Suboptimal CD4 Cell Recovery Despite Viral Suppression

Reviewed: September 25, 2025
Updated: September 25, 2025

Key Considerations and Recommendations
• Suboptimal CD4 T lymphocyte (CD4) cell recovery is associated with increased AIDS- and non–AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)–mediated viral suppression. • Promptly initiating ART in people diagnosed early with HIV provides the best opportunity for maximal CD4 cell recovery. • Adding antiretroviral (ARV) drugs to a suppressive ART regimen (ART intensification) does not improve CD4 cell recovery and therefore **is not recommended** for this purpose **(AI).** • Switching ARV drugs or drug classes in people with suppressed viral load does not improve CD4 cell recovery substantially and **is not recommended** for this purpose **(AII).** • Interleukin-2 **is not recommended** to increase CD4 counts because clinical trial data demonstrated no clinical benefit **(AI).** • Other interventions to increase CD4 counts **are not recommended** outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression **(AII).** • Efforts to decrease morbidity and mortality during ART-mediated viral suppression should focus on preventive care (e.g., opportunistic infection prophylaxis, vaccinations, cancer screening, statin therapy to reduce cardiovascular risk), addressing modifiable risk factors for chronic disease (e.g., tobacco use, alcohol and substance use, unhealthy diet, sedentary lifestyle), and optimizing management of comorbidities (e.g., hypertension, diabetes).
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Most people with HIV who achieve and maintain antiretroviral therapy (ART)–mediated viral suppression experience increases in peripheral blood CD4 T lymphocyte (CD4) cell counts over time[1-4] and recovery of CD4 counts to within the normal range (>500 cells/mm^3) of people without HIV.[5-7] However, some people who started ART at low CD4 counts do not experience recovery to the desired immunologic goal of >500 cells/mm^3 despite sustained virologic suppression on ART.[2,3,8] Promptly initiating ART in people diagnosed early with HIV provides the best opportunity for maximal CD4 cell recovery.[9,10]

There is no clear consensus on terminology to use or thresholds that define “suboptimal CD4 cell recovery.”[11,12] A common threshold used for “suboptimal CD4 cell recovery” is CD4 ≤500 cells/mm^3 after several years of suppressive ART. The term “immunologic nonresponse” also has been used to describe a lack of CD4 cell recovery, with common thresholds of <200 cells/mm^3 or <350 cells/mm^3 after several years of suppressive ART.[12] Some experts consider an increase of <200 cells/mm^3 above baseline after 24 months as an inadequate immunologic response for people with CD4 counts ≤500 cells/mm^3. The relationship between improved clinical outcomes and higher CD4 counts likely spans all ranges of CD4 counts, although incremental benefits are harder to discern once CD4 counts reach moderate-to-high levels,[13] especially beyond 500 cells/mm^3. Rarely, people with HIV may experience substantial declines in CD4 counts while maintaining virologic suppression on ART.[14]

Clinical Consequences

Persistently low CD4 counts despite ART-mediated viral suppression are associated with increased risk of morbidity, hospitalizations, and mortality. Data from two large international cohorts of people with HIV initiating ART as early as 1996 showed that individuals with HIV and CD4 counts ≤200 cells/mm^3 despite at least 3 years of suppressive ART had a 2.6-fold greater risk of mortality than those with higher CD4 counts.[15] A multicenter cohort study from Spain of individuals who started ART with low CD4 counts between 2005 and 2019 found that those whose CD4 counts remained <200 cells/mm^3 after 2 years of ART had a 4.6-fold greater risk of mortality than those with CD4 >500 cells/mm^3.[16]

People with CD4 counts <200 cells/mm^3 despite at least 1 year of suppressive ART are at increased risk of AIDS-related and non–AIDS-related events.[17-23] This population is at risk of severe infections (e.g., pneumonia) and is less likely to mount a robust immune response following vaccination.[24] In addition, these individuals have an increased risk of infection-related cancers (e.g., Epstein-Barr virus-associated lymphoma, human papillomavirus–associated malignancies, hepatocellular carcinoma associated with hepatitis B virus [HBV] or hepatitis C virus [HCV]). A cohort study of people with HIV from 1996 to 2020 demonstrated that people with CD4 <200 cells/mm^3 had a 3.5-fold higher risk of infection-related cancers compared to people with CD4 ≥500 cells/mm^3.[25] Another study found that CD4 count <350 cells/mm^3 was associated with non–AIDS-defining, smoking-related, and other malignancies.[26] People with HIV who receive chemotherapy or radiation therapy can also experience CD4 count decline. One study reported a 27% increase in mortality for every 100 cells/mm^3 decrease in CD4 count.[27] Lastly, cardiovascular disease and other comorbidities have also been observed at increased rates in people with low CD4 recovery.[15,28-35]

