The Absence of CD4+ T Cell Count Recovery Despite Receipt of Virologically Suppressive Highly Active Antiretroviral Therapy: Clinical Risk, Immunological Gaps, and Therapeutic Options

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Up to 30% of human immunodeficiency virus (HIV)–infected patients who are receiving long-term highly active antiretroviral therapy do not exhibit a marked increase in the CD4+ T cell count, despite achieving complete suppression of the HIV load. These patients are referred to as “immunological nonresponders.” When treating immunological nonresponders, the practicing clinician has several questions, including questions about the clinical risk associated with persistent immunodeficiency and about possible approaches to treatment that would provide clinical and immunological benefits. However, tentative answers to these questions require investigations of the mechanisms that underlie the lack of immune recovery, because only the deepest comprehension of the immunological gaps underlying functional defects will allow administration of highly targeted and efficacious treatment strategies. The aim of our review is to provide a thorough assessment of the clinical implications of a lack of increase in the CD4+ T cell count in immunological nonresponders, to examine the immunological gaps limiting recovery of the CD4+ T cell count, and to note possible therapeutic avenues, which may offer clinicians guidance regarding how to most efficaciously treat these critical patients.

IMMUNOLOGICAL FAILURE AND HAART

In the era of HAART, HIV/AIDS clinicians have observed a remarkable reduction in AIDS-related morbidity and mortality rates. In fact, HAART has been shown to improve survival rates among HIV-infected individuals through its ability to reduce the HIV load to undetectable levels and to increase the CD4+ lymphocyte count in peripheral blood (defined as a full response) [1, 2]. However, 15%–30% of patients have discordant responses to long-term HAART consisting of a lack of increase in the CD4+ T cell count but full suppression of HIV replication; these people are referred to as “immunological nonresponders” (INRs) [3, 4]. From a clinical standpoint, lack of CD4+ immune reconstitution during receipt of effective HAART represents an everyday issue in the clinical management of HIV/AIDS. In particular, clinicians question whether INRs have an increased risk of clinical progression to AIDS and whether it is possible to identify early predictive factors of immunological failure during HAART.

From a therapeutic standpoint, failure of CD4+ cell reconstitution during receipt of virologically suppressive HAART indicates the need for alternative treatment strategies. However, the essential premise of studies of therapeutic options in this clinical context is the deep comprehension of the pathogenetic mechanisms that underlie immunological failure. We assessed the clinical implications of a lack of a recovery in the CD4+ cell count among INRs, the immunological gaps limiting CD4+ cell count recovery, and the possible therapeutic avenues that may offer clinicians guidance regarding the most effective treatments for these critical patients.

INVESTIGATING THE CLINICAL CORRELATES OF IMMUNOLOGICAL FAILURE DURING HAART: ARE INRs AT INCREASED RISK OF HIV/AIDS DISEASE PROGRESSION AND DEATH?

An essential premise in the assessment of clinical correlates of insufficient immunological response to long-term HAART is
the definition of immunological response itself. There is no clear-cut agreement on how to assess an insufficient immune response to HAART, with particular regard to the adequate time to evaluation of immune response after the commencement of HAART. Although an interval of 12 months may be too premature to evaluate immune response to HAART [5], it is our opinion that the broadly used criteria of an increase in the CD4+ T cell count of <30% and an absolute CD4+ T cell count \( \geq 200 \) cells/\( \mu L \) during the first 6–12 months of HIV-suppressive HAART identifies immunological nonresponse [6], because immune response after 3–6 months of HAART is predictive of both immune reconstitution and HIV-related morbidity and mortality in the long term [7, 8]. However, this definition may identify an overly heterogeneous population and fail to discriminate between a real long-term nonresponse and a delayed response.

Kaufmann et al. [7] demonstrated that an incomplete immune response in the short term led to an elevated risk of Centers for Disease Control and Prevention category B and C events in the long term, indicating an augmented risk of disease progression in INRs. Additional observational studies have defined an approximately doubled relative risk of clinical progression to AIDS and an increased risk of mortality in INRs, compared with patients who had a complete response [9–13].

