HOT TOPICS

Interleukin-7 in HIV pathogenesis and therapy

Ann Chahroudi[1], Guido Silvestri[2]

[1] Division of Infectious Disease, Department of Pediatrics, Emory University School of Medicine
[2] Department of Pathology and Laboratory Medicine, Emory University School of Medicine, and Yerkes National Primate Research Center, Atlanta, USA

Correspondence: Dr. G. Silvestri, Yerkes National Primate Research Center, 954 Gatewood Rd NE, Atlanta, GA 30329, USA <gsilves@emory.edu>

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ABSTRACT. Interleukin-7 (IL-7) is a γ-chain cytokine that plays a key role in T cell development and homeostasis by signaling through its cognate receptor, IL-7R or CD127, and inducing T cell survival and/or proliferation. Owing to its ability to promote CD4+ T cell homeostasis, IL-7 has elicited significant interest as a potential immunotherapy for HIV-infected individuals. Indeed, several studies have indicated that progressive HIV infection is associated with a complex dysregulation of the IL-7/IL-7R pathway consisting of increased plasma levels of this cytokine coupled with decreased percentages of CD4+ and CD8+ T cells expressing CD127. Administration of IL-7 to antiretroviral-treated HIV-infected individuals results in a selective increase in the fraction of naive and central-memory CD4+ T cells, suggesting a beneficial effect on overall CD4+ T cell function. For this reason, and given its potential role in depleting the reservoirs of latently infected CD4+ T cells, IL-7 therapy can be considered a promising approach for improving immune function in HIV-infected individuals.

Keywords: interleukin-7, human immunodeficiency virus, CD127, central memory, immunotherapy

BIOLOGY OF INTERLEUKIN-7 AND ITS RECEPTOR

Interleukin-7 (IL-7) is a cytokine and growth factor that plays a non-redundant role in T cell development, survival, and homeostasis. Owing to its ability to stimulate thymopoesis, as well as homeostatic proliferation and survival of peripheral T cells, IL-7 has a profound effect on adaptive immunity [1]. Of note, the effects of IL-7 on thymic and peripheral T cells involve both CD4+ and CD8+ cells, with homeostatic proliferation of naive T cells occurring in response to low TCR affinity antigens, while the pool of long-lived, central memory cells is maintained by IL-7R signaling without TCR stimulation [2]. In humans, defects in the alpha chain of the IL-7 receptor (or CD127) results in a SCID phenotype characterized by a complete lack of T cells, but normal B cells and NK cells [3]. In mice, but not in humans, IL-7 has also been shown to be critical for B cell development [4]. IL-7 is constitutively produced in stromal, epithelial, and endothelial cells of lymphoid tissues (primarily the thymus and bone marrow) [2]. The major producers of IL-7 in lymph nodes appear to be fibroblastic reticular cells in the T cell zone [5]. Some mononuclear cells, including dendritic cells and macrophages, also produce IL-7 [2].

The IL-7 receptor (IL-7R) is a dimeric complex composed of a high affinity alpha chain or CD127 and the common gamma chain or CD132, which it has in common with the cytokines IL-2, IL-4, IL-9, IL-15, and IL-21 [6]. CD127 is expressed early in thymopoesis and on peripheral naive as well as central memory T cells; it is not expressed on effector or effector memory T cells [6]. CD132 is expressed throughout T cell development; thus, the presence of CD127 on the cell surface is the primary determinant of responsiveness to IL-7. In a negative feedback mechanism, IL-7 down-regulates expression of CD127 on T cells [7]. Importantly, the expression of CD127 influences which effectors become memory cells; those that remain CD127 negative are committed to die during the contraction phase of T cell responses [7]. Binding of IL-7 to the IL-7R results in activation of the JAK/STAT pathway. This is followed by induction of the anti-apoptotic mitochondrial protein Bcl-2 and other family members, with subsequent protection of T cells from programmed cell death [2]. IL-7 binding to its receptor also causes activation of the PI3K pathway that triggers T cell proliferation [2]. Similar to humans, in rhesus macaques, IL-7 has been shown to drive naive T cells to acquire a memory phenotype as well as to induce cycling of memory T cells [8].

