific CD4+ and CD8+ T cells in the durable antiviral work, eventually leading to a dysfunction of inhibiting viral expansion. PD-1, CTLA-4 and other inhibitory receptors are expressed on HIV-specific cells. Binding of these immune checkpoints to corresponding ligands may inactivate T cells, promoting virus to evade surveillance by the host immune system. In other words, dysfunctional CD4+ and CD8+ T cells both stem from the upregulation of inhibitory immune checkpoints. Among them, PD-1 is a well-studied immune checkpoint causing the dysfunction of HIV-specific CD4+ and CD8+ T cells, which may stimulate disease progression and loss of antiviral function (*14*). Although great attention has been attached to CD8+ T cell function, HIV-specific CD4+ T cells were also enhanced in ICBs. An *in vitro* study revealed that PD-1 blockade enhanced the proliferation of HIV-specific CD4+ T cells and production of IFNg, IL-2, IL-13 and IL-21, providing superior evidence for ICBs (*14,15*). In view of the above, the use of ICBs may partly restore the function of HIV-specific T cells, and enhance the host immune response to control the progression of HIV infection eventually. In this regard, immune intervention may be benefited from a comprehensive understanding of the role of immune checkpoints in HIV-specific T cells. Currently, most HIV patients, except for a few "elite controllers", still require traditional antiviral therapies. The application of anti-HIV treatment aims to control the virus and clean virus reservoir on the surface of infected T cells. Given the suppressed immune checkpoint expression, namely, on the premise of ART virus cannot be eradicated, the existence of latent virus is one of the factors for a lifelong treatment in the targeted patients. Immune checkpoint proteins were found to impair HIV-specific cytotoxic functions by promoting latent infected cells, leading to HIV persistence. Therefore, intervention using ICBs can be adopted, as an adjuvant strategy, prior to antiviral therapy, which may to some extent reverse latent infection to reduce the number of HIV reservoirs (*16*) (Figure 2).

3. The activity and safety of ICBs in PLWH

ICBs are a frequent therapeutic option for cancer patients, but not including people living with HIV (PLWH) usually. It may be attributed to the immunological deficiencies in HIV-infected patients, raising concerns among clinical researchers about their safety and impact. However, the clinical value of ICBs in HIV patients has been proposed and demonstrated in several recent studies. Here, we will continue to expound the clinical use of ICBs in PLWH to clarify these controversies. In our study, available clinical data on immune checkpoints in HIV patients are gathered to answer questions related to the efficacy and safety of ICBs and to decipher potential influential factors (Table 1-2).

3.1. Effect of ICIs on viral load and CD4+ T cells in PLWH

HIV viral load and CD4+ T lymphocyte counts are important indicators in the clinical management of HIV patients. In a phase 1 clinical trial of PD-1, CD4+ T cell counts increased in patients treated by PD-1 inhibitors (*5*), revealing potential correlation between CD4+ T cell counts and PD-1 inhibitors. In another study of 8 AIDS patients treated with cemiplimab (PD-1), Gay CL *et al*. (*17*) found that a single infusion of anti-PD-L1 antibody (BMS-936559) increased HIV-1 Gag-specific CD8+ T cell responses in 2 of 6 participants, with no significant change in median CD4+ T cell counts, CD4+ percentage, or CD4/CD8 ratio, and a decrease in CA-RNA in CD4+ T cells from 201 to 194. There was no significant difference in CA-DNA from 435 to 513. The standard HIV RNA levels remained at <40 copies/mL in all participants, and the ratio of HIV DNA to RNA/DNA in 8 participants unchanged from baseline after 28 days of observation.

Furthermore, in a prior research investigating the efficacy of different doses of CTLA-4 therapy in 24 HIV patients, Colston E *et al*. (*10*) found that 2 participants (8.3%) exhibited a significant reduction in HIV-1 RNA levels, but 8 (33.3%) showed no significant change in HIV RNA levels, all from the low-dose treatment group. Conversely, 14 participants (58.3%) demonstrated significantly increased HIV RNA levels. All individuals with obviously elevated HIV RNA (except for 1 patient) were from the high-dose group. Therefore, CTLA-4 treatment regimens showed no significant difference in

