Review Article

Incomplete Immune Recovery in HIV Infection: Mechanisms, Relevance for Clinical Care, and Possible Solutions

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Treatment of HIV-infected patients with highly active antiretroviral therapy (HAART) usually results in diminished viral replication, increasing CD4+ cell counts, a reversal of most immunological disturbances, and a reduction in risk of morbidity and mortality. However, approximately 20% of all HIV-infected patients do not achieve optimal immune reconstitution despite suppression of viral replication. These patients are referred to as immunological nonresponders (INRs). INRs present with severely altered immunological functions, including malfunction and diminished production of cells within lymphopoetic tissue, perturbed frequencies of immune regulators such as regulatory T cells and Th17 cells, and increased immune activation, immunosenescence, and apoptosis. Importantly, INRs have an increased risk of morbidity and mortality compared to HIV-infected patients with an optimal immune reconstitution. Additional treatment to HAART that may improve immune reconstitution has been investigated, but results thus far have proved disappointing. The reason for immunological nonresponse is incompletely understood. This paper summarizes the known and unknown factors regarding the incomplete immune reconstitution in HIV infection, including mechanisms, relevance for clinical care, and possible solutions.

1. Introduction

Treatment of HIV infection with highly active antiretroviral therapy (HAART) usually results in diminished viral replication and increasing CD4+ cell counts. When HAART is initiated, a biphasic response occurs with an initial high increase in CD4+ cells primarily due to reduced apoptosis and redistribution of memory CD4+ cells from lymphoid tissue, followed by a slower on-going increase in part generated from production of naïve CD4+ cells [1, 2]. For how long this increase proceeds is debatable, but cohort studies suggest CD4+ cell recovery for at least 5 years of HAART as long as the CD4+ cell count is <500 cells/μL [3]. However, approximately 20% of all HIV-infected individuals fail to restore their CD4+ cell counts despite optimal treatment and fully suppressed viral replication [2, 4, 5]. These individuals are referred to as immunological nonresponders (INRs).

The definition of INR suffers from lack of consensus impeding the comparison of findings. Most often INRs are defined as having CD4+ cell counts <200 cells/μL while the treatment duration needed for categorizing patients as INR is variable. Furthermore, some study groups define INR by the CD4+ cell increase in percentages, most commonly <20% increase from baseline [6–9]. On the other hand, there seems to be agreement that an adequate immune response to HAART should include a CD4+ cell count >500 cells/μL, mainly because HIV-infected patients with this level of immune restoration have a morbidity and mortality rate approaching or comparable to those of HIV negative individuals [10]. Patients with CD4+ cell counts <500 cells/μL are consequently classified as inadequate responders. Inadequate responders are a heterogeneous population since INR is included within this group of patients. Thus, a large group of inadequate responders, those with intermediate response with CD4+ cell counts between 200 and 500 cells/μL, are poorly described, although they may have a morbidity and mortality rate distinct from INR as well as from those with adequate immune response [11]. In contrast, the increased risk of long-term morbidity and mortality in INR is widely accepted [11–13]. This demonstrates an obvious reason for
delineating the cause of the poor immunological response seen in INR. It also emphasizes the need for additional treatment strategies for HAART. The scope of this paper is to focus on the immunological explanations for immunological nonresponse in patients with full virological responses, clinical relevance, and feasible solutions.

2. Explanations of Immunological Nonresponse

INR has been associated with a number of factors. Thus, it has been shown that older age, a long duration of the HIV infection prior to HAART, coinfection with hepatitis C, and a low CD4 nadir predispose to immunological nonresponse [13–17]. The CD4 nadir specifically appears to be critical for the recovery of CD4+ cells [14, 15]. However, none of these factors provide a full explanation for the lack of immune reconstitution in INR. As a result of this, immunological explanations have been proposed.

The CD4+ cell count in a given patient at any time is the result of production, destruction, and traffic between blood and lymphatic tissue. Thus, if the destruction exceeds the production, the CD4+ cell count decreases. INR may have alterations in the production of CD4+ cells resulting in a reduction of output as well as a destruction of CD4+ cells resulting in an increased turnover. Finally, the distribution of cells between blood and lymphatic tissue may be different in INR.

3. Production of CD4+ Cells

3.1. Thymus and Naive Cells. CD4+ cells are created from already existing CD4+ cells by proliferation, or they are produced in the thymus. The genesis of the T-cell receptor (TCR) takes place in the thymus only, and CD4+ cells generated in the thymus lead to immune reconstitution with a pool of CD4+ cells with full immunologic repertoire [1, 18]. Furthermore, HIV-infected patients with a large thymus have a better immune reconstitution and a broader immunological repertoire than patients with a small thymus [19, 20]. The thymus was thought to be only active in childhood; however it is replaced by fatty tissue with increase in age. It is now evident that the thymus can also be active in adulthood, particularly during circumstances with lymphopenia, as is the case with HIV infection [21, 22]. Thymic tissue has been visualized on computed tomography (CT) scans in HIV-infected adults, and the size of the thymus has been shown to be positively associated with naive CD4+ cell counts and total CD4+ cell counts [19, 23, 24]. However, the performance of CT scans is neither practical nor economically responsible in HIV-infected patients, and often thymic function is assessed indirectly as T-cell receptor excision circles (TRECs), as recent thymic emigrants (RTEs), or simply as the naive CD4+ cell count. TRECs are stable circular DNA fragments that are excised during the formation of TCR in the maturing T cell in the thymus, and TRECs are not replicated during cell division. Thus, the more immature CD4+ cells, the higher the TREC content. A large thymus on CT scans has been associated with a higher CD4+ TREC frequency in HIV-infected patients [19]. During the maturation process, T cells emigrate from the thymus into the periphery now classified as RTE [25], and after further maturation RTEs are classified as naive T cells. Thus, TRECS, RTEs and naive cells are all reasonable indirect measurements of thymic output, although the number of naive cells may be the result of thymic output as well as peripheral proliferation.

Thymic output is dramatically reduced with age, and the naïve cells are increasingly generated from proliferation (reviewed in [26]). RTEs express the surface marker platelet endothelial cell adhesion molecule-1 (PECAM-1) also known as CD31 [27, 28]. Proliferation leads to loss of CD31 and a lower TREC count, and therefore naïve cells in older individuals have decreasing proportions of CD31 and lower TREC counts [27, 28]. HIV leads to a disruption in the number and function of naïve CD4+ cells in blood as well as in lymphoid tissue [5, 29, 30]. After initiation of HAART, thymic output and the total numbers of naïve cells increase to subnormal levels, while the naïve T-cell proliferation decreases [5, 29–31]. Even 7 years of HAART rarely normalizes the naïve CD4+ cell counts to preinfection levels [32]. The naïve compartment in INR seems to be even more perturbed than in HIV-infected patients with a better immune reconstitution. Thus, one study found no residual thymic tissue on CT and PET scans in INR [33]. The same study found low, though detectable, thymopoiesis assessed as circulating RTE. In support of this, other studies have found decreased levels of naïve T cells and T cells expressing CD28 in INR [7, 34], suggesting an altered thymopoiesis in INR. The assumption that peripheral proliferation is a compensatory mechanism to altered thymopoiesis in INR is supported by the finding of increased proportions of the peripheral proliferation marker Ki67 in INR, although the same study found similar levels of RTE in INR versus normal responders [35]. Similar levels of TREC in INR and normal responders have also been reported [36]. It is not known if a small thymus is predictive of INR. However, in a prospective study of 30 HIV-infected individuals, thymic CT scans were obtained to investigate the role of the thymus in cellular restoration after initiation of HAART. Individuals with abundant thymic tissue had higher naïve CD4+ cell counts at weeks 2–24 than individuals with minimal thymic tissue [24]. Likewise, a large thymus has been shown to be associated with better immune reconstitution in other studies [23, 37].

Another way to assess factors influencing the capability to produce CD4+ cells is to examine the response to treatment interruption. Thus, it has been demonstrated that a small thymic volume and a low level of memory CD4+ cells predict a faster loss of CD4+ cells during treatment interruption [38, 39]. This supports thymopoiesis as being essential in immune reconstitution. Interestingly, a newly published prospective study of thymectomized children showed that thymic tissue could be identified on magnetic resonance imaging scans in the majority of these children later on in life [40]. This highlights the great plasticity of the normal immune system, and together with the aforementioned findings it substantiates the evidence for permanent damage on the thymic tissue in INR (Figure 1).
3.2. Bone Marrow and Progenitor Cells. T cells mature in the thymus, but they originate from hematopoietic progenitor cells (HPCs) in the bone marrow (BM). Thus, a functional BM is crucial for thymopoiesis and possibly for immune reconstitution. Recently, HPC has been given much attention in the hopes of realizing a functional cure for HIV infection, more relevant than ever after the newly published report of eradication of HIV by transplantation of CCR5-deficient HPC in the so-called Berlin-patient [41]. HIV influences BM and HPC. First of all, impaired hematopoiesis in HIV infection has been shown in a number of studies [42–44]. Secondly, several studies have shown that a proportion of HPCs express the HIV receptors CD4, CXCR4, and CCR5 making them potentially susceptible to HIV infection (reviewed in [45]). Recently, infection of HPC with HIV was suggested [46], although it has been difficult to determine if these HPCs are actually infected according to the complexities of purifying and maintaining HPC in culture. Also, measurements of infection may be confounded by contamination with other cell types or maturation of HPC to monocytes during in vitro culture. Furthermore, like T cells, natural killer cells and B cells, including naive B cells, seem to be depleted during HIV infection [47]. HIV-associated lymphopenia may therefore be explained by more upstream elements of lymphocyte development than reduced thymic output. In a study of BM from 12 INR compared to normal responders, an altered cytokine production was found, and a reduced growth of in vitro colonies was shown [34], suggesting impaired hematopoiesis as a contributing factor to poor immune reconstitution. However, studying the HPC is limited by the poor access to BM, and since HPCs enter the circulation [48], most studies are conducted on circulating HPC in the peripheral blood. Circulating HPCs have been found to decrease with disease progression and to be associated with CD4+ cell count [49], supporting the idea of BM and HPC as being essential in immunological reconstitution. This is further supported by in vitro studies, which has shown that treatment with the hematopoietic growth factor granulocyte-colony-stimulating factor (G-CSF) causes an increase in the numbers of circulating CD4+ cells [50]. Others have found that peripheral mononuclear blood cells (PBMCs) from HIV-infected patients placed on fetal thymus lobes from mice produced fewer CD4+ and CD8+ cells compared with PBMCs from uninfected controls. Also, fewer functional precursors in the HIV-infected patients were found [51]. This is consistent with a loss in the capacity of HIV-infected patients to produce functional T-cell progenitors in their peripheral blood. Thus, in theory dysfunctional BM and HPC might contribute to immunological nonresponse. However, so far very few studies have validated the number or function of HPC in patients with poor immune reconstitution.

