REVIEW

Incomplete immune reconstitution in HIV/AIDS patients on antiretroviral therapy: Challenges of immunological non-responders

Xiaodong Yang[1,2] | **Bin Su**[1,2] | **Xin Zhang**[1,2] | **Yan Liu**[1,2] | **Hao Wu**[1,2] |
Tong Zhang[1,2]

[1]Center for Infectious Diseases, Beijing Youan Hospital, Capital Medical University, Beijing, China

[2]Beijing Key Laboratory for HIV/AIDS Research, Beijing, China

Correspondence
Dr. Tong Zhang. Center for Infectious Diseases, Beijing Youan Hospital, Capital Medical University, Beijing 100069, China.
Email: zt_doc@ccmu.edu.cn

Abstract

The morbidity and mortality of HIV type-1 (HIV-1)-related diseases were dramatically diminished by the grounds of the introduction of potent antiretroviral therapy, which induces persistent suppression of HIV-1 replication and gradual recovery of CD4$^+$ T-cell counts. However, ~10–40% of HIV-1-infected individuals fail to achieve normalization of CD4$^+$ T-cell counts despite persistent virological suppression. These patients are referred to as "inadequate immunological responders," "immunodiscordant responders," or "immunological non-responders (INRs)" who show severe immunological dysfunction. Indeed, INRs are at an increased risk of clinical progression to AIDS and non-AIDS events and present higher rates of mortality than HIV-1-infected individuals with adequate immune reconstitution. To date, the underlying mechanism of incomplete immune reconstitution in HIV-1-infected patients has not been fully elucidated. In light of this limitation, it is of substantial practical significance to deeply understand the mechanism of immune reconstitution and design effective individualized treatment strategies. Therefore, in this review, we aim to highlight the mechanism and risk factors of incomplete immune reconstitution and strategies to intervene.

KEYWORDS

antiretroviral therapy, CD4$^+$ T cells, HIV-1 infection, immunological non-responders, immune reconstitution

1 | INTRODUCTION

The hallmark of HIV infection is the persistent destruction of CD4$^+$ T cells, resulting in progressive immunodeficiency, opportunistic diseases, and death.[1] It has been 32 years since the first antiretroviral drug, zidovudine (ZDV, formerly called AZT), was introduced to treat HIV infection. The increasing accessibility and use of antiretroviral therapy (ART) can suppress the HIV viral load to undetectable levels and to increase the CD4$^+$ T-cell counts; therefore, the acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality in HIV-1-infected individuals is sharply diminished.[2–4] However, in some patients, optimal treatment and persistent suppression of viral

TABLE 1 Definitions of immunological nonresponder and immunological responder from the literature

Definition of "immunological nonresponder"	Definition of "immunological responder"	Reference
Total CD4+ T-cell count < 500 cells/µl at 2–12 years after ART initiation, with an undetectable plasma VL.[a]	Total CD4+ T-cell count > 500 cells/µl at 2–12 years after ART initiation, with an undetectable plasma VL.	16,179,230–233
Increase in the CD4+ T-cell count < 200 cells/µl from baseline at 7 years after ART initiation, with plasma HIV RNA < 200 copies/ml.	Increase in the CD4+ T-cell count > 500 cells/µl from baseline at 7 years after ART initiation, with plasma HIV RNA < 200 copies/ml.	54
Increase in the CD4+ T-cell count < 20% from baseline and/or CD4+ T-cell counts < 200 cells/µl at 1–3 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	Increase in the CD4+ T-cell count > 20% from baseline and/or CD4+ T-cell counts > 200 cells/µl at 1–3 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	35,234,235
Increase in the CD4+ T-cell count < 100 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 50 copies/ml.	Increase in the CD4+ T-cell count > 100 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 50 copies/ml.	236
Increase in the CD4+ T-cell count < 50 cells/µl from baseline at 3–9 months after ART initiation, with an undetectable plasma VL.	Increase in the CD4+ T-cell count > 50 cells/µl from baseline at 3–9 months after ART initiation, with an undetectable plasma VL.	9,237
Total CD4+ T-cell count < 200 cells/µl at 2 years after ART initiation, with an undetectable plasma VL.	Total CD4+ T-cell count > 500 cells/µL at 2 years after ART initiation, with an undetectable plasma VL.	238,239
Increase in the CD4+ T-cell count < 200 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 50 copies/ml.	Increase in the CD4+ T-cell count > 200 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 50 copies/ml.	240
Total CD4+ T-cell count < 350 cells/µl at 2 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	Total CD4+ T-cell count > 400 cells/µl at 2 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	48,105,106,241
Total CD4+ T-cell count < 350 cells/µl and/or increase in the CD4+ T-cell count < 30% from baseline at 1–10 years after ART initiation, with an undetectable plasma VL.	Total CD4+ T-cell count > 350 cells/µl and/or increase in the CD4+ T-cell count > 30% from baseline at 1–10 years after ART initiation, with an undetectable plasma VL.	144,177,242,243
Total CD4+ T-cell count < 500 cells/µl and CD4/CD8 ratio < 1 at 8 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	Total CD4+ T-cell count > 900 cells/µl and CD4/CD8 ratio < 1 at 8 years after ART initiation, with plasma HIV RNA < 50 copies/ml.	37
Increase in the CD4+ T-cell count < 400 cells/µl from baseline at 5 years after ART initiation, with an undetectable plasma VL.	Increase in the CD4+ T-cell count > 400 cells/µl from baseline at 5 years after ART initiation, with an undetectable plasma VL.	117
Total CD4+ T-cell count < 350 cells/µl at 2 years after ART initiation, with an undetectable plasma VL	Total CD4+ T-cell count > 500 cells/µl at 2 years after ART initiation, with an undetectable plasma VL.	66,116,175,244
Total CD4+ T-cell count < 400 cells/µl at 2 years after ART initiation, with plasma HIV RNA < 20 copies/ml.	Total CD4+ T-cell count > 600 cells/µl at 2 years after ART initiation, with plasma HIV RNA < 20 copies/ml.	110,111
Total CD4+ T-cell count < 250 cells/µl at 2–3 years after ART initiation, with an undetectable plasma VL.	Total CD4+ T-cell count > 250 cells/µl at 2–3 years after ART initiation, with an undetectable plasma VL.	23,170,180,245
Increase in the CD4+ T-cell count < 50 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 40 copies/ml.	Increase in the CD4+ T-cell count > 100 cells/µl from baseline at 1 year after ART initiation, with plasma HIV RNA < 40 copies/ml.	47
Total CD4+ T-cell count < 270 cells/µl at 2 years after ART initiation, with an undetectable plasma VL.	Total CD4+ T-cell count > 270 cells/µl at 2 years after ART initiation, with an undetectable plasma VL.	176

