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Immunotherapy in HIV disease: recent developments and future directions

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ABSTRACT

Adjuvant immunotherapy, directly targeting the immune system, has been proposed as approach to modulate the immune response in HIV-infected subjects treated with HAART and without immune reconstitution. Most studies have been performed on Interleukin-2 (IL-2), focusing on immunological advantage of IL-2+HAART versus HAART alone in different stages of HIV infection. Preliminary results of two Phase III international studies, SILCAAT and ESPRIT, confirm a significant difference in CD4+ cells count, but underline that this immunological advantage does not reduce the rate of opportunistic infections and death. The authors do not provide any data of IL-2 driven immune reconstitution and this could be a bias in the interpretation of the results. Interleukin-7 (IL-7) Phase I studies are ongoing: the potential interest of IL-7 in the treatment of HIV-infection is based on its crucial role on T cell homeostasis both in thymic output and peripheral T proliferation and survival; despite SILCAAT and ESPRIT data, these studies are continuing. Finally, recently approved new class drugs, CCR5-antagonists, open a new scenario in HAART era: published results confirm an immune reconstitution better than other antiretroviral drugs.

Use of highly active antiretroviral therapy (HAART) has changed the natural history of HIV infection decreasing mortality and morbidity [1]. Clinical improvement is due to qualitative and quantitative immune reconstitution after control of viral replication. Despite use of HAART, we are not able to fully reconstitute immune competence [2]. The goal of immunotherapy strategies (cytokines, therapeutic vaccines or immunomodulators), is to accelerate or improve the immune restoration and/or control of viral replication in association with cART or after its interruption. At the state of knowledge, it is clear that the decline of CD4 is only partially explained by the level of viral load; host factors and the degree of immune activation, play an essential role in the immunodeficiency. On the other hand, the level of immune restoration achieved with cART reduces AIDS events, but is not enough to obtain of mortality and morbidity rate close to the general population, except for patients with prolonged high CD4 T levels (> 500/mm3).
Adjuvant immunotherapy with cytokines has been proposed as the ideal approach to modulate immune response by directly targeting the immune system.

Intermittent treatment with Interleukin-2 (IL-2).

Since 1995 several studies have been conducted to investigate IL-2 in HIV-infected individuals immunological non-responders [3-9]: IL-2 administration for 2-5 days every 6-8 weeks is safe and induces reconstitution of the CD4+ compartment, with no significant interference with HIV viral replication. IL-2 increases CD4+ cells, both naïve and memory [10].
In our centre, to evaluate the safety and efficacy of 3 regimens of intermittent subcutaneous IL-2, 61 patients were randomly assigned to ART plus IL-2 (three different arms with different dosage) or ART alone. Low doses (3 million IU twice a day every 4 weeks) of IL-2 induced a stable increase of peripheral CD4 cells that was indistinguishable from those associated with higher, less well-tolerated doses of IL-2 [9].
The potential effectiveness of IL-2 to maintain / restore the rate of CD4 T lymphocytes was evaluated in different stages of immunodeficiency: patients naïve to antiretroviral therapy (ANRS trial 119 - INTERSTART), in the chronic phase of infection before cessation of antiret-

roviral therapy (ANRS trial 118 - ILIADE), or in situations of immunological failure and/or virological (ANRS 123 trial - ETOILE). The ETOILE trial (ANRS 123), demonstrate clinical and biological ineffectiveness of IL-2 in very advanced patients (CD4 and viral load at entry: 5-8/mm3 and 4,9-5,1 log10 copies/ml) [10]
The results of the ANRS 119 trial [11] have shown that a IL-2 treatment strategy in asymptomatic naïve patients, with more than 300 CD4/mm3, was capable of delaying the initiation of ART thus increasing significantly CD4 count. In the ANRS 118 trial (ILIADE) ART interruption preceded by IL-2 may help to maintain CD4 T cell pool in patients willing to stop therapy for a short time. The lack of epidemiological data on clinical tolerance to long-term IL-2 led to the establishment of a cohort (ANRS cohort C014 "cohort IL-2") to collection of retrospective and prospective data on tolerance of IL-2 administered in ANRS trials. Recently, the occurrence of lymphoma was observed in trials INTERSTART and ETOILE, but not exclusively among patients receiving IL-2. These lymphomas occurred in patients receiving no antiretroviral therapy or in advanced stages of infection in severe immunovirological failure. The first data of the cohort IL-2 CO14, reported in 2006, on 745 patients who received at least one course of IL-2 and followed for a median of 35 months, showed no increased risk of non-Hodgkin's lymphoma in these patients, but a lower incidence compared to a population of 67.896 control. [12]
SILCAAT and ESPRIT are Phase III studies designed to answer clinical impact of CD4+ increase IL-2 mediated. Design of studies are similar: patients with CD4+ count between 50 and 299/mmc (SILCAAT) or ≥ 300/mmc (ESPRIT) were randomized to IL-2 plus HAART or to HAART alone. The IL-2 regimen consisted of 5-days cycles at 8-weeks intervals with additional cycles recommended to maintain the CD4 cell count. The primary endpoints were opportunistic disease (OD) or death. Serious non-AIDS events and life-threatening (grade 4) clinical events were reported as secondary endpoints. Averaged over follow-up, the CD4+ cells count was higher in the IL-2 group compared to the control group ($p<0.001$) in both studies (figure 1, 2) [13-14]. The percent with HIV-RNA ≤500 copies/ml did not differ between treatment groups. Despite a significant difference in CD4+ cells count, IL-2 did not reduce the rate of OD or death (figure 3, 4); in ESPRIT study, the addition of IL-2 was associated with more grade 4 clinical events ($p=0.003$).

