Lin *et al.*
European Journal of Medical Research (2025) 30:237
https://doi.org/10.1186/s40001-025-02427-4

European Journal of Medical Research

RESEARCH Open Access

PD-1 suppression enhances HIV reactivation and T-cell immunity via MAPK/NF-κB signaling

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Abstract

Background Programmed cell death protein 1 (PD-1) is a key immune checkpoint involved in HIV-related immune escape, but its precise role and underlying mechanisms remain unclear. This study investigates the effects of PD-1 inhibition on HIV infection and T-cell function, focusing on the MAPK and NF-κB signaling pathways.

Methods Peripheral blood mononuclear cells (PBMCs) were isolated from HIV-infected individuals and healthy controls. T-cell subsets were analyzed for PD-1 expression via flow cytometry. The impact of antiretroviral therapy (ART) on T-cell numbers, apoptosis, and PD-1 expression was assessed. PD-1 blockade was performed using pembrolizumab, and its effects on T-cell survival and cytokine secretion were evaluated. MAPK/NF-κB signaling was analyzed using Western blot and co-immunoprecipitation, while latent HIV activation was assessed by measuring HIV-1 LTR transcriptional activity in J-Lat cells. Reverse-ChIP assays explored the interaction between HIV-1 Nef protein and the PD-1 promoter.

Results PD-1 expression was higher in T cells from HIV-infected individuals compared to healthy controls, with no significant change following ART. PD-1 blockade with pembrolizumab reduced T-cell apoptosis and enhanced cytokine secretion (TNF-α, IFN-γ, IL-2). PD-1 inhibition also activated latent HIV in J-Lat cells. Western blotting revealed reduced phosphorylation of MAPK and NF-κB pathway components (p-MEK1/2, p-p38 MAPK, p-NF-κB p65), and co-immunoprecipitation confirmed a direct interaction between PD-1 and SHP-2, regulating these pathways.

Conclusions PD-1 mediates HIV immune evasion through the MAPK/NF-κB pathways. PD-1 blockade restores T-cell function and activates latent HIV, suggesting potential therapeutic strategies for HIV treatment.

Keywords PD-1, HIV infection, T-cell function, MAPK/NF-κB signaling pathway, Immune escape

Introduction

Human immunodeficiency virus (HIV) infection remains a significant global public health issue, impacting both the quality of life and survival rates of affected individuals [1]. The World Health Organization (WHO) estimates that approximately 38 million people worldwide are living with HIV, and the disease contributes to hundreds of thousands of deaths annually [2]. HIV compromises the immune system by targeting and destroying CD4 + T lymphocytes, leaving infected individuals vulnerable to opportunistic infections and certain cancers [3, 4]. While antiretroviral therapy (ART) has proven effective in suppressing viral replication

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and improving patients' quality of life, many patients still do not fully recover immune function after treatment [5]. Furthermore, the activation of the MAPK/NF-κB signaling pathways in HIV-infected T cells has not been fully elucidated. This study aims to address these knowledge gaps by investigating how PD-1 blockade affects MAPK/NF-κB signaling and its potential to reverse HIV-induced T-cell dysfunction.

Programmed death receptor-1 (PD-1) is a key immune checkpoint molecule that plays a central role in inhibiting T-cell activation and proliferation [6]. Studies have shown that PD-1 expression is significantly elevated in HIV-infected individuals, contributing to impaired T-cell function and immune evasion [7]. Therefore, investigating the role of PD-1 in HIV infection and understanding its underlying mechanisms is crucial for improving immune function in HIV-positive patients. While the inhibition of PD-1 and its role in immune reconstitution have been extensively studied, this study focuses on the novel aspect of PD-1's modulation of the MAPK/NF-κB pathways in HIV infection, and its ability to reverse HIV latency in T cells.

The MAPK/NF-κB signaling pathway has been identified as a major mediator in the progression of HIV infection [8]. Activation of this pathway following HIV infection leads to the sustained release of inflammatory cytokines, which not only support viral replication but also may contribute to the development of comorbidities [9]. In addition, certain small molecules have shown promise in reversing HIV latency by inhibiting the MAPK/NF-κB pathway [10].

Although the roles of PD-1 and the MAPK/NF-κB pathway in HIV infection have been studied, the exact mechanisms remain unclear. Investigating how PD-1 interacts with HIV infection, along with exploring its effects on the MAPK/NF-κB pathway in T cells, could provide valuable insights and open new avenues for HIV immunotherapy.

Materials and methods

Study subjects and subgroups

This study recruited HIV-infected patients and healthy controls (NC), all of whom provided informed consent. Healthy controls were selected based on the following inclusion criteria: absence of any history of chronic infections, immunocompromised states, or autoimmune diseases. HIV-infected individuals were required to have been on ART for at least 6 months, with a viral load below 50 copies/mL (virally suppressed) and a CD4 + count > 200 cells/μL at the time of enrollment. The clinical characteristics of each group are detailed in Appendix Table 1.

Cell culture and treatment

The J-Lat cell line was used as an in vitro model for latent HIV infection. Cells were cultured in RPMI 1640 medium (HyClone) supplemented with 10% fetal bovine serum (Transgen) and 1% penicillin–streptomycin (Yeasen) in a 37 °C incubator with 5% CO_2. Cells were divided into the following treatment groups: blank, 10 μg/mL pembrolizumab, 30 μM Apabetalone, and a combination of 30 μM Apabetalone and 10 μg/mL pembrolizumab.

Immunophenotyping

Lymphocytes were isolated from peripheral blood mononuclear cells (PBMCs) of HIV-infected patients and healthy controls, then expanded using the Human CD3/CD28 T-Cell Activation and Expansion Kit (IPHASE). Immunophenotyping was performed by staining with fluorescent antibodies: CD3-APC (Clone: OKT3), CD4-PE (Clone: SK3), CD8α-PE-Cy7 (Clone: OKT8), and CD279-FITC (Clone: EH12.2H7). Stained cells were analyzed using a Monisight flow cytometer (Gaugene). The apoptosis rate in each group was assessed using the Annexin V-Alexa Fluor 647/PI Apoptosis Detection Kit (Yeasen), with data analyzed by FlowJo software.