Pathogenesis

Suboptimal CD4 recovery after ART-mediated virologic suppression is typically associated with higher levels of inflammation and immune activation[36] and is most frequently observed in people with older age, prior AIDS-defining illness, lower nadir CD4 count,[16,37] and some coinfections (e.g., HCV).[38-40] The association of higher inflammation levels with persistently low CD4 counts is likely multifactorial and, to some extent, may be driven by inadequate immunologic control of other chronic viral infections, based on observed decreases in inflammation after treatment of cytomegalovirus and chronic HCV infection.[41,42] Numerous factors have deleterious effects on T-cell survival and proliferation, such as chronic coinfections, a persistently activated innate immune system (due to stimuli such as microbial translocation and dysbiosis), more severe fibrosis of lymph node tissue with disruption of naive T-cell homeostasis, potential senescence of hematopoietic progenitors, and possibly autoantibodies.[43-46]

CD4 count may occasionally decline despite suppressive ART, which may be due to a new medication, a new underlying malignancy, infection, or autoimmune disorder, including the presence of anti-CD4 autoantibodies,[44,45] and/or dysregulation of interleukin-7 (IL-7)–mediated naive T-cell homeostasis or more accentuated immune senescence.[14,47,48]

Alternative Causes of Suboptimal CD4 Cell Recovery

Evaluation of people with suboptimal CD4 cell recovery should begin with identifying modifiable causes, such as concomitant medications that reduce total white blood cells, particularly lymphocytes and CD4 cells. When possible, these drugs should be discontinued and replaced with alternatives if necessary. Untreated coinfections (e.g., HCV, *Mycobacterium avium* complex, histoplasmosis) and serious medical conditions (e.g., malignancy, autoimmune disease) may also contribute to CD4 lymphopenia, particularly in people with declining CD4 counts (and percentages) while on suppressive ART and in those with CD4 consistently <100 cells/mm^3. Treating coinfections and optimizing management of contributing conditions should be pursued when feasible.

Interventions Tested to Improve CD4 Cell Recovery

For people with suboptimal CD4 cell recovery despite suppressive ART, effective interventions to increase CD4 counts and improve clinical outcomes have not been identified.[49] Strategies to raise CD4 counts by modifying or intensifying ART regimens have been evaluated in clinical trials. Intensification strategy by adding ARV drugs to a suppressive ART regimen does not improve CD4 cell recovery[50-56] and does not reduce morbidity or mortality. Therefore, ART intensification **is not recommended** as a strategy to improve CD4 cell recovery **(AI).** Similarly, switching ARV drugs or classes has not been shown to improve CD4 cell recovery substantially for individuals with viral suppression and **is not recommended (AII).**[57,58]

Therapies targeting immunomodulatory pathways (e.g., interleukin-2 [IL-2], IL-7, growth hormone, thymosin alpha-1) have also been investigated as a strategy to increase CD4 counts.[59] Two large randomized trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of IL-2 for improving CD4 cell recovery. Although there is strong evidence linking low CD4 cell counts with increased morbidity, IL-2 adjunctive therapy did not decrease the risk of clinical events despite substantial increases in CD4 count.[60] Therefore, IL-2 is **not recommended** as a strategy to improve CD4 recovery **(AI).** Dysregulation in IL-7–mediated naive T-cell homeostasis has been reported among people with suboptimal CD4 recovery.[14,47,48] While several early-phase trials of human recombinant IL-7 treatment have shown an increase in CD4 counts among people with HIV on ART, no clinical trials designed to evaluate whether IL-7 treatment confers benefit on clinical outcomes have been performed.[61]