3.3. Cytokines. Interleukin 7 (IL-7) is crucial in the T-cell homeostasis, and the IL-7 responsiveness is determined largely by the presence or absence of the IL-7 receptor (IL-7R) which is present on most mature T cells [52]. Furthermore, IL-7 is a modulator of peripheral T-cell homeostasis involved in maintaining the naïve T-cell pool by promoting their survival and inducing proliferation without switching naïve phenotype [53]. A negative correlation between IL-7 and CD4+ cell count is described. Consequently, HIV-infected patients show high levels of IL-7 and reduced levels of IL-7R compared to healthy controls [54, 55], consistent with the need for increased production of CD4+ cells and a downregulation of the receptor due to high plasma levels. A study found that a reduction of naive CD4+ cells in INR was associated with a reduced expression of IL-7R and in increased serum levels of IL-7 [6]. In addition, a higher stromal production of IL-7 in INR compared to normal responders has been observed [34, 56]. Considering IL-7 as an inducer of CD4+ cell production, these findings are not
surprising in patients with a low CD4+ cell count. However, the interesting conclusion in relation to INR might be that the source of the CD4+ cells is impaired in INR, not the signals.

Like IL-7, interleukin 2 (IL-2) and interleukin 15 (IL-15), which are part of the gamma-chain cytokine family, are central regulators of T-cell proliferation, activation, and differentiation as well (reviewed in [57]). In contrast to IL-7, the production of IL-2 and IL-15 is compromised in HIV-infected patients (reviewed in [58] and [59]). Moreover, the production of IL-2 in blood from INR stimulated with phytohaemagglutinin has been shown to be decreased compared to HIV-infected patients with higher CD4+ cell counts [7]. Thus, in theory improving the regulation of IL-2 and IL-15 in HIV-infected patients might be beneficial as discussed later.

4. Destruction of CD4+ Cells

4.1. Immune Activation. Immune activation (IA) in the natural history of HIV infection covers a broad spectrum of cellular processes. Untreated HIV-infected patients display elevated markers of activation in most cell compartments, especially expression of the surface markers CD38 and HLA-DR on T cells [60–64]. Also, high levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), and interleukin 1b (IL-1b) have been shown in plasma as well as in lymph nodes [65–68]. IA usually reflects a normal and healthy response upon infection with any pathogen, including HIV, as an effort to evade infection. However, it is well established that IA is linked to and predictive of disease progression, and IA has an additive or stronger prognostic value than does CD4+ cell count or viral load alone [60–64, 69–71]. This is highlighted by the fact that a rare subgroup of HIV-infected patients, elite controllers, who do not progress, and sustain normal CD4+ cell counts and undetectable viral loads despite lack of treatment have a lower IA than normal progressors do [72]. Also, the natural hosts of simian immunodeficiency virus (SIV), sooty mangabeys and African green monkeys, do not show any signs of increased IA, T cell turnover, or disease progression [73, 74]. Thus, IA is a key feature in HIV infection and disease progression, elegantly supported by the fact that rats develop pneumocystic pneumonia solely as a consequence of IA [75].

The reason for the strong predictive value of IA in HIV infection is uncertain. In the setting of untreated HIV infection, the level of IA might be determinant for how fast the turnover of T cells is, thereby being related to exhaustion. Indeed, it has been proposed that IA leads to CD4+ cell depletion because it erodes the naïve T-cell pool [76]. However, untreated and treated HIV infection are two different settings. IA declines when HAART is initiated, although like most other immunological parameters, it is not normalized [77–79]. IA is one of the best valued immunological features in INR, and a number of studies have shown elevated IA in INR compared to HIV-infected patients with a better immunological recovery [6, 7, 35, 80]. Assuming INR to have a dysfunctional immune system, the high level of IA could be a consequence of rather than a reason for poor immune reconstitution. Lack of association between the extent of CD4+ cell recovery and activation of CD8+ cells beyond the first year of successful HAART [81] as well as the opposite has been found [78]. Either way, it does not answer the question whether the increased IA is the result of more upstream deficits. Finally, increased IA during primary HIV infection has been proposed to be predictive of CD4+ cell depletion and poor response to HAART [82], suggesting that preinfection host factors may predict poor immune reconstitution.

Another aspect is the findings of an overweight of residual viremia detected by ultrasensitive assays in INR, which seems to be linked to IA [83]. This might reflect release of archived viruses from cellular reservoirs and might be a contributing factor to the higher levels of IA found in INR. Also, one study reports a higher frequency of CXCR4 virus in INR. They suggest X4 virus as players in the depletion of naïve T cells in INR by triggering persistent IA and bystander apoptosis via gp120-CXCR4 interactions [84], suggesting the coreceptor dominance to be involved in the level of immune reconstitution. Moreover, it is acknowledged that CCR5 virus dominates early in infection, while X4 dominance appears later on, and increased thymic destruction has been associated with X4 viruses (reviewed in [85]).

4.2. Apoptosis and Senescence. Although the plasticity and capacity for regeneration of the immune system is prodigious, it may have boundaries. Thus, it becomes increasingly plausible that a cell can undergo a limited number of divisions and in the end will be trapped in growth arrest and immunological senescence, referred to as the Hayflick limit (reviewed in [86]). In the setting of HIV infection, this becomes relevant due to the increased production and turnover of cells. A possible way to determine the replicative history is to measure the length of the telomeres, which shorten by every cell division. The enzyme telomerase can compensate for this shortening, and indeed HIV-infected patients have been found to have shorter telomere length and dysregulated telomerase activity [87–89]. Short telomeres can lead to chromosome instability, involving growth arrest and apoptosis. Thus, not surprisingly HIV-infected patients present with elevated levels of apoptosis [90], and both early and late apoptotic CD4+ cells are more prevalent in patients with CD4+ cell counts <500 cells/μL [90–94]. The relevance of markers of immune exhaustion and senescence in relation to immune reconstitution is confirmed by the findings of the expression of the activation associated T-cell molecule programmed death-1 (PD-1). PD-1 conveys inhibitory signals to T cells (reviewed in [95]), and PD-1 is selectively upregulated by exhausted T cells during chronic viral infection [96]. Elevated levels of PD-1 in INR compared to normal responders have been reported [80, 97]. Also, PD-1 expression has been shown to be negatively correlated to CD4+ cell count, and PD-1 expressing T cells are more prone to programmed cell death ligand-mediated inhibition of T cell proliferation [97].

Finally, chronic infection with cytomegalovirus (CMV) has been associated with immunological senescence, and
a high proportion of T cells specific for CMV and CMV-viremia is associated with a low CD4+ cell count and increased mortality ([98], reviewed in [99]).

4.3. Pro- and Anti-Inflammatory T Cells. During recent years, the understanding of immune responses has changed tremendously by the discovery of T-cell subsets with pro- and anti-inflammatory properties. Th17 cells are T cells with proinflammatory properties, while regulatory T cells (Tregs) are anti-inflammatory. Tregs play a crucial role in sustaining tolerance to self-antigens [100, 101] and suppressing T-cell activation resulting in downregulation of immune activation, including reduction in antitumor immunity, graft rejection, and graft-versus-host disease ([102], reviewed in [103]). Finally, the role of Tregs in chronic viral infections, including HIV, has gained massive interest due to their immunosuppressive capabilities. Tregs themselves are CD4+ cells and susceptible to HIV infection [104]. Therefore, the absolute number of Tregs declines with disease progression, while the frequency of Tregs tends to increase and remains high on HAART [105–108]. Thus, in a prospective study Tregs were measured in 26 HIV-infected patients before and after HAART and compared to healthy controls. The level of Tregs was found to be elevated in patients compared to controls, and this level did not change despite 6 months of HAART [106]. Tregs are believed to be able to downregulate chronic immune activation in HIV infection making Tregs a key element in the understanding of the interaction between the host immune system and HIV (reviewed in [109]). However, Tregs might be beneficial as downregulators of the unbeneficial immune activation or, in contrast, they might have a harmful effect downregulating HIV-specific responses. So far, it is not clear whether Tregs accelerate or delay HIV infection.

IL-17-producing Th17 cells are closely related to Tregs. Th17 cells and Tregs share a reciprocal maturation pathway and function together in opposing ways to control the inflammatory response to infection. While Tregs inhibit autoimmunity, Th17 cells play a role in the induction of autoimmune tissue injury [110]. During acute SIV infection the rapid depletion of Th17 cells and a disturbed balance of Th17 cells and Tregs is associated with subsequent high IA and disease progression [111]. Likewise, in HIV-infection the loss of balance between Th17 cells/Tregs may play a part in inducing microbial translocation and chronic immune activation [112] (reviewed in [113]). The importance of a well-regulated balance between Tregs and Th17 cells is demonstrated by a maintained balance between Tregs and Th17 cells in HIV controllers [114] (reviewed in [115]). Finally, recent data from our own lab show disturbances in the Treg- and Th17 cell compartments as well as in the balance between them in INR, suggesting an impact on immune reconstitution [116].