RT-qPCR

Total RNA was extracted from PBMCs using chloroform and isopropanol. cDNA was synthesized using the Evo M-MLV RT Kit with gDNA Clean for qPCR (Agbio). qPCR was performed using the ChamQ SYBR qPCR Master Mix (Vazyme) on a BIO-RAD real-time PCR system. Specific primers are listed in Appendix Table 2, with β-actin used as an internal control.

ELISA

Cytokine secretion levels of TNF-α, IL-2, IFN-γ, Perforin, and Granzyme B in cell culture supernatants were measured using a commercial ELISA kit (Bersin-Bio). At least three replicates were conducted for each experimental group, with standard curves and controls provided by the kit manufacturer.

Western blot and Co-IP

The expression of MAPK/NF-κB signaling pathway proteins (p-MEK1/2, p-p38 MAPK, p-NF-κB p65, etc.) and HIV-1 Nef proteins was detected by Western blotting. The names of the antibodies used are listed in Appendix Table 3. Proteins were extracted using radioimmunoprecipitation assay (RIPA) buffer (Beyotime), separated by SDS–PAGE, transferred to PVDF membranes (Merck), and incubated overnight with primary antibodies. After secondary antibody incubation

(1:10,000; Jackson ImmunoResearch), protein bands were visualized using BeyoECL Moon (Beyotime), and densitometry was performed with Quantity One software (Bio-Rad). Incubation times were 1 h at room temperature for secondary antibody and overnight at 4 °C for primary antibodies.

For Co-immunoprecipitation (Co-IP), SHP-2 antibody was used at a 1:500 dilution, and immunoprecipitation was carried out for 2 h at 4 °C, proteins were subjected to SDS–PAGE, transferred to PVDF membranes, and detected using specific antibodies. Protein interactions were confirmed by luminescent detection following primary and secondary antibody incubation.

Reverse-ChIP

Probes complementary to the PD-1 promoter sequences were synthesized by BersinBio and biotinylated at the 3′ end (sequences in Appendix Table 4). Cells (2×10^8) were crosslinked, fixed with formaldehyde, and subjected to chromatin fragmentation. RNA was removed using RNase A, and chromatin was fragmented by sonication. Samples were separated by centrifugation and designated as Input, Reverse-ChIP AP, and Reverse-ChIP NC. The probe set was denatured, and hybridization was carried out at various temperatures (85 °C for 10 min, 37 °C for 30 min; 70 °C for 5 min, 37 °C for 30 min; and 55 °C for 2.5 min, 37 °C for 60 min). Streptavidin beads were added to capture the hybridized samples, which were then washed and eluted for western blotting. DNA was extracted for qPCR analysis.

GFP fluorescence detection

HIV-1 LTR activation in J-Lat cells was assessed using GFP fluorescence. GFP expression levels were quantified by flow cytometry after a 48-h culture period under various treatment conditions.

Statistical analysis

All experiments were performed independently at least three times. Statistical analysis was performed using paired *t* tests for comparison of two groups and one-way ANOVA for multiple group comparisons. A power analysis was conducted to ensure sufficient sample size, and all data were expressed as mean ± standard deviation.Statistical analysis was performed using GraphPad Prism software (version 8.0). A two-sample *t* test was used for comparisons between two independent groups, and analysis of variance (ANOVA) was employed for multiple comparisons. Statistical significance was defined as $p<0.05$, with significance levels indicated as follows: $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. The sample sizes for the experiments were selected based on prior studies in the field [11].

Results

Relationship between PD-1, HIV infection, and T-cell function

To explore the role of programmed cell death protein 1 (PD-1) in HIV infection and antiretroviral therapy (ART), we first analyzed peripheral blood T-cell subsets in HIV-infected patients and assessed the effect of ART on T-cell function. Our results showed a significant increase in the number of CD3 + and CD4 + cells, as well as CD3 + and CD8 + cells, in the ART-treated group compared to the untreated HIV-infected group (Fig. 1a). PD-1 gene expression was also significantly elevated in both the HIV-infected and ART groups compared to healthy controls (NC group) (Fig. 1b). However, there was no significant difference in PD-1 expression levels between the ART-treated and untreated groups.

We further examined the impact of ART on T-cell apoptosis by comparing the apoptosis rate in untreated HIV-infected and ART-treated groups. ART treatment resulted in a significant reduction in early apoptosis and an increase in CD3 + and CD4 + cell numbers (Fig. 1c). These findings indicate that ART enhances T-cell survival, though PD-1 expression remained largely unchanged.

In addition, we investigated cytokine secretion and found that levels of TNF-α, IL-2, perforin, and granzyme B were significantly reduced in the HIV-infected PD-1 low expression group (L), ART-treated group, and HIV-infected PD-1 high expression group (H) compared to healthy controls (Fig. 4a). High and low expression groups were separated by RT-qPCR. While IFN-γ levels were unchanged in the L and ART groups, they were significantly decreased in the H group (Fig. 4b). While ART significantly increases the number of CD4 + and CD8 + T cells, it also enhances cytokine secretion. These results suggest that PD-1 expression correlates with T-cell immune function.

PD-1 regulation of the MAPK/NF-κB pathway in HIV immune escape

To investigate the mechanism by which PD-1 contributes to HIV immune escape, we analyzed the activation of the MAPK/NF-κB signaling pathway. Western blotting revealed that compared to healthy controls, expression levels of pMEK1/2, p–p38 MAPK, and p-NF-κB p65 were significantly elevated in the HIV-infected, PD-1 low expression (L), PD-1 high expression (H), and ART-treated groups (Fig. 2b–d). These findings suggest that PD-1 contributes to immune escape in HIV infection by modulating the MAPK/NF-κB signaling pathway. PD-1 blockade enhances latent HIV reactivation by promoting the transcriptional activation of HIV-1 LTR. This is achieved through the upregulation of key transcription

