Effects of Recombinant Human Interleukin 7 on T-Cell Recovery and Thymic Output in HIV-Infected Patients Receiving Antiretroviral Therapy: Results of a Phase I/IIa Randomized, Placebo-Controlled, Multicenter Study

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Background. The immune deficiency of human immunodeficiency virus (HIV) infection is not fully corrected with ARV therapy. Interleukin-7 (IL-7) can boost CD4 T-cell counts, but optimal dosing and mechanisms of cellular increases need to be defined.

Methods. We performed a randomized placebo-controlled dose escalation (10, 20 and 30 µg/kg) trial of 3 weekly doses of recombinant human IL-7 (rhIL-7) in ARV-treated HIV-infected persons with CD4 T-cell counts between 101 and 400 cells/µL and plasma HIV levels <50 copies/mL. Toxicity, activity and the impact of rhIL-7 on immune reconstitution were monitored.

Results. Doses of rhIL-7 up to 20 µg/kg were well tolerated. CD4 increases of predominantly naive and central memory T cells were brisk (averaging 323 cells/µL at 12 weeks) and durable (up to 1 year). Increased cell cycling and transient increased bcl-2 expression were noted. Expanded cells did not have the characteristics of regulatory or activated T cells. Transient low-level HIV viremia was seen in 6 of 26 treated patients; modest increases in total levels of intracellular HIV DNA were proportional to CD4 T-cell expansions. IL-7 seemed to increase thymic output and tended to improve the T-cell receptor (TCR) repertoire in persons with low TCR diversity.

Conclusions. Three weekly doses of rhIL-7 at 20 µg/kg are well tolerated and lead to a dose-dependent CD4 T-cell increase and the broadening of TCR diversity in some subjects. These data suggest that this rhIL-7 dose could be advanced in future rhIL-7 clinical studies.

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Interleukin 7 (IL-7), a cytokine produced by lymph node and thymus stromal cells, has profound effects on human and murine T-cell homeostasis [1]. IL-7 is required for thymic T-cell development in the thymus and also promotes postthymic T-cell survival, proliferation and maturation (reviewed in [2]).

The heterodimeric IL-7 receptor (IL-7R) comprises a cytokine binding IL-7Rα chain and a signaling common γ chain (γc) shared by other cytokine receptors [3]. The IL-7R is expressed by lymphocyte precursors, developing thymocytes, and mature T cells. Patients with mutations
in IL-7Rαx experience severe combined immunodeficiency [3, 4] confirming that IL-7 is essential for human T-cell development. This is supported by the inverse relationship between circulating IL-7 levels and peripheral CD4 T-cell numbers consistently found in lymphopenic states, including human immunodeficiency virus (HIV) infection [5, 6]. Nonhuman primate studies showed that IL-7 administration was safe and had a significant impact on T-cell homeostasis [7–10], including T-cell trafficking and proliferation in the gut mucosa [11]. In humans, phase I HIV and cancer studies demonstrated the safety and biologic activity of single or repeated doses of nonglycosylated recombinant human IL-7 (rhIL-7) [12–15]. With a favorable safety profile, rhIL-7 was shown to increase circulating numbers of both naive and memory CD4 and CD8 T cells. However, the most well-tolerated biologically active dose of rhIL-7 that could be applied in phase Ib/III studies still remains unclear [16, 17].

We report a phase I/Ila dose escalation study of repeated administration of a glycosylated rhIL-7 in HIV-1–infected patients whose CD4 T-cell counts failed to normalize despite antiretroviral (ARV) therapy. The study objectives were to identify an optimal dosing regimen for phase IIb/III studies in HIV disease based on toxicity and efficacy and to further evaluate mechanisms of T-cell restoration with rhIL-7 therapy.

SUBJECTS AND METHODS

Subjects
Eligible subjects were chronically HIV-1–infected patients with CD4 T-cell counts of 101–400 cells/µL and plasma HIV RNA levels < 50 copies/mL for ≥6 months while receiving ARV therapy for ≥12 months. Acceptable ARVs included any protease inhibitor (with or without ritonavir) or any non-nucleoside reverse-transcriptase inhibitor combined with 2 nucleoside reverse-transcriptase inhibitors.

Recombinant Human IL-7
CYT107 is purified glycosylated 152 amino acid rhIL-7 expressed in a Chinese hamster ovary (CHO) cell line.