4.4. Secondary Lymphatic Tissue. CD4+ cell depletion occurs in the blood as well as in the secondary lymphatic tissue (SLT) of lymph nodes (LNs) and gut-associated lymphatic tissue (GALT) where the majority of the CD4+ cells reside. A vast number of cells are lost during primary infection, and by the time the infection has reached a chronic stage; more than 50% of the CD4+ cells in the LN are lost [117, 118]. With a possible damage of primary lymphatic tissue (LT) (i.e., thymic tissue and bone marrow) in mind, it seems reasonable to consider damages to SLT as a consequence of HIV infection as well, suggesting this early massive depletion as a determinant for the level of immune reconstitution following HAART. Thus, it has been proposed that HIV damages the structures in the lymphatic tissue that help sustain the normal CD4+ cell population, replacing the functional space with collagen. It was found that the greater the amount of the collagen-deposition, the lower the CD4+ cell count, and the smaller the number of naive CD4+ cells [119]. Furthermore, the amount of the collagen-deposition in LN has proven to be predictive for the degree of the immune reconstitution [120]. Also, LN biopsies from HIV and SIV-infected individuals show breakdown of the lymph node architecture and evidence of apoptosis [121].

These findings are consistent with HIV as a causative agent in damage to SLT. In light of this, it is worth noticing that SLT serves as viral reservoirs, including a pool of latently infected, resting CD4+ cells, which is believed to be a major impediment to the eradication of HIV [122]. While HAART rapidly reduces viral load in the blood, viral production is still detectable in SLT [123, 124], and it would be interesting to ascertain whether the pool of latently infected cells influences immune reconstitution. So far, it has been shown that the level of immune reconstitution is associated with certain types of cellular reservoirs. Thus, proviral DNA primarily persists in central memory cells in patients with a good immune reconstitution, while patients with a poorer reconstitution mainly host HIV proviral DNA in transitional memory cells [125]. This suggests that the viral reservoir influences immune reconstitution, and therefore it seems of interest to identify treatment strategies in addition to HAART with the ability to suppress the viral production in SLT, possibly leading to limited destruction of LT and a better immune reconstitution.

Another aspect is the fact that infection with HIV leads to redistribution of CD4+ cells between blood and lymphatic tissue. Thus, it has been demonstrated that HIV binds to resting CD4+ cells and upregulates L-selectin causing the cells to home from the blood into LN at enhanced rates [126, 127]. This has lead to the homing theory which offers an explanation for the loss of CD4+ cells due to cells leaving the blood and entering the LT (reviewed in [128]). Thus, it would be interesting to evaluate the amount of CD4+ cells outside the blood in SLT in INR, which may reveal accumulation of CD4+ cells. Indeed accumulation of Tregs has been found in SLT compared to peripheral blood in untreated HIV-infected patients [129].

5. Clinical Implications:
Relevance for Clinical Care

Treatment with HAART reduces the risk for development of AIDS and death. Consequently, a relative increase in morbidity and mortality has been described. Despite efficient treatment with HAART and suppression of viral
compared to CD4+ cell counts above 500 cells/μL comparable to HIV negative individuals [141]. Importantly, deficiency prior to the period of sustained suppression counts at baseline along with the extent of immunological rates of death increase substantially with declining CD4+ cell counts at baseline along with the extent of immunological deficiency prior to the period of sustained suppression of viral replication [11–13, 139]. Thus, INRs have a much higher risk of opportunistic diseases and death. In the UK CHIC study, the number of deaths/100 person years of follow-up was a hundred times higher in the group of patients with CD4+ cell counts below 50 cells/μL compared to CD4+ cell counts above 500 cells/μL [140]. Contrary, HIV-infected patients without risk factors and optimal response to HAART seem to have a mortality comparable to HIV negative individuals [141]. Importantly, rates of death increase substantially with declining CD4+ cell counts at baseline along with the extent of immunological deficiency prior to the period of sustained suppression of viral replication [11–13, 142]. For this reason, patients diagnosed with HIV in an advanced state of the disease (HIV late-presenters) are in higher risk of being INR (reviewed in [143]). Also, the lower the CD4 nadir, the shorter it takes for the CD4+ cell count to drop during treatment interruption [144].

Non-AIDS morbidity comprises of diseases such as cardiovascular disease (CVD), cancer, renal disease, hepatic disease, and osteoporosis. Thus, HIV-infected patients suffer more from clinical as well as subclinical atherosclerotic disease compared to the general population, and atherosclerotic (CVD) is a leading cause of death in HIV-infected patients [145]. HIV infection is associated with immune activation and inflammation. Inflammation in turn may lead to vascular damage and dysfunction increasing the risk of CVD (reviewed in [146]). Furthermore, HAART may increase the risk of myocardial infarction [147]. Either way, a consistent relation between low CD4+ cell counts and increased risk of CVD morbidity and mortality has been shown in a number of studies (reviewed in [148]). Thus, in a cross-sectional study of 1331 HIV-infected women and 600 HIV-infected men, the subclinical carotid artery lesions and common carotid artery intima-media thickness were measured by ultrasound. A low CD4+ cell count was found to be independently associated with an increased prevalence of carotid lesions [149]. The reason for this increased risk in INR is unknown, but the increased inflammation seen in patients with poor immune reconstitution as previously described seems like a more plausible reason than does the CD4+ cell count itself.

Likewise, HIV-infected patients have increased risk of cancer compared to the general population. It is well known that initially low and decreasing CD4+ cell counts during the year prior to cancer diagnosis are predictive of AIDS-defining malignancies (ADMs) such as Kaposi sarcoma and non-Hodgkin lymphoma as shown in the CASCADE study [150]. Also, the COHERE study showed that during HAART higher CD4+ cell counts are protective for the development of non-Hodgkin lymphoma [151]. Furthermore, non-AIDS-defining malignancies (non-ADM) such as anal cancer are more common in immune compromised patients (reviewed in [152]). In the D:A:D study the relationship between deaths due to ADM and non-ADM was determined, and immunodeficiency was evaluated. In a large observational cohort study including 23, 437 patients that were followed prospectively, a low CD4+ cell count was found to be predictive of death from both ADM and non-ADM in HIV-infected patients [153]. Likewise, a low current CD4+ cell count was shown to be associated with an increased incidence of certain non-ADM by the EuroSIDA group [154]. In conclusion, as expected ADMs are closely related to the CD4+ cell count. However, non-ADMs are related to the CD4+ cell count as well, presumably due to a poor immune function, especially since one study found that 48.3% of all non-ADMs were virus related [154]. All together HIV-infected patients have increased risk of developing malignancies, and more so in the group of INR.

Finally, the HIV-associated neurocognitive disorders (HANDs) have become an area of increasing interest as HIV infected patients become older and live longer. In the CHARTER study, a cross-sectional, observational study of 1,555 HIV-infected patients on HAART, the frequency and associated features of HAND were determined. Fifty-two percent of the total sample had neuropsychological impairment with higher rates in groups with greater comorbidity burden. The lowest impairment rate occurred in patients with a CD4 nadir and a current CD4+ cell count above 200 cells/μL [155]. In general, a history of low CD4 nadir seems be one of the strongest predictors of impairment [155, 156]. Future studies should identify whether early disease events (e.g., profound CD4 decline) may trigger chronic CNS changes, and whether early HAART prevents or reverses these changes.

In summary, there remains no doubt that a full immunological recovery is essential in order to reduce morbidity and mortality among HIV-infected patients. However, obtaining this goal requires improving earlier diagnosis and additional treatment to HAART. Several supplementary immune-based therapies to enhance immune reconstitution are under investigation using cytokines, hormones, and growth factors.

6. Therapeutical Possibilities

6.1. Optimizing HAART. Optimizing HAART may be a possibility to increase CD4+ cell counts in HIV-infected INR (systematically reviewed in [157]), and recent data on new drug modalities such as CCR5-antagonists, integrase
inhibitors, and fusion inhibitors increase the relevance of this matter. HIV uses CCR5 as a coreceptor for cell entry, which has led to development of several CCR5-antagonists to impede HIV infection. Currently, only Maraviroc is FDA-approved for treatment of HIV infection. The phase III randomized clinical MOTIVATION study demonstrated that addition of Maraviroc to HAART in pretreated patients resulted in a significant increase in CD4+ cell counts as well as reduced viral load [158]. Furthermore, administration of Maraviroc seems to result in decreased immune activation [159]. Underlining these findings, a meta-analysis of phase II/III clinical trials testing CCR5-antagonist in treatment-experienced HIV patients demonstrated significant increase in CD4+ cell counts by adding CCR5-antagonist [160], clearly suggesting a potential of drugs targeting CCR5 for optimizing immune reconstitution in INR. Raltegravir targets the HIV integrase, which facilitates the integration of the genetic material into the hosts DNA, and is at present the only FDA-approved integrase inhibitor. The potential of raltegravir has proven effective in the large phase III BENCHMRK study [161] showing increased CD4+ cell counts and reduced viral loads. However, two randomized clinical studies testing the effect of raltegravir in INR did not demonstrate an additional effect on immune reconstitution [162, 163]. Several clinical trials testing other integrase inhibitors are ongoing (http://www.clinicaltrials.org/), and a large phase III study comparing intensification of HAART with raltegravir and elvitegravir in treatment-experienced patients demonstrated no significant difference between the two drugs in regard with immune reconstitution [164]. Finally, enfuvirtide is the only FDA-approved fusion inhibitor. It impedes fusion of HIV to the target cell by binding to gp41. Two multicenter phase III studies (TORO 1/2) documented an effect of enfuvirtide in combination with HAART in treatment-experienced patients on both CD4+ cell count and viral load [165, 166]. However, a large randomized multicenter study (ANRS130) demonstrated no additional effect of supplementary enfuvirtide to HAART on CD4+ cell counts in treatment-naive late-presenters with low CD4+ cell count [167]. Thus, at present Maraviroc seems to be the most promising drug for HAART intensification. However, larger prospective studies assessing the effect in INR are needed to estimate the clinical benefits of HAART intensification (Figure 2).