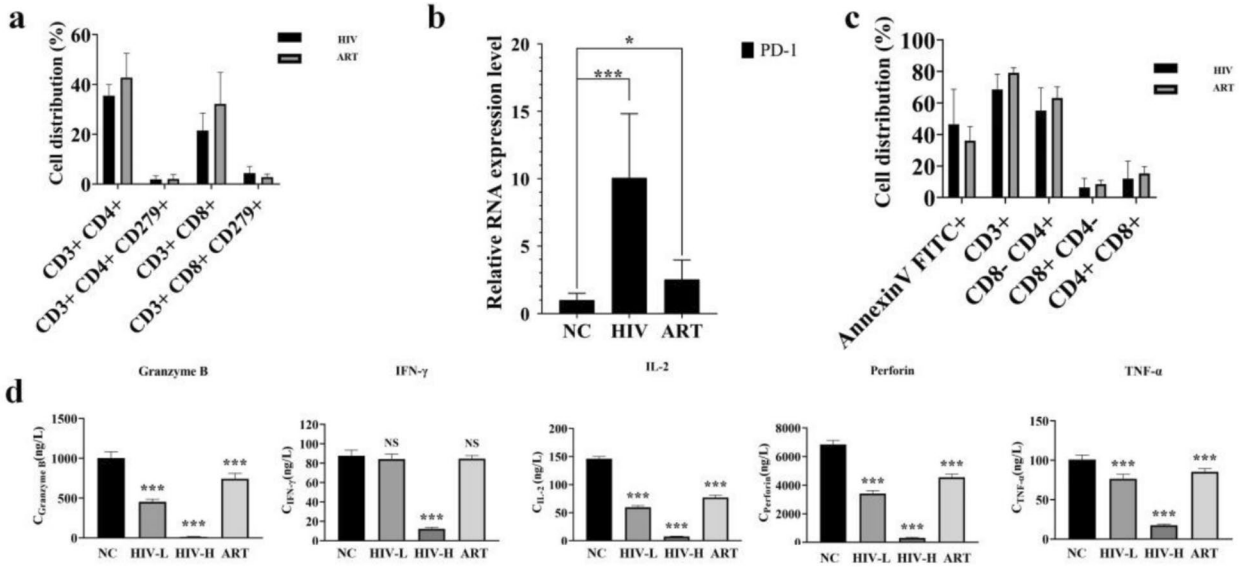

Fig. 1 Illustrates the relationship between programmed cell death-1 (PD-1) and human immunodeficiency virus (HIV) infection, as well as T-cell function. **a** T-cell subsets in the HIV and ART groups were typed by flow cytometry for the number of CD3 + , CD4 + , CD3 + , CD4 + , CD279 + , CD3 + , CD8 + , CD3 + , CD8 + , CD279 + positive cells, respectively (n = mean of 6 donors). **b** RT-qPCR quantification of PD-1 gene expression in the HIV-infected group (n = 6), ART-treated group (n = 10), and control group (n = 3). **c** Annexin V detection method was used to measure the rate of T-cell apoptosis in the HIV-infected group (n = 6), the ART-treated group (n = 10), and the control group (n = 3). **d** The ELISA was utilised to detect changes in cytokine secretion levels of IFN-γ, TNF-α, IL-2, Perforin, and Granzyme B in HIV-infected patients in the high and low PD-1 expression group and ART group (n = mean of 3 donors)

factors like NF-κB, which are typically suppressed during HIV latency.

PD-1 inhibition reactivates latent HIV

To examine the effect of PD-1 inhibition on latent HIV activation and replication, we treated J-Lat cells with pembrolizumab (10 μg/mL) and Apabetalone (30 μM), both alone and in combination. Compared to the blank control group, these treatments significantly increased HIV-1 LTR gene expression (Fig. 3a). GFP fluorescence assays confirmed that Apabetalone treatment significantly boosted GFP expression, and pembrolizumab treatment enhanced fluorescence (Fig. 3b, c). These results suggest that PD-1 inhibition can reactivate latent HIV, highlighting its potential as a therapeutic strategy.

PD-1 inhibition reduces apoptosis and restores immune function in HIV-infected T cells

To assess the impact of PD-1 inhibition on apoptosis and cytokine secretion in HIV-infected T cells, we treated PD-1 high-expressing T lymphocytes (group H) with pembrolizumab. Pembrolizumab works by inhibiting the interaction between PD-1 and its ligand PD-L1, which removes the inhibitory signals on T cells, thus enhancing T-cell activation and cytokine production. By preventing PD-1 from binding to PD-L1, Pembrolizumab restores the proliferative capacity and effector function of HIV-specific T cells, leading to improved immune responses. We observed a significant reduction in the apoptosis rate, with the most pronounced effect after 24 h of treatment (Fig. 4a, b). In addition, pembrolizumab treatment significantly increased the secretion of TNF-α, IL-2, IFN-γ, perforin, and granzyme B upon CD3/CD28 activation (Fig. 4c–f). These findings suggest that PD-1 inhibition not only reduces apoptosis but also restores immune responses in HIV-infected T cells.

PD-1 inhibition downregulates MAPK/NF-κB signaling in HIV-infected T cells

To investigate the effects of PD-1 inhibition on the MAPK/NF-κB signaling pathway in HIV-infected T cells, primary T cells from HIV-infected individuals were treated with varying concentrations of pembrolizumab (1, 5, and 10 μg/mL) for 24 h. Western blot analysis revealed that in PD-1-overexpressing T lymphocytes (group H), treatment with pembrolizumab significantly downregulated the expression of pMEK1/2, p−p38 MAPK, and p-NF-κB p65 compared to the untreated group (Fig. 5). These results suggest that PD-1 inhibition modulates the activation state of the MAPK/NF-κB pathway, which may contribute to the regulation of HIV immune escape mechanisms.