THE IL-7/IL-7R PATHWAY IN HIV AND SIV INFECTIONS

Pathogenic HIV infection of humans and SIVmac infection of macaques induce a large series of immunological

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abnormalities that eventually lead to a state of severe immune deficiency defined as AIDS. At the core of the HIV- and SIV-associated immune dysfunction is the fact that these infections cause a progressive and irreversible loss of normal CD4+ T cell homeostasis that manifests itself in many ways, including: *(i)* low CD4+ T cell counts; *(ii)* relative decrease in naive and central-memory CD4+ T cells associated with increased fractions of effector-memory CD4+ T cells; *(iii)* increased fractions of activated and/or proliferating CD4+ T cells; *(iv)* depletion of CD4+ T cells from both lymph nodes and mucosal tissues, with preferential loss of IL-17 producing cells (Th17); and *(v)* reduced proliferative ability and cytokine production by CD4+ T cells [9]. The discovery of IL-7 as a potent CD4+ T-cell-tropic cytokine prompted a series of studies of its potential role in the pathogenesis of HIV infection and AIDS. Increased levels of circulating IL-7 were observed during HIV infection, as well as in other conditions associated with lymphopenia, including chemotherapy and bone marrow transplantation. In particular, an inverse relationship between plasma levels of IL-7 and CD4+ T cell counts was found in HIV-infected patients, thus suggesting that increased production of IL-7 represents a homeostatic response to HIV-associated CD4+ T cell depletion [10]. This hypothesis is consistent with the observation that IL-7 levels typically rise in the late stages of infection, particularly when CD4+ T cell counts fall below 200 cells/uL [10]. Consistent with this paradigm is a study demonstrating that HIV-infected, long-term non-progressors have lower levels of IL-7 in their plasma compared to patients who progress to AIDS [11]. Unfortunately, these increased levels of IL-7 are not sufficient to maintain T cell homeostasis, since in the absence of antiretroviral therapy most HIV-infected patients will develop progressive CD4+ T cell decline and clinical signs of AIDS. An alternative hypothesis to explain the inverse relationship between IL-7 levels and CD4+ T cell counts is that increased levels of this cytokine result from decreased numbers of circulating CD127+ T cells resulting in reduced consumption of the cytokine [12]. Along these lines, it was proposed that owing to CD4+ T cell depletion in HIV infection, there is less competition for IL-7, thus resulting in expansion of CD8+ T cells [13]. Later in the natural history of HIV infection, when CD8+ T cells are becoming depleted and/or exhausted, increased circulating IL-7 may reflect both a homeostatic signal for increased production and reduced overall consumption.