[a]Viral load.

replication fail to restore their CD4+ T-cell counts. These patients are referred to as inadequate immunological responders, immunodiscordant responders, or immunological non-responders (INRs), and an impaired immunological response is linked to an increased risk of disease progression and death for these patients.[5–7] INRs present severe immune dysfunction, and the morbidity and mortality of AIDS and non-AIDS events (such as metabolic syndrome, liver disease, nephropathy, cardiovascular disease, non-AIDS-related malignancies, and HIV-1-related neurocognitive disorder) were significantly elevated compared with those for HIV-1-infected patients who achieved complete immune reconstitution.[8–13] In this review, we focus on recent advances to identify the various mechanisms of poor immune reconstitution in HIV-1-infected patients and explore effective, newly specific therapeutic strategies to restore immunity and thus prevent AIDS-related events.

2 | DEFINITION OF INCOMPLETE IMMUNE RECONSTITUTION

Currently, there is no worldwide consensus on the definition of INRs (Table 1). Over the years, in different studies, INRs have been defined by either a failure to meet the prescribed CD4+ T-cell count threshold (e.g., > 200 or > 250 or > 350 or > 400 or > 500/µl) or a prescribed percentage of CD4+ T-cell increase over baseline (e.g., < 5% or < 20% or < 30%). In addition, some researchers defined INRs as those with an increase in CD4+ T-cell counts from baseline, e.g., <50, <100, or <400/µl. However, the duration of ART in HIV-1-infected people varies substantially in different studies, ranging from 6 to 144 months (Table 1). The duration of ART can significantly affect the magnitude of immune reconstitution in HIV-1-infected patients, thus hindering the comparison of different findings. According to the heterogeneity

among study populations and discrepancy in definitions, the prevalence of INRs varies from 10% to 40%.[7,14,15] In contrast, an adequate immune response to ART is defined as CD4+ T-cell counts >500 cells/μl, mainly because HIV-1-infected patients with this level of immune restoration have a morbidity and mortality rate approaching or comparable to those of HIV negative individuals.[13,16–18] In addition, the Department of Health and Human Services (DHHS) considered that patients with CD4+ T-cell counts that had not increased to 350–500 cells/μl after 4–7 years of effective ART were defined as INRs.[19] The various terms used to describe this poor immune reconstitution or immune reconstitution failure in the literature are outlined in Table 1. To date, it is commonly believed that the CD4+ T-cell count is the most important predictor of immune recovery, treatment outcome, and disease progression in HIV-1 infection, but recent reports clearly indicate the need for additional markers to supplement the CD4+ T-cell count. Compared with the CD4+ T-cell count and viral load, the CD4/CD8 ratio is potentially of higher predictive and evaluative value for the recovery of immunological function especially in patients who reached a CD4+ T-cell count > 500/μl after initiation of ART.[20–22]

3 | POTENTIAL MECHANISMS OF INCOMPLETE IMMUNE RECONSTITUTION

The underlying mechanisms for this phenomenon are very complicated and may be multifactorial, including decreased hematopoiesis of bone marrow, insufficient thymic output, residual virus replication, aberrant immune activation, perturbations of cytokine secretion, and specific genetic or metabolic characteristics (Fig. 1).[14,23–25] However, none of these independent factors can fully explain the mechanism of incomplete immune reconstitution. At any time, the CD4+ T-cell counts in HIV-1-infected individuals are associated with the production, destruction, and migration between secondary lymphoid organs and peripheral tissues.[6,26] INRs may have both reduced CD4 production and excessive destruction.

3.1 | CD4+ T-cell production

3.1.1 | Bone marrow and hematopoietic progenitor cells

T cells originate from bone marrow CD34+ hematopoietic progenitor cells (HPCs) and hematopoietic stem cells (HSCs), followed by their development and maturation in the thymus.[27] Chelucci et al. found a proportion of CD34+ HPCs lineages can express the CD4 receptor together with the CXCR4 and/or CCR5 coreceptor and may thus be susceptible to HIV-1.[28,29] It has been demonstrated that HIV can infect multiple subsets of bone marrow CD34+ HPCs in vivo and in humanized mice, establishing latent cellular reservoirs.[30–32] Tsukamoto et al. utilized the in vitro OP9-DL1/HIV-1 model, cocultured cord-derived CD34+ HPCs and CXCR4-tropic HIV-1 NL4-3, and showed that CD34+CD7+CXCR4+ cells were rapidly depleted 1 week after HIV-1 infection, accompanied by dramatically diminished

numbers of CD34+CD7+CD4+ cells. These results suggest that the CXCR4-tropic HIV-1 strain may affect the differentiation rate or death rate of CD34+CD7+ lymphoid progenitor cells, resulting in impaired T-cell production capacity.[33] Li et al. found that CD34+CD38− early HPCs were preferentially depleted in HIV-1-infected individuals and humanized mice via plasmacytoid dendritic cell-dependent mechanisms, accompanied with a significant reduction in proliferation capacity, while CD34+CD38+ intermediate HPCs were rarely affected.[34] In addition, Isgro et al. found that the clonogenic capability in vitro and the level of more primitive CD34+ progenitor cells in INRs was reduced in parallel with reduced IL-2 production and increased production of TNF-α. Furthermore, Fas and Fas ligand expression was significantly up-regulated, which could lead to the apoptotic depletion of CD34+ HPCs and decreased production of naïve CD4+ T cells.[35] In addition, Sauce et al. found that the numbers of circulating CD34+ HPCs and mature lymphocyte numbers (i.e., CD8+ T cells, natural killer (NK) cells, or B cells) decreased dramatically with HIV disease progression and the number of circulating CD34+ HPCs was positively correlated with the number of CD4+ T cells, which may be due to the reduction in production of multiple lymphocyte lineages caused by bone marrow dysfunction.[36] Menkova-Garnier et al. reported that the capacity of CD34+ HPCs to differentiate into T cells is more significantly reduced in INRs than in immune responders (IRs) and healthy controls, which may be related to the significant up-regulation of the ATP receptor P2 × 7 on CD34+ HPCs in INRs. Inhibition of the P2 × 7 pathway in vitro restores the potential of CD34+ HPC differentiation into T cells in INR patients, further confirming this view.[37] The binding of ATP with its receptor, P2 × 7, induces the formation of inflammatory bodies, activates the caspase-1 signaling pathway, and promotes the secretion of the proinflammatory cytokines IL-1β and IL-18, thus inducing host cell apoptosis and pyroptosis.[38] Another study by Guo et al. found that circulating CD4+ T-cell counts correlate with the proliferation ability of HPCs and HSCs. In addition, the colony-forming ability of CD34+ HPCs and HSCs from INRs is much lower than that the colony-forming ability of those from IRs.[39] These studies suggest that incomplete immune reconstitution in HIV-1-infected individuals may be associated with impaired bone marrow hematopoietic function and decreased proliferative capacity.