Intermittent treatment with Interleukin-7 (IL-7).

Interleukin-7 (IL-7) is a critical cytokine for T-cell development, thymopoiesis, peripheral homeostasis and T-cell maturation [15]. Several studies have shown an inverse correlation between serum IL-7 and the number of CD4 T lymphocytes in patients infected with HIV, suggesting a retro-active control of the stimulation for the production of this cytokine. The results of two Phase I trials have been reported.
Twenty five patients enrolled in a US multicenter trial sponsored by AIDS Clinical Trials

Figure 1. Superior effect of interleukin-2 plus antiretroviral therapy (ART) vs ART alone on increasing absolute circulating T cells in ESPRIT trial.

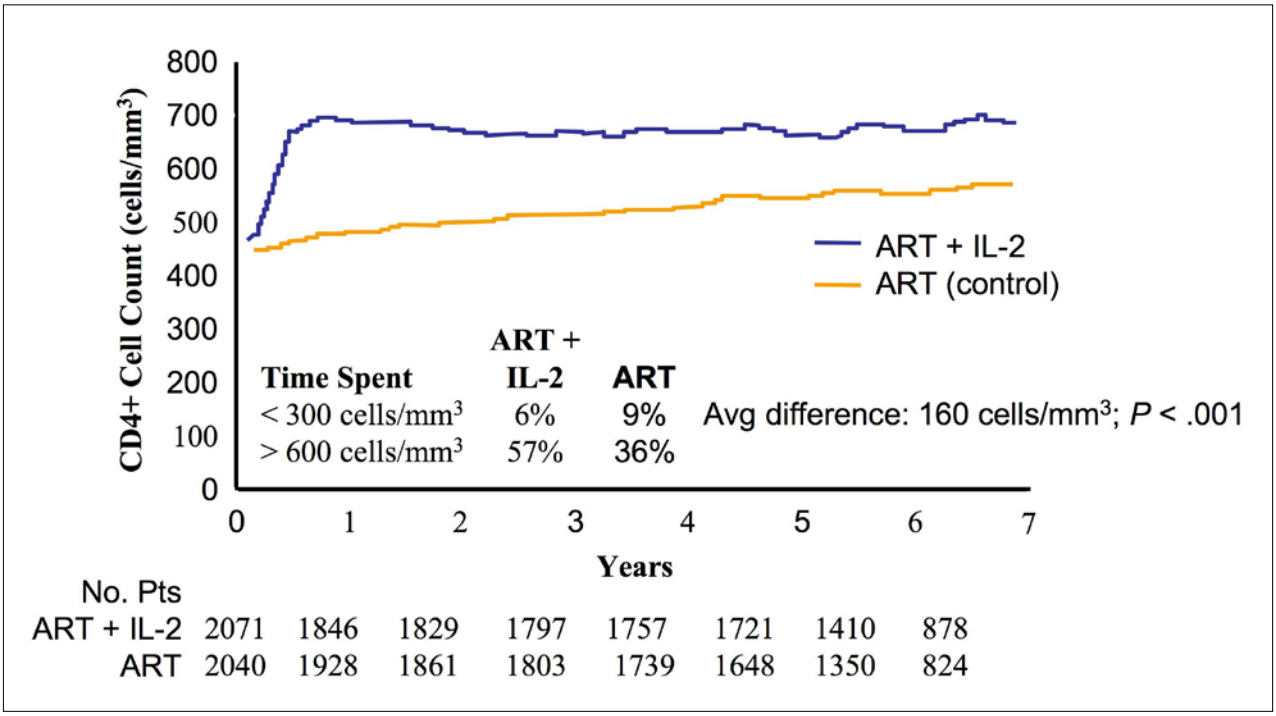


Figure 2. Superior effect of interleukin-2 (IL-2) plus antiretroviral therapy (ART) vs ART alone on increasing absolute circulating T cells in SILCAAT trial. ART+IL-2 spent less time with CD4 count < 200/mmc.