In addition, a new clinical concern was recently raised by Gutierrez et al. [12], who showed that, despite having similar proportions of new AIDS-defining events, INRs had an overall higher rate of non–AIDS-related mortality, compared with patients who had a complete response, causing additional clinical concern about the long-term risks of subclinical immunodeficiency. Accordingly, guidelines of the Department of Health and Human Services (DHHS) prefer to define immunological failure as the lack of an increase in the CD4+ T cell count to more than 350–500 cells/\( \mu L \) after receipt of 4–7 years of effective HAART [14], given recent data linking these immunological thresholds with the risk of non-AIDS clinical events [15].

**INVESTIGATION OF FACTORS ASSOCIATED WITH IMMUNOLOGICAL FAILURE DURING LONG-TERM HAART: WHICH FACTORS PREDICT IMMUNOLOGICAL NONRESPONSE?**

Having defined an overall increased risk of HIV/AIDS disease progression in INRs, we still need to assess whether the clinician can depend on specific factors for early identification of which patients are most likely to experience insufficient immune recovery while receiving HAART. As illustrated in table 1, several factors have been individually associated with immunological failure during HAART, and yet only those below have been invariably proven to predict immunological nonresponse.

Age has been reported to have a significant impact on immune recovery: the older the patient is, the more likely that he or she will experience delayed immune reconstitution [18]. Indeed, older age has been associated with a decrease of thymic function and other regenerative mechanisms, thus explaining its role as an independent predictive factor of impaired immune recovery [7, 10, 11, 16, 19]. In addition, recent data from cohort studies suggest that immune recovery in older patients may hide a more profound functional impairment, as evidenced by a persistent increased risk of AIDS-related events in these patients, even after adjustment for CD4+ T cell counts [20, 21].

Another factor presumed to affect immune recovery during HAART is concurrent viral hepatitis. In a recent meta-analysis, Miller et al. [22] showed that increases in the CD4+ T cell count during HAART are significantly lower in the course of hepatitis C virus (HCV) coinfection. The biological rationale posits that there are higher levels of T cell activation and death in HIV-HCV–coinfected patients and that there is a possible direct negative effect of HCV infection and replication inside lymphocyte subpopulations [23, 24]. However, the actual impact of HCV infection on immune recovery in HIV-infected patients still remains a matter of controversy, given the numerous confounding factors often present in the HCV-infected population, such as a history of injection drug use, poor adherence to therapy, and decreased access to health care [25–28]. Of these factors, adherence to antiretroviral therapy has been proven to be a strong independent predictor of recovery in the CD4+ T cell count and the ultimate cause of impaired immune recovery in injection drug users [29, 30].

With regard to immunovirological factors, nadir CD4+ T cell count is the most common and most reliable determinant of suboptimal immune recovery during HAART [7, 16, 17, 31, 32]. From a mechanistic standpoint, differences in CD4+ T cell nadir are indicators of differences in immunological regulatory functions over T cell homeostasis that might affect immune recovery competence [33]. However, the sole quantification of nadir CD4+ T cell count may fail to qualitatively estimate the immunological mechanism(s) that hinder CD4+ T cell count rescue, indicating a need for a more detailed assessment of immunological gaps associated with nadir-driven T cell homeostasis.