6.2. Interleukin-2 (IL-2). Several strategies to improve immune reconstitution in HIV patients have been considered during the last decade. Most of these strategies aim to increase thymus activity and/or peripheral proliferation. Of all suggested strategies supplementary treatment with recombinant human (rh)IL-2 is the best described. Thus, several studies have shown that combination therapy with rhIL-2 and HAART increases CD4+ cell counts in HIV patients compared to HAART alone (reviewed in [168]). The increased level of CD4+ cells is long-lasting and is caused by peripheral proliferation, although increased thymopoiesis may contribute as well [169]. Despite increased CD4+ cell counts, supplementary treatment with rhIL-2 did not result in clinical benefit for the treated patients, which was demonstrated in two large randomized prospective clinical trials (ESPRIT, 4111 patients, and SILCAAT, 1695 patients). The ESPRIT study revealed an increased risk of grade 4 clinical event in the IL-2-treated group. However, these data did not illustrate the (adverse) effects of supplementary rhIL-2 treatment in INR as median CD4+ cell counts were >400 cells/μL in the ESPRIT study, and <200 cells/μL in the SILCAAT study. In fact, stratified results for patients with a CD4+ cell count <200 cells/μL in the SILCAAT study showed
6.3. IL-7. As described, IL-7 is an essential regulator of the T-cell homeostasis. Administration of rhIL-7 to HIV-infected patients is being tested in several ongoing clinical trials (clinicaltrials.gov, reviewed in [172]). Animal studies [173] and phase I/II studies report that IL-7 is well tolerated, but rhIL-7 administration causes a transient increase of viral replication [174, 175]. However, concomitant HAART counteracts this adverse effect and supplementary rhIL-7 treatment has proven safe [174, 175]. Subcutaneous administration of single dose of rhIL-7 (3–100 μg/kg) [174] as well as intermittent doses (3 or 10 μg/kg) [175] results in significant dose-dependent increase in CD4+ cell counts. This increase includes both central memory cells and naive cells. Importantly, administration of rhIL-7 has been shown to increase levels of RTE, numbers of TREC, as well as lower expression of PD-1 suggestive of reduced immune activation. Thus, administration of rhIL-7 as supplementary treatment shows great promise. However, as lymphopenic HIV-infected patients present with physiological increased concentration of IL-7 [54, 55], exogenous IL-7 administration might be futile. Fortunately, animal studies [173] and phase I/II clinical trials reveal a significant increase in CD4+ cell count in individuals with low CD4+ cell counts and high IL-7 concentrations (reviewed in [172]). This finding may be due to the fact that circulating levels of IL-7 after rhIL-7 administration are much higher than physiological levels. Data from larger randomized clinical trials are warranted to determine the potential effect of adding IL-7 to HAART for immune reconstitution in INR, bearing the result of supplementary administration of IL-2 in mind.

6.4. IL-15. IL-15 is a cytokine that is structurally comparable to IL-2 and regulates proliferation and activation of T cells, and IL-15 has therefore been considered as a potential therapeutic agent in HIV infection. Treatment with IL-15 has primarily been investigated in murine and simian models [180, 181] with conflicting results. Combining IL-15 and HAART has proven to increase CD4+ cell and CD8+ cell counts in SIV-infected rhesus macaques (RMs) [182]. However, another study reported no effect of IL-15 administration on CD4+ cell counts but only on CD8+ cell counts and NK cells [181, 183]. Furthermore, administration of IL-15 in acute SIV infection resulted in increased viral load and increased disease progression [183], and similarly adding IL-15 to HAART in SIV-infected RMs resulted in decreased CD4+ cell counts. In conclusion, adding IL-15 to HAART is expected to result in limited benefit for INR.

6.5. Growth Hormone (GH). Studies with supplementary therapy with GH in patients with HIV infection have originally been conducted to examine whether GH could be used a therapeutic agent for HIV-associated wasting and lipodystrophy (reviewed in [184, 185]). However, treatment with rhGH supplement to HAART has demonstrated to increase CD4+ cell counts compared to HAART alone in randomized, prospective clinical trials [186–190], and further clinical trials are ongoing (http://www.clinicaltrials.gov/). Furthermore, the supplementary rhGH given subcutaneous in doses from 0.7 to 3 mg/day resulted in an increase in thymic size in alignment with an increase in RTE, TREC number, and naive CD4+ cells [186–190], indicating an increased thymopoiesis. The patients included in these studies had median CD4+ cell counts <400 cells/μL [187, 190] and 350 cells/μL [186], respectively, and may therefore include a group of INR. However, adverse effects such as carpal tunnel syndrome, arthralgia, glucose intolerance, or cancer progression were frequent and result in a limited use of rhGH as a therapeutic agent. A potential strategy to reduce adverse effect is by using GH releasing factor (GHRF), which seems to cause fewer adverse effects (reviewed in [191, 192]). However, so far the effects of treatment with GHRF have primarily been addressed to lipodystrophy [192], (http://www.clinicaltrials.gov/), and indeed clinical trials testing the effect of GHRF on immune reconstitution are warranted.

6.6. Keratinocyte Growth Factor (KGF). KGF causes proliferation and differentiation in thymic epithelial cells, and KGF pretreatment in mice and in rhesus macaques after myeloablative irradiation has proven to enhance thymopoiesis and increase thymic output [193–195]. However, a phase I/II randomized placebo-controlled study, originally designed to assess the effect of 40–60 μg/kg KGF per day on graft versus host disease (GVHD) in 100 patients undergoing allogeneic hematopoietic stem cell transplantation, showed no effect of KGF on absolute lymphocyte count [196, 197]. Thus, the addition of KGF to enhance immune reconstitution in INR on HAART is theoretically plausible, and results are awaited from a randomized phase II study testing the effect of palifermin (recombinant human KGF) injection at doses from 20 to 60 μg/kg per day in HIV patients on HAART with CD4 count <250 cells/μL (http://www.clinicaltrials.gov/).

6.7. Immune Suppression. The impact of immune activation is described previously. Several strategies have been suggested...
to reduce immune activation. New biological immunomodulators (inhibitors of TNF-alfa, IL-6, IL-1) for autoimmune diseases may prove to be therapeutic possibilities to suppression of immune activation in HIV infection. However, use of such immunomodulators must be done with great care taking into account the increased risks of opportunistic infections. Currently, there is limited experience, but HIV-infected patients with an autoimmune disease have been treated with TNF-α inhibitors with acceptable results for patients with CD4+ cell counts >200 cells/μL (reviewed in [198, 199]). A small study described reduced immune activation and increased CD4+ cell count in treatment naive patients after intravenous immunoglobulin (IVIG) (0.4 g/kg) [200]. However, this was not confirmed in another small study reporting no effect of high dosage IVIG (30 gram for five days) in treatment-experienced patients [201, 202], but interestingly IVIG administration resulted in a reduction of HIV reservoirs in CD4+ cell counts after treatment which may be a contributor to the failure of immune recovery in INR. Chronic coinfection with other infectious agents is a potential cause of increased immune activation in HIV-infected patients. Decreased immune activation has been documented after therapeutic clearance of HCV infection with interferon-α and ribavirin [203]. Likewise, a randomized clinical trial including 30 HIV-infected patients with CMV coinfection documented a decrease in chronic immune activation after CMV treatment in HIV patients with CD4+ cell counts <350 cells/μL [204]. However, no difference in CD4+ cell count and HIV load was found.

6.8. Microbial Translocation. Microbial translocation has been suggested as a cause of immune activation and CD4+ cell depletion in HIV-infected patients [205–207]. High levels of 16S rDNA during therapy have been shown to be associated with reduced increases in the CD4+ cell counts [208], and heightened circulating lipopolysaccharide be associated with plasma enterobacterial DNA [209]. Thus, microbial translocation may be a potential target to decrease immune activation. Probiotics have been tested in randomized clinical trial in HIV-infected patient with CD4+ cell counts above 200 cells/μL; however the results were disappointing [210]. Furthermore, the effects of hyperimmunem bovine colostrums on CD4+ cell counts in INR were tested in a randomized clinical trials including 75 patients [163]. No change in immune activation or CD4+ cell counts was found. Thus, strategies to improve immune reconstitution in INR by modulation of microbial translocation are yet to emerge.

6.9. Cox-2 Inhibitor. Finally, another approach suggested to reduce immune activation is cyclooxygenase type 2 (Cox-2) inhibitors which have been tested in clinical trials with promising results. Treatment with Cox-2 inhibitors clearly decreases immune activation in HIV-infected patients [211–213], and combination treatment with HAART and Cox-2 inhibitor resulted in increased CD4+ cell counts [212, 213]. These studies were conducted in HIV-infected patients with median CD4+ cell counts >400 cells/μL, and larger clinical trials assessing the effect of Cox-2 inhibitors in INR are needed to uncover a potential for optimizing immune recovery.

7. Conclusion and Future Directions

Following the introduction of HAART, the prognosis and life expectancy for HIV-infected patients has changed tremendously. Thus, patients with optimal immune reconstitution and lack of comorbidity have a life expectancy almost comparable to HIV negative individuals. However, rates of morbidity and mortality including both AIDS- and non-AIDS-related events increase substantially with persistent low CD4+ cell counts. Therefore, increased morbidity and mortality persist in patients who do not achieve full immune reconstitution, in particular in INR.