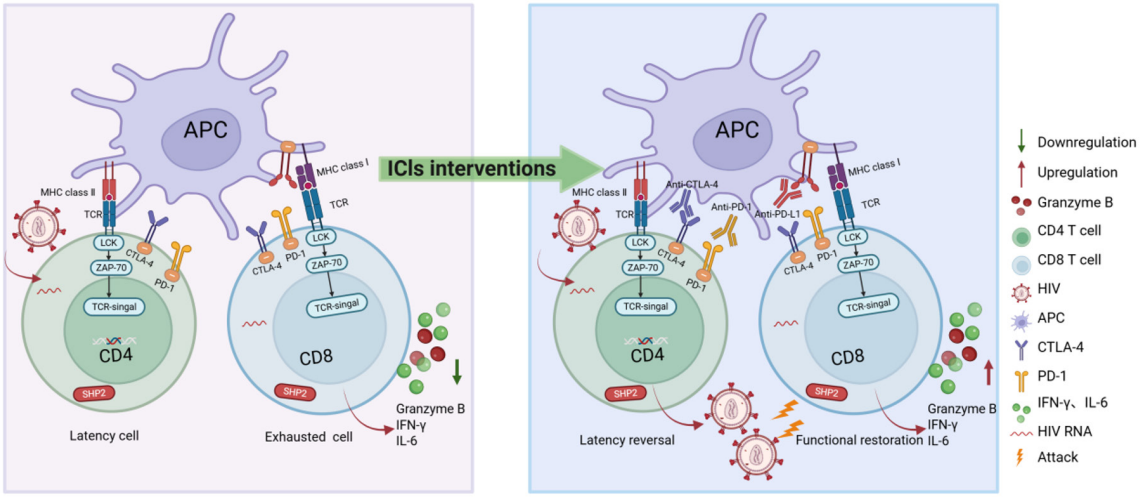

Figure 2. Immune checkpoint therapy drugs suppress HIV. After HIV infection of the host, the virus enters the receptors of CD4 T cells and hijacks the host machinery for replication. During chronic infection, sustained viral antigen exposure leads to overactivation of the CD8 T-cell TCR signaling pathway, triggering high expression of immune checkpoint molecules, leading to T-cell depletion, loss of cytotoxicity, and reduced proliferative capacity. At the same time, HIV infection leads to massive depletion of CD4 T cells, and some infected cells enter a latent state, forming a viral reservoir. Immune checkpoint inhibitors (*e.g.*, anti-PD-1 antibodies) can block inhibitory signals and partially restore the antiviral function of CD8 T cells. However, ICI may also activate latently infected CD4 T cells and induce HIV proviral transcription. Created with BioRender.com. *Abbreviations*: MHC class I: Major Histocompatibility Complex class I; MHC class II: Major Histocompatibility Complex class II; TCR: T-Cell Receptor; LCK: Lymphocyte-specific protein tyrosine kinase; CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4; PD-1: Programmed Death-1; PD-L1: Programmed Death-Ligand 1; TCR signal: T-Cell Receptor signal; SHP2: Src Homology 2 Domain-containing Phosphatase 2; Granzyme B: Granzyme B; IFN-γ: Interferon-gamma; IL-6: Interleukin-6; HIV: Human Immunodeficiency Virus; ICIs: Immune Checkpoint Inhibitors; Anti-CTLA-4: Anti-CTLA-4 Antibody; Anti-PD-1: Anti-PD-1 Antibody; Anti-PD-L1: Anti-PD-L1 Antibody; HIV RNA: HIV Ribonucleic Acid.

its overall control of viral load, and viral replication may be potentially activated in some cases when using high-dose regimen. This study may provide important insights into the effect of different dose regimens on changes in HIV RNA levels, offering a valuable basis for further investigation. Anyway, it should be acknowledged that there are still limitations in these studies, such as small number and range of subjects, despite the confirmation of potential benefit of ICB on CD4+ T cells and HIV RNA viral load in HIV patients.

3.2. Clinical response of ICIs in PLWH

With the success of ICBs in the field of oncology, this therapy has been applied in the treatment of patients with HIV-associated tumors, with some clinical benefit achieved. However, HIV patients with different tumor types may respond differently to treatment. Kaposi's sarcoma (KS) and non-small cell lung cancer (NSCLC) are two of the most representative tumor types in clinical trials of ICB for patients with HIV-associated tumors. Our literature retrieval obtained eight studies on the use of ICBs for HIV-associated tumor treatment (ClinicalTrials.gov), including five studies involving both KS and NSCLC (Table 1). In a phase 2 clinical trial of patients with HIV-KS, 12% of these participants had a complete response to PD-1 therapy, 59% had a partial response, while the overall response rate was 71% (95% CI 44-90) (*17*). Nevertheless, in another study involving 6 cases of HIV-KS, only 2 patients reached stable disease (lasting ≥ 24 weeks), and notably, one participant died of severe diffuse KSHV-associated polyclonal B-cell lymphocyte proliferation (*5*). In another on HIV-NSCLC, from real-world studies, the objective response rate (ORR) for these patients was 31% after the use of ICBs, with ORRs of 38% and 25% for first- and second-line patients, respectively (P = 0.06), with no significant inter-group difference (*8*). Significantly, patients with melanoma had an ORR of 69%, compared to only 11% for those with head and neck squamous cell carcinoma (HNSCC) (NCT03094286). Altogether, ICBs may produce varied therapeutic response for HIV combined with different tumor types, with a maximum ORR of 69% and a minimum of only 11%. Given objective factors such as limited samples, multi-center studies with expanded sample size should be performed on ICBs for patients with HIV-associated tumors (*19*). Overall, the ORR of ICBs was superbly around 70% in both KS and melanoma, but only 11% in HNSCC. In the future, multi-cohort studies should be conducted with expanded sample size and type for further verification.

