**AIDS** Reviews 2006;8:88-97

# Failure to Reconstitute CD4+ T-Cells Despite Suppression of HIV Replication under HAART

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## Abstract

***HAART in HIV-1-infected individuals has a broad spectrum of clinical outcomes. In the majority of patients, plasma viral load becomes undetectable and CD4+ T-cells increase over time. However, in a number of subjects a discrepancy between plasma viral load and the CD4+ T-cell recovery is observed. CD4+ T-cell count can rise despite persistently detectable plasma viral load (virologic nonresponders), or conversely does not increase despite full plasma viral load suppression (immunologic nonresponder).***

***Defective immune reconstitution may depend on several factors including previous therapeutic failure, duration of antiretroviral therapy, low CD4+ T-cell count at the initiation of HAART, advanced stage of disease, low adherence to HAART, and previous treatment interruption. There is no definitive evidence that age, viral strain/clade, or host genetic factors play a role in these different responses to HAART. The roles of T-cell subsets, thymic function, and cytokines have been investigated. The increased T-cell activation/apoptosis has been associated with a lack of effective immunologic response. Unabated virologic replication in lymphoid tissues, despite undetectable plasma viral load, has been proposed as the underlying mechanism of cellular activation. However, this "paradoxical response" probably can be associated with other events. Insufficient CD4+ T-cell repopulation of lymphoid tissues may be due to a thymus failure or a defect in bone marrow function. Lifelong infection, the toxic effect of antiviral drugs on T- and B-cell precursors, the stage of disease, and the low number of CD4+ T-cells before HAART may also account for thymus exhaustion and insufficient T-cell renewal. Finally, an imbalance in the production of cytokines such as TNF, IL-2 and IL-7 may also be a crucial event for the induction of immune system failure.***

***In patients in which CD4+ T-cells are not increased by HAART, therapeutic strategies aimed at increasing these cells and reducing the risk of infections are needed. IL-2 and/or other cytokines may be of benefit in this setting.***

***Some antiviral drugs may be better than others in immunologic reconstitution. Protease inhibitors may have additional, independent positive effects on the immune system. On the other hand, there may be little rationale for using immunosuppressive agents such as cyclosporine or hydroxyurea in this subgroup of immunologic nonresponder patients, as these molecules may increase T-cell decline and/or favor susceptibility to infections.*** **(AIDS Reviews 2006;8:88-97)**

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## Key words

***HIV. Immunology. HAART.***

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## Introduction

After the introduction of highly active antiretroviral therapy (HAART) several patterns of response have been observed in patients with different stages of disease caused by human immunodeficiency virus type 1

(HIV-1)[1]. With the combinations of three different classes of antiretroviral drugs, the majority of individuals that adhere to treatment show a good response as defined by the decrease of viral load to undetectable levels and an immunologic reconstitution with a significant increase of CD4+ T-cell levels from baseline values[2,3]. However, immunologic response shows a large individual variability. Some subjects with only modest virologic response occasionally have large rises of CD4+ T-cells, whereas others with undetectable viral load show only small increases of CD4+ T-cells[4]. The time and extent of immune reconstitution depend on several factors. Some are immunologic, others are virologic or host-related (i.e. genetic) factors, but all might play an important role in reconstitution of the immune system[5,6].

There is no agreement on the definition of good immune response, but in general a significant increase up to 20-30% of the CD4+ T-cell number from baseline value in the first 6-12 months of HAART has been considered positive[1]. This immune response has been observed in 70-80% of treated patients with undetectable plasma viral load (pVL). Apart from the treatment success, a certain percentage of patients may present a so-called "paradoxical response", defined as a discrepancy between the pVL values and the CD4+ T-cell count[7].

Two main situations relevant for the course of the disease may occur. The first is characterized by a CD4+ T-cell count rise despite persistently detectable pVL as defined in virologic nonresponders and immunologic responder patients. This may be due to a selection of mutant viruses with low fitness induced by HAART compared to wild-type viruses, or by a modest benefit from antiviral drugs that causes only a partial reduction of pVL in comparison to baseline values[8-10]. This condition could also be sustained, with some benefits to the immune system, directly induced by protease inhibitors (PI) that may act independently from their antiviral effects[11-13].