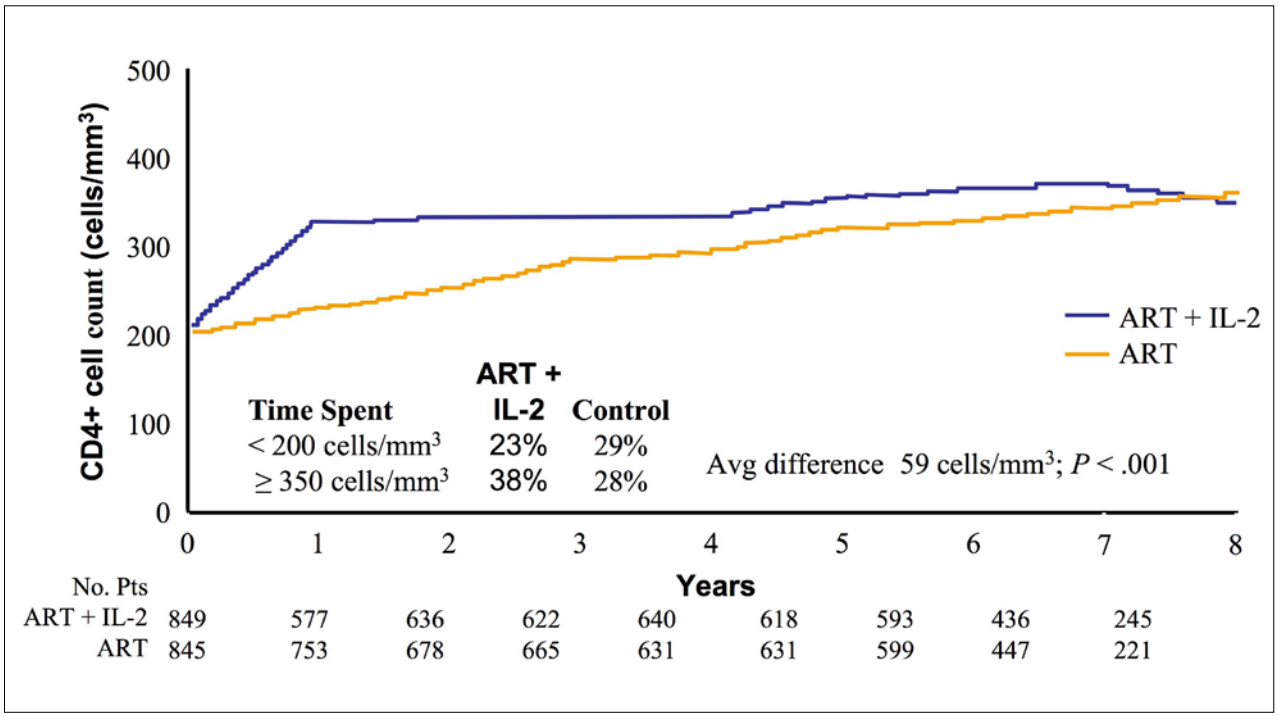
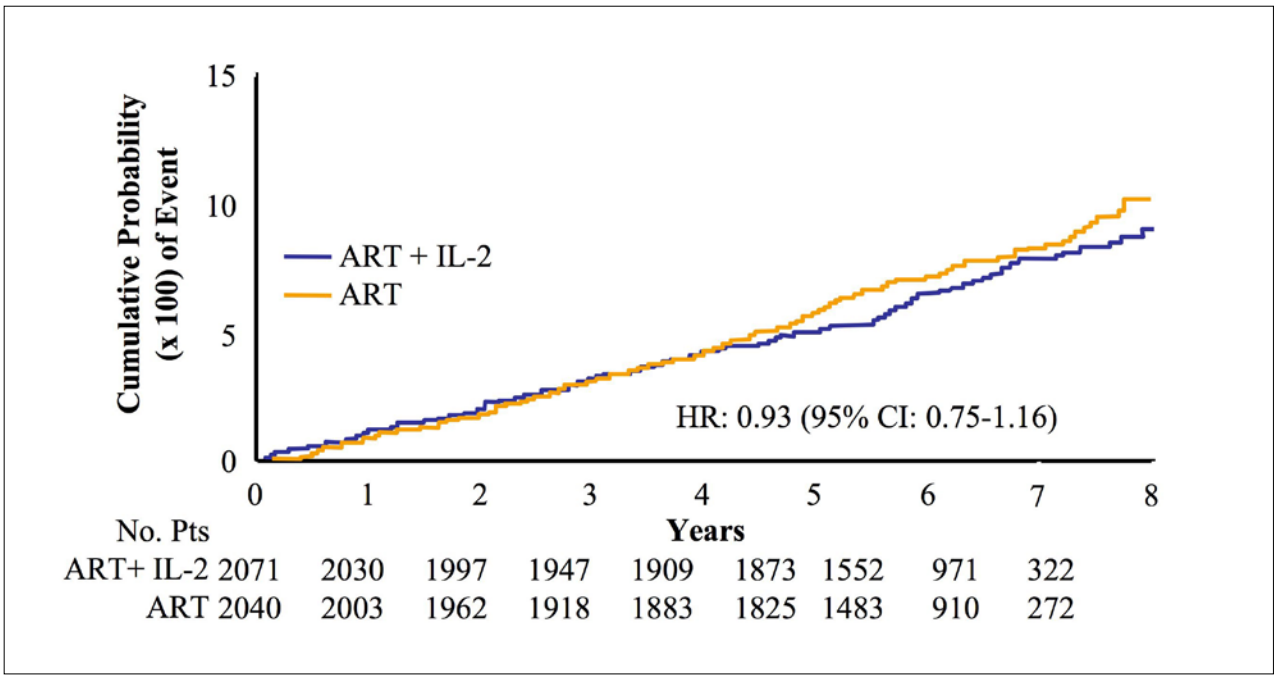