The identification of immunopathogenetic models behind the negative impact of age, HCV coinfection, and nadir CD4+ cell count on immune recovery raises an additional clinical question: are there immunological, virological, or genetic markers that can be directly exploited, from bench to bedside, to predict immunological failure during HAART in at-risk patients? Although Spritzler et al. [34] demonstrate that peripheral immunophenotype has a limited ability to predict HAART response, only the most thorough investigation of immunovirological correlates of discordant responses will allow for a targeted immune-based treatment approach.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study population</th>
<th>ART regimen(s)</th>
<th>Definition of “incomplete immunological response”</th>
<th>No. (%) of patients</th>
<th>Statistical analysis</th>
<th>Risk factors found by statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grabar et al. [9]</td>
<td>2000</td>
<td>2236 PI-naive patients (77.3% were ART experienced and 22.7% were ART naive)</td>
<td>2 NRTIs plus a PI</td>
<td>Increase in the CD4+ T cell count &lt;50 cells/μL at 6 months after ART introduction, with a decrease in the plasma HIV load &gt;1 log_{10} copies/mL or a plasma HIV load &lt;1000 copies/mL</td>
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<td></td>
<td></td>
<td>387 (17.3)</td>
<td>Kruskal-Wallis and χ² tests</td>
<td>IDU, higher baseline CD4+ T cell count, and lower baseline plasma HIV load</td>
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<tr>
<td>Kaufmann et al. [16]</td>
<td>2002</td>
<td>95 Patients (52% were NRTI experienced and 48% were NRTI naive)</td>
<td>2 NRTIs plus a PI, 2 NRTIs plus an NNRTI, an NRTI plus 2 PIs, an NNRTI plus a PI, or 2 NRTIs</td>
<td>Total CD4+ T cell count &lt;500 cells/μL at 4 years after ART introduction, with plasma HIV load &lt;400 copies/mL</td>
<td>22 (23)</td>
<td>Univariate logistic regression</td>
<td>Lower nadir CD4+ T cell count and lower baseline CD4+ T cell count</td>
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<td>Multivariate logistic regression</td>
<td>Lower nadir CD4+ T cell count</td>
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<tr>
<td>Dronda et al. [5]</td>
<td>2002</td>
<td>255 ART-naive patients</td>
<td>2 NRTIs plus a PI or 2 NRTIs plus an NNRTI</td>
<td>Increase in the CD4+ T cell count &lt;100 cells/μL 24 months after ART introduction, with plasma HIV load &lt;50 copies/mL</td>
<td>42 (16.5)</td>
<td>Univariate logistic regression</td>
<td>Lower baseline plasma HIV load, higher baseline CD4+ T cell count, and previous IDU</td>
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<td></td>
<td>Multivariate logistic regression</td>
<td>Previous IDU</td>
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<tr>
<td>Florence et al. [17]</td>
<td>2003</td>
<td>780 Patients (61% were NRTI experienced and 39% were NRTI naive)</td>
<td>NRTIs plus a PI, NRTIs plus an NNRTI, or an NNRTI plus a PI</td>
<td>Increase in the CD4+ T cell count &lt;50 cells/μL by month 6 or &lt;75 cells/μL by month 12, with a plasma HIV load &lt;500 copies/mL</td>
<td>225 (29)</td>
<td>Univariate logistic regression</td>
<td>Older age, interval between HIV infection diagnosis to commencement of HAART, NRTI experience, lower nadir CD4+ T cell count, greater increase in CD4+ T cell count with previous ART, lower baseline and peak plasma HIV loads, and previous KS</td>
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<td>Multivariate logistic regression</td>
<td>Older age, lower nadir CD4+ T cell count, lower baseline CD4+ T cell count, greater increase in CD4+ T cell count with previous ART, and lower baseline plasma HIV load</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Method</td>
<td>Combination</td>
<td>Time to Increase</td>
<td>CD4+ T cell count</td>
<td>Method</td>
<td>Factors Associated</td>
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<tr>
<td>Kaufmann et al. [7]</td>
<td>2005</td>
<td>293 ART-naive patients</td>
<td>2 NRTIs plus a PI, 2 NRTIs plus an NNRTI, an NRTI plus 2 PIs, an NRTI plus an NNRTI and a PI, or 3 NRTIs</td>
<td>Total CD4+ T cell count &lt;500 cells/μL 5 years after ART introduction, with a plasma HIV load &lt;1000 copies/mL</td>
<td>105 (35.8)</td>
<td>Univariate logistic regression</td>
<td>Older age, duration of HIV infection, HCV antibody positivity, CDC infection categories B and C, and lower baseline CD4+ T cell count</td>
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<tr>
<td>Moore et al. [10]</td>
<td>2005</td>
<td>1527 ART-naive patients</td>
<td>2 NRTIs plus a PI or 2 NRTIs plus an NNRTI</td>
<td>Increase in the CD4+ T cell count &lt;50 cells/μL 3–9 months after ART introduction, with a plasma HIV load &lt;500 copies/mL</td>
<td>235 (15.4)</td>
<td>Multivariate logistic regression</td>
<td>Older age and HAART backbone of 3TC plus ZDV</td>
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<tr>
<td>Nicastri et al. [11]</td>
<td>2005</td>
<td>2143 Patients (74.2% were NRTI experienced and 25.8% were NRTI naive)</td>
<td>2 NRTIs plus a PI</td>
<td>Increase in the CD4+ T cell count &lt;100 cells/μL 12 months after ART introduction, with a plasma HIV load &lt;500 copies/mL</td>
<td>336 (15.7)</td>
<td>Multivariate logistic regression</td>
<td>Older age, ART naive, and baseline CD4+ T cell count &gt;350 cells/μL</td>
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<tr>
<td>Gutiérrez et al. [12]</td>
<td>2008</td>
<td>650 ART-naive patients</td>
<td>2 NRTIs plus a PI, 2 NRTIs plus an NNRTI, 3 NRTIs, or an NNRTI plus a PI</td>
<td>Increase in the CD4+ T cell count &lt;50 cells/μL 12 months after ART introduction, with a plasma HIV load &lt;500 copies/mL</td>
<td>108 (16.6)</td>
<td>Univariate logistic regression</td>
<td>Older age, patient sex, lower baseline plasma HIV load, and higher baseline CD4+ T cell count</td>
</tr>
<tr>
<td>Tan et al. [13]</td>
<td>2008</td>
<td>404 ART-naive patients</td>
<td>2 NRTIs plus a PI, 2 NRTIs plus an NNRTI, or 3 NRTIs</td>
<td>Increase in the CD4+ T cell count &lt;50 cells/μL 3–9 months after ART introduction, with an undetectable plasma HIV load</td>
<td>35 (8.7)</td>
<td>Multivariate logistic regression</td>
<td>No factors</td>
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</table>