Study Design and End Points
A randomized, placebo-controlled, single-blind, interpatient, dose escalation design was chosen to facilitate the replacement of subjects as needed and also because injection site reactions would unblind study staff. The study was approved by ethics committees or institutional review boards of all participating institutions in France, Italy, United States, and Canada and was registered in the EudraCT database (http://eudract.emea.eu/; protocol 2006–00624-20A) and at clinicaltrials.gov (NCT0047732), IND 100538, and CTA 9427-C2666/1-21C. All participants signed written informed consent before enrollment.

The subjects received 3 weekly subcutaneous (SC) injections of rhIL-7 on days 0, 7, and 14. Three different doses of CYT107—10, 20, and 30 µg/kg—were tested sequentially. Ten patients (8 receiving rhIL-7, 2 receiving placebo [sodium chloride]) were randomized in each dose group and were seen on days 0, 7, 14, 21, 28, and 35, weeks 9 and 12, and then quarterly until week 52. The primary end point was safety, which was assessed through the reporting of adverse events using the Division of AIDS (December 2004) toxicity grading scale. Dose-limiting toxicity was defined as any grade 3 or 4 adverse event, a rash of grade ≥2, or an immune restoration inflammatory syndrome event; a confirmed increase in plasma HIV RNA levels to >0.75 log10 copies/mL on day 28 or 35; detection of plasma IL-7 neutralizing antibodies at dilutions ≥1:400; any diagnosis of lymphoma; or adenopathy compromising or threatening organ function. Secondary end points included changes from baseline in CD4 and CD8 T-cell counts (the baseline was defined as the mean of 4 values, including 2 obtained in the 6 months prior to study entry, the initial screening value, and the day 0 value).

Immunophenotyping
Flow cytometric analyses were performed on cryopreserved peripheral blood mononuclear cells (PBMCs). Labeled cells were acquired with an LSRII cytometer and analyzed using DiVa software (Version 6.0). Nine T-cell subsets (Supplementary Table 1) and phenotypes were defined using the following antibodies: CD3-AmCyan, CD4-PB, CD8-PerCP-Cy5.5, CD45RA-ECD, CD27-APC-Alexa-750, CCR7-PE-Cy7, CD31-PE-Cy7, CD38-FITC, Foxp3-Alexa700, and Ki-67-FITC.

T-Cell Receptor Excision Circle Quantifications
Parallel quantification of sj T-cell receptor excision circle (TRECs) and each of the 13 Djβ TRECs, together with the CD3γ gene (used as a housekeeping gene), was performed using LightCycler technology (Roche Diagnostics), as described elsewhere [18]. The sj/Dj TREC ratio was calculated as described elsewhere (sj/Dj TREC = sj TRECs/105 cells)/(Djβ1 TRECs/105 cells + Djβ2 TRECs/105 cells).

Repertoire Diversity
The T-cell receptor (TCR) repertoire was measured using the ImmunTraCkeR test (ImmunoID Technologies) and diversity (Divpenia and NDL score) was analyzed using Constel’ID software (ImmunoID). Briefly, 5 x 106 PBMCs were thawed and re-suspended in EasyID buffer containing proteinase K. Multiplex polymerase chain reaction (PCR) analysis was performed on the genomic DNA, as described elsewhere [19, 20].

HIV DNA Quantification
HIV-1 DNA was quantified in whole blood obtained at day 0, day 28, and week 12 using a real-time PCR method [21].
Results were converted into copies per $10^6$ CD4 T lymphocytes using lymphocyte, monocyte, and CD4 T-cell counts, according to the following formula: $[\text{HIV DNA (copies/10}^6 \text{ CD4 T cells)} = \text{HIV DNA (copies/10}^6 \text{ PBMCs)} \times (\text{PBMCs/µL})/\text{CD4 T cells/µL}].$ HIV DNA levels were also calculated in copies per mL of whole blood: $[\text{HIV DNA (copies/mL whole blood)} = (\text{HIV DNA (copies/10}^6 \text{ PBMCs)} \times (\text{lymphocytes/µL})/1000].$

Statistical Analysis

All patients who received $\geq 1$ injection were included in safety analyses. Immunologic activity was evaluated in patients who received all 3 weekly administrations. Changes in CD4 T-cell counts were calculated as absolute values, whereas changes in marker expression were reported as fold changes from baseline using the Wilcoxon test for paired samples. Statistical analysis was performed with SAS software, version 9.2 (SAS Institute).

