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Immune Checkpoint Modulation and Reservoir Persistence in People Living with HIV

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ABSTRACT

Despite effective antiretroviral therapy, people living with HIV harbored a latent viral reservoir in long-lived memory CD4+ T cells that prevents cure. Immune checkpoint molecules, initially recognized for their role in maintaining peripheral tolerance and preventing autoimmunity, have emerged as critical regulators of T cell exhaustion and viral persistence in chronic HIV infection. This review examined the bidirectional relationship between immune checkpoint expression and HIV reservoir dynamics, evaluating how checkpoint pathways contributed to reservoir establishment, maintenance, and potential therapeutic targeting. A comprehensive analysis of literature published between 2015 and 2024 was conducted, focusing on studies investigating checkpoint molecule expression, reservoir quantification, and experimental interventions in people living with HIV. Programmed cell death protein 1 (PD-1), cytotoxic T lymphocyte associated protein 4 (CTLA-4), T cell immunoglobulin and mucin domain containing protein 3 (TIM-3), and lymphocyte activation gene 3 (LAG-3) are preferentially expressed on HIV-infected cells and correlate with reservoir size. Checkpoint blockade enhanced HIV-specific immune responses in vitro and animal models, yet clinical trials have shown limited reservoir reduction despite immune activation. The reservoir persists in checkpoint-high memory subsets that exhibit metabolic quiescence and epigenetic modifications favoring latency. Combination approaches targeting multiple checkpoints alongside latency reversal agents demonstrate enhanced viral reactivation but raise safety concerns. Immune checkpoint modulation represented a promising but complex strategy for HIV reservoir elimination, requiring careful consideration of tissue compartmentalization, immune reconstitution potential, and the balance between viral reactivation and immune-mediated clearance.

Keywords: Immune checkpoints, HIV reservoir, Latency reversal, T cell exhaustion, Antiretroviral therapy.

INTRODUCTION

Immune checkpoint molecules constitute a sophisticated regulatory network that modulates T cell activation, proliferation, and effector function to maintain immunological homeostasis [1, 2]. Under physiological conditions, these coinhibitory receptors prevent excessive immune activation and protect against autoimmunity by attenuating T cell receptor signaling following antigen recognition. In the context of chronic viral infections, however, sustained antigen exposure drives progressive upregulation of multiple checkpoint receptors on virus-specific CD8+ and CD4+ T cells, culminating in a state of functional exhaustion characterized by diminished cytokine production, impaired cytotoxic capacity, and reduced proliferative potential [3]. The checkpoint landscape in HIV infection is particularly complex, as the virus directly infects CD4+ T cells that express these inhibitory molecules, creating a microenvironment that simultaneously favors viral persistence and suppresses antiviral immunity. Emerging evidence indicates that checkpoint expression is not merely a consequence of chronic immune activation but actively shapes the cellular and molecular characteristics of cells harboring replication-competent provirus.

The relationship between immune checkpoint expression and the HIV latent reservoir has garnered substantial attention as a potential therapeutic vulnerability in efforts to achieve viral eradication or functional cure [4, 5]. The latent reservoir, comprised predominantly of resting memory CD4+ T cells containing integrated but transcriptionally silent proviral DNA, persists indefinitely despite suppressive antiretroviral therapy and rapidly rebounds upon treatment interruption. Checkpoint-expressing CD4+ T cells exhibit preferential infection susceptibility and enhanced survival following integration, characteristics that may explain their overrepresentation within the reservoir [6, 7]. Furthermore, checkpoint-mediated signaling pathways intersect with cellular metabolic programs, epigenetic regulatory mechanisms, and transcriptional machinery that collectively determine latency

establishment and reversal potential. Understanding these molecular connections has important implications for designing cure strategies, as interventions that modulate checkpoint pathways may influence both reservoir stability and the capacity of the immune system to eliminate reactivated infected cells. The objective of this review is to critically evaluate current evidence linking immune checkpoint molecule expression to HIV reservoir dynamics in people living with HIV, with particular emphasis on the mechanisms by which checkpoint pathways contribute to reservoir persistence, the impact of checkpoint blockade on viral latency and immune function, and the translational potential of checkpoint-targeted interventions as components of HIV cure strategies.