As described in the above studies, all patients received ART, with no significant difference in baseline CD4 + T cell count (> 200). Baseline CD4+ T lymphocyte count emerges as a pivotal prognostic biomarker, with its clinical predictive value rooted in its central role in orchestrating adaptive immune responses (*8,19*). The tumor microenvironment (TME) exhibits

Table 1. Clinical trials of checkpoint blockades in HIV infection

Trials	Region	Phase	Drug	Trearment	Participants	Characteristic	Efficiency	irAES	*Ref.*
NCT03469804	France	2	Pembrolizumab (PD-1)	200 mg, every 3 weeks for 6 months	30	HIV-related Kaposi sarcoma	/	12% (2/17) Grade ≥3	*18*
NCT02595866	United States	1	Pembrolizumab (PD-1)	200 mg, every 3 weeks	30	HIV and advanced cancer	23% (7/30) had detectable HIV viremia; no significant viral load breakthrough	73% (22/30) irAEs (Grade 1-2); 20% (6/30) Grade ≥3	*5*
NCT03239899	United States	1	Pembrolizumab (PD-1)	Single dose of 2 mg/kg at Week 0	20	HIV infection	/	/	*39*
NCT04091932	China	2	Pembrolizumab (PD-1)	2 mg/kg, every for 3 months	10	AIDS-related PML	Data under analysis	/	*40*
NCT03367754	United States	1	Pembrolizumab (PD-1)	200 mg	60	HIV infection	/	/	*41*
NCT04514484	United States	1	Nivolumab (PD-1)	Day 1 every 28 days for up to 1 year	18	HIV and advanced cancer	/	/	*42*
NCT03304093	France	2	Nivolumab (PD-1)	3 mg/kg, every 2 weeks	16	HIV infection	/	/	*39*
NCT05187429	Australia, Singapore	1, 2	Nivolumab (PD-1)	Cohort A: 0.1/0.3/1.0 mg/kg single dose on Day 7; Cohort B: Single dose on Day 0	42	HIV infection	/	/	*43*
NCT03316274	United States	1	Nivolumab (PD-1)	Cohort A: 10 mg every 2 weeks for 4 doses; Cohort B: Response-based dosing	12	HIV-related Kaposi sarcoma	/	/	*44*
NCT04929028	United States	2	Nivolumab (PD-1)	Cohort A: 1 mg/kg for 12 weeks; Cohort B: 2.5 mg/kg for 12 weeks	53	HIV-associated anal cancer	/	/	*45*
NCT03787095	United States	1, 2	Cemiplimab (PD-1)	0.3/1/3/10 mg/kg at weeks 0 and 6	5	HIV infection	25%(1/4) increased HIV-1-specific T-cell responses and transiently increased HIV-1 expression	100% (4/4) experienced Grade 1-2	*9*
NCT03407105	United States	1	Ipilimumab (CTLA-4)	0.1, 1, 3, or 5 mg/kg 2 or 4 doses of every 28	24	HIV infection	41.7% (10/24) CD4+ counts increased; 16.7% (4/24) decreased	37.5% (9/24) Grade 1; 41.7%(10/24)Grade 2; 4.2% (1/24) Grade 3	*10*
NCT02028403	United States	1	BMS-936559 (PD-L1)	0.3 mg/kg single dose	8	HIV infection	33.3% (2/6) increased HIV-1 Gag-specific CD8+ responses	16.7% (1/6) asymptomatic hypophysitis	*17*

Table 1. Clinical trials of checkpoint blockades in HIV infection (continued)

Trials	Region	Phase	Drug	Trearment	Participants	Characteristic	Efficiency	irAES	*Ref.*
NCT05330143	China	2	ASC22 (PD-L1)	Cohort A: 1 mg/kg for 12 weeks; Cohort B: 2.5 mg/kg for 12 weeks	30	HIV infection	Latent reservoir activation analysis ongoing	/	*46*
NCT04499053	United States	2	Durvalumab (PD-L1)	1500 mg, every 3 weeks for 4 cycles	18	HIV-infected with NSCLC	/	/	*47*
NCT03094286	Spain	2	Durvalumab (PD-L1)	1500 mg, every 4 weeks	20	HIV-1-infected patients with advanced cancer	CD4+ and CD8+ T-cell counts and plasma HIV-1 viremia remained stable	75% (15/20) Grade 1; 50% (10/20) Grade 2; 5% (1/20) Grade 3; 5% (1/20) Grade 4; 10% (2/20) Grade 5	*19*