The second type of "paradoxical response" occurs when the CD4+ T-cell count does not increase despite a full suppression of viral replication: this condition includes virologic responders but immunologic nonresponder individuals, briefly defined as immunologic nonresponders. The CD4+ T-cell count may remain stable from baseline values or below the critical threshold of 200 cell/mm$^3$. This could occur in 10-27% of patients treated with HAART[14-16]. Several other papers reported patients treated with HAART with a delayed immune response. In these patients, immunologic response may occur after one year from the beginning of HAART because of the slow decline of pVL[5]. We will not include these patients in the definition of immunologic nonresponder patients.

Since low levels of viral replication are also able to damage the immune system, we believe that only the patients with sustained undetectable viral load (< 50 HIV-RNA copies/ml) for a prolonged period (at least one year) of HAART may be considered virologic responders. In the majority of studies, the rise of CD4+ T-cells was considered defective when the CD4+ T-cells increased < 50/mm$^3$ from baseline in six months, while in others they were considered defective when they did not increase, or decline at all, despite sustained undetectable viral load[15-17]. We suggest in the future considering as immunologic nonresponders only those patients that do not show any (or a very low) increase in their CD4+ T-cells (< 50/mm$^3$) after one year of continuous HAART because these subjects will probably never ameliorate their immune response.

Several factors are associated with impaired CD4+ T-cell reconstitution, including older age, previous therapeutic failure, previous duration of antiretroviral therapy, low level of CD4+ T-cells before HAART, persistent HIV-1 replication at lymphoid tissues, low adherence to HAART, and previous treatment interruption[17].

The studies describing HIV-1 positive patients under HAART with a good viral control and a poor immunologic response were of two types: the first were retrospective cohort (monocentric or multicentric) and the second prospective monocentric[9,18-21]. This difference demonstrates one of the difficulties in having homogeneous data. In addition, a variation also depends on the heterogeneity of the cohorts, such as demographics, CDC stage, years of infection, previous therapy, nadir of CD4+ T-cells, levels of pVL, presence of coinfections, type of HAART, associated treatments for opportunistic infections, and adherence to therapy. In some patients the absence of CD4+ T-cell increase was observed after a period of 6-12 months, in others only within the first six months[5,22].

Risk factors for a poor immune reconstitution after HAART have been analyzed by several investigators in large, multicenter studies by using a logistic regression model, or in a single center with a low number of enrolled patients by sample statistical methods. Other studies were conducted in order to investigate the biologic factors responsible for the absence of immune response. We shall briefly focus our attention on the following factors summarized in table 1.

## Factors involved in the pathogenesis of immunologic nonresponse despite effective HAART

### *Demographic factors*

An important sex-related difference in immune recovery is suggested in several studies, showing a remarkably greater increase in CD4+ T-cell counts after HAART in women[23-25]. None of these studies reported a significant relevance of ethnic origin (Hispanic, Caucasian, Black, Asian) or HIV-1 transmission groups (drug abusers, previous drug abusers, homosexuals, heterosexuals). No studies are available on hemophiliacs or blood-transfused individuals, probably because of the low number of persons involved in these trials. In contrast, the majority of papers reported the importance of age. In the evaluation of immune recovery under HAART, younger age predicted greater early CD4+ T-cell gain, supporting the importance of thymic function or its surrogate[6,26,27]. Older patients were more likely to experience poorer immunologic response[28]. In one study, older age seems to correlate with a decreased number of low responder patients to HAART[6], while in another paper advanced age seems not to be correlated to the absence of immune response; however no statistical difference has been reported[29]. These discrepancies probably are correlated to the low number of investigated persons or to the different stage of their disease[29].

### *Stage of HIV disease*

The stage of the disease, according to the CDC classification, is not relevant to the degree of the immune reconstitution. In fact, patients belonging to stage C, corresponding to full-blown AIDS, seem to respond to HAART as well as patients in stage A or B, whereas in another study, patients with previous AIDS seem to have lesser immune response than stage B or A. The duration of the disease as evaluated from the period of the seroconversion or from the diagnosis of AIDS is not relevant in terms of the presence or absence of immune reconstitution[5,6,21,29].