3.1.2 | Thymus and naïve cells

The thymus is crucial for the generation of naïve CD4 and CD8 cells with a broad T-cell receptor repertoire. The most reliable method for evaluating thymic function is to perform a thymic biopsy. However, it is neither practical nor economical in HIV-1-infected individuals; therefore, thymic function is indirectly assessed by T-cell receptor excision circles (TRECs), or recent thymus emigrants (RTEs) or naïve CD4+ T-cell counts. After ART initiation, the thymic output improved significantly in HIV-1-infected adults and children, indicating that early ART initiation is essential for immune reconstitution in HIV-1-infected patients.[40,41] It has been reported that the thymic volume, as evaluated by computed tomographic scans, is a powerful independent predictor of the magnitude of CD4+ T-cell recovery in HIV-1-infected individuals
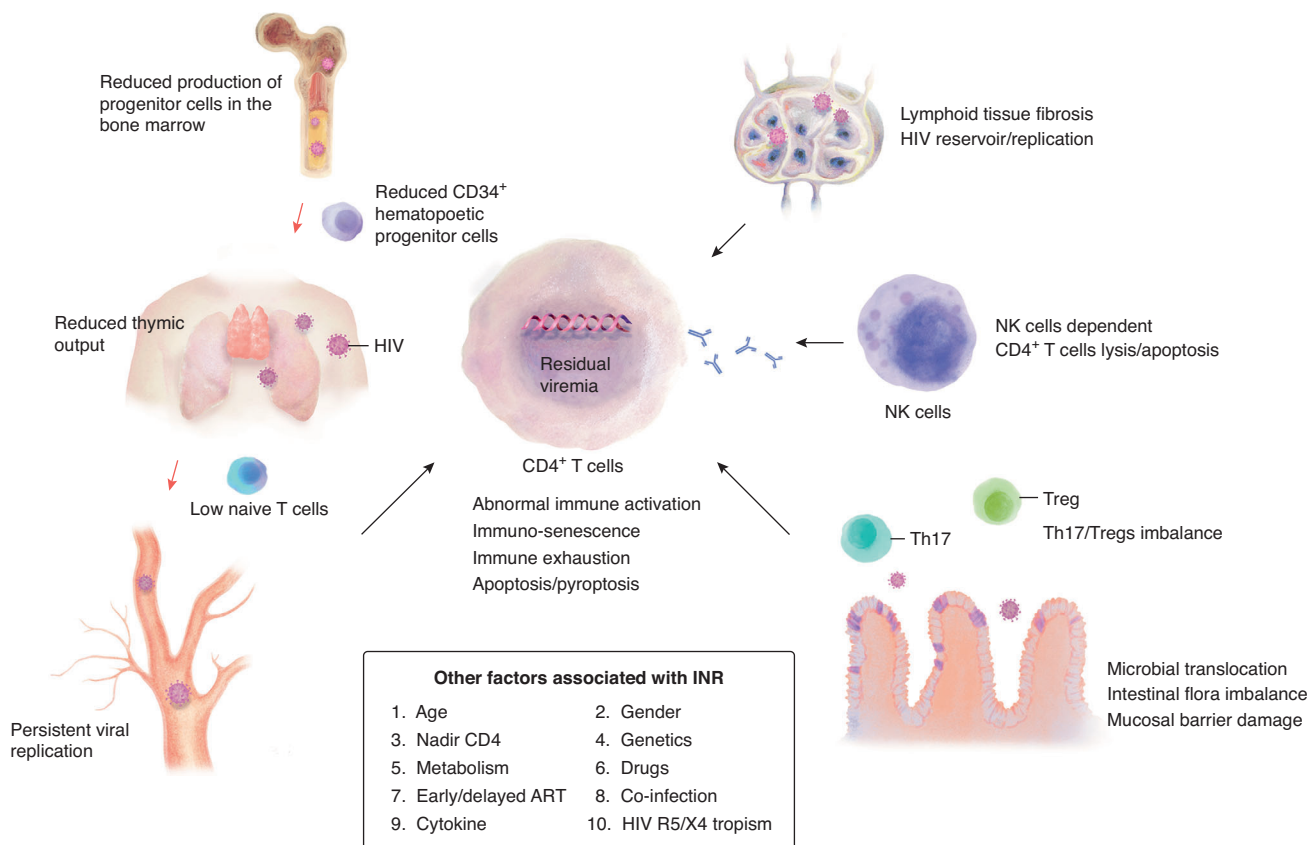
FIGURE 1 **Factors associated with immunological non-responders**. Current understanding of the mechanism of incomplete immune reconstitution. INRs show severe immune dysfunction, including reduced production of progenitor cells in the bone marrow; thymic dysfunction; reduced CD34+ hematopoietic progenitor cells; abnormal immune activation; immune exhaustion; immunoregulatory cell imbalance, such as Treg and Th17 cells; increased immune-senescence and cell apoptosis/pyroptosis, lymphoid tissue fibrosis, and microbial translocation; and persistent viral replication due to the HIV reservoir, and so on. Arrows in red highlight the maturation route of CD4+ T cells, while arrows in black indicate the factors associated with incomplete immune reconstitution. Th: helper T cell; Treg: regulatory T cell; NK: natural killer

receiving ART.[42–44] Simultaneously, other studies demonstrated that the thymic volume is associated with increased CD4+ TRECs content, CD4+ naïve cells and total CD4+ T-cell counts in ART-experienced HIV-1-infected individuals.[45,46] These studies suggest that in the case of lymphopenia, ongoing thymopoies may contribute to immune recovery in adult HIV-1-infected individuals. It has been shown that the frequency of CD4+ RTE cells, the numbers of sj-TRECs and the sj/β-TREC ratios are markedly lower in INRs than in IRs and healthy individuals, indicating that lower thymic output is the main cause of incomplete immune recovery in these patients.[37,47–49] Furthermore, Menkova-Garnier et al. found that the frequency of CD4+ RTEs was positively correlated with the peripheral CD4+ T-cell count.[37] A study by Li et al. showed that INRs had a lower naïve CD4+ T-cell increase and a lower percentage of CD4+ RTE than immunological responders and healthy controls, indicating that reduced thymic output may be a major mechanism of incomplete immune reconstitution.[50] In accordance, it has been reported that thymic function, measured by the sj/β-TREC ratio or CD4+ RTE%, can predict HIV-1 disease progression in HIV-1-infected adults and adolescents with perinatally acquired HIV-1.[51,52] These studies indicate that reduced thymic output may play