Additional interventions have been studied in early-phase trials, and some have demonstrated improvements in CD4 counts among people with HIV on ART with suboptimal CD4 cell recovery. These studies were not designed to evaluate clinical endpoints. Examples include the use of novel antivirals,[62] repurposed medications,[63,64] probiotics,[65,66] plants and herbal treatments with medicinal properties,[67-69] and other nutritional supplements,[70] as well as human umbilical cord mesenchymal stem cell infusions[71,72] or allogenic natural killer cell immunotherapy.[73] As demonstrated by the IL-2 clinical trial results, randomized trials with clinical endpoints will be needed to establish clinical benefit. Because of the lack of clinical efficacy data from these alternative interventions, the use of adjunct therapies to improve immune recovery **is not recommended,** except in the context of a clinical trial **(AII).**

Prevention of Clinical Consequences

With continuous ART and viral suppression, life expectancy for people with HIV is approaching that of people without HIV. However, persistently low CD4 counts despite ART-mediated viral suppression are associated with higher rates of both AIDS and non–AIDS-related morbidity and mortality over the long term. Reducing AIDS- and non–AIDS-related morbidity and mortality remains a cornerstone of HIV treatment and is especially important for people with suboptimal CD4 recovery, given the increased risk of such outcomes. Risk for opportunistic infections (OIs) is generally low for people on ART with viral suppression, but some primary or secondary prophylaxis may need to be extended for certain OIs among people who do not experience CD4 recovery above certain thresholds (see the Adult OI Guidelines for specific guidance).

Given the increased risk for severe manifestations and/or poor outcomes from infections such as tuberculosis, HBV, and HCV, guidelines for screening for such infections should be followed closely, and treatments should be initiated promptly when indicated. Clinicians should also be vigilant about ensuring that people with HIV are up to date on vaccinations for preventable infections. It should be noted that live virus vaccines are contraindicated for people with CD4 counts <200 cells/mm^3 (see Immunizations for Preventable Diseases in Adults and Adolescents With HIV in the Adult OI Guidelines for detailed recommendations).

For non-AIDS-related morbidities, providers should offer preventive counseling, evaluate and manage cardiovascular risk factors (see Cardiovascular Complications), ensure that screening for malignancies (e.g., colorectal cancer, anal or cervical cancer, hepatocellular carcinoma, lung cancer, breast cancer) is up to date (see Primary Care Guidance), initiate statin therapy when indicated (see Statin Therapy in People With HIV), and provide prompt care and referrals when appropriate.[74] As for all people with HIV, regardless of CD4 count, preventive counseling should address lifestyle modifiable risk factors, including but not limited to smoking cessation, abstinence from alcohol and substance use, dietary modification, regular exercise, and treatment optimization for comorbidities such as hypertension and diabetes.

References

1. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS*. 2001;15(11):1369-1377. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11504958.

2. Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis*. 2009;48(6):787-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19193107.

3. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. *AIDS*. 2010;24(12):1867-1876. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20467286.

4. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26192873.

5. Bishop JD, DeShields S, Cunningham T, Troy SB. CD4 count recovery after initiation of antiretroviral therapy in patients infected with human immunodeficiency virus. *The American Journal of the Medical Sciences*. 2016;352(3):239-244. Available at: https://www.sciencedirect.com/science/article/pii/S0002962916300246.

6. Collazos J, Valle-Garay E, Carton JA, et al. Factors associated with long-term CD4 cell recovery in HIV-infected patients on successful antiretroviral therapy. *HIV Medicine*. 2016;17(7):532-541. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/hiv.12354.

7. Lundgren JD, Babiker AG, Sharma S, et al. Long-term benefits from early antiretroviral therapy initiation in HIV infection. *NEJM Evid*. 2023;2(3). Available at: https://pubmed.ncbi.nlm.nih.gov/37213438.

8. Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin Infect Dis*. 2007;44(3):441-446. Available at: https://pubmed.ncbi.nlm.nih.gov/17205456https://pubmed.ncbi.nlm.nih.gov/17205456/.

9. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230. Available at: https://pubmed.ncbi.nlm.nih.gov/23323898.

10. Sharma S, Schlusser KE, de la Torre P, et al. The benefit of immediate compared with deferred antiretroviral therapy on CD4+ cell count recovery in early HIV infection. *AIDS*. 2019;33(8):1335-1344. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6561661.