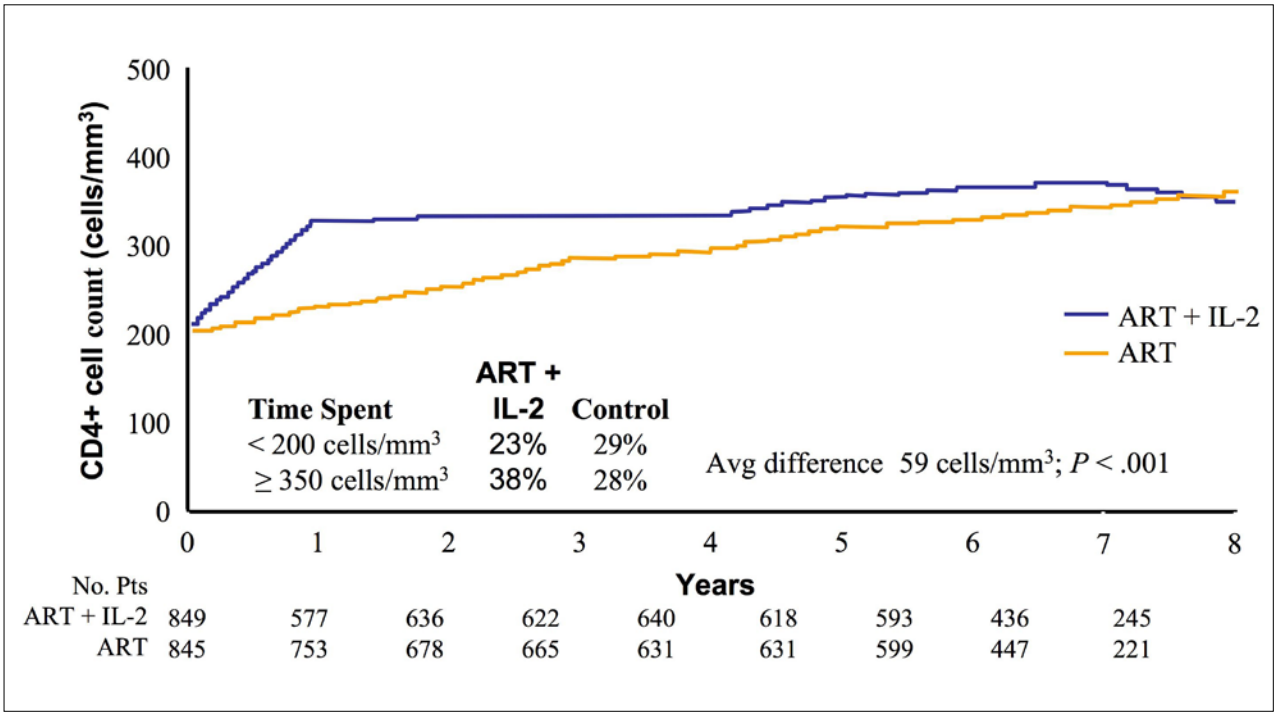