Immune Checkpoint Molecules in HIV Pathogenesis

Immune checkpoint receptors represent a diverse family of cell surface proteins that deliver inhibitory signals upon engagement with their cognate ligands, thereby dampening T cell effector responses [8]. During HIV infection, several checkpoint molecules become dysregulated, with PD-1 emerging as the most extensively studied marker of T cell exhaustion. PD-1 expression is elevated on both HIV-specific $CD8^+$ T cells and $CD4^+$ T cells throughout infection, correlating with disease progression markers including viral load and $CD4^+$ T cell decline in untreated individuals [9, 10]. The PD-1 ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), are upregulated on antigen-presenting cells and infected cells, creating multiple inhibitory axes that suppress antiviral responses. CTLA-4, which competes with the costimulatory molecule CD28 for binding to B7 ligands on antigen-presenting cells, is also elevated in HIV infection and contributes to impaired T cell priming and clonal expansion. Additional checkpoint molecules including TIM-3, LAG-3, T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), and CD160, are coexpressed on exhausted T cells, with the degree of coexpression correlating with the severity of functional impairment.

The functional consequences of checkpoint upregulation extend beyond simple inhibition of T cell activation. Checkpoint signaling actively modulates intracellular metabolic programs, shifting cells away from glycolytic metabolism required for effector function toward oxidative phosphorylation and fatty acid oxidation characteristic of memory differentiation and quiescence [11]. This metabolic reprogramming may promote the survival of infected cells within the reservoir by reducing cellular activation and minimizing expression of viral antigens that could trigger immune recognition. Furthermore, checkpoint receptor engagement influences epigenetic modifications at the HIV long terminal repeat and cellular genes involved in viral transcription, potentially reinforcing latency. Studies employing single-cell RNA sequencing have revealed that checkpoint-high $CD4^+$ T cells exhibit distinct transcriptional profiles enriched for genes associated with cellular longevity, survival signaling, and resistance to apoptosis, characteristics that favor reservoir persistence [12, 13]. The checkpoint landscape differs across T cell memory subsets, with central memory and transitional memory populations displaying particularly high checkpoint expression and harboring disproportionate levels of integrated proviral DNA.

Checkpoint Expression as a Marker of Reservoir Cells

Multiple lines of evidence support the association between checkpoint molecule expression and HIV reservoir localization. Flow cytometric analyses combined with quantitative viral outgrowth assays have demonstrated that PD-1-expressing $CD4^+$ T cells from antiretroviral therapy-suppressed individuals contain significantly higher levels of inducible replication-competent virus compared to PD-1-negative counterparts [14]. This enrichment is particularly pronounced in cells coexpressing multiple checkpoint receptors, suggesting that progressive checkpoint accumulation identifies cells with the greatest reservoir burden. Mechanistic studies indicate that checkpoint-high cells are preferentially infected during acute and early infection phases due to their activated phenotype and elevated expression of HIV coreceptors. Following integration, checkpoint signaling promotes cell survival through multiple pathways including upregulation of antiapoptotic proteins, enhanced DNA repair mechanisms, and resistance to cytotoxic T lymphocyte-mediated killing. Importantly, antiretroviral therapy initiation does not normalize checkpoint expression, and elevated levels persist for years despite viral suppression, indicating that checkpoint dysregulation is at least partially independent of ongoing viral replication.