11. Yang X, Su B, Zhang X, Liu Y, Wu H, Zhang T. Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: challenges of immunological non-responders. *J Leukoc Biol*. 2020;107(4):597-612. Available at: https://pubmed.ncbi.nlm.nih.gov/31965635.

12. Guedes MCS, Lopes-Araujo HF, Dos Santos KF, Simões E, Carvalho-Silva WHV, Guimarães RL. How to properly define immunological nonresponse to antiretroviral therapy in people living with HIV? an integrative review. *Front Immunol*. 2025;16:1535565. Available at: https://pubmed.ncbi.nlm.nih.gov/40260259.

13. Young J, Psichogiou M, Meyer L, et al. CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med*. 2012;9(3):e1001194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22448150.

14. Lisco A, Wong CS, Lage SL, et al. Identification of rare HIV-1-infected patients with extreme CD4+ T cell decline despite ART-mediated viral suppression. *JCI Insight*. 2019;4(8). Available at: https://pubmed.ncbi.nlm.nih.gov/30996137.

15. Engsig FN, Zangerle R, Katsarou O, et al. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. *Clin Infect Dis*. 2014;58(9):1312-1321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24457342.

16. Martin-Iguacel R, Reyes-Urueña J, Bruguera A, et al. Determinants of long-term survival in late HIV presenters: the prospective PISCIS cohort study. *EClinicalMedicine*. 2022;52:101600. Available at: https://pubmed.ncbi.nlm.nih.gov/35958520.

17. Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 >=500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. *Int J Epidemiol*. 2012;41(2):433-445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22493325.

18. Baker JV, Peng G, Rapkin J, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS*. 2008;22(7):841-848. Available at: https://pubmed.ncbi.nlm.nih.gov/18427202https://pubmed.ncbi.nlm.nih.gov/18427202/.

19. Achhra AC, Amin J, Law MG, et al. Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients. *AIDS*. 2010;24(12):1877-1886. Available at: https://pubmed.ncbi.nlm.nih.gov/20588170https://pubmed.ncbi.nlm.nih.gov/20588170/.

20. Smurzynski M, Wu K, Benson CA, Bosch RJ, Collier AC, Koletar SL. Relationship between CD4+ T-cell counts/HIV-1 RNA plasma viral load and AIDS-defining events among persons followed in the ACTG longitudinal linked randomized trials study. *J Acquir Immune Defic Syndr*. 2010;55(1):117-127. Available at: https://pubmed.ncbi.nlm.nih.gov/20622677 https://pubmed.ncbi.nlm.nih.gov/20622677/.

21. Aksak-Wąs BJ, Kowalska JD, Ząbek P, et al. Immune restoration affects 10-year survival in people living with HIV/AIDS. *HIV Med*. 2023;24(3):325-334. Available at: https://pubmed.ncbi.nlm.nih.gov/36054430.

22. Liu J, Wang L, Hou Y, et al. Immune restoration in HIV-1-infected patients after 12 years of antiretroviral therapy: a real-world observational study. *Emerg Microbes Infect*. 2020;9(1):2550-2561. Available at: https://pubmed.ncbi.nlm.nih.gov/33131455.

23. Castillo-Rozas G, Tu S, Luz PM, et al. Clinical outcomes and risk factors for immune recovery and all-cause mortality in Latin Americans living with HIV with virological success: a retrospective cohort study. *J Int AIDS Soc*. 2024;27(3):e26214. Available at: https://pubmed.ncbi.nlm.nih.gov/38494667.

24. Khaimova R, Fischetti B, Cope R, Berkowitz L, Bakshi A. Serological response with Heplisav-B® in prior hepatitis B vaccine non-responders living with HIV. *Vaccine*. 2021;39(44):6529-6534. Available at: https://pubmed.ncbi.nlm.nih.gov/34600748.

25. Nicolau IA, Moineddin R, Brooks JD, et al. Associations of CD4 cell count measures with infection-related and infection-unrelated cancer risk among people with HIV. *J Acquir Immune Defic Syndr*. 2024;96(5):447-456. Available at: https://pubmed.ncbi.nlm.nih.gov/38985442.

26. Han WM, Ryom L, Sabin CA, et al. Risk of cancer in people with HIV experiencing varying degrees of immune recovery with sustained virological suppression on antiretroviral treatment for more than 2 years: an international, multicentre, observational cohort. *Clin Infect Dis*. 2025. Available at: https://pubmed.ncbi.nlm.nih.gov/40368374.