**NOTE.** CDC, Centers for Disease Control and Prevention; IDU, injection drug use; KS, Kaposi sarcoma; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine; ZDV, zidovudine.
INVESTIGATION OF THE PATHOGENETIC CORRELATES OF INRS: WHICH IMMUNOVIROLOGICAL AND GENETIC MECHANISMS LIMIT IMMUNE RECOVERY DURING LONG-TERM HAART?

Failure in De Novo CD4+ T Cell Production

The pathogenesis of immunological nonresponse may be secondary to specific failure of the T cell armamentarium machinery (i.e., failure of the bone marrow to produce hematopoietic stem cells) or to a deficiency in thymic output (figure 1) [35].

The role of bone marrow. Decreased bone marrow progenitor cell growth and abnormal stromal microenvironment have been described in patients with HIV/AIDS [36] and have been partly restored after the commencement of HAART [37, 38]. Recent observations support the hypothesis that the lack of immune recovery in INRs may be due, at least in part, to persistent bone marrow impairment, despite receipt of HAART, that is possibly characterized by altered clonogenic capability and stromal cell function (figure 1) [39–41].

The role of thymic output. The failure to restore circulating CD4+ T cells during HAART may partially be caused by deficiencies in thymopoietin [42–45]. Indeed, several studies have demonstrated a trend toward smaller thymuses and lower thymopoietin levels in INRs (figure 1) [35, 46–48]. Given that a hypofunctional thymus may account for the immunological failure in INRs, a question remains whether the thymus itself is unable to respond to thymopoietic signals (e.g., IL-7) or whether the latter are insufficient to drive thymic-dependent immune reconstitution.