The spatial distribution of checkpoint-expressing reservoir cells extends beyond peripheral blood to include lymphoid tissues, the gastrointestinal tract, and the central nervous system, compartments that are relatively sheltered from immune surveillance and antiretroviral drug penetration [15]. In lymphoid follicles, a subset of $CD4^+$ T follicular helper cells expressing high levels of PD-1, CXCR5, and BCL6 constitutes a significant reservoir component that is maintained through homeostatic proliferation and exhibits distinct susceptibility to latency reversal agents [16, 17]. Checkpoint expression profiles vary across anatomical sites, with tissue-resident memory T cells displaying unique combinations of inhibitory receptors that reflect local inflammatory environments and antigen exposure histories. Advanced imaging studies utilizing immunohistochemistry and in situ hybridization have visualized HIV RNA-positive cells within lymphoid tissues and demonstrated their colocalization with checkpoint molecule expression and markers of immune exhaustion.

Checkpoint Blockade and Latency Reversal

The success of checkpoint blockade immunotherapy in cancer has stimulated investigation of similar approaches for HIV reservoir reduction. In vitro studies using $CD4^+$ T cells from suppressed individuals have shown that antibodies

blocking PD-1, PD-L1, or CTLA-4 enhance T cell proliferation, cytokine production, and HIV-specific immune responses [18, 19]. When combined with latency reversal agents such as histone deacetylase inhibitors or protein kinase C agonists, checkpoint blockade augments viral reactivation from latently infected cells, potentially increasing the visibility of reservoir cells to immune effectors. Animal models, particularly humanized mice and simian immunodeficiency virus-infected macaques, have provided proof-of-concept evidence that checkpoint blockade can delay viral rebound following antiretroviral therapy interruption and reduce reservoir size when combined with therapeutic vaccination or broadly neutralizing antibodies. These preclinical successes generated optimism for clinical translation.

Clinical trials evaluating checkpoint blockade in people living with HIV have yielded more modest results. Studies administering anti-PD-1 or anti-CTLA-4 antibodies to individuals with HIV-associated malignancies demonstrated acceptable safety profiles and tumor responses comparable to HIV-negative populations, but showed minimal impact on HIV reservoir size as measured by total or integrated HIV DNA, cell-associated HIV RNA, or quantitative viral outgrowth assays [20, 21]. Transient increases in plasma viremia and cell-associated HIV RNA have been observed in some participants, suggesting viral reactivation, but these changes have not translated into durable reservoir reduction. Explanations for the limited efficacy include insufficient immune reconstitution to clear reactivated cells, anatomical and functional sanctuary sites protected from checkpoint blockade effects, and the possibility that checkpoint inhibition alone is inadequate to reverse the multiple mechanisms maintaining latency. Furthermore, the theoretical risk of exacerbating immune activation and inflammation, hallmarks of treated HIV infection associated with non-AIDS morbidity and mortality, has tempered enthusiasm for checkpoint blockade monotherapy.

Immunometabolic Regulation and Reservoir Dynamics

The intersection of immune checkpoint signaling and cellular metabolism represents a critical determinant of reservoir persistence. Checkpoint receptors regulate metabolic reprogramming through modulation of the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway and AMP-activated protein kinase (AMPK) signaling, master regulators of cellular bioenergetics [22]. PD-1 engagement inhibits glycolysis and glutaminolysis while promoting fatty acid oxidation, metabolic shifts that favor the quiescent phenotype characteristic of latently infected memory $CD4^+$ T cells. These metabolic states influence HIV transcription through multiple mechanisms including regulation of cellular transcription factor availability, modulation of chromatin accessibility, and control of metabolite pools that serve as substrates or cofactors for epigenetic modifying enzymes. Metabolomic profiling of sorted checkpoint-expressing $CD4^+$ T cells has revealed distinct metabolite signatures including elevated ratios of oxidized to reduced nicotinamide adenine dinucleotide (NAD+/NADH), increased ceramide species, and altered amino acid pools, metabolic features associated with cellular longevity programs.