Perhaps not surprisingly, a correlation between increase in IL-7 levels and disease progression has also been found following SIVmac239 infection of rhesus macaques [14]. Similar to that which was observed in HIV-infected individuals, the elevated plasma levels of IL-7 found in SIV-infected macaques were not associated with restoration of CD4+ T cell homeostasis. In the rare macaques that display a slow-progressor phenotype with low viral loads, IL-7 levels are similarly increased compared to the normal, progressor macaques, even though CD4+ T cell counts are relatively normal [14]. This interesting observation suggests that it is the level of virus replication, rather than IL-7, that appears to have the greatest effect on disease progression, although the interplay of these factors is probably complex. Of note, a timely increase in the plasma levels of IL-7 was observed in the early stages of non-pathogenic SIV infection of sooty mangabeys, a natural host African monkeys species in which infection is associated with preserved CD4+ T cell homeostasis despite continuous high-level virus replication [15]. This apparent beneficial effect of IL-7 on CD4+ T cell homeostasis suggests a potentially important role for IL-7 early in this model of non-pathogenic SIV infection. This idea is supported by the observation that, in SIV-infected mangabeys, increased levels of bone marrow CD4+ T cell proliferation are associated with better preservation of overall CD4+ T cell homeostasis [16]. Pathogenic HIV and SIV infections are also associated with a complex dysregulation of the expression of the IL-7 receptor, which is commonly assessed by staining for the alpha-chain CD127. Several studies have demonstrated that HIV infection is associated with a progressive reduction of the fraction of both CD4+CD127+ and CD8+CD127+ T cell subsets that often declines below 50% of peripheral T cells [17-21]. In HIV-infected individuals the loss of CD127 expression on CD8+ T cells defines an expansion of a subset of cells, specific for HIV as well as other antigens, that show phenotypic as well as functional features of effector T cells [18]. These CD8+CD127- cells do not express CCR7 or CD62L and produce IFNγ, but not IL-2. Of note, the levels of CD8+CD127- T cells in HIV-infected persons correlated directly with the main markers of disease progression (*i.e.* plasma viremia and CD4+ T cell count), as well as with the indices of overall T cell activation [18]. CD4+ T cells of HIV-infected individuals display a less dramatic reduction in the fraction of CD127 expression when compared to CD8+ T cells [19, 20]. Dunham *et al.* have shown that HIV infection is associated with a relative expansion of effector-like (*i.e.* IFNγ-producing and perforin-expressing) CD4+CD127- T cells that correlates directly with the levels of total CD4+ T cell depletion and immune activation [22]. The HIV-associated perturbation of the IL-7/IL-7R pathway may also involve an abnormal activation of the JAK/STAT5 pathway [23].Using the rhesus macaque model, it was demonstrated that SIV infection also results in a loss of CD127+ T cells, both CD4+ and CD8+, in the blood, spleen, GI tract and GU tract, when compared to uninfected macaques [24]. The decrease in CD127-expressing cells correlated directly with the CD4+ T cell count. While the mechanism for the observed reduced fraction of CD127+ T cells during HIV and SIV infections has not been fully elucidated, several theories have been proposed, including preferential infection and death of CD127+ cells, chronic antigen stimulation, expansion of CD127 negative cells, negative feedback from increased IL-7 levels, and an effect of HIV Tat protein [13].

An additional role of IL-7 in T cell homeostasis involves influencing CD95 (Fas)-mediated apoptosis. IL-7 has been shown to increase the expression of CD95 on CD127+ T cells (both naive and memory populations), and thus potentially promote the CD95-dependent activation-induced cell death that is present during HIV infection [25-27]. In a contrasting role, IL-7 has also

been shown to protect CD4+ and CD8+ T cells from HIV-induced apoptosis by upregulating Bcl-2 [28, 29], although this finding is controversial [30]. Thus, chronically elevated levels of IL-7, in the setting of T cell depletion induced by HIV, may support T cell reconstitution and survival as well as increased immune activation and T cell apoptosis. This apparent paradox emphasizes the complexity of the role of IL-7 in T cell homeostasis, under normal conditions and after infection with HIV.

In addition to the direct effects of IL-7 on the immune system, several groups have reported that IL-7 enhances HIV replication. Modulation of HIV transcription by IL-7-mediated signaling, following engagement of its receptor, may occur as a consequence of activation of STAT5 binding to the HIV LTR [31]. IL-7 both increases the susceptibility of naive $CD4^+$ T cells to HIV infection and enhances HIV replication in these cells [32, 33]. Importantly, IL-7 has been demonstrated to induce HIV replication by latently infected cells of HIV-infected patients *in vitro* [34, 35]. This effect of IL-7 has a potential therapeutic role during HIV infection if, in conjunction with ART, virus replication can be activated from latently infected cells and then targeted by drugs. It should be noted however, that administration of high doses of exogenous IL-7 to non-human primates does not impact SIV plasma viremia [36-38], thus calling into question the *in vivo* significance of the above *in vitro* studies.