Table 2. Clinical trials of immune checkpoint combination therapy in HIV

Trials	Region	Phase	Combination Drug	Trearment	Participant	Characteristic	Effiency	irAES	*Ref.*
NCT05129189	China	2	ASC22 (PD-L1) + Chidamide (HDACi)	ASC22: 2 mg/kg every 2 weeks	15	HIV infection	CA-HIV RNA increased from baseline to week 4; CA-RNA/DNA ratio returned to baseline by week 24. Plasma HIV VL showed no significant change from baseline at weeks 4 and 8.	46.7% (7/15) Grade 1-2; 6.7% (1/15) Grade 3	*28*
NCT05646082	UK	1	Dostarlimab (PD-1) + cART	Dostarlimab: 500 mg every 3 weeks (first 4 doses), then 1000 mg every 6 weeks until week 48	20	HIV-associated Kaposi sarcoma	/	/	*48*
NCT03354936	France	/	Pembrolizumab (PD-1) or Durvalumab (PD-L1) or Ipilimumab (CTLA-4)	/	50	HIV-infected and cancer	/	/	*49*
NCT05597800	Italy	2	Nivolumab (PD-1) + Ipilimumab (CTLA-4)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg every 3 weeks for 4 cycles	30	HIV infection with NSCLC	/	/	*50*
NCT02408861	United States	1	Nivolumab (PD-1) + Ipilimumab (CTLA-4)	Cohert A: nivolumab 30 minutes on day 1; Cohert B: ipilimumab 90 minutes on day 1 of every third cycle of nivolumab;Cohert C: Ipilimumab 90 minutes on day 1 of every sixth cycle of nivolumab. Treatment repeats every 14 days for up to 46 cycles	96	HIV-related classical Hodgkin lymphoma	/	/	*51*

remarkable variability across varied cancer types (*20*), resulting in profound impact on the therapeutic outcomes. This variability was strikingly evident in a cohort of 461 NSCLC patients. The study demonstrated that in tumors with high PD-1 expression, the level of programmed death-ligand 1 (PD-L1) emerged as a pivotal predictor of therapeutic response (*21*). Moreover, the abundance of host-derived cells within the TME plays a decisive role in shaping treatment outcomes. The therapeutic sensitivity and resistance may be dictated collectively by the intricate interplay between host cells and tumor cells, which is mediated through cytokine secretion, immune response modulation, and bidirectional signaling. Consequently, variations in host cell density across tumors may result in divergent responses to immunotherapy.

3.3. Immune-related adverse events (irAEs) associated with ICIs in PLWH

In real-world studies, approximately 20% of HIV patients experienced any grade of irAEs, with a rate of grade ≥ 3 irAEs reaching 7.7% in this group of patients. Specifically, 19% and 39% of HIV patients treated with ICBs combined chemotherapy or targeted agents experienced any grade of irAEs, with 5.9% and 13% experiencing grade ≥ 3 irAEs. and 13%, respectively. Moreover, irAEs of any grade occurred in 16% of PWH with baseline CD4+ T-cell counts < 200 cells/μL, and 7.8% of which were grade ≥ 3. Of these, the most common irAEs were pneumonia and endocrine, both at 4.7%; moreover, 4% of PWH with baseline CD4+ T-cell counts ≥ 200 cells/μL experienced any grade of irAEs, 9.9% of which were grade ≥ 3 (*8*). Collectively, the frequency of irAEs varies considerably among HIV-infected individuals, depending on the treatment strategies and host CD4+ T cells.

The occurrence of irAEs may be related to multiple different risk factors, which were reported to be associated with the type of tumors found (*22,23*), over-expression of PD-1/PD-L1 and smoking history. However, studies on the use of ICBs in HIV patients are currently limited to efficacy, necessitating further in-depth investigation on irAEs. Special attention should be given to the study of irAEs in HIV patients, a special group of immunodeficient population.

3.4. Cooperation benefits: Combined immune checkpoint therapy strategies

The combination of anti-PD-1 and anti-CTLA-4 therapies has previously been shown in SIV studies to reverse latency compared to ICB monotherapy (*24*). Recently, in a clinical trial on the combination of PD-1 and CTLA-4, Harper J et.al. found a 1.44-fold (interquartile range, 1.16-1.89) increase in median CA-US HIV RNA in patients receiving nabulizumab+ibritumomab compared with nabulizumab monotherapy (P = 0.031) (*25*), offering a useful perspective for combination therapy.

As for clinical trials on ICBs in HIV patients, the majority of patients also adhere to ART during treatment. In patients with viremic HIV patients, a study of CTLA-4 (ipilimumab) found a smaller increase in baseline HIV-1 RNA in patients who were not on ART compared to those who were on ART (0.93 *vs*. 0.8), yet without significant difference between groups (*10*). Moreover, in clinical trials on the use of ICBs alone versus jointly, combination therapy with PD-1 and CTLA-4 in patients with HIV resulted in improved latency reversal efficiency, as evidenced by a rise in HIV ART, and monitoring of the change in HIV virus load in 43% of PWH who received nivolumab+ipilimumab in this context, these HIV virus load data point before or after the initiation of ICBs (*8*). Thus, HIV RNA was increase, yet without statistical significance, during treatment for HIV patients treated with ART or not with ICBs.

In another phase II clinical trial of ASC22 (PD-1) combined with histone deacetylase (HDAC) inhibitors in HIV patients, conducted by a research team from Shanghai, China, compared to the baseline level, CA HIV RNA levels increased progressively at week 4 and significantly increased by week 8 (4.27-fold, P = 0.004), but gradually declined after week 8 and returned to the baseline by week 24 (*26*). Therefore, PD-1 combination therapy may have potential in activating the latent reservoir.