Therapeutic interventions targeting cellular metabolism have shown promise in preclinical reservoir studies. Metformin, an AMPK activator and mTOR inhibitor commonly used for type 2 diabetes management, has demonstrated the capacity to reduce immune activation markers and modestly decrease HIV DNA levels in observational studies of people living with HIV [23, 24]. Mechanistically, metformin-induced metabolic reprogramming may render latently infected cells more susceptible to immune clearance or alter the balance of proviral transcription. Conversely, approaches that transiently boost glycolytic metabolism, such as treatment with interleukin 2 or interleukin 7, can drive latency reversal but simultaneously may expand checkpoint-expressing cell populations, highlighting the complexity of metabolically targeted interventions. The interplay between checkpoint signaling, metabolic state, and reservoir dynamics underscores the need for integrated therapeutic strategies that coordinate immune modulation with metabolic manipulation.

Combination Strategies and Future Therapeutic Directions

Recognition that HIV persistence results from multiple overlapping mechanisms has driven the development of combination cure strategies incorporating checkpoint modulation alongside complementary interventions. The "shock and kill" paradigm, which pairs latency reversal agents with immune enhancement to reactivate and eliminate reservoir cells, has been refined to include checkpoint blockade as an immune enhancement component. Early phase clinical trials are evaluating regimens combining broadly neutralizing antibodies, which can mediate antibody-dependent cellular cytotoxicity against reactivated cells, with checkpoint inhibitors to enhance cytotoxic T lymphocyte function. Preliminary data suggest that dual or triple checkpoint blockade targeting PD-1, CTLA-4, and LAG-3 simultaneously may achieve greater immune reconstitution than single-agent approaches, though toxicity profiles require careful monitoring [25, 26]. Therapeutic vaccines designed to boost HIV-specific T cell responses are being tested in combination with checkpoint inhibitors to overcome exhaustion and improve effector function against reactivated reservoir cells.

Alternative approaches focus on preventing reservoir establishment and maintenance rather than the elimination of existing reservoirs. Administration of checkpoint inhibitors during acute HIV infection, when the immune system retains greater functional capacity and the reservoir is smaller, represents an attractive strategy currently under investigation in nonhuman primate models. Ex vivo studies suggest that blocking checkpoint pathways during

antiretroviral therapy initiation may limit reservoir seeding and preserve immune function, though clinical validation is needed [27]. Gene editing technologies, including CRISPR-Cas9, are being explored to disrupt checkpoint receptor genes in autologous T cells before reinfusion, creating populations resistant to exhaustion that might better control reactivated virus. The feasibility and safety of checkpoint-targeted gene therapy remain to be established. Concerns regarding immune-related adverse events, particularly autoimmune phenomena observed in cancer immunotherapy contexts, necessitate careful patient selection and monitoring protocols. The development of biomarkers to predict which individuals will respond to checkpoint-based interventions, potentially including checkpoint expression profiles, reservoir characteristics, and immune functional assays, will be essential for advancing personalized cure strategies.

Challenges, Controversies, and Research Gaps

Despite significant advances in understanding checkpoint biology in HIV infection, substantial knowledge gaps and controversies persist. The causal relationship between checkpoint expression and reservoir persistence remains incompletely defined, as it is unclear whether checkpoint upregulation actively promotes latency or simply marks cells that have become latently infected for other reasons. Longitudinal studies tracking checkpoint expression dynamics from acute infection through chronic suppressed phases, combined with paired reservoir measurements, are needed to resolve this question. The tissue-specific roles of different checkpoint molecules remain poorly characterized, with most studies relying on peripheral blood samples that may not reflect reservoir dynamics in anatomical sanctuaries. Advanced tissue sampling techniques, including lymph node biopsies, colorectal biopsies, and cerebrospinal fluid sampling, combined with single-cell multiomics approaches, would provide more comprehensive insights into compartmentalized reservoir biology [28].