INRs have immunological dysfunctions in both production and destruction of CD4+ cells. A well-functioning bone marrow, a large thymus with adequate function, and a high output of naïve cells are all critical components for production of CD4+ cells and immune reconstitution. It is plausible that dysfunctions in one or more of these parameters contribute to the low CD4+ cell counts in INR. Also, INRs have higher levels of immune activation and apoptotic cells indicating a higher loss of CD4+ cells. With the known significant impact of immune activation on the prognosis in HIV-infected individuals, it is reasonable to conclude that a high level of immune activation is a contributing factor to poor immune reconstitution as well. Furthermore, a dysregulated balance between pro- and anti-inflammatory T cells in INR may have an influence on immune reconstitution, but definitive documentation is lacking. Finally, it is likely that disruptions in the secondary lymphatic tissue may contribute to lack of immune reconstitution. However, with the present level of knowledge, it is difficult to determine whether these immunological disturbances are reflecting a poor immunological reconstitution rather than causing them. Only well-designed large prospective studies can help clarify this.

So far, a range of supplementary treatment to HAART has been suggested to improve immune reconstitution. The only thoroughly investigated candidate has been IL-2 that unfortunately proved not to be beneficial for clinical outcome. Several candidates seem promising including supplementary treatment with IL-7, GH releasing analogues, and possibly Cox-2 inhibitors. Furthermore, using Maraviroc as an integrated component of HAART does seem to result in higher CD4+ cell counts, but at present, the possibilities of improving the immune reconstitution in INR using supplementary treatment are limited. Some predictive factors can be avoided. Early diagnosis could be improved, reducing the risk for a low CD4 nadir, and coinfection with hepatitis C can be treated. However, understanding and improving immune reconstitution in HIV-infected patients remains an important field of research.

Conflict of Interests

The authors have no conflict of interests.
References

[1] N. G. Pakker, D. W. Notermans, R. J. De Boer et al., “Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation,” Nature Medicine, vol. 4, no. 2, pp. 208–214, 1998.

[2] B. Autran, G. Carcelain, T. S. Li et al., “Restoration of the immune system with anti-retroviral therapy,” Immunology Letters, vol. 66, no. 1-3, pp. 207–211, 1999.

[3] A. Mocroft, A. Phillips, J. Gatell et al., “Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study,” Lancet, vol. 370, no. 9585, pp. 407–413, 2007.

[4] C. Piketty, P. Castiel, L. Belec et al., “Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease,” AIDS, vol. 12, no. 7, pp. 745–750, 1998.

[5] B. Autran, G. Carcelain, T. S. Li et al., “Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease,” Science, vol. 277, no. 5322, pp. 112–116, 1997.

[6] M. Marziali, W. De Santis, R. Carello et al., “T-cell homeostasis alteration in HIV-1 infected subjects with low CD4 T-cell count despite undetectable virus load during HAART,” AIDS, vol. 20, no. 16, pp. 2033–2041, 2006.

[7] C. Erikstrup, G. Kronborg, N. Rohse, O. S. Rye, J. Gerstoft, and H. Ullum, “T-cell dysfunctions in HIV-1-infected patients with impaired recovery of CD4 cells despite suppression of viral replication,” Journal of Acquired Immune Deficiency Syndromes, vol. 53, no. 3, pp. 303–310, 2010.

[8] G. Marchetti, L. Gazzola, D. Trabattoni et al., “Skewed T-cell maturation and function in HIV-infected patients failing CD4+ recovery upon long-term virologically suppressive HAART,” AIDS, vol. 24, no. 10, pp. 1455–1460, 2010.

[9] T. Li, N. Wu, Y. Dai et al., “Reduced thymic output is a major mechanism of immune reconstitution failure in HIV-infected patients after long-term antiretroviral therapy,” Clinical Infectious Diseases, vol. 53, no. 9, pp. 944–951, 2011.

[10] C. Lewden, G. Chêne, P. Morlat et al., “HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population,” Journal of Acquired Immune Deficiency Syndromes, vol. 46, no. 1, pp. 72–77, 2007.

[11] “Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies,” Lancet, vol. 372, no. 9635, pp. 292–299, 2008.

[12] C. Piketty, L. Weiss, F. Thomas, A. S. Mohamed, L. Belec, and M. D. Kazatchkine, “Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen,” Journal of Infectious Diseases, vol. 183, no. 9, pp. 1328–1335, 2001.

[13] F. N. Engsig, J. Gerstoft, G. Kronborg et al., “Long-term mortality in HIV patients virally suppressed for more than three years with incomplete CD4 recovery: a cohort study,” BMC Infectious Diseases, p. 318, 2010.

[14] R. D. Moore and J. C. Keruly, “CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression,” Clinical Infectious Diseases, vol. 44, no. 3, pp. 441–446, 2007.

[15] R. D’Amico, Y. Yang, D. Mildvan et al., “Lower CD4+ T lymphocyte nadirs may indicate limited immune reconstitution in HIV-1 infected individuals on potent antiretroviral therapy: analysis of immunophenotypic marker results of AACTG 5067,” Journal of Clinical Immunology, vol. 25, no. 2, pp. 106–115, 2005.

[16] G. R. Kaufmann, H. Furrer, B. Ledergerber et al., “Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/μL in HIV type 1-infected individuals receiving potent antiretroviral therapy,” Clinical Infectious Diseases, vol. 41, no. 3, pp. 361–372, 2005.

[17] G. Greub, B. Ledergerber, M. Battegay et al., “Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the swiss HIV cohort study,” Lancet, vol. 356, no. 9244, pp. 1800–1805, 2000.

[18] L. Kolte, C. Strandberg, A. M. Dreves et al., “Thymic involvement in immune recovery during antiretroviral treatment of HIV infection in adults; comparison of CT and sonographic findings,” Scandinavian Journal of Infectious Diseases, vol. 34, no. 9, pp. 668–672, 2002.

[19] L. Kolte, A. M. Dreves, A. K. Erbsell et al., “Association between larger thymic size and higher thymic output in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy,” Journal of Infectious Diseases, vol. 185, no. 11, pp. 1578–1585, 2002.

[20] A. Vigano, S. Vella, N. Principi et al., “Thymus volume correlates with the progression of vertical HIV infection,” AIDS, vol. 13, no. 5, pp. F29–F34, 1999.

[21] D. C. Douek, R. A. Vescio, M. R. Betts et al., “Assessment of thymic output in adults after haematopoietic stem-cell transplantation and prediction of T-cell reconstitution,” Lancet, vol. 355, no. 9218, pp. 1875–1881, 2000.

[22] B. F. Haynes, M. L. Markert, G. D. Sempowski, D. D. Patel, and L. P. Hale, “The role of the thymus in immune reconstitution in aging, bone marrow transplantation, and HIV-1 infection,” Annual Review of Immunology, vol. 18, pp. 529–560, 2000.

[23] J. M. McCune, R. Loftus, D. K. Schmidt et al., “High prevalence of thymic tissue in adults with human immunodeficiency virus-1 infection,” Journal of Clinical Investigation, vol. 101, no. 11, pp. 2301–2308, 1998.

[24] K. Y. Smith, H. Valdez, A. Landay et al., “Thymic size and lymphocyte restoration in patients with human immunodeficiency virus infection after 48 weeks of zidovudine, lamivudine, and ritonavir therapy,” Journal of Infectious Diseases, vol. 181, no. 1, pp. 141–147, 2000.

[25] B. D. Jamieson, D. C. Douek, S. Killian et al., “Generation of functional thymocytes in the human adult,” Immunity, vol. 10, no. 5, pp. 569–575, 1999.

[26] G. Khoury, R. Rajasuriar, P. U. Cameron, and S. R. Lewin, “The role of naïve T-cells in HIV-1 pathogenesis: an emerging key player,” Clinical Immunology, vol. 141, no. 3, pp. 253–267, 2011.

[27] S. Kimmig, G. K. Przybylski, C. A. Schmidt et al., “Two key characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/μL in HIV type 1-infected individuals receiving potent antiretroviral therapy,” Clinical Infectious Diseases, vol. 370, no. 9, pp. 141–147, 2011.

[28] S. Junge, B. Kloecckner-Gruissem, R. Zufferrey et al., “Correlation between recent thymic emigrants and CD31+(PECAM-1) CD4+ T cells in normal individuals during aging and in lymphopenic children,” European Journal of Immunology, vol. 37, no. 11, pp. 3270–3280, 2007.
A. Marandin, A. Katz, E. Oksenhendler et al., “Loss of R. Van Gent, A. W. L. Schadenberg, S. A. Otto et al., “Long-term loss of T-cell receptor excision circle content of the naïve T-cell population in HIV-1 infection,” Nature Medicine, vol. 6, no. 9, pp. 1036–1042, 2000.

D. C. Douek, R. D. McFarland, P. H. Kéiser et al., “Changes in thymic function with age and during the treatment of HIV infection,” Nature, vol. 396, no. 6712, pp. 690–695, 1998.

L. Zhang, S. R. Lewin, M. Markowitz et al., “Measuring recent thymic emigrants in blood of normal and HIV-1-infected individuals before and after effective therapy,” Journal of Experimental Medicine, vol. 190, no. 5, pp. 725–732, 1999.

N. Vrisekoop, R. Van Gent, A. B. De Boer et al., “Restoration of the human T-cell compartment after long-term highly active antiretroviral therapy without phenotypical signs of accelerated immunological aging,” Journal of Immunology, vol. 181, no. 2, pp. 1573–1581, 2008.

S. T. Tanaskovic, S. Fernandez, M. A. French et al., “Thymic tissue is not evident on high-resolution computed tomography and [18F]Fluoro-deoxy-glucose positron emission tomography scans of aviraemic HIV patients with poor recovery of CD4+ T-cells,” AIDS, vol. 25, no. 9, pp. 1235–1237, 2011.