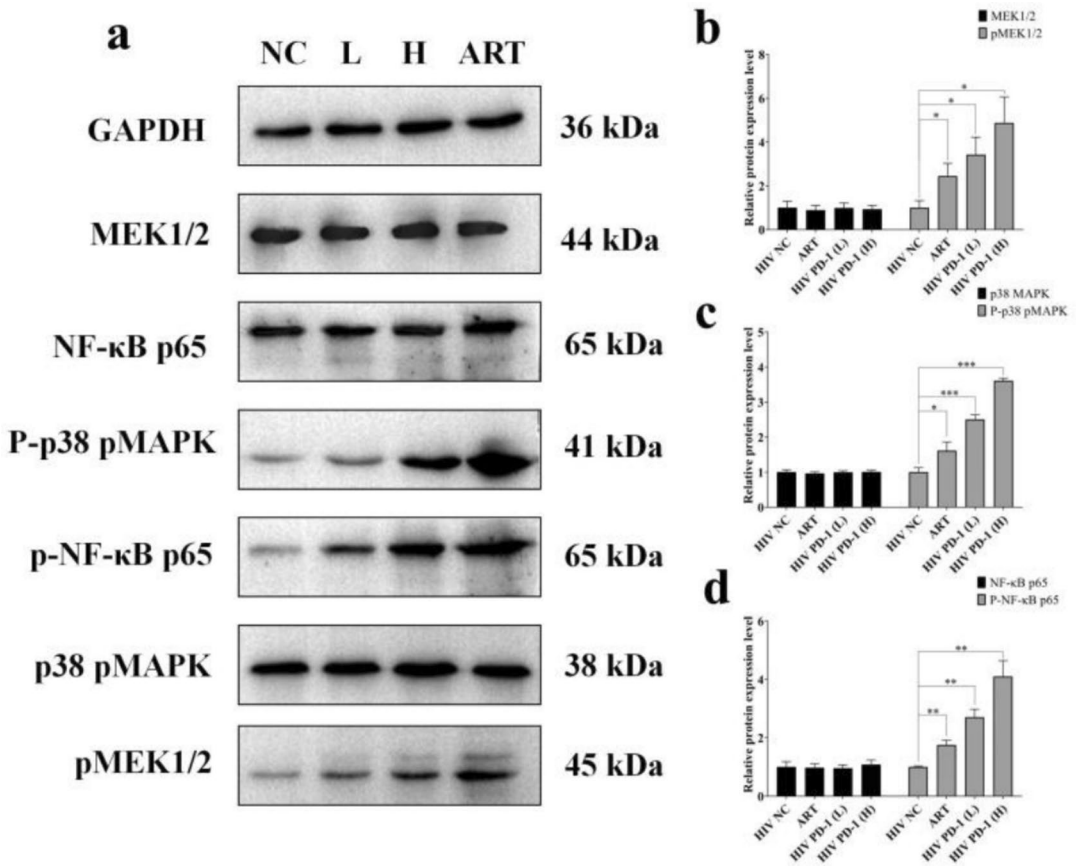

Fig. 2 Analysis of MAPK/NF-κB signaling pathway activation status. **a–d** Representative immunoblots and statistical comparisons of MAPK/NF-κB signaling pathway-related protein expression in the healthy control group (NC group), the HIV-infected PD-1 low-expression group (L group), the HIV-infected PD-1 high-expression group (H group), and the antiretroviral therapy (ART) treatment group (ART group) ($n = 3$)

PD-1 inhibition alters protein interactions and reduces c-Raf phosphorylation in HIV-infected T cells

To further elucidate the molecular mechanisms of PD-1 action in HIV-infected cells, we conducted co-immunoprecipitation (Co-IP) experiments to analyze protein interactions between PD-1 and MAPK/NF-κB pathway-related proteins. In PD-1-overexpressing T lymphocytes (group H), both SHP-2 and SHP-1 proteins were detected in the input and immunoprecipitated groups (Fig. 6a). Furthermore, pembrolizumab treatment significantly reduced the expression of p–c-Raf (Ser338) compared to the blank control group (Fig. 6b, c). These findings suggest that PD-1 facilitates MAPK/NF-κB pathway activation through interactions with SHP-2, influencing the immune escape mechanisms of HIV-infected T cells.

HIV infection upregulates PD-1 expression via Nef protein

To explore the mechanism by which HIV infection regulates PD-1 expression, we examined the levels of HIV-1 Nef protein. Western blot analysis revealed that HIV-infected individuals with low PD-1 expression (group L) exhibited lower Nef protein levels compared to the PD-1 high expression group (group H), where Nef expression was significantly upregulated (Fig. 7a, b). Co-IP experiments confirmed an interaction between HIV-1 Nef protein and PD-1 (Fig. 7c), suggesting that Nef may contribute to HIV immune escape by modulating PD-1 expression. RT-qPCR results further supported this finding, showing that the Nef protein successfully interacted with PD-1 in cells (Fig. 7d). Nef protein directly interacts with the PD-1 promoter region, upregulating PD-1 transcription and increasing PD-1 expression on T cells. This interaction is critical for inducing T-cell exhaustion and immune suppression in HIV-infected individuals. The Nef-induced upregulation of PD-1 enhances the immune evasion capacity of HIV by limiting T-cell function.

Discussion

This study provides an in-depth investigation into the role of PD-1 in T-cell dysfunction and immune escape during HIV infection, as well as its underlying mechanisms. PD-1 suppresses T-cell proliferation and