The optimal checkpoint targets for therapeutic intervention remain debated. While PD-1 has received the most attention, emerging evidence suggests that other checkpoint molecules, including TIGIT, which is preferentially expressed on a subset of highly functional HIV-specific $CD8^+$ T cells, or CD39, an ectonucleotidase that generates immunosuppressive adenosine, may represent superior or complementary targets [29, 30]. The timing and duration of checkpoint blockade relative to latency reversal and other interventions require optimization, as transient versus sustained inhibition may yield different effects on reservoir and immune function. Concerns about the durability of responses following checkpoint blockade, the potential for viral evolution and escape, and the risk of immune-related adverse events in a population already experiencing chronic inflammation remain substantial barriers to widespread clinical application. Furthermore, the applicability of checkpoint modulation strategies across diverse populations, including individuals with advanced immunosuppression, opportunistic infection histories, or comorbid conditions, requires careful evaluation. The cost and accessibility of checkpoint inhibitor therapies, which are expensive biologics requiring intravenous administration, pose additional challenges for global implementation, particularly in resource-limited settings where the HIV burden is greatest [31].

CONCLUSION

Immune checkpoint molecules play multifaceted roles in HIV pathogenesis, simultaneously serving as markers of reservoir cells, mediators of T cell exhaustion, and regulators of cellular metabolic and transcriptional programs that influence viral latency. The preferential expression of PD-1, CTLA-4, TIM-3, LAG-3, and other checkpoint receptors on HIV-infected $CD4^+$ T cells reflects both the activated state required for initial infection and the immunosuppressive microenvironment that promotes long term reservoir persistence. While checkpoint blockade has demonstrated the capacity to enhance HIV-specific immune responses and augment latency reversal in preclinical models, clinical trials have revealed limited efficacy as monotherapy for reservoir reduction. These disappointing results highlight the complexity of HIV persistence mechanisms and the inadequacy of single-target interventions. The integration of checkpoint modulation into combination cure strategies, potentially including latency reversal agents, therapeutic vaccines, broadly neutralizing antibodies, and metabolic modulators, represents the most promising path forward. Critical research priorities include defining optimal checkpoint targets and combination regimens, characterizing tissue-specific reservoir dynamics and checkpoint expression patterns, developing biomarkers to predict treatment response, and establishing safety profiles for checkpoint-based interventions in people living with HIV. The success of checkpoint-directed immunotherapy in oncology provides proof-of-concept that reshaping immune regulation can achieve clinically meaningful outcomes, yet the unique challenges posed by HIV reservoirs, including their anatomical distribution, genetic diversity, and integration into long-lived memory cells, necessitate tailored approaches. Achieving an HIV cure will likely require comprehensive strategies that coordinate immune reconstitution, viral reactivation, and enhanced clearance mechanisms, with checkpoint modulation serving as one component of this multifaceted effort. It is recommended to prioritize multi-site longitudinal studies combining deep tissue sampling, single-cell multiomics profiling, and functional immune assays to define tissue-specific checkpoint expression patterns and reservoir characteristics that can guide rational design of checkpoint-targeted combination cure strategies for people living with HIV.