IL-7 IN HIV THERAPY: PRE-CLINICAL AND CLINICAL TRIALS

Owing to its potentially beneficial effect on CD4+ T cell homeostasis, IL-7 has been tested as immunotherapy for HIV and SIV infection. The primary goal of this intervention was to increase the CD4+ T cell count by selectively expanding the pool of naive and central-memory cells that are known to express CD127 and to be progressively depleted during pathogenic HIV and SIV infection. In this context, the strongest effect on T cell reconstitution by exogenous IL-7 would, in theory, be obtained when patients are treated at earlier stages of infection, *i.e.* when there is still a sizeable population of CD127+ naive and central-memory CD4+ T cells that can be successfully expanded. In contrast, a less dramatic effect may be expected in patients with severe CD4+ T cell depletion and the presence of few CD127+ cells within the CD4+ T cell pool, *i.e.* a situation in which even major increases in endogenous IL-7 do not effectively replenish the CD4+ T cell pool. As such, providing IL-7 as an immune-based adjunct to optimal background antiretroviral therapy earlier in the course of infection would be expected to boost CD4+ T cell counts more rapidly and/or to levels above those obtained by ART alone. In this context, a point to emphasize is that the expected effect of exogenous IL-7 therapy on CD4+ T cell counts is markedly different from that of IL-2, another CD4+ T cell-tropic cytokine that has been extensively studied as an immune therapy for HIV infection. IL-2 administration to HIV-infected patients resulted in a significant increase in CD4+ T cells, but no additional clinical benefit when compared to ART alone [39]. This lack of effect was likely due to the fact that IL-2 preferentially expands a population of regulatory T cell-like CD4+ lymphocytes that express the IL-2 receptor (CD25), but whose function is unclear. In contrast, the fact that IL-7 selectively acts on CD127+ naive and central-memory cells suggests a much stronger rationale for this cytokine.

Preclinical studies of IL-7 therapy in ART-naïve, SIV-infected rhesus macaques resulted in a significant increase in T cell numbers that was likely due to increased proliferation (as indicated by high fractions of cells expressing the Ki-67 antigen) of peripheral naive and memory T cells [36, 37]. The rise in T cell counts was associated with a dramatic, albeit transient, down-modulation of CD127 expression [36]. Preclinical studies of IL-7 therapy in SIV-infected, ART-treated rhesus macaques have also shown an increase in memory CD4+ and CD8+ T cells, as well as naive T cells [38]. The effect of stimulating proliferation was expected based on the observed induction of peripheral T cell cycling when IL-7 was administered to uninfected cynomolgus monkeys and rhesus macaques [8, 36]. Similarly, markers of T cell activation, including HLA-DR, CD25, and Fas, were upregulated in SIV-infected rhesus macaques following IL-7 administration [36-38]. Importantly, the IL-7-induced increase in CD4+ T cell proliferation was not associated with any significant increase in viral load [36-38]. The molecular basis for the absence of viral load increase, despite higher levels of activated CD4+ T cells, is currently unknown, but may be related to a lack of CCR5 expression on cells that are recruited into the cell cycle by IL-7, as well as additional post-entry mechanisms. In these non-human primate studies, the increase in T cell proliferation proved to be relatively transient, with T cell levels returning to baseline approximately one month following cessation of IL-7 therapy, coincident with the development of anti-IL-7 antibodies [38]. Interestingly, more recent work has identified tissues such as lymph nodes, the GI tract, and skin as the sites of T cell expansion following treatment of rhesus macaques with IL-7, suggesting that a process of T cell homing from blood to tissues then back to the periphery occurs during homeostatic proliferation [40].

As we mentioned earlier, the fact that endogenous IL-7 is elevated in HIV-infected patients with low CD4+ T cell counts raises a theoretical debate as to the usefulness of IL-7 therapy. In this regard, the work in SIV-infected, non-human primates helped to provide a rationale for treatment of CD4+ T cell-depleted, HIV-infected patients, as exogenous IL-7 administration successfully increased T cell production, perhaps because the levels of circulating cytokine achieved by therapeutic administration were much greater than that seen naturally. Further rationale for the use of IL-7 during HIV infection derived from studies in which IL-7 was used in lymphopenic cancer patients suffering from metastatic melanoma or metastatic sarcoma for example, that demonstrated an expansion of circulating, fully functional naive and central-memory CD4+ and CD8+ T cells with a broadened TCR repertoire, and a relative decrease in CD4+ regulatory T cells

[41, 42]. The conclusions from these studies were that IL-7 therapy is well-tolerated and may have therapeutic benefit in lymphopenic states.