RESULTS

Study Design and Subjects

Forty-seven subjects were screened, and 32 were enrolled (10, 12, and 10 in the 10, 20, or 30 µg/kg groups, respectively) (Supplementary Figure 1). The baseline characteristics are listed in Table 1. Overall, 6 patients received placebo (2 in each dose group). At 10 µg/kg, 7 subjects received 3 injections each, and 1 subject received a single injection. At 20 µg/kg, 8 of 10 subjects received 3 injections, and 2 discontinued treatment after 1 or 2 injections (the first because the total dose was given in a single administration and the second because of a dispensing error). At 30 µg/kg, 6 of 8 subjects received 3 injections, and 2 received 1 injection because of a dose-limited toxic event after the first injection. All subjects completed the study follow-up.

rhIL-7 Induction of Dose-Dependent Sustained Increase in T Lymphocytes

The subjects in the 10, 20, and 30 µg/kg and placebo groups had baseline CD4 T-cell counts of 268, 240, 276, and 280 cells/µL, respectively. At week 12, CD4 T cells were 419, 563, 799, and 259 cells/µL ($P < .002$ representing changes from baseline for each dose group compared with placebo) (Figure 1A). Increases were dose dependent (+188, +323, and +551 cells/µL, respectively). CD8 T-cell counts were 761, 659, 415, and 502 cells/µL at baseline in the 10, 20, and 30 µg/kg and placebo groups and at week 12, increased to 1081, 1210, 1011, and 487 cells/µL, respectively (Figure 1B) ($P < .002$ representing changes from baseline for each dose group, compared with placebo). At week 52, CD4 T-cell counts remained significantly higher than baseline in all rhIL-7 dose groups (change, +154, +172 and +209 cells/µL, respectively; all $P < .005$). CD8 T-cell counts also remained significantly higher in rhIL-7–treated subjects compared with baseline ($P < .01$).

A biologically active dose was defined as one that induced a CD4 T-cell increase of $\geq 50%$ above baseline at week 12 in 6 of 8 treated subjects. Both the 20 and 30 µg/kg doses were biologically active. The median time to reach a threshold of CD4 T-cell count of 500 cells/µL at all doses of rhIL-7 was 14 days; and at week 12, 62.5% (5 of 8 subjects) and 100% (6 of 6 subjects) in the 20 and 30 µg/kg groups maintained a CD4 T-cell count $\geq 500$ cells/µL (data not shown).

Table 1. Baseline Participant Characteristics by Dose Group

| Characteristic                  | 10 µg/kg (n = 8) | 20 µg/kg (n = 10) | 30 µg/kg (n = 8) | Placebo (n = 6) |
|--------------------------------|-----------------|------------------|-----------------|----------------|
| Age, years                     | 43 (27–66)      | 42 (35–52)       | 49 (41–52)      | 53 (48–59)     |
| Male-female ratio              | 5:3             | 9:1              | 8:0             | 3:3            |
| Time since HIV diagnosis, years | 5 (2–22)        | 5 (2–8)          | 21 (19–23)      | 14 (3–24)      |
| Duration of ARV, years         | 4 (1–16)        | 1 (1–3)          | 6 (1–15)        | 9 (3–17)       |
| CD4a, cells/µL                 | 268 (152–373)   | 240 (197–323)    | 276 (207–370)   | 280 (203–344)  |
| CD8c, cells/µL                 | 761 (530–857)   | 659 (376–1090)   | 415 (209–1524)  | 502 (393–1123) |
| Nadir CD4                      | 100 (10–278)    | 98 (8–206)       | 128 (8–254)     | 45 (6–210)     |
| CD4/CD8 ratio                  | 0.35 (0.18–0.62) | 0.39 (0.18–0.64) | 0.5 (0.19–1.45) | 0.50 (0.17–0.80) |
| Proviral HIV DNA, log$_{10}$ copies/10$^6$ CD4 cells | 3.65 (2.79–4.20) | 4.04 (3.27–4.41) | 3.13 (1.69–4.33) | 3.37 (3.05–3.50) |

Except for the sex ratios, all values represent medians (ranges). There were no significant differences between groups in any of the listed variables. All subjects had plasma HIV RNA levels <50 copies/mL.