With respect to the above, ICBs therapy still has some problems in its safety and efficacy, despite successive clinical trials in HIV patients. Firstly, similar to cancer patients, irAEs are inevitable in HIV patients treated with ICBs and cover all grades, necessitating more effective risk mitigation strategies. Furthermore, the majority of ICBs currently used in HIV patients are inhibitors targeting PD-1/PD-L1 and CTLA-4. There is inadequate investigation on other antibody drugs including TIGIT, LAG-3, and TIM-3, which may restrict our understanding of the safety and efficacy of ICBs. For example, HVEM and BLAT could negatively regulate T cells, and TIGIT was significantly up-regulated in clonally competent pairs of latent cells, according to the study of HIV on immune cell phenotype library. Secondly, the host is also a pivotal factor affecting the efficacy of ICBs. There are early studies showing that gender, age and heredity can affect the effect of ICBs (*27,28*). The clinical trials of ICBs on AIDS patients are mostly concentrated on males, blacks or whites, *etc*., and distributed in developed countries and regions such as Europe and the United States. A study of combination therapy with ICBs for HIV patients in Shanghai, China, provides an important clinical basis for promoting the treatment program (*26*), while AIDS occurs frequently in some developing countries and regions such as Africa. As described previously, ICBs are commonly adopted for patients with HIV-associated tumors, mainly

for NSCLC and KS patients, exhibiting cancer type-dependent varied response rates. Besides, T-cell failure is an important hallmark of chronic infectious diseases, and HIV patients are predominately prone to acquiring various opportunistic infections caused by autoimmune deficiencies, including hepatitis B and tuberculosis, *etc*. At this study, there is a need to conduct additional clinical trials of ICBs for patients with HIV-associated tumors. In terms of therapeutic strategies, preliminary findings support the importance of combining ICIs, which, by integrating the complementary advantages of different mechanistic therapies, have demonstrated significant breakthroughs in viral clearance, immune reconstitution, and long-term control, and that the ICI combination strategy is currently the most promising strategic pathway to achieving a functional cure for HIV (Figure 3).

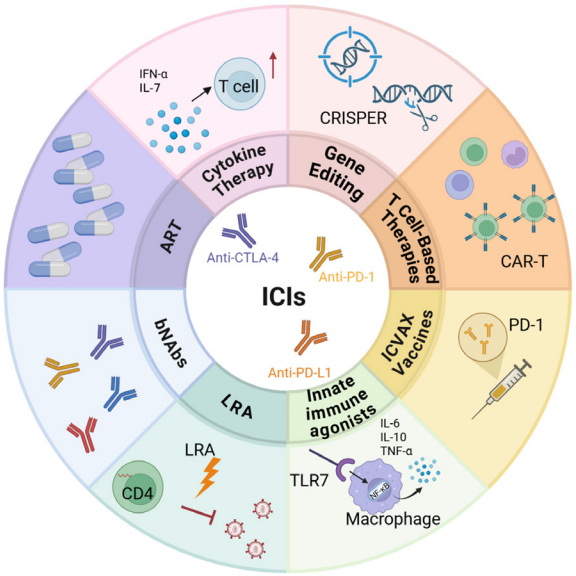

Figure 3. Schematic Overview of ICI Based Combination Strategies. The following strategies can be used to intervene in HIV treatment based on ICI therapy combined with other treatments. Treatments such as gene editing CRISPR-Cas9 target viral DNA or host genes to remove the viral reservoir. Latency reversal agents (LRA) such as histone deacetylase inhibitors (HDACi), which expose the latent virus to the immune system by activating it, or drug therapy. In cytokine therapy, cytokines such as IFN-α, and IL-7 enhance HIV-specific T cell survival and killing and modulate follicular helper T cell function to combat HIV. Various immunotherapies have been developed based on the body's immune system, and T cell immunotherapy targets and removes HIV-infected host cells by modifying T cells. Innate immune agonists enhance the antiviral immune response by activating pattern recognition receptors (PRRs). HIV-neutralising antibodies block the onset of infection by interfering with the entry of HIV-1 into target cells, primarily by binding to viral infectious process exposures. Therapeutic vaccines (*e.g.*, ICVAX) are designed to activate specific B/T cell immune responses by delivering HIV antigens to establish long-lasting immune memory. When it comes to immune checkpoint inhibitor therapy, combination therapy such as ICI in combination with ART synergistically reduces the viral reservoir by controlling viral replication while restoring T-cell function as compared to single inhibitor therapy. Created with BioRender.com. *Abbreviations*: ICI: immune checkpoint inhibitor; ART: antiretroviral therapy; LRA: latency reversing agent; CAR-T: chimeric antigen receptor T cell; TLR: toll-like receptor; bNAbs: broadly neutralizing antibodies ; IFN-α: interferon-alpha.

4. Immune checkpoint: Research progress as biomarkers for disease prediction

ICBs have emerged as a promising strategy to restore antiviral immunity in PLWH. However, the heterogeneous responses of CD4+ and CD8+ T cell subsets to ICBs highlight the necessity for precision-guided therapeutic approaches. To improve efficacy, sophisticated immunotherapeutic strategies may be found by integrating the findings of recent clinical and preclinical studies.