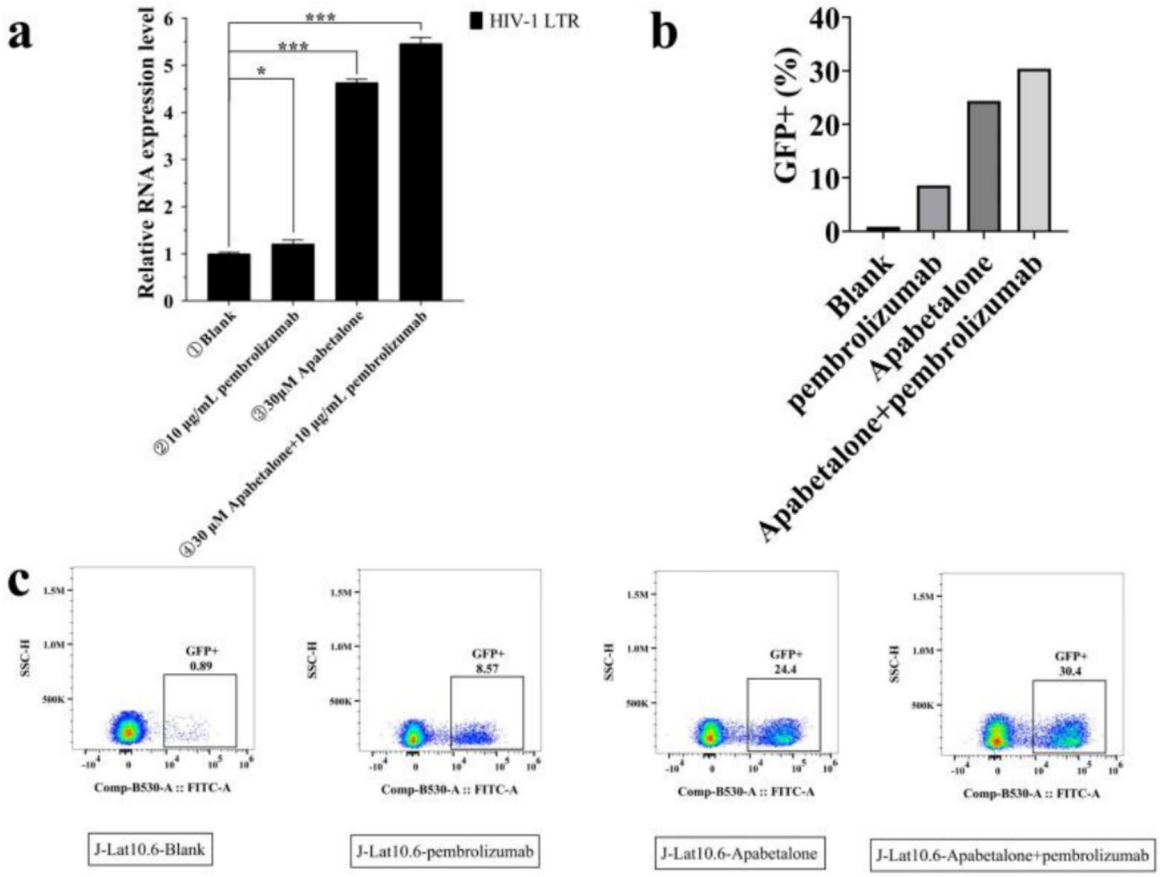

Fig. 3 PD-1 inhibition promotes latent HIV activation and replication. **a** RT-qPCR quantification of HIV-1 LTR gene expression in the Blank group, the 10 μg/mL pembrolizumab-treated group, the 30 μM Apabetalone-treated group, and the 30 μM Apabetalone combined with 10 μg/mL pembrolizumab-treated group. **b**, **c** Flow cytometry quantification of changes in GFP fluorescence expression in the Blank group, the 10 μg/mL pembrolizumab-treated group, the 30 μM Apabetalone-treated group, and the 30 μM Apabetalone combined with 10 μg/mL pembrolizumab-treated group

cytokine secretion, and its continuous upregulation in HIV infection leads to immune exhaustion, which allows the virus to persist. Specifically, PD-1 acts as a crucial regulator of T-cell exhaustion through inhibiting CD8 + and CD4 + T-cell activity, reducing viral clearance, and fostering viral persistence by impeding host immune surveillance Our findings demonstrate that antiretroviral therapy (ART) significantly increases the number of CD4 + and CD8 + T cells while reducing early T-cell apoptosis, suggesting that ART has a beneficial impact on immune recovery. However, despite these improvements in T-cell count and survival, PD-1 expression was not fully reversed by ART. This indicates that ART may not completely restore PD-1-associated immune suppression, which could be a key factor limiting T-cell functional recovery. Previous studies have shown that elevated PD-1 expression is closely linked to T-cell exhaustion in HIV infection, and PD-1-mediated T-cell depletion is a critical mechanism for HIV to evade host immune surveillance [12]. The interaction between PD-1 and its ligand, PD-L1, has been found to inhibit T-cell proliferation and cytokine production, leading to T-cell dysfunction in chronic HIV infection, a phenomenon that persists even after ART [13].

Further assessment of T-cell function revealed that HIV infection significantly suppresses cytokine production, particularly in patients with high PD-1 expression. In this study, PD-1 inhibition notably reduced T-cell apoptosis and restored cytokine secretion. This aligns with findings in cancer immunotherapy, where PD-1 blockade has been shown to enhance T-cell function. These results highlight PD-1 as a crucial regulator of T-cell immune function recovery in HIV, and growing evidence supports its potential in HIV immune therapy, particularly in reversing immune dysfunction and overcoming HIV's immune evasion mechanisms. Studies indicate that immune checkpoint inhibitors can restore HIV-specific T-cell function, overcome immune