The role of IL-7. IL-7, which is mainly produced by thymic and bone marrow stromal cells, is a vital cytokine for thymocyte development for which production is up-regulated in lymphopenic conditions [49, 50]. A relative deficiency in IL-7 production or function may occur in INRs. Studies have found that plasma IL-7 levels in INRs are comparable to those in patients who had complete responses, suggesting maintenance of the IL-7 compensatory loop [47, 48]. Marziali et al. [47] reported a reduction in IL-7R expression on CD4+ T cells obtained from INRs, compared with CD4+ T cells obtained from persons who had complete responses, as well as a positive correlation between peripheral percentage of CD4+ T cells and those expressing IL-7R, leading to speculation about defective IL-7R expression. Additional studies are needed to aid com-

Figure 1. Differences in CD4+ T cell dynamics between persons who experienced a full immunological response (FRs; A) and immunological nonresponders (INRs; B). Compared with FRs, INRs are notable for reduced bone marrow and thymic output of naive T cells in peripheral circulation, greater HIV- and antigen-driven T cell activation, and reduced content of T regulatory cells, ultimately leading to increased cellular death by apoptosis. Despite significantly lower CD4+ T cell counts in the periphery, a similar stimulation of the IL-7 compensatory loop is displayed by INRs and FRs. However, compared with FRs, INRs are characterized by reduced IL-7R expression on different T cell populations, thus potentially limiting the compensatory effect of IL-7. Different T cell pools are represented: recent thymic emigrants, naive T cells, resting memory T cells, activated T cells, T regulatory cells, and hematopoietic stem cell precursors (HSCPs). The size of the boxes and the number of cells represent the relative amount of each cell pool and are not to scale. IL-7R is represented on T cell surface according to its expression, not to scale. Ag, antigen.
Excessive CD4+ T Cell Destruction

As illustrated in figure 1, INRs may also be characterized by augmented levels of CD4+ T cell loss in the periphery [35].

CD4+ T cell hyperactivation. CD4+ T cell hyperactivation has been demonstrated to persist even after HAART virological suppression occurs and to have a significant effect on recovery of the CD4+ T cell count during HAART [52, 53]. Indeed, despite complete suppression of the HIV load, INRs maintain CD4+ T cell hyperactivation comparable to that in patients who have not experienced viral suppression (figure 1) [48, 54].

Although highlighting the possible pathogenetic role of enhanced CD4+ T cell activation in insufficient CD4+ T cell count recovery, these findings also raise questions on the driver(s) of persistently elevated CD4+ T cell activation.

Ongoing viral replication. Even in the context of complete viral suppression, INRs have been shown to have higher levels of proviral DNA in total, memory, and naive CD4+ T cells, reinforcing the role of increased HIV antigen–driven CD4+ T cell activation as a driving force of continuous loss of CD4+ T cells in INRs [48]. On the one hand, despite control of plasma viral loads, the persistence of residual low-level viral replication at levels less than the detection limit of the most-sensitive methods, either in blood or in other compartments, maintains the HIV DNA burden in the reservoir; on the other hand, it represents a continuous trigger of immune activation [55, 56].

Persistent antigenic stimulation. CD4+ T cell hyperactivation may also be secondary to ongoing chronic inflammatory disease. Recently, a pathogenetic model of increased translocation of microbial bioproducts from the gastrointestinal lumen has been proposed as a continuous trigger of immune activation in patients with HIV/AIDS [57, 58]. Brenchley et al. [59] elegantly demonstrated that high levels of plasma lipopolysaccharide—an indicator of microbial translocation—in HIV-infected patients correlate with immune hyperactivation and are only partially restored by HAART. We reported a consistent trend toward higher lipopolysaccharide levels in INRs, compared with levels in persons who had a complete response, that correlated with the proportion of activated Ki67+ CD4+ and CD8+ cells. Taken together, these data allow speculation that microbial translocation, by perpetuating peripheral CD4+ T cell activation, may contribute to the inefficient recovery in the CD4+ T cell count in INRs [60]. Consistent with this finding is the fact that HIV-driven dysfunction of CD4+ T cell homeostasis in the gut mucosa, with local immune activation, has been shown to persist after commencement of HAART [61–64]. However, a clear-cut correlation between mucosal immune restoration and immunological and clinical outcome during HAART is still missing [64, 65].

Immunoregulatory mechanisms. T regulatory cells are a specialized T cell subpopulation with the ability to down-modulate immune activation and function [66]. Indeed, Marziali et al. [47] reported a significant reduction in T regulatory cell count in INRs, compared with patients who had complete responses, inversely correlating with activated CD4+ T cells, allowing one to hypothesize that persistently low levels of T regulatory cells, which are unable to turn off immune activation, could partly account for immune reconstitution failure in INRs [47].