Figure 3. Cumulative probability of event in ESPRIT. Despite CD4 rise, no clinical benefits in IL-2 arm were observed. .



Group (ACTG) received a single dose of CYT 99 007, the non glycosylated form of IL-7. The trial was randomized against a placebo and stratified according to viral load at entry. In the first stratum (undetectable viral load at entry), 17 patients were enrolled in 4 cohorts corresponding to dose levels between 3 and 60 µg/dose of CYT 99 007; 13 patients received CYT 99 007. In stratum 2 (50 to 50,000 copies/mL of HIV RNA at entry), 8 patients were enrolled in 2 cohorts, corresponding to 2 dose levels (3 and 10 µg/kg); 6 patients received CYT 99 007. Dose escalation has stopped in both strata and preliminary unblinded results are available for stratum 1: maximum tolerated dose was 30µg/Kg; at this dose level, most common AEs were transient LFT elevation and local reactions. Single-dose rhIL-7 induced T-cell proliferation, down-regulation of IL-7Ra, and transient T-cell increases. The maximum

Figure 4 . Cumulative probability of event in ESPRIT. Despite CD4 rise, no clinical benefits in arm were observed. Number of patients decreased during follow up.



tolerated dose was 30 µg/kg. Biologic activity at all tested doses suggests a favourable therapeutic index of this cytokine for potential use in HIV infection [16].

Phase I/II multicentric study evaluated the safety and biological effects of escalating doses of recombinant human IL-7 (CYT 99-007) in HIV-infected patients with CD4 between 100 and 400 cells/mmc and viral load below 50 copies/ml [17]. They received 8 subcutaneous injections 3 times/week. Median CD4 counts increased of 95% at day 21 and remained significantly above baseline at week 12 ($p<0.01$); CD4 increase was dependent on the dose (3 and 10 mcg / kg) and it was durable for up to 48 weeks after cessation of IL-7. The possible effect of IL-7 on viral replication is being investigated in phase I / II under way, with a glycosylated form of IL-7 administered once a week subcutaneously. Glycosilated form of IL-7 have these expected advantages: it shows less or no immunogenicity in primates and its pharmacokinetic and pharmacodynamic profile may allow for a greater interval between doses. Our centre is involved in this Phase I/IIa randomized placebo controlled, single-blind multicenter dose-escalation study of subcutaneous intermittent Interleukin-7 (CYT107) in chronically HIV-infected patients with CD4+ cells count between 101-400/mmc and plasma HIV-RNA<50 copies/ml after at least 12 months of HAART. The primary objective of the study is to determine the safety and identify a biologically active dose of CYT107.

Future studies are necessary to understand clinical benefits of CD4+ rise.

CCR5 antagonists

The therapeutic armamentarium against HIV has recently gained Maraviroc belonging to a novel class of antiretrovirals, the CCR5 antagonists. In MOTIVATE 1 and 2 [18, 19] studies Maraviroc, as compared with placebo, resulted in significantly greater suppression of HIV-RNA at 48 weeks in previously treated patients with R5 HIV-1 who received optimized background therapy. Interestly, the change from baseline in CD4 counts was also greater with maraviroc ($p<0.001$). These results are confirmed at 96 weeks [20]. A metanalysis of different drug combinations showed that CCR5 antagonists increase CD4 count better than other drugs. This new class, with new mechanism of action, could be considered an immunomodulator. In fact these are first drugs with virological action but also with direct action on immune system. Our published data suggest that some antiretroviral combinations containing maraviroc could rise CD4 significantly [21, 22]; CD4 increase is better with association with one or two active drugs [18, 19].

Discussion

IL-2 represented the most promising immunomodulant approach of HIV-infection treatment. Several studies confirmed qualitative and quantitative immune reconstitution of adjunct IL-2 versus HAART alone. Unfortunately, results of Phase III clinical trials SILCAAT and ESPRIT, with extensive follow up (median years of follow up 7.7) underline

that this immunological advantage does not translate into clinical benefits; in some cases immune reconstitution should be a disadvantage, with major risk of inflammatory-based events.
Results of these trials change the scenario of immunotherapy in HIV disease: Phase I results of IL-7 trials are encouraging, but in terms of CD4+ rise too, not in terms of clinical outcome.
Could immunotherapy have another chance after these results?

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