Abbreviations: ARV, antiretroviral; HIV, human immunodeficiency virus; rhIL-7, recombinant human interleukin 7.

a Derived data.

b The baseline CD4 T-cell count was defined as the mean of 4 values, 2 in the 6 months prior to study entry, 1 at screening, and 1 at day 0.

c The baseline CD8 T-cell count was defined as the mean of results at screening and at day 0.
Effects of rhIL-7 Administration on CD4 and CD8 T-Cell Populations

We next investigated the phenotype of the rhIL-7–expanded T cells. We found a dose-dependent effect of rhIL-7 on both naive and central memory CD4 T cells at day 28 that remained significantly different from baseline at week 12 (day 77) in groups treated with the 2 highest doses ($P < .05$) (Figure 1C and 1D). Less-pronounced effects were seen for effector memory and terminal effector memory cells (data not shown). IL-7 effects were substantially more pronounced on naive than on memory...
CD8 T-cell subsets (Figure 1E and 1F), reaching statistical significance in both subsets on days 28 and 77 (P < .05) (week 12).

Recent results of interleukin 2 (IL-2)–based therapy trials in HIV-infected patients have raised concerns that the phenotypes of expanded CD4 cells [22] and regulatory T cells (Tregs) have similar features [23, 24]. In the current study, CD4 expansion also transiently increased the absolute numbers of Tregs (CD4+CD25+CD127−FoxP3+) in all treated groups on day 28 (P < .001) (Figure 1G). However, the relative frequency of Tregs decreased significantly in the rhIL-7–treated subjects at day 28 (P = .0005 compared with placebo) (Figure 1G), as other CD4 subsets had greater expansions.

**Effects of rhIL-7 Administration on Markers of T-Cell Homeostasis**

Compared with the placebo group, all doses of rhIL-7 increased the frequency of Ki-67 expression among naive, central memory, and effector memory CD4 T cells (pooled groups, all P < .001 at day 7) (Figure 2A). This effect peaked on day 7, after 1 dose of rhIL-7 in each group. A similar effect of rhIL-7 was noted among CD8 T-cell subsets (Figure 2A). This effect was not dose dependent, and the frequency of cycling T cells returned to baseline on day 28 in all groups (Figure 2A). As shown elsewhere in cancer patients [15], a significant transient increase in CD4 and CD8 T cells expressing Bcl-2 was observed during rhIL-7 therapy (at days 7 and 14 for pooled rhIL-7 groups, P < .001); these counts subsequently returned to values lower than baseline (P < .001 at week 12 [day 77]) (Supplementary Figure 2).

**Effects of rhIL-7 on T-Cell Expression of Programmed-Death 1**

The proportion of T cells expressing Programmed-Death 1 (PD-1), a marker of activation or exhaustion in HIV-infected subjects [25], was also evaluated. As shown in Figure 2B, the frequency of CD4+PD-1+ and CD8+PD-1+ T cells decreased significantly from baseline (up to a 40% decrease for subjects treated with 20 or 30 µg/kg rhIL-7; P < .05) for both CD4 and CD8 and memory T cells at days 28 and 77. Administration of rhIL-7 did not significantly change the frequency of CD4 and CD8 T cells coexpressing the activation marker CD38+/DR+ (Supplementary Figure 3).

**Effects of rhIL-7 on Thymocyte Proliferation and the T-Cell Repertoire**

We next quantified the proportion of recent thymic emigrants (RTE) among naive CD4 T cells, cells containing T-cell receptor excision circles (TRECs), and TCR diversity using a quantitative real-time PCR method. As shown in Figure 3A, for subjects treated with the highest doses (20 or 30 µg/kg), rhIL-7 increased both naive and RTE CD4 T cells at day 77 (P < .05 for both subsets as compared with baseline). We also found an increase in the sj/β TREC ratio (a reflection of thymic output [18]) from 46 at day 0 to 68.7 at week 12 (day 77), (mean fold increase, 1.8; P = .06). There was a significant inverse relationship between the change in sj/β TREC ratio and the CD4 T-cell count at day 0 and the nadir (r = 0.40; P = .01; Spearman’s test) (Figure 3B).