Nevertheless, there is currently a lack of sufficient biomarker research for AIDS patients, but it is also important to validate the already identified biomarkers clinically. More comprehensive strategies are required to provide precise selection criteria for patients undergoing ICI-based monotherapy or combination therapy.

4.1. Monitoring of ICIs Efficacy

An intimate correlation of PD-1 expression has previously been established with the depletion of CD8 + T cell function, yet without the discovery of direct effect of PD-1 on CD8 + T cell counts. Therefore, PD-1 may act primarily by inhibiting the antiviral activity of cytotoxic T cells, rather than directly regulating its counts. Furthermore, PD-1 expression was significantly associated with reduced CD4 + T cell counts, which could be recovered after using a PD-1 inhibitor (*5*). Another study documented a significant elevation of the HIV RNA in 58.3% of participants in the high-dose group of CTLA-4 inhibitors, possibly related to excessive immune activation, which might result in expanded viral repertoire or increased inflammatory response (*12*). Specifically, the PD-1 pathway mainly affects the count and function of CD4 + T cells, while the regulation of CTLA-4 is more complex and dose-dependent (*10*). A precise regulation is required to balance the immune reconstitution and viral control when applying ICIs for HIV treatment. PD-1 inhibitors can improve the number and function of CD4 + T cells, providing a new strategy for immune recovery in HIV patients, with additional attention on its safety and resistance during long-term medication. At present, in order to balance the antiviral effect with the risk of immunopathology, there is a need to determine the optimal dose of CTLA-4 inhibitors by more clinical trials.

4.2. Immune activation and inflammatory markers

The modulatory effects of ICIs on CD38 expression during HIV infection reveal a novel dimension of virus-host interactions. As a multifunctional immunoregulatory molecule (*29*), CD38 critically influences T cell

functionality and disease progression, with genetic deficiency of CD38 directly impairing regulatory T cell development and accelerating autoimmune disorders (*30*). Notably, while PD-1/PD-L1 checkpoint blockade demonstrates remarkable efficacy in solid tumors, HIV exploits CD4+ T cell surface co-receptors (CCR5/CXCR4) to upregulate immune markers such as CD38, thereby establishing a proviral immune microenvironment. In this pathological context, therapeutic application of ICIs may further upregulate CD38 expression through IFN-γ-mediated immune activation, potentially contributing to ICI resistance (*31*). So far, there is limited investigations into HIV-associated immune marker dynamics under checkpoint inhibition, necessitating further studies of mechanisms to delineate these regulatory networks.

4.3. Combined therapy strategies

In terms of combined therapies available at present, dual blockade of PD-1/CTLA-4 has demonstrated significant therapeutic potential in HIV management recently. Preclinical SIV models and subsequent clinical trial data consistently indicate that such combination therapy can activate latent viral reservoirs more effectively compared to monotherapy. For example, Rahman *et al*. classified SIV treatment into treatment with PD-1 + vaccine and vaccine only under ART inhibition, and DNA vaccination induced high-frequency proliferation of CD8+ T cells with cytolytic potential. In their research, after analytical treatment interruption, SIV-specific IFNλ+ CD4+ and CD8+ T cells expanded further for 2 to 4 weeks in the vaccine + PD-1 group, preserving the function and breadth of antiviral T cells after ART interruption (*26*). Noticeably, two SIVs (50%) in the other PD-1 blockade + vaccine group died of AIDS symptoms during the experiment, whereas all eight (100%) SIVs survived in the other two vaccine-only and control groups throughout the study. The median fold change in SIV plasma viral load relative to set point was 1.82-fold in the PD-1 blockade + vaccine group, accounting for double the fold change in the vaccine-only group; moreover, PD-1 blockade accelerated potential reservoir reactivation and AIDS progression in chronically SIV-infected rhesus macaques after ART interruption. However, at this study, there is insufficient SIV trials that provide a valid basis for ICBs + vaccine therapy in the treatment HIV. Importantly, existing data all suggested that effective activation of potential reservoirs provides robust evidence, which should be validated in the clinical setting (*27*).

Furthermore, other combination therapies are also available for application. ICIs have made remarkable progress in tumor treatment, among which TIM 3 + PD-1 therapy show excellent immunomodulatory ability, offering another novel solution for tumor immunotherapy. It is worth noting that the successful experience of these ICIs in tumor treatment also provides additional insights for HIV treatment. As we known, it is crucial to restore and maintain the immune function of patients during HIV treatment. In view of this, it highlights the clinical significance and research value of ICIs for the treatment of HIV (*32*). Meanwhile, IBI321 is regarded as the first dual-targeting IC (TIGIT/PD-1) bispecific antibody