Genetic Influence

A role of genetic polymorphisms involved in CD4+ T cell homeostasis has also been postulated in dictating the magnitude of recovery in the CD4+ T cell count during HAART. In a recent multivariate analysis, Haas et al. [67] found a significant association between CD4+ T cell count recovery and polymorphisms in genes encoding TNF-related apoptosis-induced ligand, TNF-α, Bcl-2–interacting molecule, and IL-15/IL-15R. Similarly, diverse polymorphisms in chemokine or chemokine receptors and HLA genes have been associated with the response to HAART, although different association patterns were demonstrated by different authors [68–70]. In conclusion, it seems reasonable that multiple genetic variants may be involved in the pathogenesis of immunological nonresponse vis-a-vis complex immune phenotypes in these individuals.

INVESTIGATION OF THE THERAPEUTIC OPTIONS FOR INRS: WHICH STRATEGIES MAY IMPROVE IMMUNE RECOVERY IN INRS?

Having assessed the clinical risk and the immunological defects that may be potential targets for adjuvant approaches in INRs, additional questions arise on the actual direction for an effective therapeutic strategy. Should we aim at improving peripheral T cell production and expansion or rather, should we seek immune activation control, enhancing peripheral survival of CD4+ T cells?

MOLECULES THAT SUSTAIN THE CD4+ T CELL COUNT IN THE PERIPHERY

IL-2. Thus far, several controlled studies have been conducted to investigate the effect of IL-2 in INRs, concluding that IL-2 is safe and efficacious in inducing a rapid and significant reconstitution of the CD4+ T cell compartment, with no significant impact on HIV load [71–73]. Most interestingly, data showing no HIV-related events among IL-2–treated patients, compared with recipients of HAART alone, suggest that the IL-2–driven increases in the CD4+ T cell count may also be effective in preserving an adequate cellular immunity [72, 74–76], even though the ultimate evidence of IL-2 clinical impact is still being sought [14, 77].
Nonetheless, major constraints to the clinical use of IL-2 in INRs include a time-limited immune benefit in sustaining CD4+ T cell counts and inefficacy in a minor group of nonresponding patients. Although a possible way to overcome such limitations has recently been proposed (consisting of induction maintenance strategies of long-term IL-2 treatment [78]), it is clear that IL-2 immunotherapy alone for the treatment of INRs failed to meet the initial expectations. Given these controversies and possible drug-associated adverse effects in IL-2 recipients, DHHS guidelines recommend the use of IL-2 immunotherapy only in the context of clinical trials [14].

**IL-7.** Two recent trials have demonstrated a sustained dose-dependent increase in naive and memory CD4+ and CD8+ T cells after administration of IL-7 to HIV-infected patients [79–81]. However, the opportunity to use IL-7 as an immune adjuvant in INRs is still controversial, given evidence that endogenous plasma IL-7 levels are already elevated in INRs. In our opinion, a possible way to understand this controversy is analysis of IL-7 production and signaling in INRs that would yield evidence on the functional status of the IL-7 axis and, thus, to the possible benefits of its exogenous administration. However, DHHS guidelines recommend use of IL-7 immunotherapy only in the context of clinical trials [14].

**Modulation of T regulatory cells.** Although they are an intriguing target for immune therapy, no clear-cut consensus has been reached on whether and how to exogenously modulate T regulatory cell function and/or activity [82]. Thus far, data on the effects of IL-2 and IL-7 immunotherapy on T regulatory cells have been discordant [83, 84], indicating the importance of investigating the role of cytokine-based approaches to this particular T cell population.

**STRATEGIES AIMED AT TURNING OFF IMMUNE HYPERACTIVATION**

**Antiretroviral therapy strategies.** Differences in CD4+ T cell response may exist among different drug classes. Controversial data on a greater immunological efficacy of protease inhibitor–containing regimens have been generated [85]. Indeed, a recent randomized clinical trial that compared first-line regimens including nonnucleoside reverse-transcriptase inhibitors versus protease inhibitor reported a superior immune response to the latter regimen, but this occurred only in the long term, and there was doubt about its clinical significance [86]. Furthermore, data on thymidine analogue-associated mitochondrial toxicity and oxidative stress have accumulated recently. These findings suggest a role for thymidine analogues—including nucleoside reverse-transcriptase–based regimens—in cell dysfunction [87], possibly hampering recovery of the CD4+ T cell count.