an important role in the incomplete immune reconstitution of HIV-1-infected individuals. Conversely, Cobos Jiménez et al. found in HIV-1-infected ART-experienced 45-year-old adults with detectable viremia (<50 copies/ml) for at least 1 year, the percentage of CD31+CD4+ cells and Sj-TREC content in PBMCs are much higher than those in healthy controls. However, there was no correlation between Sj-TREC content and CD4+ T-cell recovery.[53] In addition, a study by Delobel et al. found that the level of intrathymic proliferation, measured by the sj/β-TREC ratio, as well as the frequency of CD31+ RTEs in INRs was comparable to that found in IRs despite their reduced numbers of naïve CD4+ T cells.[54] These studies suggest that reduced thymic output does not help to explain the loss of CD4+ T-cell counts. Our group recently found that INRs had a low number of CD3+CD4−CD8− T cells after long-term ART and that the number of these cells positively correlated with the CD4+ T-cell count. This study demonstrates that low double CD3+CD4−CD8− T-cell counts may play a role in the incomplete restoration of CD4+ T cells.[55] In conclusion, these studies indicate that a functional thymus is of vital importance for the maintenance of T-cell homeostasis and achievement of optimal immune reconstitution.

3.1.3 | Cytokines

Interleukin-7 (IL-7), which is mainly produced by stromal cells in primary and secondary lymphoid organs, such as bone marrow stromal cells, thymic epithelial cells, fibroblastic reticular cells, and lymphatic endothelial cells, and IL-7 receptor (IL-7R), consisting of a common γ-chain (CD132) and an IL-7R-specific α-chain (CD127), are crucial for CD4$^+$ T-cell homeostasis due to promotion of survival, proliferation, and de novo production of T cells.[56,57] It has been reported that in HIV-1-infected individuals, a decreased percentage of CD127$^+$CD4$^+$ T cells and an increased percentage of CD127$^+$CD8$^+$ central memory T cells are associated with incomplete immune reconstitution.[58,59] However, a study by Hartling et al. demonstrated that neither the plasma level of IL-7 nor CD127 expression on CD4$^+$ T cells was associated with an increase in the total CD4$^+$ T-cell count after initiation of ART. In contrast, they found positive associations between baseline CD127 density on CD4$^+$ T cells and an increase in CD4$^+$ RTE cell counts and naïve CD4$^+$ T-cell counts after 2 years of effective ART, indicating that CD127 expression on CD4$^+$ T cells is a predictor of increased thymic output after 2 years of suppressive ART.[60] Furthermore, a few studies have found that in INRs, plasma levels of IL-7 were elevated and CD127 expression both on CD4$^+$ and CD8$^+$ T cells was decreased; however, there was no statistically significant correlation between the baseline plasma IL-7 level and absolute CD4$^+$ T-cell count after successful ART.[61] Furthermore, others have shown a positive association[59,62] or a negative association[63–65] between baseline plasma IL-7 levels and CD4 recovery in HIV-1-infected individuals after ART initiation. CD4$^+$ T cells from INRs exhibited diminished CD127 expression and reduced IL-7-mediated proliferation responsiveness.[66,67] These studies demonstrated that IL-7 responsiveness is impaired in INRs and may be related to downregulation of CD127. In addition, a study by Cote et al. showed that Th17 cells (a subset of CD4$^+$ T cells) from aviremic HIV-1-infected individuals have increased CD127 expression but impaired IL-7-induced proliferation, indicating that this reduction in proliferation is not the result of the lack or dysfunction of the IL-7 receptor.[68] Accordingly, perturbations in the IL-7/IL-7R system may not be a reliable predictor of incomplete immune reconstitution. It has been reported that in HIV-1-infected individuals with incomplete immune reconstitution, elevated plasma levels of IL-6, and increased CD4$^+$ T cell turnover are already present before ART initiation.[69,70] A study by Shive et al. showed that pre-exposure of PBMCs from healthy subjects to IL-1β or IL-6 can drive CD4$^+$ T cell turnover, downregulate CD127 expression, and diminish CD4$^+$ T-cell responsiveness to IL-7.[71] While numerous studies have found that plasma IL-6 levels[69,72,73] and lymphoid tissue IL-1 levels[71] are elevated in HIV-1-infected individuals, these levels did not normalize even after effective ART. In addition, thymic atrophy and fibrosis in lymphoid tissues may hinder IL-7 access, which seems to be related to the continuous expression of type I IFNs and decreased expression of IL-7R induced by IL-1 and IL-6, which is linked to cell death and reduced thymopoiesis.[74] Therefore, IL-1β and IL-6 induce thymic atrophy and fibrosis in lymphoid tissues, increasing CD4$^+$ T-cell turnover, and diminished T-cell responsiveness to IL-7 may partially explain the lack of CD4$^+$ T-cell recovery in aviremic HIV-1-infected individuals.

3.2 | CD4$^+$ T-cell destruction

3.2.1 | Coinhibitory receptors

Coinhibitory or immune checkpoint receptors (ICRs), including programmed cell death 1 (PD-1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and ITIM domain (TIGIT), T cell immunoglobulin and mucin domain-containing molecule-3 (Tim-3), lymphocyte activation gene-3 (Lag-3), and 2B4 (CD244), play a vital role in regulating immune responses against HIV-1 infection. In HIV-1 infection up-regulation of ICRs is associated with T-cell exhaustion, which is characterized by decreased proliferation and production of cytokines.[75,76] Furthermore, ICRs also participate in the establishment and maintenance of viral reservoirs, which is the main obstacle of HIV-1 eradication.[77–80] Numerous studies have shown that expression of ICRs (such as PD-1, Tim-3, CTLA-4, and Lag-3) on CD4 and CD8 T cells is substantially up-regulated in untreated HIV-1-infected individuals and decreased after ART initiation, which is positively correlated with plasma viral load and negatively with CD4$^+$ T-cell count, and blockade of the corresponding pathways resulted in enhanced HIV-specific CD4 and CD8 T-cell proliferation and effector functions.[81–88] These studies indicate that ICR expression on T cells is associated with T-cell exhaustion and disease progression.