REFERENCES

1. Abdeladhim, M., Karnell, J.L., Rieder, S.A.: In or out of control: Modulating regulatory T cell homeostasis and function with immune checkpoint pathways. Front. Immunol. 13, (2022). https://doi.org/10.3389/fimmu.2022.1033705
2. Zhang, Y., Zheng, J.: Functions of Immune Checkpoint Molecules Beyond Immune Evasion. In: Xu, J. (ed.) Regulation of Cancer Immune Checkpoints: Molecular and Cellular Mechanisms and Therapy. pp. 201–226. Springer, Singapore (2020)
3. Alum, E.U., Uti, D.E., Ugwu, O.P.-C., Alum, B.N.: Toward a cure – Advancing HIV/AIDs treatment modalities beyond antiretroviral therapy: A Review. Medicine. 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768
4. Li, K., Zhang, Q.: Eliminating the HIV tissue reservoir: current strategies and challenges. Infectious Diseases. 56, 165–182 (2024). https://doi.org/10.1080/23744235.2023.2298450
5. Lau, J.S.Y., McMahon, J.H., Gubser, C., Solomon, A., Chiu, C.Y.H., Dantanarayana, A., Chea, S., Tennakoon, S., Zerbato, J.M., Garlick, J., Morcilla, V., Palmer, S., Lewin, S.R., Rasmussen, T.A.: The impact of immune checkpoint therapy on the latent reservoir in HIV-infected individuals with cancer on antiretroviral therapy. AIDS. 35, 1631 (2021). https://doi.org/10.1097/QAD.0000000000002919
6. Obeagu, E.I., Obeagu, G.U., 2School of Nursing Science, Kampala International University, Uganda., Odo, E.O., School of General Studies (Physical and Health Education Unit) Michael Okpara University of Agriculture, Umudike, Nigeria, Igwe, M.C., Department of Public Health, Kampala International University, Uganda, Ugwu, O.P.-C., Department of Publication and Extensions, Kampala International University, Uganda, Alum, E.U., 5Department of Publication and Extensions, Kampala International University, Uganda, 6Department of Biochemistry, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria., Okwaja, P.R., Department of Public Administration and Development Studies, Kampala International University, Uganda.: Revolutionizing HIV Prevention in Africa: Landmark Innovations that Transformed the Fight. IAA-JAS. 11, 1–12 (2024). https://doi.org/10.59298/IAAJAS/2024/1.3.5288
7. Tokarev, A., McKinnon, L.R., Pagliuzza, A., Sivro, A., Omole, T.E., Kroon, E., Chomchey, N., Phanuphak, N., Schuetz, A., Robb, M.L., Eller, M.A., Ananworanich, J., Chomont, N., Bolton, D.L.: Preferential Infection of α4β7+ Memory CD4+ T Cells During Early Acute Human Immunodeficiency Virus Type 1 Infection. Clin Infect Dis. 71, e735–e743 (2020). https://doi.org/10.1093/cid/ciaa497
8. Zhang, Y., Zheng, J.: Functions of Immune Checkpoint Molecules Beyond Immune Evasion. In: Xu, J. (ed.) Regulation of Cancer Immune Checkpoints: Molecular and Cellular Mechanisms and Therapy. pp. 201–226. Springer, Singapore (2020)
9. Rallón, N., García, M., García-Samaniego, J., Cabello, A., Álvarez, B., Restrepo, C., Nistal, S., Górgolas, M., Benito, J.M.: Expression of PD-1 and Tim-3 markers of T-cell exhaustion is associated with CD4 dynamics during the course of untreated and treated HIV infection. PLOS ONE. 13, e0193829 (2018). https://doi.org/10.1371/journal.pone.0193829
10. Scharf, L., Tauriainen, J., Buggert, M., Hartogensis, W., Nolan, D.J., Deeks, S.G., Salemi, M., Hecht, F.M., Karlsson, A.C.: Delayed Expression of PD-1 and TIGIT on HIV-Specific CD8 T Cells in Untreated HLA-B*57:01 Individuals Followed from Early Infection. Journal of Virology. 94, 10.1128/jvi.02128-19 (2020). https://doi.org/10.1128/jvi.02128-19
11. van der Windt, G.J.W., Pearce, E.L.: Metabolic switching and fuel choice during T-cell differentiation and memory development. Immunological Reviews. 249, 27–42 (2012). https://doi.org/10.1111/j.1600-065X.2012.01150.x
12. Alum, E.U.: Career Advancement towards Nascent Technologies: RNA in Focus. IDOSR-JSR. 9, 49–53 (2024). https://doi.org/10.59298/IDOSRJSR/2024/9.2.4953.100
13. Durek, P., Nordström, K., Gasparoni, G., Salhab, A., Kressler, C., de Almeida, M., Bassler, K., Ulas, T., Schmidt, F., Xiong, J., Glažar, P., Klironomos, F., Sinha, A., Kinkley, S., Yang, X., Arrigoni, L., Amirabad, A.D., Ardakani, F.B., Feuerbach, L., Gorka, O., Ebert, P., Müller, F., Li, N., Frischbutter, S., Schlickeiser, S., Cendon, C., Fröhler, S., Felder, B., Gasparoni, N., Imbusch, C.D., Hutter, B., Zipprich, G., Tauchmann, Y., Reinke, S., Wassilew, G., Hoffmann, U., Richter, A.S., Sieverling, L., Chang, H.-D., Syrbe, U., Kalus, U., Eils, J., Brors, B., Manke, T., Ruland, J., Lengauer, T., Rajewsky, N., Chen, W., Dong, J., Sawitzki, B., Chung, H.-R., Rosenstiel, P., Schulz, M.H., Schultze, J.L., Radbruch, A., Walter, J., Hamann, A., Polansky, J.K.: Epigenomic Profiling of Human CD4+ T Cells Supports a Linear Differentiation Model and Highlights Molecular Regulators of Memory Development. Immunity. 45, 1148–1161 (2016). https://doi.org/10.1016/j.immuni.2016.10.022
14. Fromentin, R., DaFonseca, S., Costiniuk, C.T., El-Far, M., Procopio, F.A., Hecht, F.M., Hoh, R., Deeks, S.G., Hazuda, D.J., Lewin, S.R., Routy, J.-P., Sékaly, R.-P., Chomont, N.: PD-1 blockade potentiates HIV latency reversal ex vivo in CD4+ T cells from ART-suppressed individuals. Nat Commun. 10, 814 (2019). https://doi.org/10.1038/s41467-019-08798-7