Several clinical trials have been completed or are underway of IL-7 therapy in HIV-infected patients receiving ART. Of note, IL-7 is hypothesized to have the most impact on immunological low- or non-responders to ART (*i.e*. 5-30% of all treated HIV-infected subjects), who achieve full and persistent viral suppression, but do not recover their CD4+ T cell counts. The first study of IL-7 therapy in HIV infection used a non-glycosylated recombinant human IL-7 (rhIL-7), and consisted of an open-label prospective phase I/IIa trial including patients with CD4+ T cell counts between 100 and 400 cells/μL and viral loads < 50 copies/mL plasma for at least six months while on ART for at least 12 months [43]. This trial, that had an extended follow-up period of 48 weeks, demonstrated a significant and sustained increase in the number of CD4+ and CD8+ T cells, of both the naive and central memory subsets, in the peripheral blood. Interestingly, the authors did not observe a statistically significant increase in T cell activation during the IL-7 treatment. At the higher dose of IL-7 used, a transient increase in viremia (to a maximum of 630 copies/mL plasma) was observed in four out of eight patients. No safety concerns were raised [43]. The second study of IL-7 therapy for HIV infection is the ACTG 5214 trial the results of which were published in June 2009 [44]. In this Phase I prospective, randomized, placebo-controlled, double-blinded, multicenter study, a single subcutaneous injection of non-glycosylated rhIL-7 was administered with consecutive dose escalation. Key inclusion criteria were CD4+ T cell counts > 100 cells/uL and HIV RNA < 50,000 copies/mL plasma, as well as treatment with ART for at least 12 months. Transient increases in plasma HIV-RNA levels were observed in six out of 11 IL-7-treated patients. As expected, single-dose administration of rhIL-7 was followed by a transient down-regulation of CD127 in both CD4+ and CD8+ T cells and, more importantly, by a significant although transient increase in the numbers of circulating CD4+ and CD8+ T cells, predominantly of central memory phenotype [44]. Interim data on the INSPIRE Study, a Phase I/IIa study of recombinant human IL-7 in HIV-infected patients with CD4+ T cell counts between 101 and 400 cells/μL and viral load < 50 copies/mL plasma after at least 12 months of HAART, was released in September 2009 [Oral, late breaker session, 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 12-15, 2009, San Francisco, California, USA]. In this multicenter, prospective, randomized, placebo-controlled, single-blind, dose-escalation study, the enrolled patients that were classified as immunological nonresponders experienced a dose-dependent and sustained increase in CD4+ T cell counts. Of note, this study was the first to use a glycosylated form of the recombinant human IL-7, *i.e*. second generation product that was generated *via* a recombinant mammalian cell culture system. Final results from this trial are eagerly anticipated.

The potential beneficial role of IL-7 in maintaining CD4+ T cell homeostasis and promoting memory T cell differentiation has been also explored in studies of preventative or therapeutic HIV vaccines. Specific candidate AIDS vaccines have been constructed to encode HIV antigens as well as cytokines such as IL-7. In a recent report, SIVmac251-infected ART-treated rhesus macaques were immunized with live canarypox vaccines containing SIV genes and inter-currently treated with subcutaneous IL-7 [45]. IL-7 was administered prior to immunization to increase the number of naïve T cells, and was continued during the vaccination protocol to expand the memory pool specific for antigens encoded by the vaccine. While vaccination appeared to transiently decrease viral load following discontinuation of ART, IL-7 administration had no additional effect [45]. Further studies will be needed to better assess the potential immune-adjuvant role of IL-7 in the context of HIV vaccines.