A. Isgrò, W. Leti, W. De Santis et al., “Altered clonogenic capability and stromal cell function characterize bone marrow of HIV-infected subjects with low CD4+ T-cell counts despite viral suppression during HAART,” Clinical Infectious Diseases, vol. 46, no. 12, pp. 1902–1910, 2008.

P. Deolobo, M. T. Nugeyre, M. Cazabet et al., “Naïve T-cell depletion related to infection by X4 human immunodeficiency virus type 1 in poor immunological responders to highly active antiretroviral therapy,” Journal of Virology, vol. 80, no. 20, pp. 10229–10236, 2006.

G. Marchetti, A. Gori, A. Casabianca et al., “Comparative analysis of T-cell turnover and homeostatic parameters in HIV-infected patients with discordant immune-virological responses to HAART,” AIDS, vol. 20, no. 13, pp. 1727–1736, 2006.

L. Kolte, L. P. Ryder, E. Albrecht-Beste, F. K. Jensen, and S. D. Nielsen, “HIV-infected patients with a large thymus maintain higher CD4 counts in a 5-year follow-up study of patients treated with highly active antiretroviral therapy,” Scandinavian Journal of Immunology, vol. 70, no. 6, pp. 608–613, 2009.

S. Molina-Pinelo, J. Vivancos, B. De Felipe et al., “Thymic volume predicts CD4 T-cell decline in HIV-infected adults under prolonged treatment interruption,” Journal of Acquired Immune Deficiency Syndromes, vol. 42, no. 2, pp. 203–206, 2006.

F. García, M. Planá, G. Mestre et al., “Immunological and virological factors at baseline may predict response to structured therapy interruption in early stage chronic HIV-1 infection,” AIDS, vol. 16, no. 13, pp. 1761–1765, 2002.

R. Van Gent, A. W. L. Schadenberg, S. A. Otto et al., “Long-term restoration of the human T-cell compartment after thymectomy during infancy: a role for thymic regeneration?” Blood, vol. 118, no. 3, pp. 627–634, 2011.

G. Hütter and S. Ganepola, “Eradication of HIV by transplantation of CCX5-deficient hematopoietic stem cells,” The Scientific World Journal, vol. 11, pp. 1068–1076, 2011.

A. Marandin, A. Katz, E. Oksenhendler et al., “Loss of primitive hematopoietic progenitors in patients with human immunodeficiency virus infection,” Blood, vol. 88, no. 12, pp. 4568–4578, 1996.

A. Isgrò, W. Leti, W. De Santis et al., “Altered clonogenic capability and stromal cell function characterize bone marrow of HIV-infected subjects with low CD4+ T-cell counts despite viral suppression during HAART,” Clinical Infectious Diseases, vol. 46, no. 12, pp. 1902–1910, 2008.

P. Deolobo, M. T. Nugeyre, M. Cazabet et al., “Naïve T-cell depletion related to infection by X4 human immunodeficiency virus type 1 in poor immunological responders to highly active antiretroviral therapy,” Journal of Virology, vol. 80, no. 20, pp. 10229–10236, 2006.

G. Marchetti, A. Gori, A. Casabianca et al., “Comparative analysis of T-cell turnover and homeostatic parameters in HIV-infected patients with discordant immune-virological responses to HAART,” AIDS, vol. 20, no. 13, pp. 1727–1736, 2006.

L. Kolte, L. P. Ryder, E. Albrecht-Beste, F. K. Jensen, and S. D. Nielsen, “HIV-infected patients with a large thymus maintain higher CD4 counts in a 5-year follow-up study of patients treated with highly active antiretroviral therapy,” Scandinavian Journal of Immunology, vol. 70, no. 6, pp. 608–613, 2009.

S. Molina-Pinelo, J. Vivancos, B. De Felipe et al., “Thymic volume predicts CD4 T-cell decline in HIV-infected adults under prolonged treatment interruption,” Journal of Acquired Immune Deficiency Syndromes, vol. 42, no. 2, pp. 203–206, 2006.

F. García, M. Planá, G. Mestre et al., “Immunological and virological factors at baseline may predict response to structured therapy interruption in early stage chronic HIV-1 infection,” AIDS, vol. 16, no. 13, pp. 1761–1765, 2002.

R. Van Gent, A. W. L. Schadenberg, S. A. Otto et al., “Long-term restoration of the human T-cell compartment after thymectomy during infancy: a role for thymic regeneration?” Blood, vol. 118, no. 3, pp. 627–634, 2011.

G. Hütter and S. Ganepola, “Eradication of HIV by transplantation of CCX5-deficient hematopoietic stem cells,” The Scientific World Journal, vol. 11, pp. 1068–1076, 2011.

A. Marandin, A. Katz, E. Oksenhendler et al., “Loss of primitive hematopoietic progenitors in patients with human immunodeficiency virus infection,” Blood, vol. 88, no. 12, pp. 4568–4578, 1996.
treatment,” Current HIV Research, vol. 7, no. 1, pp. 83–90, 2009.

[58] A. Ahmad, R. Ahmad, A. Iannello, E. Toma, R. Morisset, and S. T. A. K. Sindhu, “IL-15 and HIV infection: lessons for immunotherapy and vaccination,” Current HIV Research, vol. 3, no. 3, pp. 261–270, 2005.

[59] D. Sirskyj, J. Thiéze, A. Kumar, and M. Kryworuchko, “Disruption of the γc cytokine network in T cells during HIV infection,” Cytokine, vol. 43, no. 1, pp. 1–14, 2008.

[60] M. D. Hazenberg, S. A. Otto, B. H. B. van Benthem et al., “Persistent immune activation in HIV-1 infection is associated with progression to AIDS,” AIDS, vol. 17, no. 13, pp. 1881–1888, 2003.

[61] Z. Liu, W. G. Cumberland, L. E. Hultin, A. H. Kaplan, R. Detels, and J. V. Giorgi, “CD8+ T-lymphocyte activation in HIV-1 disease reflects an aspect of pathogenesis distinct from viral burden and immunodeficiency,” Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, vol. 18, no. 4, pp. 332–340, 1998.

[62] Z. Liu, W. G. Cumberland, L. E. Hultin, H. E. Prince, R. Detels, and J. V. Giorgi, “Elevated CD38 antigen expression on CD8+ T cells is a stronger marker for the risk of chronic HIV disease progression to AIDS and death in the multicenter AIDS Cohort Study than CD4+ cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression,” Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, vol. 16, no. 2, pp. 83–92, 1997.

[63] Z. Liu, L. E. Hultin, W. G. Cumberland et al., “Elevated relative fluorescence intensity of CD38 antigen expression on CD8+ T cells is a marker of poor prognosis in HIV infection: results of 6 years of follow-up,” Communications in Cytometry, vol. 26, no. 1, pp. 1–7, 1996.

[64] J. V. Giorgi, Z. Liu, L. E. Hultin, W. G. Cumberland, K. Hennessey, and R. Detels, “Elevated levels of CD38/CD8+ T cells in HIV infection add to the prognostic value of low CD4+ T cell levels: results of 6 years of follow-up,” Journal of Acquired Immune Deficiency Syndromes, vol. 6, no. 8, pp. 904–912, 1993.

[65] L. Weiss, N. Haefnner-Cavaillon, M. Laude, J. Gilquin, and M. D. Kazatchkine, “HIV infection is associated with the spontaneous production of interleukin-1 (IL-1) in vivo and with an abnormal release of IL-1α in vitro,” AIDS, vol. 3, no. 11, pp. 695–699, 1989.

[66] J. M. Molina, D. T. Scadden, R. Byrn, C. A. Dinarello, and J. E. Groopman, “Production of tumor necrosis factor α and interleukin 1β by monocyctic cells infected with human immunodeficiency virus,” Journal of Clinical Investigation, vol. 84, no. 3, pp. 733–737, 1989.

[67] D. Emilie, M. Peuchmair, M. C. Maillot et al., “Production of interleukins in human immunodeficiency virus-1-replicating lymph nodes,” Journal of Clinical Investigation, vol. 86, no. 1, pp. 148–159, 1990.

[68] D. L. Birx, R. R. Redfield, K. Tencer, A. Fowler, D. S. Burke, and G. Tosato, “Induction of interleukin-6 during human immunodeficiency virus infection,” Blood, vol. 76, no. 11, pp. 2303–2310, 1990.

[69] J. V. Giorgi, L. E. Hultin, J. A. McKeating et al., “Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage,” Journal of Infectious Diseases, vol. 179, no. 4, pp. 859–870, 1999.
immunological responders to combination antiretroviral therapy,” *PloS ONE*, vol. 4, no. 10, Article ID e7658, 2009.

[84] P. Delobel, S. Flament, M. Hamdane et al., “Abnormal Tau phosphorylation of the Alzheimer-type also occurs during mitosis,” *Journal of Neurochemistry*, vol. 83, no. 2, pp. 412–420, 2002.

[85] R. Hazra and C. Mackall, “Thymic function in HIV infection,” *Current HIV/AIDS Reports*, vol. 2, no. 1, pp. 24–28, 2005.

[86] R. B. Effros and G. Pavlec, “Repetitive senescence of T cells: does the Hayflick Limit lead to immune exhaustion?” *Immunology Today*, vol. 18, no. 9, pp. 450–454, 1997.

[87] K. C. Woltthers, G. B. A. Wisman, S. A. Otto et al., “T cell telomere length in HIV-1 infection: no evidence for increased CD4+ T cell turnover,” *Science*, vol. 274, no. 5292, pp. 1543–1547, 1996.

[88] M. Dagarag, H. Ng, R. Lubong, R. B. Effros, and O. O. Yang, “Differential impairment of lytic and cytokine functions in senescent human immunodeficiency virus type 1-specific cytotoxic T lymphocytes,” *Journal of Virology*, vol. 77, no. 5, pp. 3077–3083, 2003.