### *Drug-naive or experienced patients and type of therapy*

No differences have been reported on the degree of immune reconstitution according to the type of HAART (PI-sparing regimen or not). In a retrospective cohort study on 600 antiretroviral-naive patients who started HAART in 1996, PI, boosted PI and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are not significantly different in achieving increased CD4+ T-cell counts in individuals who commence therapy with a low CD4+ T-cell count (< 200 cells/mm$^3$)[30]. In early stages of HIV-1 infection, a PI-based regimen was more effective than an NNRTI-based treatment in reducing plasma and lymphoid tissue-associated HIV-RNA to undetectable levels. However, the effectiveness in improving the immune system function was similar in both groups, although the PI was more effective in increasing the CD4+ T-cell counts and in reducing disease-induced T-cell activation[31,32]. A therapeutic PI-containing regimen may have a positive action on the recovery of CD4+ T-cell numbers as well as of T-cell functions that is independent from the antiviral effect[33-36]. Recently, some investigators demonstrated a decrease of apoptosis of T-cell subsets and an increase of colony-forming cells (CFC) at bone marrow level in patients under HAART[37]. Such positive effects on the immune system have also been demonstrated *in vitro* in bone marrow cells of normal subjects exposed to PI[13].

An increased prevalence of immunologic nonresponse in patients treated with two nucleoside reverse transcriptase inhibitors (NRTI) plus tipranavir in comparison to one NRTI plus one NNRTI or a PI plus tipranavir has been recently described[38]. In this case it may be hypothesized that the combination of two NRTI may be responsible for the accumulation of purine toxic metabolites with a situation similar to that observed in children affected by congenital deficiency of purine nucleoside phosphorylase (PNP)[39]. The accumulation of purine bases may be responsible for the damage in cells with a high proliferative activity, such as thymocytes, bone marrow cells, T- and B-cells, platelets, and erythrocyte progenitor cells[40].

### *Role of coinfections*

In some studies[41,42], hepatitis C virus (HCV) coinfection has been associated with a poorer immunologic response to HAART and a greater risk of clinical progression, although not all investigators have agreed on this[22]. Because HCV replicates in lymphoid tissue in coinfected patients, it has been suggested that HCV is directly pathogenic to the immune system and this may impede the immune recovery[42]. Moreover, in a recent meta-analysis by Miller, et al.[43] it has been shown that patients with HIV-HCV coinfection have less immune reconstitution, as determined by CD4+ T-cell counts after 48 weeks of HAART, in comparison with patients with HIV-1 infection alone.

**Table 1. Factors involved in the immunologic nonresponder status**

| Cause | Degree of evidence | References |
|---|---|---|
| Residual viral replication in tissues | evidence | Furtado et al. N Engl J Med 1999<br>Garcia, et al. J Acquir Immune Defic Syndr 2004<br>Ostrowski, et al. J Infect Dis 2005 |
| Type of virus | not defined | Hejdeman, et al. AIDS Res Hum Retroviruses 2001 |
| CDC Stage (3 >1 and 2) | controversial data | Palella, et al. N Engl J Med 1998<br>Egger, et al. Lancet 2002 |
| Previous type of therapy (mono or dual therapy or three NRTI) | evidence | Viora, et al. Immul Infectious Dis 1994<br>Grabar, et al. Ann Intern Med 2000<br>Benveniste, et al. Eur J Clin Microbiol Infect Dis 2001 |
| Previous HAART failure | evidence | Knobel, et al. AIDS Patient Care STDs 2001 |
| Adherence | controversial data | Reynolds, et al. AIDS Reader 1999<br>Casado, et al. Antivir Ther 1999<br>Smith, et al. Patient Educ Couns 2003 |
| Age and race | not defined | Viard, et al. J Infect Dis 2001<br>Kaufmann, et al. AIDS 2002<br>Frater, et al. AIDS 2002<br>Tumbarello, et al. BMC Infect Dis 2004 |
| Gender | controversial data | Moore, et al. J Acquir Immune Defic Syndr 2001<br>Poundstone, et al. AIDS 2001 |
| Genetic factors | not defined | Nasi, et al. Immunogenetics 2005 |
| Baseline CD4+ T-cell levels (< 200/mm$^3$) | strong evidence | Grabar, et al. Ann Intern Med 2000<br>Kaufmann, et al. AIDS 2002 |
| Bone marrow failure | evidence | Isgrò, et al. AIDS Res Hum Retroviruses 2005 |
| Thymus failure | evidence | Teixeira, et al. AIDS 2001 |
| Defective naive T-cell production | strong evidence | Fleury, et al. Proc Natl Acad Sci USA 2000<br>Hellerstein, et al. Nat Med 1999 |
| Increased (or persistent) T-cell activation and apoptosis | strong evidence | Sloand, et al. Blood 1999<br>Benveniste, et al. J Infect Dis 2005 |