When compared with the T-cell repertoire diversity of historical controls, the repertoire diversity of patients varied from 36% to 83% (median, 63%) at baseline (Figure 3C). Diversity scores did not increase significantly at day 28 (71.5%) or week 12 (64.3%) (Figure 3C). Subjects with normal TCR diversity at baseline remained in stable condition. Four subjects with a low baseline diversity score who received rhIL-7 exhibited increased TCR diversity, from 49%, 55%, 36%, and 50% at entry to 75%, 61%, and 59% (two patients) at day 28 (Figure 3C), and this change persisted at week 12 (67%, 70%, 52%, and 61%); changes were not noted in a fifth subject who received placebo. A detailed analysis of the clonotypes from 1 rhIL-7 and 1 placebo recipient is shown in Figure 3D.

**Effects of rhIL-7 Administration on HIV Replication**

No changes in plasma HIV RNA levels were noted in subjects in the placebo and 10 µg/kg groups. In contrast, 4 and 2 subjects in the 20 and 30 µg/kg dose groups, respectively, experienced transient increases of plasma HIV RNA during or immediately after rhIL-7 administration (<400 copies/mL in 5 and 1023 copies/mL in the sixth). No modifications of highly active ARV therapy or compliance issues were recognized in these subjects. All subsequent plasma HIV RNA levels remained below detection through week 52, except in 2 subjects (85 and 52 copies/mL).

Table 2 shows the evolution of the total amount of cell-associated DNA from HIV. There were no significant changes in intracellular HIV-1 DNA levels when these levels were expressed per 10^6 PBMC or 10^6 CD4 T cells, irrespective of the treatment group at week 12 (Table 2). In contrast, when expressed as log_{10} copies per milliliter of blood, HIV-1 DNA significantly increased in subjects treated with 20 µg/kg (median change, 0.4 log_{10} copies/mL; P = .03 compared with day 0) or 30 µg/kg (median change, 0.5 log_{10} copies/mL; P = .006 compared with day 0).

**Safety, Tolerability, and Pharmacokinetics of rhIL-7**

At 10 or 20 µg/kg, rhIL-7 was well tolerated. At 30 µg/kg, dose-limiting toxicity was observed in 2 subjects, one with a transient grade 3 alanineaminotransferase increase and the other with a grade 2 rash. No neutralizing anti–IL-7 antibodies were detected. The pharmacokinetic analysis showed loss of the linear relationship between the area under the curve and dose at 30 µg/kg (Supplementary Figure 4).
DISCUSSION

This study was designed to identify a well-tolerated dose of rhIL-7 that would achieve the main desirable biologic effect of IL-7, namely, expansion of the CD4 T-cell pool in HIV-1–infected subjects. We show substantial and sustained CD4 T-cell expansions for as long as 1 year after IL-7 treatment, decreases in the proportions of PD-1+ T cells, and improved thymopoiesis with broadening of the T-cell repertoire in a few subjects.

IL-7 consistently increases circulating T cells in HIV-infected patients, as was shown with previous formulations [12] and different schedules of administration [26]. The new formulation of rhIL-7 (CYT107) given as a cycle of 3 weekly injections led to a safe and significant increase in circulating

Figure 2. Cycling of CD4 and CD8 T-cell subsets in response to recombinant human interleukin 7 (rhIL-7). A, Flow cytometry was used to determine Ki-67 expression in T-cell subsets. Increased naive, central memory (CM), and effector memory T-cell cycling was seen on day 7 (pooled rhIL-7 groups compared with placebo, \(P<.001\)), returning to baseline by day 28 (median, Quarter 1–Quarter 3). The increase was not dose dependent and occurred in both CD4 and CD8 subsets. B, PD-1 expression decreased on both CD4 and CD8 T cells 28 days after 20 and 30 \(\mu\)g/kg rhIL-7 administration (\(P<.05\) for each). The decrease persisted until day 77 (\(P<.05\)). C, CM subsets showed decreased expression of PD-1. Abbreviations: CM, central memory; EM, effector memory; N, naive.
CD4 T cells. In addition, based on tolerance and biologic activity, we identified the 20 µg/kg dose as ideal for future studies.