[89] O. Franzese, R. Adamo, M. Pollicita et al., “Telomerase activity, hTERT expression, and phosphorylation are down-regulated in CD4+ T lymphocytes infected with human immunodeficiency virus type 1 (HIV-1),” *Journal of Medical Virology*, vol. 79, no. 5, pp. 639–646, 2007.

[90] L. Meyaard, S. A. Otto, R. R. Jonker, M. J. Mijnster, R. P. M. Keet, and F. Miedema, “Programmed death of T cells in HIV-1 infection,” *Science*, vol. 257, no. 5067, pp. 217–219, 1992.

[91] L. Meyaard, S. A. Otto, I. P. M. Keet, M. T. L. Roos, and F. Miedema, “Programmed death of T cells in human immunodeficiency virus infection. No correlation with progression to disease,” *Journal of Clinical Investigation*, vol. 93, no. 3, pp. 982–988, 1994.

[92] F. Bottarel, S. Bonissoni, M. B. Lucia et al., “Decreased function of Fas in patients displaying delayed progression of HIV-induced immune deficiency,” *Hematology Journal*, vol. 2, no. 4, pp. 220–227, 2001.

[93] M. L. Gougeon, H. Lecoeur, A. Dulioust et al., “Programmed cell death in peripheral lymphocytes from HIV-infected persons: increased susceptibility to apoptosis of CD4 and CD8 T cells correlates with lymphocyte activation and with disease progression,” *Journal of Immunology*, vol. 156, no. 9, pp. 3509–3520, 1996.

[94] S. Piconi, D. Trabattoni, A. Gori et al., “Immune activation, apoptosis, and treg activity are associated with persistently reduced CD4+ T-cell counts during antiretroviral therapy,” *AIDS*, vol. 24, no. 13, pp. 1991–2000, 2010.

[95] M. E. Keir, M. J. Butte, G. J. Freeman, and A. H. Sharpe, “PD-1 and its ligands in tolerance and immunity,” *Annual Review of Immunology*, vol. 26, pp. 677–704, 2008.

[96] D. L. Barber, E. J. Wherry, D. Masopust et al., “Restoring function in exhausted CD8+ T cells during chronic viral infection,” *Nature*, vol. 439, no. 7077, pp. 682–687, 2006.

[97] K. Grabmeier-Pfistshammer, P. Steinberger, A. Rieger, J. Leitner, and N. Kohrgruber, “Identification of PD-1 as a unique marker for failing immune reconstitution in HIV-1-infected patients on treatment,” *Journal of Acquired Immune Deficiency Syndromes*, vol. 56, no. 2, pp. 118–124, 2011.

[98] V. Appay, S. Fastenackels, C. Katlama et al., “Old age and anticytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients,” *AIDS*, vol. 25, no. 15, pp. 1813–1822, 2011.
and TH17 cells in HIV-1-infected elite controllers," Journal of Acquired Immune Deficiency Syndromes, vol. 57, no. 2, pp. 101–108, 2011.

[115] D. J. Harrigan-O’Connor, L. A. Hirao, J. M. McCune, and S. Dandekar, “Th17 cells and regulatory T cells in elite control over HIV and SIV,” Current Opinion in HIV and AIDS, vol. 6, no. 3, pp. 221–227, 2011.

[116] J. Gaardbo et al., “Regulatory T cells (Tregs) are extremely prevalent in HIV infected individuals with immunological non-response, oral presentation PS12/2,” European AIDS Clinical Society. In press.

[117] J. J. Mattapallil, D. C. Douek, B. Hill, Y. Nishimura, M. Martin, and M. Roederer, "Massive infection and loss of memory CD4 T cells in multiple tissues during acute SIV infection," Nature, vol. 434, no. 7037, pp. 1093–1097, 2005.

[118] M. Guadalupe, E. Reay, S. Sankaran et al., "Severe CD4 T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy," Journal of Virology, vol. 77, no. 21, pp. 11708–11717, 2003.

[119] T. W. Schacker, P. L. Nguyen, G. J. Beilman et al., "Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis," Journal of Clinical Investigation, vol. 110, no. 8, pp. 1133–1139, 2002.

[120] T. W. Schacker, C. Reilly, G. J. Beilman et al., "Amount of lymphatic tissue fibrosis in HIV infection predicts magnitude of HAART-associated change in peripheral CD4 cell count," AIDS, vol. 19, no. 18, pp. 2169–2171, 2005.

[121] T. H. Finkel, G. Tudor-Williams, N. K. Banda et al., "Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes," Nature Medicine, vol. 1, no. 2, pp. 129–134, 1995.

[122] D. Finzi, M. Hermankova, T. Pierson et al., "Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy," Science, vol. 278, no. 5341, pp. 1295–1300, 1997.

[123] W. Cavert, D. W. Notermans, K. Staskus et al., "Kinetics of response in lymphoid tissues to antiretroviral therapy of HIV-1 infection," Science, vol. 276, no. 5314, pp. 960–964, 1997.

[124] T. W. Chun, D. C. Nickle, J. S. Justement et al., "Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy," Journal of Infectious Diseases, vol. 197, no. 5, pp. 714–720, 2008.

[125] N. Chomont, M. El-Far, P. Ancuta et al., "HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation," Nature Medicine, vol. 15, no. 8, pp. 893–900, 2009.

[126] L. Wang, C. W. Robb, and M. W. Cloyd, "HIV induces homing of resting T lymphocytes to lymph nodes," Virology, vol. 228, no. 2, pp. 141–152, 1997.

[127] L. Wang, J. J. Chen, B. B. Gelman, R. Konig, and M. W. Cloyd, "A novel mechanism of CD4 lymphocyte depletion involves effects of HIV on resting lymphocytes: induction of lymph node homing and apoptosis upon secondary signaling through homing receptors," Journal of Immunology, vol. 162, no. 1, pp. 268–276, 1999.

[128] M. W. Cloyd, J. J. Chen, P. Adeqboyega, and L. Wang, "How does HIV cause depletion of CD4 lymphocytes? A mechanism involving virus signaling through its cellular receptors," Current Molecular Medicine, vol. 1, no. 5, pp. 545–550, 2001.

[129] H. J. Eppe, C. Loddenkemper, D. Kunkel et al., "Mucosal but not peripheral FOXP3+ regulatory T cells are highly increased in untreated HIV infection and normalize after suppressive HAART," Blood, vol. 108, no. 9, pp. 3072–3078, 2006.

[130] K. Bhaskaran, O. Hamouda, M. Sannes et al., "Changes in the risk of death after HIV seroconversion compared with mortality in the general population," JAMA - Journal of the American Medical Association, vol. 300, no. 1, pp. 51–59, 2008.

[131] F. Fedele, N. Bruno, and M. Mancone, "Cardiovascular risk factors and HIV disease," AIDS Reviews, vol. 13, no. 2, pp. 119–129, 2011.

[132] S. K. Grinspoon, "Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus," The American Journal of Medicine, vol. 118, supplement 2, pp. 235–285, 2005.

[133] S. G. Deeks, "Antiretroviral treatment of HIV infected adults," British Medical Journal, vol. 332, no. 7556, pp. 1489–1493, 2006.

[134] N. R. Reynolds, "Cigarette smoking and HIV: more evidence for action," AIDS Education and Prevention, vol. 21, no. 3, pp. 106–121, 2009.

[135] H. Van Tiem and B. A. Koblin, "HIV, alcohol, and noninjection drug use," Current Opinion in HIV and AIDS, vol. 4, no. 4, pp. 314–318, 2009.

[136] A. A. Adimora and J. D. Auerbach, "Structural interventions for HIV prevention in the United States," Journal of Acquired Immune Deficiency Syndromes, vol. 55, no. 2, supplement, pp. S132–S135, 2010.

[137] R. Greener and S. Sarkar, "Risk and vulnerability: do socioeconomic factors influence the risk of acquiring HIV in Asia?" AIDS, vol. 24, no. 3, supplement, pp. S3–S11, 2010.

[138] J. D. Lundgren, A. Babiker, W. El-Sadr et al., "Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ cell counts and HIV RNA levels during follow-up," Journal of Infectious Diseases, vol. 197, no. 8, pp. 1145–1155, 2008.

[139] F. Gutiérrez, S. Padilla, M. Masiá et al., "Patients’ characteristics and clinical implications of suboptimal CD4 T-cell gains after 1 year of successful antiretroviral therapy," Current HIV Research, vol. 6, no. 2, pp. 100–107, 2008.

[140] A. N. Phillips, B. Gazzard, R. Gilson et al., "Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count," AIDS, vol. 21, no. 13, pp. 1717–1721, 2007.

[141] R. C. Griesinger, K. H. O'Neil, G. Kronborg et al., "Impact of socioeconomic factors and HIV disease, clinical implications and management," Expert Review of Anti-Infective Therapy, vol. 9, no. 10, pp. 877–889, 2011.

[142] C. Smith, "Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study: the data collection on adverse events of anti-HIV drugs (D:A:D) study group," AIDS, vol. 24, no. 10, pp. 1537–1548, 2010.

[143] L. Waters and C. A. Sabin, "Late HIV presentation: epidemiology, clinical implications and management," Expert Review of Anti-Infective Therapy, vol. 9, no. 10, pp. 877–889, 2011.

[144] C. Mussini, "CD4 cell-monitored treatment interruption in patients with a CD4 cell count > 500 × 106 cells/l," AIDS, vol. 19, no. 3, pp. 287–294, 2005.

[145] J. D. Lundgren, "Combination antiretroviral therapy and the risk of myocardial infarction: the data collection on adverse
events of anti-HIV drugs (DAD) Study Group," *New England Journal of Medicine*, vol. 349, no. 21, pp. 1993–2003, 2003.

[146] J. V. Baker, W. K. Henry, and J. D. Neaton, "The consequences of HIV infection and antiretroviral treatment for cardiovascular disease risk: shifting paradigms," *Current Opinion in HIV and AIDS*, vol. 4, no. 3, pp. 176–182, 2009.