## General immunologic factors

Several immunologic factors were independently associated with a poor immunologic reconstitution after HAART initiation and might be involved in immunologic nonresponder status. Some of them have been clearly demonstrated in the past few years.

Several groups attempted to study the relationship between full viral suppression and CD4+ T-cell gains[5,9]. Some authors have reported data on long-term CD4+ T-cell trends in patients with sustained HAART-induced viral suppression, showing a failure to achieve a CD4+ T-cell count > 500/mm$^3$ in the majority of patients with CD4+ T-cells < 200/mm$^3$ pretherapy[6,44]. On the contrary, according to Hunt, et al.[23], irreversible depletion of circulating CD4+ T-cells appears to be uncommon in patients with advanced immunodeficiency (CD4+ < 350/mm$^3$) as long as durable treatment-mediated viral suppression can be maintained. Moreover, starting HAART with more severe immune suppression (CD4+ < 100/mm$^3$) does not seem to influence the long-term immune recovery in one study by Smith, et al.[45]. In fact, those starting HAART at low CD4+ T-cell levels appeared to respond in a similar manner to those starting at higher CD4+ T-cell counts. Similar results were reached in another retrospective study[46], showing that immune recovery is possible regardless of baseline CD4+ T-cell count. In HIV-1-infected subjects, the rate of CD4+ T-cell gain is comparable after one year of commencing HAART to the rate of naive CD4+ T-cell increase observed in HIV-1-uninfected adults following intensive chemotherapy[47]. This slow

rate of CD4+ T-cell recovery may be also due to an HIV-1-induced process that limits T-cell production (i.e. thymic or bone marrow damage) or enhances peripheral destruction, because T-cell activation is dependent on other stimuli[48-50]. Moreover, in another paper we demonstrated that immune recovery, as tested by T-cell function assays and CD4+ T-cell subsets, is less pronounced in patients starting HAART with severe immunodeficiency[51]. According with these findings, a depressed bone marrow activity with impaired numbers of CFC and long-term culture-initiating cells (LTC-IC) have been observed before therapy in advanced patients treated with HAART. Controlling HIV-1 replication by HAART could determine a restoration of stem cell activity, probably because of the suppression of factors that inhibit normal hematopoiesis[50,51].

Anthony, et al.[52] showed that a persistently elevated level of CD4+ T-cell turnover after HAART is associated with incomplete CD4+ T-cell recovery despite that the HIV-RNA level was < 50 copies/ml. The increased levels of T-cell turnover are closely linked to immune activation, revealed by the persistent elevation of CD4+ and CD8+ T-cells expressing activation markers[53], even after long-term HAART. A possible explanation for this ongoing T-cell activation and turnover is that compartmentalized viral antigens provide continuous immune stimulation[54]. Moreover, in patients initiating HAART with CD4+ T-cell counts < 350/mm$^3$, these findings are more pronounced than in subjects with less severe immune suppression. These data strongly suggest that T-cell activation and turnover may influence the potential for immune reconstitution in patients with low CD4+ T-cells before therapy[55,56]. We recently studied a group of immunologic nonresponder patients demonstrating a defective proliferation of naive T-cells, particularly of thymic origin, associated with increased expression of CD95 on CD4+ T-cells. In addition, a reduced proliferation of progenitor cells, together with decreased production of interleukin (IL)-2, interferon-γ (IFN-γ) and IL-12 and increased values of tumor necrosis factor (TNF)-β has been observed at bone marrow level (Marziali M, in preparation). These data indicate the important role of cytokine production in immune reconstitution.