Noyan et al. found that the frequencies of PD-1, CTLA-4, and TIGIT expression on CD4$^+$ T cells in HIV-1 elite controllers (ECs), who can spontaneously control HIV-1 replication in the absence of ART and maintain a high CD4$^+$ T-cell count, were comparable with those in healthy individuals and significantly lower than those in untreated viremic subjects and ART-treated aviremic subjects. In addition, all of these ICR coexpressed CD4$^+$ T cells were positively correlated with pVL and negatively correlated with the CD4$^+$ T-cells count and CD4/CD8 ratio, suggesting that the state of CD4$^+$ T-cell exhaustion in ECs is equivalent to that in healthy subjects.[88] It has been reported that INRs had significantly higher levels of PD-1 than IRs on total CD4$^+$ T cells,[87,89–91] and that PD-1 expression on CD4$^+$ T cells was significantly inversely associated with the CD4$^+$ T-cell count.[87,89] A study by Saidakova et al. showed that both CD4$^+$ T-cell cycling (expression of Ki-67) and the exhaustion rate were significantly elevated in HIV-1-infected INRs on suppressive ART compared to those in IRs. In addition, the percentages of CD4$^+$Ki-67$^+$ CM and EM T lymphocytes were inversely related to the CD4$^+$ T-cell counts, and the frequency of CD4$^+$Ki$^-$67$^+$ CM T cells was significantly positively related to the proportion of CD4$^+$PD-1$^+$ cells, suggesting that lymphopenia-induced intensive homeostatic proliferation of CD4$^+$ T cells is associated with CD4$^+$ T-cell exhaustion and poor CD4$^+$ T-cell recovery.[91] In conclusion, these studies indicate that inhibitory receptor-mediated T-cell exhaustion may have an important role in incomplete immune reconstitution in HIV-1-infected individuals.

3.2.2 | Immune activation

Immune activation is manifested by mainly the acquisition of an activated phenotype by innate and adaptive immune cells and the secretion of soluble inflammatory mediators, such as IFN-α, IL-1β, IL-6, IL-8, TNF, TGF-β, sCD14, sCD163, MIP-1α, MIP-1β, RANTES,

and IP-10. During HIV-1 infection, persistent immune activation and inflammation are driven by multiple factors, including residual virus replication, inflammatory lipids, gut microbial translocation, and co-infection.[92–94] Although long-term effective ART substantially reduces the level of immune activation and inflammation in HIV-1-infected individuals, it fails to normalize the activation and inflammation.[95–99] It was reported that persistent T-cell activation was associated with decreased CD4^{+} T-cell gains in HIV-1-infected individuals during ART.[53,100–103] Hunt et al. found that for every 5% increase in the percentage of activated CD4^{+} T cells, the CD4^{+} T-cell counts decreased by 45 cells/μl in the first 3 months of ART. Similarly, for every 5% increase in the percentage of activated CD8^{+} T cells, the CD4^{+} T-cell counts decreased by 35 cells/μl after 3 months of ART.[100] In addition, a study by Cobos Jiménez et al. found that the plasma sCD14 and sCD163 levels and the percentages of activated (coexpressing CD38^{+}HLA-DR^{+}) CD4^{+} and CD8^{+} T cells were higher in ART-treated HIV-1-infected individuals than in healthy controls. The sCD14 and sCD163 levels were positively associated with the percentage of activated CD4^{+} T cells. Furthermore, the percentage of activated CD4^{+} T cells was significantly inversely associated with the CD4^{+} T-cell count and CD4^{+} T-cell recovery after starting ART. This study indicated that T-cell activation driven by monocyte activation and bacterial translocation, as demonstrated by sCD14 and sCD163 levels, is associated with poor immune recovery in HIV-1-infected individuals.[53] In support of this finding, Khoury et al. also found that activated CD4^{+} T cells were significantly inversely correlated with current and nadir CD4^{+} T-cell counts.[79] It was reported that INRs showed increased levels of immune activation, mainly in CD4^{+} T cells; increased levels of proliferation; and increased rates of spontaneous CD4^{+} T-cell death by apoptosis.[48,104–109] These studies indicate that activated-mediated CD4^{+} T-cell hyperproliferation and spontaneous cell death may impede immune recovery in HIV-1-infected individuals. Stiksrud et al. showed that INRs displayed higher activation of both monocytes and DCs than IRs and that this increase was correlated with enhanced CD4^{+} and CD8^{+} T-cell activation. HIV-1-specific monocyte plasma IFN-inducible protein-10 (IP-10, also known as CXCL-10, a marker of monocyte activation) responses were shown to be negatively associated with future CD4 gain.[110] This group also found that INRs had elevated plasma IP-10 levels. Furthermore, the plasma IP-10 levels and IDO-1 enzyme activity, measured as the kynurenine/tryptophan ratio, were inversely associated with the CD4^{+} T-cell count 2 years after inclusion.[111] IDO is predominantly expressed in macrophages and DCs and is the rate-limiting enzyme for the catabolism of tryptophan into kynurenines. Therefore, IDO activity may serve as a marker of inflammation and immune activation.[112] Others have demonstrated that elevated IDO-1 activity is associated with reduced CD4^{+} T-cell recovery in HIV-1-infected individuals on ART.[113,114] A study by Luo et al. showed that the frequency of activated NK cells was significantly increased in IRs and healthy controls and that NK cell activation was inversely correlated with peripheral CD4^{+} T-cell counts in HIV-1-infected individuals on ART. Furthermore, NK cells from INRs had the ability to induce uninfected CD4^{+} T-cell death via cytotoxic effects. These results suggest that activated NK cells may play a role in unsatisfactory CD4^{+} T-cell recovery in HIV-1-infected individuals on long-term ART.[115]

In addition, Bandera et al. found that the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family, pyrin domain containing 3 (NLRP3) inflammasome and caspase-1 were significantly up-regulated in INRs compared to those in IRs and that NLRP3-mediated activation of caspase-1 could induce CD4^{+} T-cell loss via persistent immune activation and pyroptosis, resulting in unsatisfactory CD4^{+} T-cells recovery.[116] It was reported that INRs had a higher frequency of CXCR4-tropic viruses than IRs and that CXCR4-tropic virus can trigger persistent T-cell activation and bystander apoptosis through the interaction of gp120-CXCR4, thus resulting in the depletion of naïve T cells, and may play a role in the impaired immune reconstitution in INRs.[54,117]