CONCLUSION AND FUTURE DIRECTIONS

The IL-7/IL-7 receptor pathway is crucial for maintaining CD4+ T cell homeostasis, and is clearly dysregulated during chronic HIV and SIV infections. For this reason, and also owing to the potential role of IL-7 in depleting the reservoirs of latently infected CD4+ T cells, there has been significant interest in exploring the role of IL-7 as an immune-based intervention for HIV-infected individuals. The results of the two initial clinical trials were indeed quite promising, and show that administration of IL-7 to ART-treated, HIV-infected individuals with fully suppressed virus replication results in a global rebalancing of the pool of CD4+ T cells, with selective increases in both naive and central-memory CD4+ T cells. In our view, the results of these two pilot studies suggest that further investigation of this cytokine, for the clinical management of HIV-infected individuals, is warranted.

In particular, we think that additional clinical studies should include: *(i)* the long-term assessment of the effect of IL-7 on CD4+ T cell homeostasis; *(ii)* a detailed analysis of the possible impact of IL-7 on the residual immune activation and immune senescence observed in ART-treated, HIV-infected individuals; and *(iii)* an assessment of the impact of IL-7 on the size, cellular distribution, and dynamic evolution of the reservoirs of latently infected CD4+ T cells. In this regard, we also think that further studies of the effects of IL-7 in pre-clinical, non-human primate models of both pathogenic and non-pathogenic SIV infections would be extremely useful in elucidating specific aspects of the physiopathology of the IL-7/IL-7R pathway during lentiviral infections that are hard or impossible to test in humans. Finally, a better mechanistic understanding of how IL-7 signaling results in preserved CD4+ T cell homeostasis could pave the way to a second generation of IL-7-based interventions that would fully exploit this pathway for the treatment of HIV-induced immune deficiency.