## Specific immunologic factors

### *Immune activation*

Persistent chronic activation of T-cells is a characteristic of HIV-1-infected immunologic nonresponder subjects and may contribute in explaining the immunologic nonresponse status. Several mechanisms are involved in this condition and lead to an upregulation of apoptosis[54,57]. This upregulation is suggested by the presence of high levels of activation marker expressions on the T-cell surface of immunologic nonresponder patients. This may be explained by the persistence of low level viral replication *in vivo*, perhaps in compartments not accessible for the measurements. We also found that when studying T-cell receptor expression during several years of effective HAART, an increased expansion of both CD4+ and CD8+ T-cell repertoire could be observed[58]. So, despite the absence of viral replication in plasma, stimulation of the immune system continues to occur at lymphoid tissue level for the persistent activation of memory cells[54]. An alternative explanation is that other antigenic stimuli by viral or bacterial antigens may be involved in chronic immune stimulation in HIV-1 infection[58]. It is well known that regulatory T-cells, characterized by the expression of $CD4^+CD25^{bright}CD62L^{high}$ on their surface, are actively involved in the downregulation of the immune system. Recently, their loss during HIV-1 infection has been associated with the high levels of CD4+ and CD8+ T-cell activation in the advanced stages of the disease[59]. Moreover, it might be hypothesized that a persistent skewed rate of regulatory T-cells could be involved in the persistence of a low number of CD4+ T-cells in immunologic nonresponder subjects who show high levels of T-cell activation.

### *Immune phenotype of immunologic nonresponder patients*

In order to explain the pathogenesis of the failure of immune response, several investigators studied T-cell subsets, thymus function, and production of cytokines. In a recent paper, the two main characteristics observed were the increased mortality rate of T-cells and the decrease of proliferation and *de novo* central production of T-cells[21]. It has been observed that in these patients there is an increased apoptosis in comparison to immunologic responder subjects, and increased Fas activation both at peripheral blood and bone marrow levels. The mechanisms involved in this excessive apoptosis are still unclear. Persistent low levels of viral replication and/or an unbalanced pattern of cytokine production might be involved. In addition, after one year of HAART the immunologic nonresponder individuals showed lower levels of naive T-cells as tested by CD45RA+CD62L+ phenotype or by T-cell rearrangement excision circles (TREC) in comparison to normal controls or immunologic responder patients[60,61], confirming that thymopoiesis in these patients is altered.

In these immunologic nonresponder individuals there is also a defective production of some cytokines (i.e. IL-2, IL-4, IL-12), whereas the TNF levels are increased[62-64]. Besides the thymus defect, an impaired immune restoration in immunologic nonresponder subjects could be attributed to a defective activity of the other central immune system organ, the bone marrow[64]. According to our recent observations studying bone marrow progenitor cells activity in immunologic nonresponder patients, we were able to demonstrate a severe proliferative defect in bone marrow progenitor cells of these subjects using CFC assays[65].

The role of Fas/FasL interactions in the homeostasis of the immune system and during HIV-1 infection has been well known for several years[66,67]. Recently, the role of the Fas/FasL gene polymorphisms in the immune reconstitution after antiretroviral therapy was investigated[68], showing that some polymorphisms of these genes can affect the increase in CD4+ T-cells during HAART. Starting therapy with low CD4+ T-cell numbers in the presence of unfavorable Fas/FasL genes could be a cause of poor CD4+ T-cell recovery.

Due to the positive effects of IL-7 on survival and homeostatic proliferation of T-cells, a recent demonstration has shown that the downregulation of the alpha IL-7 receptor on T-cells correlates with the depletion of CD4+ T-cells in HIV-1 infected subjects, including increased concentration of serum IL-7[69].