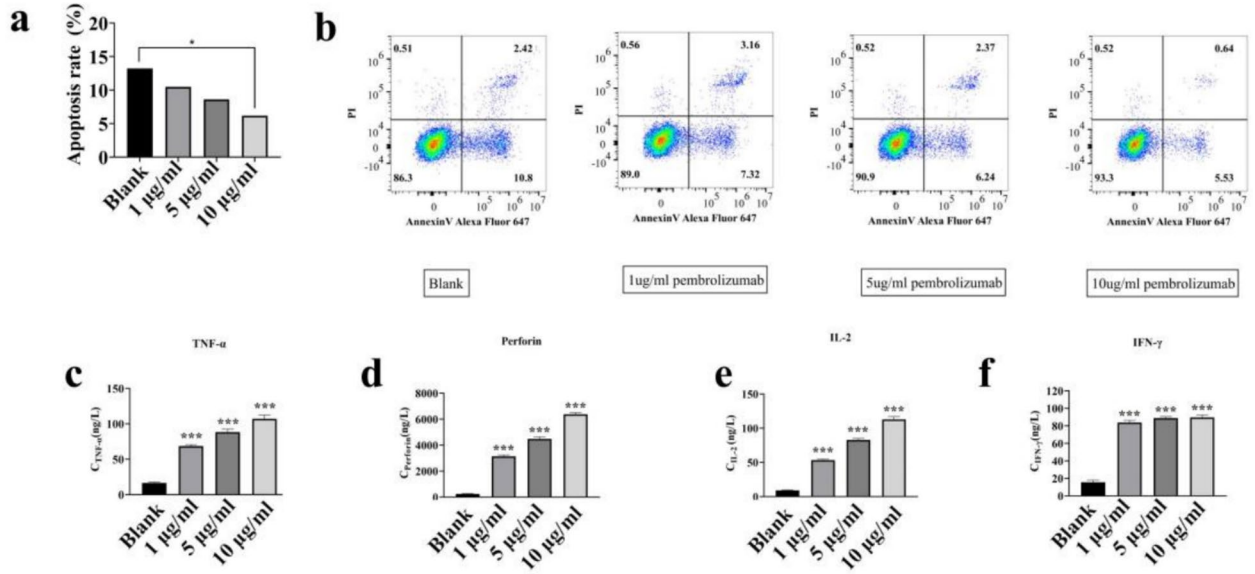

Fig. 4 Effect of PD-1 monoclonal antibody treatment on T-cell apoptosis rate. **a**, **b** Annexin V has been utilized to detect alterations in the rate of T-cell apoptosis subsequent to treatment with Pembrolizumab. **c**–**f** Enzyme-linked immunosorbent assay (ELISA) has been employed to detect alterations in the secretion of TNF-α, IL-2, IFN-γ, perforin, and granzyme B in the PD-1 monoclonal antibody treatment group following CD3/CD28 activation ($n = 3$)

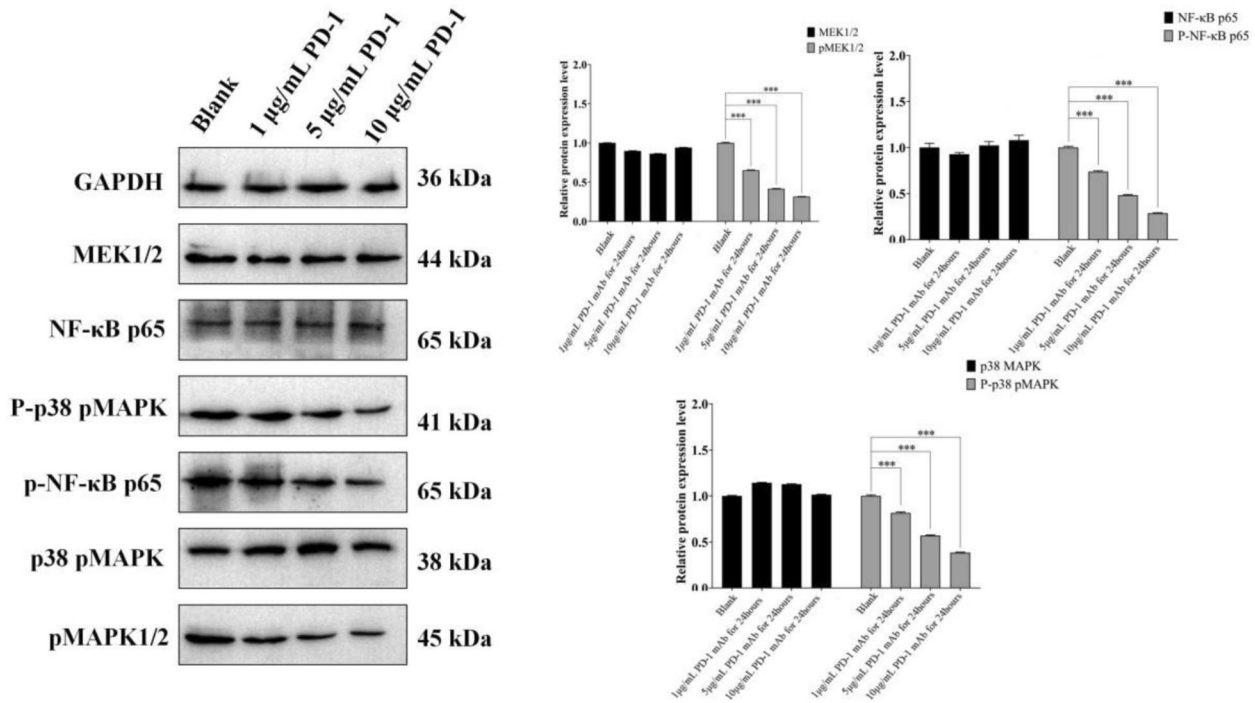

Fig. 5 Present study investigates the effects of PD-1 inhibition on MAPK/NF-κB signaling in HIV-infected T cells. To this end, the effects of different concentrations of PD-1 monoclonal antibody treatment on the expression of MAPK/NF-κB signaling pathway-related proteins were analyzed by Western blot

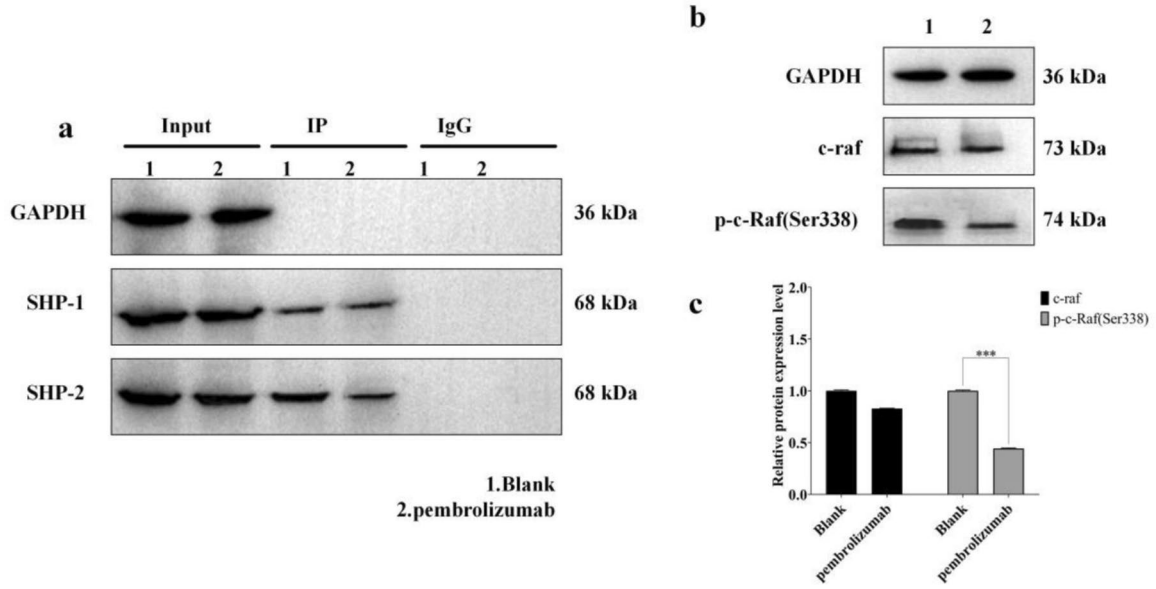

Fig. 6 PD-1 inhibits altered protein interaction with SHP-2 and reduces c-Raf phosphorylation in HIV-infected T cells. **a** Co-IP assay analysis showing the interaction of SHP-2 and SHP-1 in PD-1 high-expressing T lymphocytes. **b**, **c** Western blot analysis of p–c-Raf (Ser338) and p–c-Raf expression in Pembrolizumab-treated samples