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REFERENCES

1. Lee SK, Surh CD. Role of interleukin-7 in bone and T-cell homeostasis. *Immunol Rev* 2005; 208: 169.
2. Jiang Q, Li WQ, Aiello FB, *et al.* Cell biology of IL-7, a key lymphotrophin. *Cytokine Growth Factor Rev* 2005; 16: 513.
3. Puel A, Ziegler SF, Buckley RH, Leonard WJ. Defective IL7R expression in T(-)B(+)NK(+) severe combined immunodeficiency. *Nat Genet* 1998; 20: 394.
4. Von Freeden-Jeffry U, Vieira P, *et al.* Lymphopenia in interleukin (IL)-7 gene-deleted mice identifies IL-7 as a nonredundant cytokine. *J Exp Med* 1995; 181: 519.
5. Link A, Vogt TK, Favre S, *et al.* Fibroblastic reticular cells in lymph nodes regulate the homeostasis of naive T cells. *Nat Immunol* 2007; 8: 1255.
6. Mazzucchelli R, Durum SK. Interleukin-7 receptor expression: intelligent design. *Nat Rev Immunol* 2007; 7: 144.
7. Capitini CM, Chisti AA, Mackall CL. Modulating T-cell homeostasis with IL-7: preclinical and clinical studies. *J Intern Med* 2009; 266: 141.
8. Moniuszko M, Fry T, Tsai WP, *et al.* Recombinant interleukin-7 induces proliferation of naive macaque CD4+ and CD8+ T cells *in vivo*. *J Virol* 2004; 78: 9740.
9. Ortiz AM, Silvestri G. Immunopathogenesis of AIDS. *Curr Infect Dis Rep* 2009; 11: 239.
10. Napolitano LA, Grant RM, Deeks SG, *et al.* Increased production of IL-7 accompanies HIV-1-mediated T-cell depletion: implications for T-cell homeostasis. *Nat Med* 2001; 7: 73.
11. Fluur C, Rethi B, Thang PH, *et al.* Relationship between serum IL-7 concentrations and lymphopenia upon different levels of HIV immune control. *AIDS* 2007; 21: 1048.
12. Fry TJ, Mackall CL. The many faces of IL-7: from lymphopoiesis to peripheral T cell maintenance. *J Immunol* 2005; 174: 6571.
13. Rethi B, Vivar N, Sammicheli S, Chiodi F. Limited efficacy of endogenous interleukin-7 levels in T cell reconstitution during HIV-1 infection: will exogenous interleukin-7 therapy work? *AIDS* 2009; 23: 745.
14. Muthukumar A, Wozniakowski A, Gauduin MC, *et al.* Elevated interleukin-7 levels not sufficient to maintain T-cell homeostasis during simian immunodeficiency virus-induced disease progression. *Blood* 2004; 103: 973.
15. Muthukumar A, Zhou D, Paiardini M, *et al.* Timely triggering of homeostatic mechanisms involved in the regulation of T-cell levels in SIVsm-infected sooty mangabeys. *Blood* 2005; 106: 3839.
16. Paiardini M, Cervasi B, Engram JC, *et al.* Bone marrow-based homeostatic proliferation of mature T cells in nonhuman primates: implications for AIDS pathogenesis. *Blood* 2009; 113: 612.
17. MacPherson PA, Fex C, Sanchez-Dardon J, Hawley-Foss N, Angel JB. Interleukin-7 receptor expression on CD8(+) T cells is reduced in HIV infection and partially restored with effective antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001; 28: 454.
18. Paiardini M, Cervasi B, Albrecht H, *et al.* Loss of CD127expression defines an expansion of effector CD8+ T cells in HIV-infected individuals. *J Immunol* 2005; 174: 2900.
19. Rethi B, Fluur C, Atlas A, *et al.* Loss of IL-7Ralpha is associated with CD4 T-cell depletion, high interleukin-7 levels and CD28 down-regulation in HIV infected patients. *AIDS* 2005; 19: 2077.
20. Koesters SA, Alimonti JB, Wachihi C, *et al.* IL-7Ralpha expression on CD4+ T lymphocytes decreases with HIV disease progression and inversely correlates with immune activation. *Eur J Immunol* 2006; 36: 336.
21. Sasson SC, Zaunders JJ, Zanetti G, *et al.* Increased plasma interleukin-7 level correlates with decreased CD127 and increased CD132 extracellular expression on T cell subsets in patients with HIV-1 infection. *J Infect Dis* 2006; 193: 505.
22. Dunham RM, Cervasi B, Brenchley JM, *et al.* CD127 and CD25 expression defines CD4+ T cell subsets that are differentially depleted during HIV infection. *J Immunol* 2008; 180: 5582.
23. Juffroy O, Bugault F, Lambotte O, *et al.* Dual mechanism of impairment of interleukin -7 (IL-7) responses in human immunodeficiency virus infection: decreased IL-7 binding and abnormal activation of the JAK/STAT5 pathway. *J Virol* 2010; 84: 96.
24. Moniuszko M, Edghill-Smith Y, Venzon D, *et al.* Decreased number of CD4+ and CD8+ T cells that express the interleukin-7 receptor in blood and tissues of SIV-infected macaques. *Virology* 2006; 356: 188.
25. Jaleco S, Swainson L, Dardalhon V, Burjanadze M, Kinet S, Taylor N. Homeostasis of naive and memory CD4+ T cells: IL-2 and IL-7 differentially regulate the balance between proliferation and Fas-mediated apoptosis. *J Immunol* 2003; 171: 61.
26. Lelievre JD, Petit F, Arnoult D, Ameisen JC, Estaquier J. Interleukin 7 increases human immunodeficiency virus type 1 LAI-mediated Fas-induced T-cell death. *J Virol* 2005; 79: 3195.
27. Fluur C, De Milito A, Fry TJ, *et al.* Potential role for IL-7 in Fas-mediated T cell apoptosis during HIV infection. *J Immunol* 2007; 178: 5340.
28. Guillemard E, Nugeyre MT, Chene L, *et al.* Interleukin-7 and infection itself by human immunodeficiency virus 1 favors persistence in mature CD4(+)CD8(-)CD3(+) thymocytes through sustained induction of Bcl-2. *Blood* 2001; 98: 2166.
29. Vassena L, Proschan M, Fauci AS, Lusso P. Interleukin 7 reduces the level of spontaneous apoptosis in CD4+ and CD8+ T cells from HIV-1-infected individuals. *Proc Natl Acad Sci USA* 2007; 104: 2355.
30. Zaunders JJ, Moutouh-de Parseval L, Kitada S, *et al.* Polyclonal proliferation and apoptosis of CCCR5+ T lymphocytes during primary human immunodeficiency virus type 1 infection: regulation by interleukn (IL)-2, IL-15, and Bcl-2. *J Infect Dis* 2003; 187: 1735.
31. Selliah N, Zhang M, DeSimone D, *et al.* The gammac-cytokine regulated transcription factor STAT5, increases HIV-1 production in primary CD4 T cells. *Virology* 2006; 344: 283.
32. Unutmaz D. KewelRamani VN, Marmon S, Littman DR. Cytokine signals are sufficient for HIV-1 infection of resting human T lymphocytes. *J Exp Med* 1999; 189: 1735.
33. Managlia EZ, Landay A, Al-Harthi L. Interleukin-7 induces HIV replication in primary naive cells through a nuclear factor of activated T cell (NFAT)-dependent pathway. *Virology* 2006; 350: 443.
34. Scripture-Adams DD, Brooks DG, Korin YD, Zack JA. Interleukin-7 induces expression of latent human immunodeficiency virus type 1 with minimal effects on T-cell phenotype. *J Virol* 2002; 76: 130077.
35. Wang FX, Xu Y, Sullivan J, *et al.* IL-7 is a potent and proviral strain-specific inducer of latent HIV-1 cellular reservoirs of infected individuals on virally suppressive HAART. *J Clin Invest* 2005; 115: 128.
36. Fry TJ, Moniuszko M, Creekmore S, *et al.* IL-7 therapy dramatically alters peripheral T-cell homeostasis in normal and SIV-infected nonhuman primates. *Blood* 2003; 101: 2294.
37. Nugeyre MT, Monceaux V, Beq S, *et al.* IL-7 stimulates T cell renewal without increasing viral replication in simian immunodeficiency virus-infected macaques. *J Immunol* 2003; 171: 4447.