## Virologic factors

It has recently been demonstrated that viral replication might continue in patients with undetectable HIV-RNA levels[70,71]. Intensification of HAART in this condition leads to significant reduction of virus replication and T-cell activation[72,73]. Low level viremia may be associated with T-cell activation and higher proviral DNA levels, and these findings indicate that periods of low level viremia during HAART are negatively associated with CD4+ T-cell gain and immune reconstitution[74]. Moreover, a higher proviral DNA is associated with an increased proportion of effector CD4+ T-cells and a reduction of naive CD4+ and CD8+ T-cells. So, the presence of proviral DNA interferes with immune reconstitution during HAART and this finding may be attributed to replication-competent or replication-defective genomes through the production of viral proteins. The presence of residual HIV-1 replication in central or peripheral lymphoid tissue through the mechanisms illustrated below could be one of the determinants of the immunologic nonresponder status[74].

## Therapeutic approaches for the correction of the immunologic nonresponder status

### *The role of IL-2*

Progressive depletion of CD4+ T-cells is associated with an increased risk of opportunistic infections and is the hallmark of HIV-1 disease. HAART has been shown to have a profound impact in reducing mortality, hospital admission and AIDS-defining illnesses also in subjects with discordant immuno-virologic response[75,76], but these findings were lost when the discordant status persisted during time[20]. IL-2 is a T-cell growth factor relevant for the function of the immune system[77]. HIV-1 infection is characterized by an impairment of antigen-induced IL-2 production[78,79]. Starting from 1995, several clinical studies[80,81] using intermittent administration of recombinant (r) IL-2, alone or in combination with antiretroviral therapy, in patients with HIV-1 infection have revealed that this regimen gives rise to significant and sustained increases in peripheral CD4+ T-cell counts without a significant impact on virus load[82,83]. Following rIL-2 administration, memory CD4+ T-cells initially contributed to the CD4+ T-cell increase, but the subsequent expansion of the CD4+ T-cell population was a consequence of an increase in naive T-cells. A significant rise in CD4+CD28+ T-cells (CD28 is a costimulatory molecule important for antigen presentation) was seen in the rIL-2 recipients. These findings also suggest that the expansion of T-cells achieved with the use of rIL-2 is functionally competent[84,85]. Consequently, rIL-2 has been proposed as the treatment of choice for immunologically discordant patients with low CD4+ T-cell counts after HAART. These patients have a higher risk of developing AIDS-defining events, and rIL-2 may increase CD4+ T-cell counts even in the presence of a severely immunocompromised condition (CD4+ < 50/mm$^3$) and should be considered as part of the treatment in patients with an immuno-virologic discordant response to HAART[86].

### *The possible role of immunosuppressive drugs, cytokine inhibitors and other cytokines in the correction of the immunologic nonresponder status*

#### Immunosuppressive drugs

To reduce immune activation and/or the apoptosis of T-cell subsets, some investigators attempted to use cyclosporine-A[87,88] or hydroxyurea, in addition to anti-

retroviral drugs, in the treatment of patients at different stages of HIV-1 disease[89,90]. At present, there are no studies with these drugs in immunologic nonresponder patients. We believe that in the immunologic nonresponder condition the theoretical advantage derived from the use of drugs capable of inducing a reduction of T-cell activation will be overwhelmed by the dangerous immunosuppressive effect exerted in patients with low CD4+ T-cell counts despite HAART.

### Anti-TNF treatments

Anti-TNF drugs have been successfully used in patients affected by rheumatoid arthritis and other autoimmune disorders, and the beneficial effects observed in these conditions have been correlated with the reduction of the immune activation that characterizes the disease, but at the cost of heightened susceptibility to a variety of infections[91]. The possible use of anti-TNF in the treatment of patients with HIV-1 infection, despite its ability to reduce immune activation of T-cells, could be dangerous due to the high risk of severe infections and tuberculosis in these patients[92]. Experience in treating individuals with HIV-1 infection with anti-TNF based therapies is limited, but collectively suggests that such therapies may be given with a reasonable ratio of benefits to risks only if the patients' underlying infections are controlled and they are not severely immunosuppressed[93-95].