27. Calkins KL, Chander G, Joshu CE, et al. Immune status and associated mortality after cancer treatment among individuals with HIV in the antiretroviral therapy era. *JAMA Oncology*. 2020;6(2):227-235. Available at: https://jamanetwork.com/journals/jamaoncology/fullarticle/2757078.

28. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641. Available at: https://pubmed.ncbi.nlm.nih.gov/16908797 https://pubmed.ncbi.nlm.nih.gov/16908797/.

29. Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS*. 2008;22(16):2143-2153. Available at: https://pubmed.ncbi.nlm.nih.gov/18832878 https://pubmed.ncbi.nlm.nih.gov/18832878/

30. Liu Z, Zhang J, Yang X, et al. The dynamic risk factors of cardiovascular disease among people living with HIV: a real-world data study. *BMC Public Health*. 2024;24(1):1162. Available at: https://pubmed.ncbi.nlm.nih.gov/38664682.

31. Noiman A, Esber A, Wang X, et al. Clinical factors and outcomes associated with immune non-response among virally suppressed adults with HIV from Africa and the United States. *Sci Rep*. 2022;12(1):1196. Available at: https://pubmed.ncbi.nlm.nih.gov/35075147.

32. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012;26(4):465-474. Available at: https://pubmed.ncbi.nlm.nih.gov/22112603.

33. Lin W, Zhong H, Wen C, et al. Persistently low CD4 cell counts are associated with hepatic events in HCV/HIV coinfected patients: data from the National Free Antiretroviral Treatment Program of China. *Chin Med J (Engl)*. 2022;135(22):2699-2705. Available at: https://pubmed.ncbi.nlm.nih.gov/36574222.

34. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. 2010;51(4):435-447. Available at: https://pubmed.ncbi.nlm.nih.gov/20597691https://pubmed.ncbi.nlm.nih.gov/20597691/.

35. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2011;57(3):205-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21522014.

36. Lederman MM, Calabrese L, Funderburg NT, et al. Immunologic failure despite suppressive antiretroviral therapy is related to activation and turnover of memory CD4 cells. *J Infect Dis*. 2011;204(8):1217-1226. Available at: https://pubmed.ncbi.nlm.nih.gov/21917895.

37. Negredo E, Massanella M, Puig J, et al. Nadir CD4 T cell count as predictor and high CD4 T cell intrinsic apoptosis as final mechanism of poor CD4 T cell recovery in virologically suppressed HIV-infected patients: clinical implications. *Clin Infect Dis*. 2010;50(9):1300-1308. Available at: https://pubmed.ncbi.nlm.nih.gov/20367229.

38. Gazzola L, Tincati C, Bellistrì GM, Monforte Ad, Marchetti G. The absence of CD4+ T cell count recovery despite receipt of virologically suppressive highly active antiretroviral therapy: clinical risk, immunological gaps, and therapeutic options. *Clin Infect Dis*. 2009;48(3):328-337. Available at: https://pubmed.ncbi.nlm.nih.gov/19123868.

39. Potter M, Odueyungbo A, Yang H, Saeed S, Klein MB. Impact of hepatitis C viral replication on CD4+ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy. *AIDS*. 2010;24(12):1857-1865. Available at: https://pubmed.ncbi.nlm.nih.gov/20479633.

40. Boatman JA, Baker JV, Emery S, et al. Risk factors for low CD4+ count recovery despite viral suppression among participants initiating antiretroviral treatment with CD4+ counts > 500 cells/mm^3: findings from the Strategic Timing of AntiRetroviral Therapy (START) trial. *J Acquir Immune Defic Syndr*. 2019;81(1):10-17. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6456414.

41. Karimi-Sari H, Piggott DA, Scully EP, et al. Changes in inflammatory cytokines after chronic hepatitis C treatment among people living with HIV. *Open Forum Infect Dis*. 2024;11(1):ofad623. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC10773550.

42. Hunt PW, Martin JN, Sinclair E, et al. Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy. *J Infect Dis*. 2011;203(10):1474-1483. Available at: https://pubmed.ncbi.nlm.nih.gov/21502083.