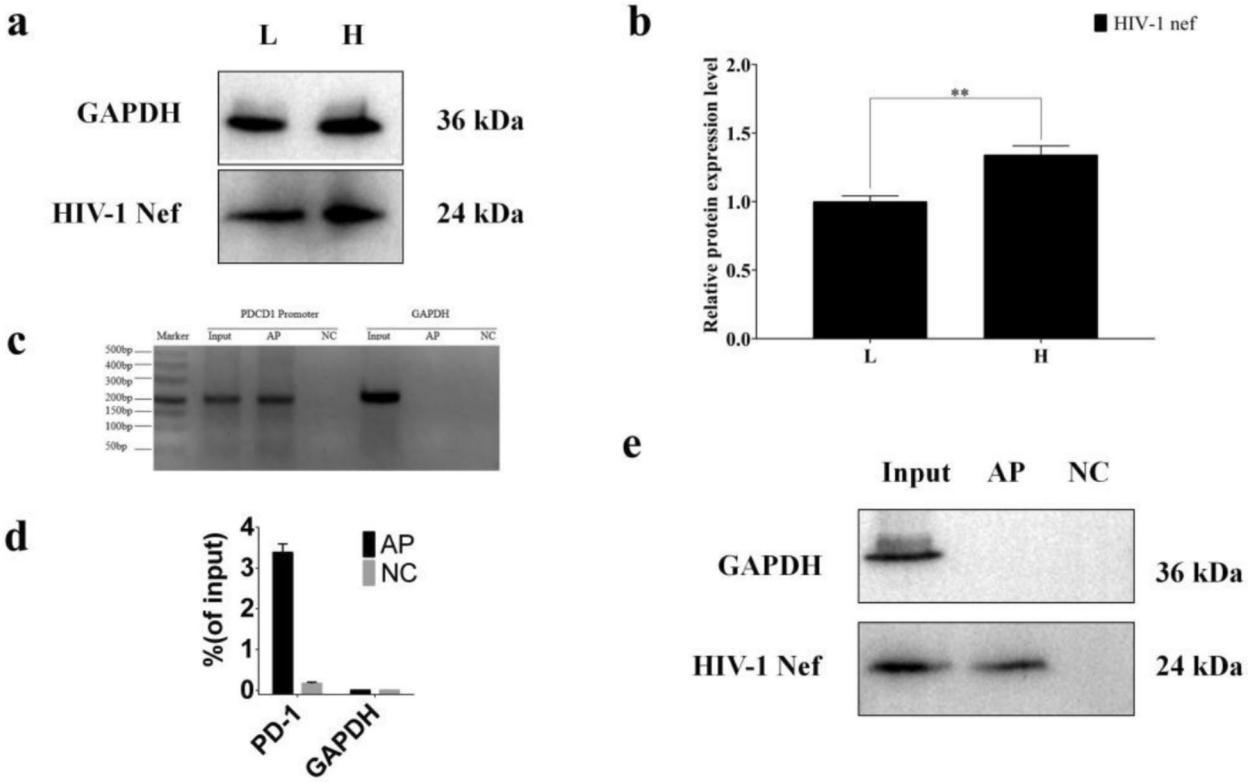

Fig. 7 HIV infection upregulates PD-1 expression through Nef protein. **a**, **b** Changes in HIV-1 Nef protein expression were analyzed by Western blot in HIV-infected PD-1 low-expression group and in PD-1 high-expression group. **c**, **d** Co-IP with RT-qPCR to analyze the interaction of HIV-1 Nef protein with PD-1. **e** Changes in HIV-1 Nef protein expression within Input, Reverse-ChIP AP and Reverse-ChIP NC groups were analyzed by Western blot

tolerance, and potentially aid in clearing latent HIV reservoirs [14].

Regarding signaling pathways, Western blot and Co-IP analyses showed significantly elevated expression of key molecules in the MAPK/NF-κB pathway—such as pMEK1/2, p-p38 MAPK, and p-NF-κB p65—in HIV-infected cells. After PD-1 monoclonal antibody treatment, the expression of these pathway-related proteins decreased significantly. The MAPK/NF-κB pathway plays a vital role in T-cell activation, proliferation, and functional maintenance, and is often hyperactivated in HIV-induced immune evasion. Overactivation of the MAPK and NF-κB pathways has been identified as a major mechanism underlying the functional exhaustion of HIV-specific T-cells. This study further reveals that PD-1 facilitates the activation of the MAPK/NF-κB pathway by recruiting SHP-2 and SHP-1, thereby suppressing T-cell immune function. This mechanism is also implicated in tumor immune evasion, suggesting that PD-1 inhibition could provide a new avenue for HIV immune therapy [15].

In terms of latent HIV infection, accumulating evidence suggests that immune checkpoint inhibitors may play a role in eliminating HIV reservoirs. Our experiments demonstrate that PD-1 monoclonal antibody (pembrolizumab), alone or in combination with Apabetalone, significantly upregulated HIV-1 LTR transcription, suggesting that PD-1 not only contributes to immune escape during HIV infection but may also promote the persistence of latent infection. Recent studies have shown that immune checkpoint inhibitors can activate latent HIV transcription, providing a potential strategy for eradicating long-term hidden HIV reservoirs [16]. For instance, combining CTLA-4 and PD-1 monoclonal antibodies has been shown to enhance HIV-specific CD8 + T-cell function and reduce latent HIV reservoirs [17].