[147] N. Friis-Møller, P. Reiss, C. A. Sabin et al., "Class of antiretroviral drugs and the risk of myocardial infarction," *New England Journal of Medicine*, vol. 356, no. 17, pp. 1723–1735, 2007.

[148] A. N. Phillips, J. Neaton, and J. D. Lundgren, "The role of HIV in serious diseases other than AIDS," *AIDS*, vol. 22, no. 18, pp. 2409–2418, 2008.

[149] R. C. Kaplin, L. A. Kingsley, S. J. Gange et al., "Low CD4 T-cell count as a major atherosclerosis risk factor in HIV-infected women and men," *AIDS*, vol. 22, no. 13, pp. 1615–1624, 2008.

[150] H. W. Jaffe, B. L. De Stavola, L. M. Carpenter, K. Porter, and D. R. Cox, "Immune reconstitution and risk of Kaposi sarcoma and non-Hodgkin lymphoma in HIV-infected adults," *AIDS*, vol. 25, no. 11, pp. 1395–1403, 2011.

[151] J. Bohlius, K. Schmidlin, D. Costagliola, G. Fatkenheuer, M. May, and A. M. Caro-Murillo, "Incidence and risk factors of HIV-related non-Hodgkin’s lymphoma in the era of combination antiretroviral therapy: a European multicohort study," *Antiviral Therapy*, vol. 14, no. 8, pp. 1065–1074, 2009.

[152] E. Zanet, M. Berretta, F. Martellotta et al., "Anal cancer: focus on HIV-positive patients in the HAART era," *Current HIV Research*, vol. 9, no. 2, pp. 70–81, 2011.

[153] A. D. Monforte, D. Abrams, C. Fradier et al., "HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies," *AIDS*, vol. 22, no. 16, pp. 2143–2153, 2008.

[154] J. Reekie, C. Kosa, F. Engsig el al., "Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies," *Cancer*, vol. 116, no. 22, pp. 5306–5315, 2010.

[155] R. K. Heaton, D. B. Clifford, D. R. Franklin et al., "HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: charter Study," *Neurology*, vol. 75, no. 23, pp. 2087–2096, 2010.

[156] R. J. Ellis, J. Badiee, F. Vaida et al., "CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy," *AIDS*, vol. 25, no. 14, pp. 1747–1751, 2011.

[157] J. A. Bartlett, M. J. Fath, R. DeMasi et al., "An updated systematic overview of triple combination therapy in antiretroviral-naïve HIV-infected adults," *AIDS*, vol. 20, no. 16, pp. 2051–2064, 2006.

[158] R. M. Gulick, J. Lalezari, J. Goodrich et al., "Maraviroc for previously treated patients with RS HIV-1 infection," *New England Journal of Medicine*, vol. 359, no. 14, pp. 1429–1441, 2008.

[159] T. Wilkin et al., "Maraviroc intensification for suboptimal CD4 cell response despite sustained virologic suppression: ACTG 5256," in *Proceedings of the 17th Conference on Retrovirus and Opportunistic Infections (CROI ’10)*, abstract 285, 2010.

[160] T. J. Wilkin, H. R. Ribaudo, A. R. Tenorio, and R. M. Gulick, "The relationship of CCR5 antagonists to CD4 T-cell gain: a meta-regression of recent clinical trials in treatment-experienced HIV-infected patients," *HIV Clinical Trials*, vol. 11, no. 6, pp. 351–358, 2010.

[161] R. T. Steigbigel, D. A. Cooper, H. Tepler, J. J. Eron, J. M. Gatell, and P. N. Kumar, "Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials," *Clinical Infectious Diseases*, vol. 50, no. 4, pp. 605–612, 2010.

[162] H. Hatao, T. L. Hayes, V. Dahl et al., "A randomized, controlled trial of raltegravir intensification in antiretroviral-treated, HIV-infected patients with a suboptimal CD4 T-cell response," *Journal of Infectious Diseases*, vol. 203, no. 7, pp. 960–968, 2011.

[163] H. Byakwaga, M. Kelly, D. F. Purcell et al., "Intensification of antiretroviral therapy with raltegravir or addition of hyper-immune bovine colostrum in HIV-infected patients with suboptimal CD4 T-cell response: a randomized controlled trial," *Journal of Infectious Diseases*, vol. 204, no. 10, pp. 1532–1540, 2011.

[164] J.-M. Molina, A. LaMarca, J. Andrade-Villanueva et al., "Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study," *The Lancet Infectious Diseases*, vol. 12, no. 1, pp. 27–35, 2012.

[165] J. P. Lalezari, K. Henry, M. O’Hearn et al., "Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America," *New England Journal of Medicine*, vol. 348, no. 22, pp. 2175–2185, 2003.

[166] A. Lazzarin, B. Clotet, D. Cooper et al., "Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia," *New England Journal of Medicine*, vol. 348, no. 22, pp. 2186–2195, 2003.

[167] V. Joly et al., "Intensification of HAART through the addition of enfuvirtide in naive HIV-infected patients with severe immunosuppression does not improve immunological response: results of a prospective randomised multicenter trial," in *Proceedings of the 17th Conference on Retrovirus and Opportunistic Infections (CROI ’10)*, abstract 282, 2010.

[168] S. L. Pett, A. D. Kelleher, and S. Emery, "Role of interleukin-2 in patients with HIV infection," *Drugs*, vol. 70, no. 9, pp. 1115–1130, 2010.

[169] G. Carcelain, P. Saint-Mézard, H. K. Altes et al., "IL-2 therapy and thymic production of naive CD4 T cells in HIV-infected patients with severe CD4 lymphopenia," *AIDS*, vol. 17, no. 6, pp. 841–850, 2003.

[170] F. Sabbatini, A. Bandera, G. Ferrario et al., "Qualitative immune modulation by interleukin-2 (IL-2) adjuvant therapy in immunological non responder HIV-infected patients," *PLoS ONE*, vol. 5, no. 11, Article ID e14119, 2010.

[171] G. Marchetti, L. Meroni, S. Varchetta et al., "Low-dose production of naive CD4 T cells in HIV-infected patients with severe CD4 lymphopenia," *AIDS*, vol. 17, no. 6, pp. 841–850, 2003.

[172] C. L. MacKall, T. J. Fry, and R. E. Gress, "Harnessing the biology of IL-7 for therapeutic application," *Nature Reviews Immunology*, vol. 11, no. 5, pp. 330–342, 2011.

[173] A. Leone, M. Rohankhedkar, A. Okoye et al., "Increased CD4 T cell levels during IL-7 administration of antiretroviral therapy-treated simian immunodeficiency virus-positive macaques are not dependent on strong proliferative responses," *Journal of Immunology*, vol. 185, no. 3, pp. 1650–1659, 2010.
[202] T. Mellberg, V. D. Gonzalez, A. Lindkvist et al., “Rebound of residual plasma viremia after initial decrease following addition of intravenous immunoglobulin to effective antiretroviral treatment of HIV,” *AIDS Research and Therapy*, vol. 8, article 21, 2011.

[203] V. D. Gonzalez, K. Falconer, K. G. Blom et al., “High levels of chronic immune activation in the T-cell compartments of patients coinfected with hepatitis C virus and human immunodeficiency virus type 1 and on highly active antiretroviral therapy are reverted by alpha interferon and ribavirin treatment,” *Journal of Virology*, vol. 83, no. 21, pp. 11407–11411, 2009.

[204] P. W. Hunt, J. N. Martin, E. Sinclair et al., “Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy,” *Journal of Infectious Diseases*, vol. 203, no. 10, pp. 1474–1483, 2011.

[205] P. W. Hunt, “Th17, gut, and HIV: therapeutic implications,” *Current Opinion in HIV and AIDS*, vol. 5, no. 2, pp. 189–193, 2010.

[206] E. Merlini, F. Bai, G. M. Bellistrì, C. Tincati, A. d’Arminio Monforte, and G. Marchetti, “Evidence for polymicrobial flora translocating in peripheral blood of HIV-infected patients with poor immune response to antiretroviral therapy,” *PLoS ONE*, vol. 6, no. 4, article e18580, 2011.

[207] J. M. Brenchley, D. A. Price, T. W. Schacker et al., “Microbial translocation is a cause of systemic immune activation in chronic HIV infection,” *Nature Medicine*, vol. 12, no. 12, pp. 1365–1371, 2006.

[208] W. Jiang, M. M. Lederman, P. Hunt et al., “Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection,” *Journal of Infectious Diseases*, vol. 199, no. 8, pp. 1177–1185, 2009.

[209] G. Marchetti, G. M. Bellistrì, E. Borghi et al., “Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy,” *AIDS*, vol. 22, no. 15, pp. 2035–2044, 2008.

[210] R. Hummelen, J. Changalucha, N. L. Butamanya et al., “Effect of 25 weeks probiotic supplementation on immune function of HIV patients,” *Gut Microbes*, vol. 2, no. 2, pp. 80–85, 2011.

[211] F. O. Pettersen, E. A. Torheim, A. E. Dahm et al., “An exploratory trial of cyclooxygenase type 2 inhibitor in HIV-1 infection: downregulated immune activation and improved T cell-dependent vaccine responses,” *Journal of Virology*, vol. 85, no. 13, pp. 6557–6566, 2011.

[212] D. Kvale, V. Ormaasen, A. M. B. Kran et al., “Immune modulatory effects of cyclooxygenase type 2 inhibitors in HIV patients on combination antiretroviral treatment,” *AIDS*, vol. 20, no. 6, pp. 813–820, 2006.

[213] C. C. Johansson, T. Bryn, E. M. Aandahl et al., “Treatment with type-2 selective and non-selective cyclooxygenase inhibitors improves T-cell proliferation in HIV-infected patients on highly active antiretroviral therapy,” *AIDS*, vol. 18, no. 6, pp. 951–952, 2004.