43. Gómez-Mora E, García E, Urrea V, et al. Preserved immune functionality and high CMV-specific T-cell responses in HIV-infected individuals with poor CD4(+) T-cell immune recovery. *Sci Rep*. 2017;7(1):11711. Available at: https://pubmed.ncbi.nlm.nih.gov/28916780.

44. Muñoz-Muela E, Trujillo-Rodríguez M, Serna-Gallego A, et al. Anti-CD4 autoantibodies in immunological nonresponder people with HIV: cause of CD4+ T-cell depletion? *AIDS*. 2022;36(9):1207-1214. Available at: https://journals.lww.com/aidsonline/fulltext/2022/07150/anti_cd4_autoantibodies_in_immunological.1.aspx.

45. Epling BP, Lisco A, Manion M, et al. Impact of anti-CD4 autoantibodies on immune reconstitution in people with advanced human immunodeficiency virus. *Clinical Infectious Diseases*. 2024. Available at: https://doi.org/10.1093/cid/ciae562.

46. Vos W, Navas A, Meeder EMG, et al. HIV immunological non-responders are characterized by extensive immunosenescence and impaired lymphocyte cytokine production capacity. *Front Immunol*. 2024;15:1350065. Available at: https://pubmed.ncbi.nlm.nih.gov/38779686.

47. Schacker TW, Bosch RJ, Bennett K, et al. Measurement of naive CD4 cells reliably predicts potential for immune reconstitution in HIV. *J Acquir Immune Defic Syndr*. 2010;54(1):59-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20182359.

48. Zeng M, Southern PJ, Reilly CS, et al. Lymphoid tissue damage in HIV-1 infection depletes naive T cells and limits T cell reconstitution after antiretroviral therapy. *PLoS Pathog*. 2012;8(1):e1002437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22241988.

49. Utay NS, Hunt PW. Role of immune activation in progression to AIDS. *Curr Opin HIV AIDS*. 2016;11(2):131-137. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4750472.

50. Gandhi RT, Zheng L, Bosch RJ, et al. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. *PLoS Med*. 2010;7(8). Available at: https://pubmed.ncbi.nlm.nih.gov/20711481.

51. Hatano H, Strain MC, Scherzer R, et al. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. *J Infect Dis*. 2013;208(9):1436-1442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23975885.

52. Hunt PW, Shulman NS, Hayes TL, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. *Blood*. 2013;121(23):4635-4646. Available at: https://pubmed.ncbi.nlm.nih.gov/23589670.

53. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. *Proc Natl Acad Sci USA*. 2009;106(23):9403-9408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19470482.

54. Cuzin L, Trabelsi S, Delobel P, et al. Maraviroc intensification of stable antiviral therapy in HIV-1-infected patients with poor immune restoration: MARIMUNO-ANRS 145 study. *J Acquir Immune Defic Syndr*. 2012;61(5):557-564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22986949.

55. Buzón MJ, Massanella M, Llibre J M, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med*. 2010;16(4):460-465. Available at: https://pubmed.ncbi.nlm.nih.gov/20228817.

56. Rusconi S, Vitiello P, Adorni F, et al. Maraviroc as intensification strategy in HIV-1 positive patients with deficient immunological response: an Italian randomized clinical trial. *PLoS One*. 2013;8(11):e80157. Available at: https://pubmed.ncbi.nlm.nih.gov/24244635.

57. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS*. 2010;24(11):1697-1707. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20467288.

58. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(7):e357-e365. Available at: https://pubmed.ncbi.nlm.nih.gov/29925489.

59. Chadwick D, Pido-Lopez J, Pires A, et al. A pilot study of the safety and efficacy of thymosin alpha 1 in augmenting immune reconstitution in HIV-infected patients with low CD4 counts taking highly active antiretroviral therapy. *Clin Exp Immunol*. 2003;134(3):477-481. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC1808897.

60. Abrams D, Levy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361(16):1548-1559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19828532.

61. Thiébaut R, Jarne A, Routy JP, et al. Repeated cycles of recombinant human interleukin 7 in HIV-infected patients with low CD4 T-cell reconstitution on antiretroviral therapy: results of 2 phase II multicenter studies. *Clin Infect Dis*. 2016;62(9):1178-1185. Available at: https://pubmed.ncbi.nlm.nih.gov/26908786.