Moreover, reverse-ChIP and Western blot analyses revealed that the HIV-1 Nef protein interacts with the PD-1 promoter to upregulate PD-1 transcription. Nef is a crucial regulator of HIV immune evasion, modulating host immune responses through various mechanisms, including PD-1 upregulation, which promotes T-cell exhaustion and immune suppression. Recent studies have highlighted that Nef influences host immune cell function and immune checkpoint expression, including PD-1, contributing to HIV's ability to evade immune surveillance [18].

In summary, this study highlights the pivotal role of PD-1 in HIV infection by regulating the MAPK/NF-κB signaling pathway and promoting T-cell exhaustion. HIV utilizes the Nef protein to interact with the PD-1 promoter, leading to increased PD-1 expression, which further enhances T-cell immune suppression and sustains viral persistence. PD-1 monoclonal antibody (pembrolizumab) reduces T-cell apoptosis, restores immune function, and activates latent HIV-1 transcription, offering new insights into potential therapeutic strategies for HIV infection. Future research should focus on further elucidating the regulatory mechanisms of PD-1 and its potential as a therapeutic target, particularly in combination with novel immune checkpoint inhibitors, to provide more effective treatment options for individuals living with HIV [19]. While PD-1 is a key immune checkpoint in HIV immune evasion, other immune checkpoints such as CTLA-4, LAG-3, and TIM-3 also play significant roles in immune modulation [20, 21]. These molecules contribute to T cell exhaustion and may synergize with PD-1 to facilitate HIV persistence. Future research should investigate the interplay between these checkpoints and their potential in combination therapies for more effective HIV treatment.

Conclusion

Overall, this research advances our understanding of PD-1's role in HIV immunopathogenesis and supports the potential of PD-1 blockade as a therapeutic tool in HIV treatment. Future studies should explore the clinical applications of these findings, particularly in combination with other immune checkpoint inhibitors, to improve treatment outcomes for HIV-infected patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02427-4.

Supplementary Material 1.

Acknowledgements
Not applicable.

Author contributions
XR L and SC L contributed to the study conception and design. XR L, B S, LJ C, L Z, SY L, X W, XH C and SC L performed the experiments and interpreted the data. XR L was a major contributor in writing the manuscript. SC L and XH C was responsible for the manuscript revision, and all authors have read and approved the final manuscript for publication.

Funding
This work was not supported by any external funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University (No. 2024-Ethics Review-06). Consent to participate is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 7 January 2025 Accepted: 3 March 2025
Published online: 04 April 2025

References

1. Faulhaber JR, et al. Update in human immunodeficiency virus and aging. Infect Dis Clin North Am. 2023;37(1):153–73.
2. Engels EA, et al. State of the science and future directions for research on HIV and cancer: summary of a joint workshop sponsored by IARC and NCI. Int J Cancer. 2024;154(4):596–606.
3. Moir S, Chun TW, Fauci AS. Pathogenic mechanisms of HIV disease. Annu Rev Pathol. 2011;6:223–48.
4. Bakhanashvili M. The role of tumor suppressor p53 protein in HIV-host cell interactions. Cells. 2024;13(18):1512.
5. Siripurapu R, Ota Y. Human immunodeficiency virus: opportunistic infections and beyond. Neuroimaging Clin N Am. 2023;33(1):147–65.
6. Yi M, et al. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer. 2022;21(1):28.
7. Day CL, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature. 2006;443(7109):350–4.
8. Guo Q, et al. NF-kappaB in biology and targeted therapy: new insights and translational implications. Signal Transduct Target Ther. 2024;9(1):53.
9. Youn GS, et al. HDAC6 mediates HIV-1 tat-induced proinflammatory responses by regulating MAPK-NF-kappaB/AP-1 pathways in astrocytes. Glia. 2015;63(11):1953–65.
10. Yang X, et al. PEBP1 suppresses HIV transcription and induces latency by inactivating MAPK/NF-kappaB signaling. EMBO Rep. 2020;21(11): e49305.
11. Jiang Z, et al. HIV-1-specific CAR-T cells with cell-Intrinsic PD-1 checkpoint blockade enhance anti-HIV efficacy in vivo. Front Microbiol. 2021;12:684016.
12. Fenwick C, et al. T-cell exhaustion in HIV infection. Immunol Rev. 2019;292(1):149–63.
13. McBrien JB, Kumar NA, Silvestri G. Mechanisms of CD8(+) T cell-mediated suppression of HIV/SIV replication. Eur J Immunol. 2018;48(6):898–914.
14. Benito JM, et al. Immune checkpoint inhibitors as potential therapy for reverting T-cell exhaustion and reverting HIV latency in people living with HIV. Front Immunol. 2023;14:1270881.
15. Christofides A, et al. SHP-2 and PD-1-SHP-2 signaling regulate myeloid cell differentiation and antitumor responses. Nat Immunol. 2023;24(1):55–68.
16. Boyer Z, Palmer S. Targeting immune checkpoint molecules to eliminate latent HIV. Front Immunol. 2018;9:2339.
17. Harper J, et al. CTLA-4 and PD-1 dual blockade induces SIV reactivation without control of rebound after antiretroviral therapy interruption. Nat Med. 2020;26(4):519–28.
18. Kwon Y, et al. Structural basis of CD4 downregulation by HIV-1 Nef. Nat Struct Mol Biol. 2020;27(9):822–8.
19. Su H, Mueller A, Goldstein H. Recent advances on anti-HIV chimeric antigen receptor-T-cell treatment to provide sustained HIV remission. Curr Opin HIV AIDS. 2024;19(4):169–78.
20. Munoz-Muela E, et al. HIV-1-specific T-cell responses and exhaustion profiles in people with HIV after switching to dual therapy vs. maintaining triple therapy based on integrase inhibitors. Biomed Pharmacother. 2023;168:115750.
21. Chiu CY, et al. Soluble immune checkpoints as correlates for HIV persistence and T cell function in people with HIV on antiretroviral therapy. Front Immunol. 2023;14:1123342.

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