3.2.3 | Microbial translocation and intestinal flora imbalance

In the early stage of HIV-1 infection, massive amounts of CD4^{+} T cells in the gut are depleted, especially T helper (Th) 17 cells and Th22 cells, which play an important role in maintaining the integrity of the gut. HIV-1 infection is also associated with gut epithelial barrier damage characterized by villous atrophy, enterocyte apoptosis, crypt hyperplasia, decreased expression of tight junction proteins, and increased gastrointestinal inflammation, which contributes to increased intestinal permeability.[118–120] These abnormalities eventually result in alteration of the intestinal microbiota composition (dysbiosis) and release of bacterial products into the circulation (microbial translocation), leading to chronic immune activation and inflammation.[74,121,122] A study by Jiang et al. found that bacterial ribosomal 16S RNA, a marker of microbial translocation from the gastrointestinal tract, was substantially elevated in HIV-1-infected subjects on effective ART compared with that in healthy controls and was positively associated with the levels of T-cell activation and inversely associated with the levels of CD4^{+} T-cell restoration.[123] In addition, Mehraj et al. reported that plasma levels of the fungal antigen βDG, a component of fungal cell walls that serves as a potent pathogen-associated molecular pattern in triggering antifungal immunity, were significantly elevated in HIV-1-infected individuals and did not normalize despite long-term ART. βDG content correlated positively with activated CD4^{+} and CD8^{+} T cell levels, IDO-1 enzyme activity, and plasma sCD14 and Lipopolysaccharide levels and inversely with CD4^{+} T-cell counts.[124] These studies suggest that microbial product translocation from the gut to the circulation was associated with immune activation and imply CD4^{+} T-cell depletion during suppressive ART treatment. HIV-1 infection is associated with a decrease in intestinal microbial diversity.[118,121] Nowak et al. found that the alpha-diversity of the gut microbiota, measured as the number of observed bacterial species and Shannon index, was significantly lower in HIV-1-infected individuals, both at baseline and after ART initiation, than in healthy controls. The alpha diversity correlated with CD4^{+} T-cell counts and inversely with markers of microbial translocation and monocyte activation. For every increase in the number of bacterial species, the CD4^{+} T-cell count increased by 0.88 cells/μl. This

study suggests a pivotal role of microbiota diversity in host immune homeostasis.[125] Several studies have found that HIV-1-infected individuals have a significant increase in the relative abundance of the Gram-negative bacteria *Prevotella* in conjunction with a decrease in *Bacteroides* abundance compared to those in healthy controls.[126–130] A study by Kaur et al. also found that the abundance of *Prevotella* was significantly higher in perinatal HIV-1-infected children than in uninfected controls despite ART. The relative abundance of *Prevotella* positively correlated with the levels of IP-10 and sCD14, a marker of monocyte activation and microbial translocation, and was inversely associated with the CD4+ T-cell count.[131] In addition, Dillon et al. reported that the relative abundance of *Prevotella* was strongly positively associated with the number of activated mucosal CD4+ and CD8+ T cells and the level of myeloid DC activation.[127,132] These studies suggest that enrichment of *Prevotella* may be detrimental to immune reconstitution by driving immune activation. Lee et al. found that INRs had a higher abundance of *Fusobacterium* than IRs and healthy controls. The relative abundance of *Fusobacterium* abundance was positively correlated with CD4+ T-cell activation but negatively correlated with CD4+ T-cell counts, suggesting that the enrichment of *Fusobacterium* may be associated with poor CD4+ T-cell recovery.[133] In addition, Lu et al. showed that INRs were enriched with *Faecalibacterium prausnitzii*, unclassified *Subdoligranulum* sp., and *Coprococcus comes* compared with those in IRs. Moreover, the relative abundances of unclassified *Subdoligranulum sp.* and *C. comes* were positively correlated with CD8+ T-cell activation and inversely associated with CD4+ T-cell counts.[130] A study by Pérez-Santiago et al. found that gut *Lactobacillales* was associated with an increased CD4 percentage, reduced microbial translocation, and decreased systemic immune activation during HIV infection, which may be related to the fact that *Lactobacillus* can regulate the anti-inflammatory immune response and participate in maintenance of intestinal mucosal barrier integrity, thereby reducing the level of immune activation and the destruction of CD4+ T cells.[134] These observations suggest that altered intestinal microbiota communities may be associated with systemic immune activation and microbial translocation, thus contributing to incomplete immune recovery in HIV-1-infected individuals. A study by Serpa et al. showed that long-term use of proton pump inhibitors was associated with increased microbial translocation, innate immune activation, and poor immune reconstitution in HIV-1-infected individuals on suppressive ART.[135]

3.2.4 | Coinfection

Numerous studies have found that hepatitis B virus (HBV),[136–139] hepatitis C virus (HCV),[140–142] and CMV coinfections[143,144] were associated with poor CD4+ T-cell immune recovery in HIV-1-infected individuals on ART. The precise mechanism by which HBV, HCV, and CMV coinfections may have deleterious effects on CD4+ T-cell count recovery is unclear. The impaired immunological recovery in HBV-, HCV-, or CMV-coinfected patients could be due to the destruction of CD4+ T cells by coinfection-mediated CD4+ T-cell activation, apoptosis, or exhaustion.[145–149] Others studies did not show an

association between HBV,[142,150,151] HCV,[152,153] or CMV[154] coinfection and immunological recovery. Demographic characteristics (such as age, sex, and ethnicity), baseline CD4+ T-cell counts, follow-up time, duration of ART, and coinfection status might have contributed to this discrepancy.

3.2.5 | Secondary lymphatic organs

Lymphatic tissue structure and function is of vital importance in T-cell homeostasis. HIV-1 infection is associated with persistent chronic immune activation and inflammation, which results in progressive collagen deposition in the parafollicular T-cell zone and lymphoid tissues fibrosis, which replaces the fibroblastic reticular cell network (FRCn), a structure that is vital to normal immune function, the FRCn also produce the T-cell homeostatic cytokine IL-7.[155] Several studies demonstrated the evidence of dramatically paracortical T-cell zone damage was associated with the deposition of collagen in lymphoid tissues (LT), and the magnitude of collagen deposition in LT was inversely correlated with both the size of the CD4+ T-cell population in the LT and the increase of peripheral CD4+ T-cell counts in HIV-1-infected individuals on effective ART.[156–158] Consistently, the extent of loss of the FRCn and collagen in the LT predicts the degree of the restoration of both naïve T cells and peripheral total CD4+ T cells after 6 months of ART.[159,160] These studies suggest that collagen deposition and loss of the FRCn in the LT limit the magnitude of the CD4+ T-cell recovery in HIV-1-infected individuals under long-term ART.