15. Saksena, N.K., Wang, B., Zhou, L., Soedjono, M., Ho, Y.S., Conceicao, V.: HIV reservoirs in vivo and new strategies for possible eradication of HIV from the reservoir sites. HIV AIDS (Auckl). 2, 103–122 (2010). https://doi.org/10.2147/hiv.s6882
16. Eivazi, S., Bagheri, S., Hashemzadeh, M.S., Ghalavand, M., Qamsari, E.S., Dorostkar, R., Yasemi, M.: Development of T follicular helper cells and their role in disease and immune system. Biomedicine & Pharmacotherapy. 84, 1668–1678 (2016). https://doi.org/10.1016/j.biopha.2016.10.083
17. F, P.-C., Na, T., Mt, R.: CD8+ T-Cell Response to HIV Infection in the Era of Antiretroviral Therapy. Front Immunol. 10, 1896–1896 (2019). https://doi.org/10.3389/fimmu.2019.01896
18. Baksh, K., Weber, J.: Immune Checkpoint Protein Inhibition for Cancer: Preclinical Justification for CTLA-4 and PD-1 Blockade and New Combinations. Seminars in Oncology. 42, 363–377 (2015). https://doi.org/10.1053/j.seminoncol.2015.02.015
19. Fromentin, R., DaFonseca, S., Costiniuk, C.T., El-Far, M., Procopio, F.A., Hecht, F.M., Hoh, R., Deeks, S.G., Hazuda, D.J., Lewin, S.R., Routy, J.-P., Sékaly, R.-P., Chomont, N.: PD-1 blockade potentiates HIV latency reversal ex vivo in CD4+ T cells from ART-suppressed individuals. Nat Commun. 10, 814 (2019). https://doi.org/10.1038/s41467-019-08798-7
20. Benito, J.M., Restrepo, C., García-Foncillas, J., Rallón, N.: Immune checkpoint inhibitors as potential therapy for reverting T-cell exhaustion and reverting HIV latency in people living with HIV. Front. Immunol. 14, (2023). https://doi.org/10.3389/fimmu.2023.1270881
21. Rajdev, L., Jackie Wang, C.-C., Joshi, H., Lensing, S., Lee, J., Ramos, J.C., Baiocchi, R., Ratner, L., Rubinstein, P.G., Ambinder, R., Henry, D., Streicher, H., Little, R.F., Chiao, E., Dittmer, D.P., Einstein, M.H., Cesarman, E., Mitsuyasu, R., Sparano, J.A., Consortium, for the A.M.: Assessment of the safety of nivolumab in people living with HIV with advanced cancer on antiretroviral therapy: the AIDS Malignancy Consortium 095 Study. Cancer. 130, 985–994 (2024). https://doi.org/10.1002/cncr.35110
22. Ni, C.-X., Xu, J.-J., Pang, Y., Xu, J.-J.: Treatment strategies targeting the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin pathway against triple-negative breast cancer. World J Clin Oncol. 16, 104623 (2025). https://doi.org/10.5306/wjco.v16.i5.104623
23. Duan, W., Ding, Y., Yu, X., Ma, D., Yang, B., Li, Y., Huang, L., Chen, Z., Zheng, J., Yang, C.: Metformin mitigates autoimmune insulitis by inhibiting Th1 and Th17 responses while promoting Treg production. Am J Transl Res. 11, 2393–2402 (2019)