### Other cytokines

IL-7 plays an important role at various stages of T-cell development, from the T-cell precursors at bone marrow level to the mature T-cells in the peripheral bloodstream. Despite the well-known thymopoietic and lymphopoietic effects of IL-7 in humans, its role in the course of HIV-1 disease is controversial. It has been demonstrated that IL-7 induces virus replication and increases proviral DNA levels in naturally infected CD8+ peripheral blood mononuclear cell (PBMC) cultures and augments naive T-cell susceptibility to HIV-1 *in vitro*[96,97]. Wang, et al.[98] showed that IL-7 was significantly more effective in enhancing HIV-1 proviral reactivation than either IL-2 alone or IL-2 combined with phytohemagglutinin (PHA) in CD8-depleted PBMC. IL-7 also showed a positive trend for inducing proviral reactivation from resting CD4+ T-cells from HIV-1-infected patients on suppressive HAART. However, studies in nonhuman primates infected with simian immunodeficiency virus (SIV) have shown that IL-7 administration could stimulate T-cell renewal and peripheral T-cell expansion without increasing viral replication[99,100]. Therefore, whether the beneficial effects on T-cell recovery will outweigh the risk of HIV-1 reactivation needs to be assessed in further studies. In HIV-1 infected subjects, we observed the decline of elevated stromal IL-7 levels when CD4+ T-cell recovery occurred following effective antiviral therapy[101]. In addition, elevated IL-7 levels have been observed in HIV-1 infected adults with low CD4+ T-cell counts. These findings suggest that IL-7, through its potent effect on mature T-cells, plays a central role in modulating peripheral T-cell expansion in the presence of T-cell depletion[102]. Another interesting cytokine is IL-15, which has been demonstrated to exert various roles in the innate and adaptive immune systems, including the development, activation, homing, and survival of immune effector T-cells. IL-15 plays a role in the survival and antigen-independent expansion of naive and memory CD8+ T-cells[103]. IL-15 production by PBMC was significantly decreased in antiretroviral-naive patients and in those with treatment failure. On the contrary, in patients with good response to HAART, IL-15 production was comparable to that of healthy donors[104]. IL-15 is also able to stimulate the anti-HIV-1 response, as determined by IFN-γ secretion *in vitro.* Recently, the adjuvant activity of recombinant human IL-7 (rhIL-7) and rhIL-15 has been studied by Melchionda, et al.[105]. The results confirm the adjuvant activity of rhIL-15 and demonstrate that rhIL-7 also serves as a potent vaccine adjuvant. In fact, IL-7 is able to broaden vaccinal immunity by augmenting responses to subdominant antigens and improving the survival of the CD8+ T-cell memory pool. These findings suggest that IL-15, as well as IL-7, or the combination of both, alone or in association with IL-2, could be used as immunomodulatory agents in a novel anti-HIV-1 strategy, particularly in patients with poor immunologic response after HAART[106]. However, only extensive trials with these cytokines will give answers on the safety and efficiency of this therapeutic approach in immunologic nonresponder patients.

## Conclusions

The persistence of a low grade virologic replication, as recently also confirmed in subjects who achieve full virologic suppression (HIV-RNA < 50 copies/ml) during HAART, has been proposed as one of the causes of cellular activation and increased apoptosis associated with the occurrence of a discordant response. There is no difference in the burden of proviral DNA between

immunologic responders and those subjects who do not show any increase in CD4+ T-cells. This "paradoxical response" probably recognizes the intervention of other mechanisms; differences in the capability of achieving an extensive immune repopulation might be altered in these patients due to a thymus failure or to a defect at the bone marrow precursor level. The real problem is that, despite several hypothetical mechanisms proposed so far, we do not know exactly why CD4+ T-cells decrease in the course of HIV-1 infection. What are the true causes of the progressive immune system depletion? Probably the viral replication control achieved using HAART is able to positively act on some mechanisms involved in the CD4+ T-cell depletion associated with HIV-1 disease, but not in all individuals. In other subjects, perhaps with different genetic characteristics, or in whom the immune system damage has been more pronounced, the antiretroviral treatment also fails to partially reconstitute the immune system. Immunologic nonresponder patients actually represent a paradigm of our poor knowledge on several pathogenetic aspects of HIV-1 disease. This condition urges appropriately based guidelines regarding both structural interventions to improve therapeutic strategies to stimulate immune system and to reduce the higher risk of opportunistic infections.

## Acknowledgements

This paper was supported by Istituto Superiore di Sanità grants nr. 40F.3, 40F.39 and 40F.53 (2004). We would like to thank Prof. R. Paganelli for his contribution in the discussion of this paper.

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