3.3 | Other factors associated with immune reconstitution

In addition to the factors mentioned above, older age,[18,161–163] male sex,[164–166] lower nadir CD4 T-cell counts,[18,167,168] lower CD4/CD8 ratios, and a lower naïve/memory CD4+ T-cell ratio[167,169,170] have been associated with a blunted immunological response to ART treatment. Ethnic origin is also associated with immune recovery.[171–174] Furthermore, host genetic factors, metabolic characteristics, and specific ART regimens may play a role in incomplete immune recovery. Luo et al. reported that HIV-1-infected INRs had significantly increased surface-bound IgG on CD4+ T cells compared to that in IRs and healthy controls. The percentage of auto-IgG binding on CD4+ T-cell surfaces was associated with increased CD4+ T-cell apoptosis and inversely correlated with absolute CD4+ T-cell counts. Furthermore, purified anti-CD4 IgG from HIV-1-infected INRs bound to CD4+ T cells and induced cell apoptosis through NK-mediated Ab-dependent cell-mediated cytotoxicity (ADCC) in vitro.[175] This study suggests that autoreactive anti-CD4 IgG may play a vital role in unsatisfactory CD4+ T-cell reconstitution despite effective ART. In addition, Lisco et al. demonstrated that anti-CD4 antibody-mediated ADCC and aberrant inflammasome/caspase-1 activation may be an important cause of extreme CD4+ T-cell count decline in HIV-1-infected individuals with ART-mediated viral suppression.[176] A study by Tincati et al. showed that the level of HIV-1 reservoirs, measured as the frequencies of cells harboring total and integrated HIV-DNA as well as 2 long terminal repeat circles, in both peripheral CD4+ T cells and intestinal tissue

was comparable between HIV-1-infected INRs and IRs. However, HIV reservoirs in both peripheral blood and the gut negatively correlate with CD4+ T-cell reconstitution, suggesting that poor immune recovery on ART may be associated with increased HIV reservoirs.[177] Agrati et al. reported that the frequency of myeloid-derived suppressor cells (MDSCs) was significantly elevated during primary HIV-1 infection and did not normalize after 48 weeks of successful ART. Furthermore, an inverse correlation was also observed between the frequency of MDSCs and the CD4+ T-cell count at 48 weeks after ART initiation, indicating that the persistence of MDSCs may impede CD4+ T-cell recovery.[178] HIV-1-infected INRs had remarkably higher levels of $\alpha 4\beta 7$, a marker of lymphocyte gut-homing, on CD4+ T cells than healthy controls despite effective ART treatment, suggesting that an increase in the trafficking of CD4+ T cells to gut-associated lymphatic tissue may contribute to unsatisfactory CD4+ T-cell recovery.[179,180] A study by Sennepin et al. reported that the expression of NKp44L, the cellular ligand of an activating NK cell receptor, was remarkably up-regulated on CD4+ T cells in HIV-1-infected INRs compared with that on CD4+ T cells in IRs and healthy controls. NKp44L expression was associated with a significant expansion and apoptosis of highly differentiated, multifunctional CD4+ T cells, indicating that a rapid CD4+ T-cell turnover in HIV-1-infected individuals may prevent immune recovery.[181]

3.3.1 | Host genetic factors

Previous studies have shown that host genetic factors can influence CD4+ T-cell recovery during suppressive ART treatment. The CCL3L1-CCR5 genotypes,[182] polymorphisms in CD14 and TLR4,[183] mitochondrial haplogroup H,[184,185] and IL18 G variant allele and genotype[186] were associated with enhanced long-term CD4+ T-cell recovery in HIV-1-infected patients on suppressive ART. The IL-7 receptor subunit alpha (IL7RA) rs6897932 CT/TT genotype was related to a faster and better CD4+ T-cells recovery compared to that of the CC genotype; a potential mechanism is that signal transduction and proliferation in response to IL-7 was is substantially higher in the "TT" genotype compared to that in the "CC" genotype in HIV-infected individuals.[187–189] A study by Greenblatt et al. showed that 41 genes harbored variations that were independently predictive of CD4 recovery. Many of these genes are associated with the cell cycle, apoptosis, lymphocyte migration, or CD4+ T-cell homeostasis.[163] Conversely, the CCR2 rs1799864-AG genotypes,[190] HLA-A68 and HLA-B15 alleles,[191] TLR9 1635AA genotype,[192] polymorphism rs1385129 in the glut1 gene SLC2A1,[193] and polymorphisms in the IFN-γ and IL19 genes[194] are linked to poor CD4+ T-cell recovery in HIV-1-infected individuals.

3.3.2 | Host metabolic factors

Numerous studies have shown that a higher baseline body mass index (BMI) was associated with enhanced immune reconstitution in HIV-1-infected individuals on suppressive ART.[195–198] In support of this finding, others have shown that an increasing BMI was an independent predictor of elevated CD4+ T-cell counts in HIV-1 uninfected individuals.[199–201] These studies indicate that adipose tissue

may affect peripheral CD4+ T-cell recovery. Glucose metabolism plays a vital role in supporting the growth, proliferation, and effector functions of T cells. Glucose transporter-1 (Glut1) is a kind of glucose transporter with high affinity for glucose and is the main glucose transporter in T cells. Glut1 can also serve as a marker of glycolysis activation. The percentage of circulating CD4+Glut1+ T cells was significantly elevated in HIV-1-infected individuals and did not normalize despite long-term effective ART. In addition, the proportion of CD4+Glut1+ T cells correlates positively with the percentage of activated CD4+ T cells and inversely with the absolute CD4+ T-cell count irrespective of HIV treatment status. This group also demonstrated that Glut1 was up-regulated on exhausted and senescent CD4+ T cells. Thus, these observations indicate that hyperactivation of glycolysis in CD4+ T cells during HIV infection facilitates metabolic exhaustion that drives CD4+ T-cell depletion.[193,202] Vitamin D (VitD) is a key regulator of host defense against infections by activating genes and pathways that enhance innate and adaptive immunity.[203] Several studies have demonstrated that baseline VitD deficiency in HIV-1-infected individuals was associated with diminished CD4+ T-cell recovery after ART initiation.[204–207] This effect may be partially explained by the fact that sufficient VitD levels can reduce inflammation and T cell activation, restrain HIV-1 infection in T cells, and promote the proliferation of CD4+ T cells induced by APCs.[207,208] These observations suggest that the baseline metabolic characteristics may be associated with impaired immune reconstitution in HIV-1-infected individuals during ART.