38. Beq S, Nugeyre MT, Ho Tsong Fang R, *et al.* IL-7 induces immunological improvement in SIV-infected rhesus macaques under antiviral therapy. *J Immunol* 2006; 176: 914.

39. INSIGHT-ESPRIT Study Group, SILCAAT Scientific Committee, Abrams D, Levy Y, Losso MH, *et al.* Interleukin-2 therapy in patients with HIV infection. *N Engl J Med* 2009; 361: 1548.

40. Beq S, Rozlan S, Gautier D, *et al.* Injection of glycosylated recombinant simian IL-7 provokes rapid and massive T-cell homing in rhesus macaques. *Blood* 2009; 114: 816.

41. Rosenberg SA, Sportes C, Ahmadzadeh M, *et al.* IL-7 adminstration to humans lead to expansion of CD8+ and CD4+ cells but a relative decrease of CD4+ T-regulatory cells. *J Immunother* 2006; 29: 313.

42. Sportes C, Hakim FT, Memon SA, *et al.* Administration of rh-IL7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naïve T cell subsets. *J Exp Med* 2008; 205: 1701.

43. Levy Y, Lacabaratz C, Weiss L, *et al.* Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment. *J Clin Invest* 2009; 119: 997.

44. Sereti I, Dunham RM, Spritzler J, *et al.*, ACTG 5214 Study Team. IL-7 adminstration drives T cell-cycle entry and expansion in HIV-infection. *Blood* 2009; 113: 6304.

45. Hryniewicz A, Price DA, Moniuszko M, *et al.* Interleukin-15 but not interleukin-7 abrogates vaccine-induced decrease in virus level in simian immunodeficiency virus mac251-infected macaques. *J Immunol* 2007; 178: 3492.