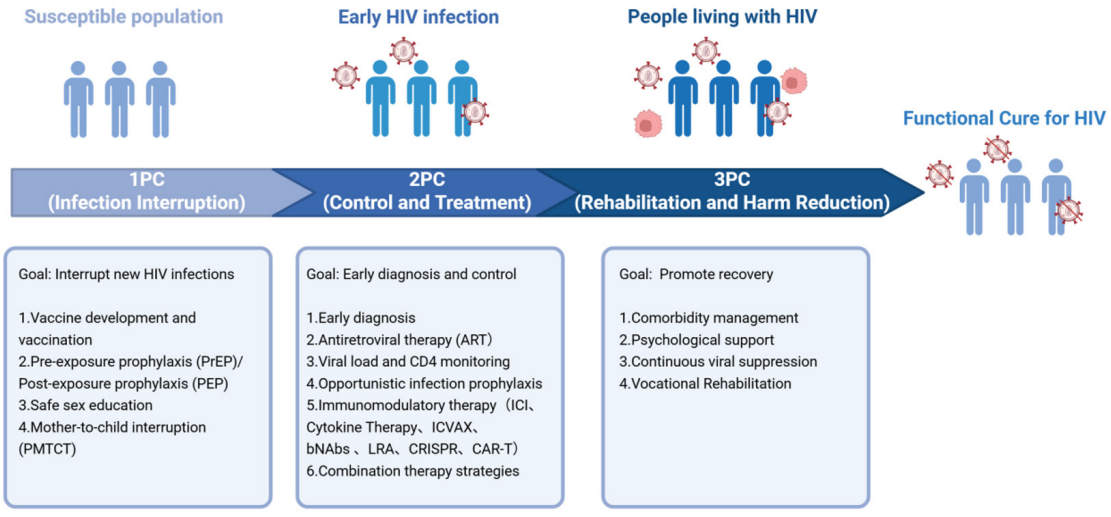

Figure 4. Tertiary prevention and control strategies to achieve a functional cure for HIV. In pursuit of a functional cure for HIV, a three-dimensional prevention and control system of prevention, interruption, and cure is being built. The vaccine-driven source prevention and control system includes prevention in high-risk groups and research and development of innovative vaccines. Secondary prevention is based on post-infection treatment-based interventions, and the immunomodulatory combination strategy of immunotherapy highlights the unique advantages and development potential of many HIV treatments, making a major step forward in achieving a functional cure for HIV. Tertiary prevention focuses on recovery promotion and harm reduction, supported by multidimensional strategies that encourage sustained technological innovation and policy synergy networks. *Abbreviations:* PC: prevention and control. Created with BioRender.com.

available clinically, which has been highly concerned considering its performance in tumor treatment. A study was designed to evaluate the safety, tolerability, and antitumor activity (NCT04911894) of IBI321 in 16 patients with advanced malignant solid tumors who did not respond to standard therapy. Corresponding data are not yet available, although the trial is currently completed. In the future, we will continue to focus on the therapeutic outcome of IBI321, aiming at providing possible foundation for the effectiveness and safety of HIV treatment, and advancing HIV treatment (*33*).

Besides, TLR7 is an innate immune receptor that recognizes single- and short double-stranded RNA. It is a active participant in antiviral immunity that functions to stimulate dendritic cell maturation, promote cytokine secretion and antigen presentation, thereby enhancing the adaptive immune response. Vesatolimod (GS-9620) is a potent and selective TLR7 agonist that can moderately induce PBMC infection to produce HIV, activate T cells, and enhance antibody-mediated HIV + CD4 T cell killing *in vitro*. For example, by establishing a rhesus macaque model with chronic SIV infection and long-term ART inhibition, a previous study investigated the therapeutic potential of PD-1 blocking antibodies alone or in combination with the TLR7 agonist vesatolimod (*34*). However, this combination therapy generated no significant effectiveness. More in-depth statistical analyses of the collected data should be conducted to search for possible subgroup effects or treatment effects under specific conditions, and actively explore the possibility of combination regimens with other immunomodulators or antiviral drugs to form a more effective treatment combination.

4.4 Other influential factors related to precision therapy

Safety must be taken into consideration for patients before treatment, and CD4 cell count is a protective factor to reduce the risk of irAEs. Biomarker detection should also be performed throughout the whole process (*8*). Meanwhile, individual differences have been reported in the response to ICIs, even with the occurrence of severe irAEs in some patients (*35*), thus necessitating biomarker detection for predicting disease progression. These biomarkers may serve dual predictive roles. To be specific and firstly, biomarkers can determine whether baseline levels of immune checkpoint molecules can forecast the therapeutic efficacy of ICBs (*36*). Secondly, it can benefit the assessment of the correlation of dynamic changes in these markers during treatment with subsequent development of drug resistance and irAEs (*37*).

For instance, in the treatment of melanoma, the biweekly 10 mg/kg pembrolizumab regimen demonstrated marginally reduced ORR compared to the triweekly 10 mg/kg schedule (33.7% *vs.* 32.9%), whereas the 3 mg/kg ipilimumab cohort exhibited significantly lower ORR than the pembrolizumab group (11.9% *vs.* 33.7%) (*38*). In HIV immunotherapy trials, 90% of high-dose regimen recipients showed significant elevation in the absolute counts of CD4+ T cells, yet with the absence of linear correlation between CD4+ percentage changes and absolute count increments underscores, requiring expanded sample sizes to validate dose-response relationships (*10*). Furthermore, spatial multi-omics profiling can be integrated to decode the potential associations between patient-specific biomarker signatures and therapeutic responses, which may facilitate the elucidation of spatial regulatory mechanisms of immunotherapy sensitivity within the TME (*21*). In addition, pharmacokinetic monitoring models linking biomarker trajectories to ICI plasma concentrations may also contribute to enhanced efficacy prediction accuracy and guide personalized therapeutic optimization.