62. Fan L, Hu Y, Li R, et al. Enhanced immune reconstitution with albuvirtide in HIV-infected immunological non-responders. *Front Cell Infect Microbiol*. 2024;14:1397743. Available at: https://pubmed.ncbi.nlm.nih.gov/38975330.

63. Valdés-Ferrer SI, Crispín JC, Belaunzarán-Zamudio PF, et al. Add-on pyridostigmine enhances CD4(+) T-cell recovery in HIV-1-infected immunological non-responders: a proof-of-concept study. *Front Immunol*. 2017;8:1301 Available at: https://pubmed.ncbi.nlm.nih.gov/29093707.

64. Bäckdahl T, Hedberg P, Vesterbacka J, Carlander C, Sönnerborg A, Nowak P. Metformin treatment and immune reconstitution in people with HIV and type 2 diabetes: a matched retrospective study. *Open Forum Infect Dis*. 2025;12(4):ofaf110. Available at: https://pubmed.ncbi.nlm.nih.gov/40160340

65. Rousseau RK, Walmsley SL, Lee T, et al. Randomized, blinded, placebo-controlled trial of De Simone Formulation Probiotic during HIV-associated suboptimal CD4+ T cell recovery. *J Acquir Immune Defic Syndr*. 2022;89(2):199-207. Available at: https://pubmed.ncbi.nlm.nih.gov/34693932.

66. Mortezazadeh M, Kalantari S, Abolghasemi N, et al. The effect of oral probiotics on CD4 count in patients with HIV infection undergoing treatment with ART who have had an immunological failure. *Immun Inflamm Dis*. 2023;11(6):e913. Available at: https://pubmed.ncbi.nlm.nih.gov/37382253.

67. Twinomujuni SS, Atukunda EC, Mukonzo JK, Nicholas M, Roelofsen F, Ogwang PE. Evaluation of the effects of Artemisia annua l. and Moringa oleifera lam. on CD4 count and viral load among PLWH on ART at Mbarara Regional Referral Hospital: a double-blind randomized controlled clinical trial. *AIDS Res Ther*. 2024;21(1):22. Available at: https://pubmed.ncbi.nlm.nih.gov/38627722.

68. Cao W, Liu X, Han Y, et al. (5R)-5-hydroxytriptolide for HIV immunological non-responders receiving ART: a randomized, double-blinded, placebo-controlled phase II study. *Lancet Reg Health West Pac*. 2023;34:100724. Available at: https://pubmed.ncbi.nlm.nih.gov/37283977.

69. Li T, Xie J, Li Y, et al. Tripterygium wilfordii hook F extract in cART-treated HIV patients with poor immune response: a pilot study to assess its immunomodulatory effects and safety. *HIV Clin Trials*. 2015;16(2):49-56. Available at: https://pubmed.ncbi.nlm.nih.gov/25874991.

70. Geng ST, Zhang JB, Wang YX, et al. Pre-digested protein enteral nutritional supplementation enhances recovery of CD4(+) T cells and repair of intestinal barrier in HIV-infected immunological non-responders. *Front Immunol*. 2021;12:757935. Available at: https://pubmed.ncbi.nlm.nih.gov/35003070.

71. Wang L, Zhang Z, Xu R, et al. Human umbilical cord mesenchymal stem cell transfusion in immune non-responders with AIDS: a multicenter randomized controlled trial. *Signal Transduct Target Ther*. 2021;6(1):217. Available at: https://pubmed.ncbi.nlm.nih.gov/34103473.

72. Zhang Z, Fu J, Xu X, et al. Safety and immunological responses to human mesenchymal stem cell therapy in difficult-to-treat HIV-1-infected patients. *AIDS*. 2013;27(8):1283-1293. Available at: https://pubmed.ncbi.nlm.nih.gov/23925377.

73. Xia H, Wang Y, Sun HL, et al. Safety and efficacy of allogeneic natural killer cell immunotherapy on human immunodeficiency virus type 1 immunological non-responders: a brief report. *Chin Med J (Engl)*. 2020;133(23):2803-2807. Available at: https://pubmed.ncbi.nlm.nih.gov/33273328.

74. Horberg M, Thompson M, Agwu A, et al. Primary care guidance for providers who care for persons with human immunodeficiency virus: 2024 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2024. Available at: https://doi.org/10.1093/cid/ciae479.