24. Fert, A., Richard, J., Marchand, L.R., Planas, D., Routy, J.-P., Chomont, N., Finzi, A., Ancuta, P.: Metformin Enhances Antibody-Mediated Recognition of HIV-Infected CD4+ T-Cells by Decreasing Viral Release. bioRxiv. 2024.02.15.580166 (2024). https://doi.org/10.1101/2024.02.15.580166
25. Kreidieh, F.Y., Tawbi, H.A.: The introduction of LAG-3 checkpoint blockade in melanoma: immunotherapy landscape beyond PD-1 and CTLA-4 inhibition. Ther Adv Med Oncol. 15, 17588359231186027 (2023). https://doi.org/10.1177/17588359231186027
26. Huang, R.-Y., Francois, A., McGray, A.R., Miliotto, A., Odunsi, K.: Compensatory upregulation of PD-1, LAG-3, and CTLA-4 limits the efficacy of single-agent checkpoint blockade in metastatic ovarian cancer. OncoImmunology. 6, e1249561 (2017). https://doi.org/10.1080/2162402X.2016.1249561
27. Lau, J.S.Y., McMahon, J.H., Gubser, C., Solomon, A., Chiu, C.Y.H., Dantanarayana, A., Chea, S., Tennakoon, S., Zerbato, J.M., Garlick, J., Morcilla, V., Palmer, S., Lewin, S.R., Rasmussen, T.A.: The Impact of Immune Checkpoint Therapy on the Latent reservoir in HIV Infected Individuals with Cancer on Antiretroviral Therapy. AIDS. 35, 1631–1636 (2021). https://doi.org/10.1097/QAD.0000000000002919
28. Shishido, S.N., Marvit, A., Pham, D., Luo, T., Xu, L., Mason, J., Priceman, S.J., Portnow, J., Kuhn, P.: Multi-Omic Characterization of Single Cells and Cell-Free Components Detected in the Cerebrospinal Fluid of Patients with Leptomeningeal Disease. Cancers. 16, 3746 (2024). https://doi.org/10.3390/cancers16223746
29. Scharf, L., Tauriainen, J., Buggert, M., Hartogensis, W., Nolan, D.J., Deeks, S.G., Salemi, M., Hecht, F.M., Karlsson, A.C.: Delayed Expression of PD-1 and TIGIT on HIV-Specific CD8 T Cells in Untreated HLA-B*57:01 Individuals Followed from Early Infection. Journal of Virology. 94, 10.1128/jvi.02128-19 (2020). https://doi.org/10.1128/jvi.02128-19
30. Chu, X., Tian, W., Wang, Z., Zhang, J., Zhou, R.: Co-inhibition of TIGIT and PD-1/PD-L1 in Cancer Immunotherapy: Mechanisms and Clinical Trials. Mol Cancer. 22, 93 (2023). https://doi.org/10.1186/s12943-023-01800-3
31. Madu, C.V., Alum, E.U., Aloh, H.E., Ugwu, O.P.C., Obeagu, E.I., Uti, D.E., Egba, S.I., Ukaidi, C.U.A., Alum, N.B.: The price of progress: Assessing the financial costs of HIV/AIDS management in East Africa. Medicine (Baltimore). 104, e42300 (2025). https://doi.org/10.1097/MD.0000000000042300

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