5. Conclusion

In conclusion, patients with HIV may not be able to benefit equally from ICBs given the existing clinical data. It is necessary to consider precision medicine, and to improve the selection of appropriate ICBs therapies for an individual with a view to maximising the therapeutic benefit. Biomarkers can assist in disease diagnosis and prognosis, and guide personalized treatment, which is an important tool for the implementation of precision medicine. Biomarkers may benefit the determination of appropriate treatment regimens during ICB therapy. However, due to the complexity of HIV itself and the challenge of uncovering its associated biomarkers, mining biomarkers is still one of the most important means to advance the functional cure of AID patients.

Massive existing studies have reported the expression of TIGIT, TIM-3, LAG-3, *etc*. on T cells of HIV patients, and relevant *in vitro* studies have documented the potential of ICBs.

Currently, available choices of ICBs are limited as relevant clinical trials are still in the preliminary stage. In combination therapy, dual-target ICB therapy can activate the viral latent reservoir. ICBs in combination with vaccines have shown potential in reducing latent reservoirs. In the comparison of pre- and post-treatment DNA reservoirs, the viral reservoirs after treatment using vaccine in combination with PD-1 therapy were reduced even more significantly as (3.5 *vs.* 2.1) levels compared to DNA vaccine only. However, there are few trials on the use of ICBs + vaccine in SIV, necessitating further investigation concerning the on-going gap in clinical validation.

However, there are several questions that need to be answered about its strategy in combination with ICB therapy, despite the indispensability of conventional ART as described above. The first problem is it necessary to use ART through the course of ICB therapy. Consequently, multi-cohort studies are required to

investigate the viral suppression with ART and the viral suppression utility of ICBs.

The second problem is how should ICI be applied as a predictive marker after ART treatment interruption. ICB has been revealed to be a new and effective modality for patients when ART treatment is interrupted after the emergence of drug resistance and viraemia, *etc*.. Extensive studies have documented the value of PD-1 in indicating depletion or even activation. For instance, the effects of PD-1, TIM-3, and LAG-3 in the CD4+ and CD8+ T cells in predicting a significant effect on viral rebound, suggesting a role in strongly predicting viraemic relapse events after treatment interruption. The final question is whether resistance or increased drug toxicity occurs during treatment using ICB as an immunosuppressant for ART. Currently, the core treatment option for HIV remains ART, with limitations such as the inability to clear latent viral reservoirs, the need for lifelong medication, and the potential risk of drug resistance, which warrants a thorough investigation of the use of combination treatment strategies as opposed to monotherapy.

The immune system is a key breakthrough in achieving a functional cure for HIV. For example, strategies such as activating the self-regenerative capacity of immune cells, precisely targeting latent viral reservoirs, and developing therapeutic vaccines and broad-spectrum neutralizing antibodies hold the promise of achieving a functional cure for HIV without the need for lifelong drug therapy.

To achieve this long-term goal, it is necessary to integrate diversified therapeutic means: combining cutting edge technological breakthroughs with traditional interventions, and constructing a prevention and control system of prevention and control at the source - early blockade - immune reconstruction, to promote a paradigm shift from passive control to active elimination of HIV treatment.

The first level of the prevention and control system is vaccine-driven, focusing on the protection of susceptible populations and the research and development of innovative vaccines. For example, the development of the latest therapeutic vaccine, IVCAX, is based on the regulation of immune checkpoints on effector T-cells to achieve functional inhibition by suppressing viral replication, marking an important advance in vaccine development.

The second tier of the prevention and control system focuses on early intervention after infection, forming a network of 'early screening and early treatment - virus reservoir monitoring - joint immune regulation'. Currently, the synergistic strategy of immune checkpoint inhibitors (ICIs) and antiretroviral therapy (ART) has highlighted its unique advantages: while ART controls viral replication, ICIs can restore T-cell function and target the removal of latent infected cells, significantly reducing the size of the viral reservoir.

The third level of prevention and control focuses on immune reconstitution and long-term recovery, such as remodeling the immune function through the establishment of an autologous memory T-cell bank or targeting the glucose metabolism pathway to enhance the persistence of CD8+ T-cells, which provides long-term immune protection for patients.

In summary, a functional cure for HIV requires a multi-dimensional strategy: continuous promotion of technological innovations (*e.g.*, gene editing, innate immune agonists, chimeric antigen receptor T cells, *etc*.), improvement of the policy synergy network, and construction of a global HIV governance framework. Through the technological empowerment of the three-tier prevention and control system, it is expected to achieve effective control of new infections and a significant increase in the functional cure rate in the future, providing a replicable and innovative model for the prevention and control of chronic infectious diseases.

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