The negative impact of low-level residual HIV levels to less than suppressive threshold during CD4+ immune recovery in INRs led to the hypothesis that intensification of HAART may improve immunological responses in INRs [88–92]. The availability of new drug classes, such as fusion and integrase inhibitors, which provide the strongest suppression of HIV loads and HIV DNA burden and the greatest immunological efficacy [93, 94], makes this issue more relevant and current. Recently, CCR5 antagonists have been suggested to have the potential to yield the greatest CD4+ T cell count gains, given their specific effect in the suppression of immune activation [95]. Indeed, a very recent meta-analysis investigated the differences in increases in the CD4+ T cell count among patients enrolled in phase II/III trials of new antiretrovirals and found an enhanced CD4+ T cell response in recipients of CCR5 antagonist–containing regimens, compared with recipients of other regimens, that was independent of suppression of the HIV load [96]. Even if the durability and clinical meaning of this finding remain to be determined, these data support deeper investigation of this approach in INRs.

In addition to identification of the “best” antiretroviral strategy for INRs, a major challenge for clinicians is the identification of the “best” CD4+ T cell range for initiation of HAART. Indeed, given the persistence of different trajectories for the recovery of the CD4+ T cell count based on different baseline ranks, with some individuals barely achieving a protective CD4+ T cell count of <200 cells/μL after 5 years of HAART, the impact of commencement of HAART should be evaluated in patients with a high risk of becoming INRs, such as older patients [21, 97].

**Immunosuppressive agents.** Because there has been interest in “turning off” excessive immune activation, various immunosuppressive agents have been investigated [98–103]. In addition to providing positive data on the efficacious control of immune activation, these trials have also demonstrated an immunological benefit in terms of increases in the CD4+ T cell count [99, 101]. Unfortunately, trials assessing the benefit of administration of immunosuppressive drugs to INRs are still lacking, the major concern being the potential risk of administering immunosuppressive agents to patients with a highly depleted CD4+ T cell compartment. In our opinion, a promising approach may be the identification of targeted interventions to interact with pathways of immune activation that are specific to INRs, thus allowing for a more efficacious and less dangerous intervention.

**CONCLUSIONS AND FUTURE DIRECTIONS**

The absence of a recovery in the CD4+ T cell count during long-term, virologically suppressive HAART is an unquestionable source of anxiety to HIV-infected patients and their treating clinicians, given the long-term risks of disease progression and death, underscoring the need for means of identifying early predictive factors and treatment options. Furthermore, INRs may be viewed as a merging point between clinical practice and basic science: while HIV/AIDS clinicians investigate which
treatment most effectively sustains peripheral the CD4+ T cell count, bench scientists, by investigating the immunovirological pathways behind insufficient recovery of the CD4+ T cell count, may provide tools both to forecast immunological failure and to investigate new therapeutic strategies. Unfortunately, even though several approaches have been suggested and investigated, no consensus has been reached yet on the most efficacious treatment for immunological nonresponse. Thus, we are now facing a dichotomy, whereby the ever-growing list of new-class antiretrovirals provides us with the most potent weapons against HIV/AIDS, while we still lack a full grasp on the most proper means of administering them to INRs. However, even though such research has not yet provided a unique treatment protocol, research has revealed diverse immunovirological and even genetic patterns behind impaired CD4+ T cell count recovery, indicating the need for novel treatment scenarios tailored to different INRs, possibly including antiretrovirals and immunomodulants. Thus, with regard to the frustrating lack of concrete therapeutic options, we strongly advocate the continuous investigation of the correlates of the failure of CD4+ T cell counts to recover during HAART to aid HIV/AIDS clinicians who treat INRs today, to find the most effective and timely therapeutic options in the future.

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