3.3.3 | Antiretroviral drugs and immune reconstitution

Numerous studies have demonstrated that the CD4+ T-cell count recovery was superior under the raltegravir-containing regimen compared with that under the efavirenz-containing regimen when combined with tenofovir/emtricitabine in HIV-1-infected ART-utilizing individuals after long-term ART.[209–212] Others have shown that HIV-1-infected individuals receiving the dolutegravir-abacavir-lamivudine (DTG-ABC-3TC) regimen had a shorter median time to viral suppression, as well as greater increases in CD4+ T-cell count, than those receiving the efavirenz–tenofovir disoproxil fumarate–emtricitabine (EFV-TDF-FTC) regimen.[213,214] Tanuma et al. reported that stavudine (d4T)-based regimens (OR 0.51, vs AZT) and nevirapine (NVP)-based regimens (OR 0.53, vs EFV) were associated with impaired immune recovery.[165] Furthermore, a study by Zhang et al. showed that the risk of suboptimal immunologic recovery among patients with AZT-containing regimens or d4T-containing regimens was 2.1 and 2.4 times higher, respectively, compared with that among patients with TDF-containing regimens.[215] These studies suggest that a specific ART regimen may also affect the level of immune reconstitution in HIV-1-infected individuals.

4 | INTERVENTION MEASURES FOR POOR IMMUNE RECONSTITUTION

Thus far, it is not clear which treatment can maximize the recovery of CD4+ T cells in INRs. Although researchers have made

various attempts to improve the level of immune reconstitution in INRs, these specific interventions have not yet achieved convincing results except for standard ART regimes, mainly because the mechanism of immune reconstitution in INRs has not yet been clarified. As mentioned above, the occurrence of poor immune reconstitution in HIV-1-infected people may involve a variety of mechanisms, and the relative contributions of these mechanisms vary greatly among individuals. Therefore, precise individualized treatment should be selected according to the pathogenesis presented. In HIV-1 infection, persistent immune activation contributes to rapid T-cell turnover, immune exhaustion, and increased cell death. Several studies have evaluated the effect of other strategies, such as intensification with maraviroc or raltegravir, the immunomodulatory agents chloroquine and its analogue hydroxychloroquine, statins, aspirin, and prebiotics and probiotics in combination with a standard ART regimen, in limiting immune activation and immune reconstitution. As it is not possible to eradicate HIV, the current intervention strategies to limit residual immune activation are marginally successful.[216]

VitD deficiency is associated with an increased plasma HIV viral load, decreased peripheral blood CD4^{+} T cells, and rapid AIDS progression.[203] Coelho et al. reported that plasma 25(OH)D levels were significantly positively correlated with CD4^{+} T-cell counts after 24 weeks of VitD supplementation and that each 1.0 ng/ml increase in 25(OH)D during repletion therapy was associated with a 3.3 cell/μl increase in the CD4^{+} T-cell count.[217] Although others have found that VitD supplementation is associated with reduced immune activation and CD4^{+} T-cell exhaustion levels, it has no effect on CD4^{+} T-cell recovery in both untreated and treated HIV-1-infected individuals.[218–220] Therefore, additional investigation is needed to determine whether VitD can promote immune reconstitution.

IL-2 is a cytokine that regulates the proliferation and differentiation of lymphocytes and may help to reconstitute the immune system. A systematic review summarized the role of IL-2 supplementation in HIV-1-infected individuals receiving ART treatment and found that IL-2 in combination with ART increases the CD4^{+} T-cell count in HIV-1-infected individuals compared with that of ART alone. However, combining IL-2 therapy with ART does not confer any significant clinical benefit in terms of mortality and the occurrence of opportunistic infections and may increase grade 3 or 4 adverse effects. Therefore, IL-2 is not recommended as a therapeutic adjunct in the treatment of HIV infection.[221]

IL-7 plays a vital role in thymopoiesis as well as in the peripheral proliferation and survival of mature T cells. Multiple phase I/II clinical trials have evaluated the effect of recombinant human IL-7 supplementation on immune reconstitution in HIV-1-infected individuals receiving ART treatment. The administration of r-hIL-7 resulted in a substantial and sustained increase in the numbers of circulating CD4^{+} and CD8^{+} T cells, as well as enhanced cell proliferation and thymic output.[222–227] IL-7 therapy is also associated with apparent improvement in gut barrier integrity and decreased systemic inflammatory and immune activation. However, a study by Katlama et al. demonstrated that despite IL-7 administration and dual ART intensification inducing a significant expansion of central memory CD4^{+} T-cells, a mild HIV reactivation

and an amplification of the HIV reservoir was also observed.[228] Taken together, these studies revealed that patients may benefit from intermittent therapy with IL-7 in combination with ART, but we should also pay attention to the side effects caused by HIV-1 reactivation.

Mesenchymal stem cells (MSCs) can interact with cells of both the innate and adaptive immune systems and inhibit their activation and release of proinflammatory cytokines. A study by Zhang et al. found that umbilical cord-MSCs transfusions are well tolerated and can substantially reduce the level of systemic immune activation, immune exhaustion, and the inflammatory response as well as efficiently increase circulating naïve and central memory CD4^{+} T-cell counts in HIV-1-infected INRs, suggesting that such interventions may be helpful for immune reconstitution in INRs.[229]

5 | CONCLUSIONS

In conclusion, numerous studies on the mechanism of INRs have focused on mainly isolated portions of the complex processes of CD4^{+} T-cell production, differentiation, survival, and destruction. However, poor immune reconstitution in HIV-1-infected individuals is related to many factors. Thus far, there is no precise mechanism to explain INRs, which may be due to the combination of several factors leading to poor immune reconstitution. Moreover, it should be noted that different patients may have different dominant mechanisms of poor immune reconstitution. These two aspects can affect the best treatment choice for INRs. Therefore, precise individualized treatment should be selected according to the specific pathogenic mechanism presented. In summary, a further understanding and improvement of immune reconstitution in HIV-1-infected patients remains an important field of scientific research.

AUTHORSHIP

All authors made a substantial, direct, and intellectual contribution to the work. X.Y. and B.S. wrote the article, and T.Z. supervised the manuscript. All authors read and approved the final manuscript. X.Y. and B.S. contributed equally to the article.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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