HIV infection is characterized by a progressive depletion of CD4 T cells due to direct killing, decreased survival of activated cells, and an impairment of thymic production and naive
Table 2. Changes in Total Cell-Associated HIV DNA Levels

| Day | Change in HIV DNA Level From Baseline, Median (IQR) | Log10 Copies/µL | PBMCs | Log10 Copies/µL | PBMCs | Log10 Copies/µL | PBMCs | Log10 Copies/µL | PBMCs |
|-----|----------------------------------------------------|----------------|--------|----------------|--------|----------------|--------|----------------|--------|
| Day 0 | Placebo (n = 6) | 2.75 (2.62–2.98) | 2.47 (2.32–2.70) | 3.37 (3.33–3.41) | 3.27 (3.24–3.37) | 3.33 (3.60–4.15) | 3.29 (3.61–3.84) | 3.33 (3.60–4.15) | 3.27 (3.24–3.37) |
|     | rhIL-7 dose, µg/kg | 10 (n = 6) | 2.63 (2.34–2.52) | 2.76 (2.32–2.79) | 3.11 (3.06–3.44) | 3.20 (3.09–3.39) | 3.30 (3.09–3.39) | 3.20 (3.09–3.39) | 3.30 (3.09–3.39) |
|     | 20 (n = 6) | 2.47 (2.32–2.79) | 2.67 (2.62–2.79) | 3.49 (3.36–3.54) | 3.49 (3.36–3.54) | 3.95 (3.82–4.10) | 3.95 (3.82–4.10) | 3.95 (3.82–4.10) | 3.95 (3.82–4.10) |
|     | 30 (n = 6) | 2.51 (2.21–2.75) | 2.51 (2.21–2.75) | 3.46 (3.33–3.58) | 3.46 (3.33–3.58) | 3.96 (3.83–4.10) | 3.96 (3.83–4.10) | 3.96 (3.83–4.10) | 3.96 (3.83–4.10) |

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PBMCs, peripheral blood mononuclear cells; rhIL-7, recombinant human interleukin 7.

Recent experience with IL-2 therapy in HIV-infected patients shows that an increase in CD4 T cells does not necessarily confer a clinical benefit. Analyses of IL-2-expanded cells have shown a predominant expansion of CD25 T cells [28] with a long half-life [29] that share molecular and functional characteristics of Tregs [24]. In contrast, we find that most expanded CD4 T cells in rhIL-7–treated subjects did not exhibit Treg features, resulting in a relative decrease in Tregs within the total CD4 T-cell population. Other important differences between IL-2 and IL-7 are the concomitant expansion of CD8 T cells, the improved safety profile, and the pharmacokinetic characteristics of rhIL-7 that could make weekly injections feasible [24].

To date, the long-term effects and safety of rhIL-7 are unknown. In previous studies of rhIL-7, transient elevations in plasma HIV RNA levels were noted. A recent study suggested that the population of cells that harbor HIV DNA may be targeted and expanded by IL-7 [30]. In the present study, about 1 in 4 subjects experienced a transient increase in plasma HIV RNA levels, and though there was no increase in the proportion of cells containing HIV DNA, the concentration of HIV DNA per milliliter of blood increased. Although statistically significant, the clinical relevance of this observation remains to be determined and will be evaluated in future studies.

From a clinical perspective, rhIL-7 may prove to be an attractive therapeutic adjuvant in HIV disease. If shown to be safe in longer-term studies, repeated administration of rhIL-7 may help patients reach and sustain normal circulating CD4 T-cell expansion capacity [27]. We show that rhIL-7 increases predominantly the naive and central memory CD4 and CD8 T-cell subsets. Cellular proliferation, as indicated by Ki-67 staining, is probably a major mechanism. Although difficult to measure in vivo, improved T-cell survival due to rhIL-7 could not be ruled out. Such an effect was suggested by the decreased expression of the exhaustion markers (PD-1) on T cells and transient increases in Bcl-2 expression, as shown in the current study and elsewhere in cancer patients [15].

A novel aspect of the present study was the characterization of the naive T-cell compartment through phenotypic and molecular measurements. Our findings of an increase in RTE and β2/β TREC were compatible with an effect of rhIL-7 on thymic output and the production and/or expansion of a younger cell population (eg, naive T cells). We also found changes in the TCR repertoire in a few subjects with the lowest TCR diversity at entry. These observations require validation in additional patients and with a long-term follow-up. Although in the current study we cannot relate these phenotypic and molecular changes to a restoration of T-cell function, an earlier study by our group has shown that IL-7–expanded CD4 T cells respond well in vitro to mitogens, recall antigens, and HIV peptides [22]. Similar observations have been made among patients with cancer who received rhIL-7 [15].
counts. Several epidemiologic studies have indicated that the circulating CD4 T-cell count is an important predictor of morbidity including cardiovascular, malignant, renal and hepatic disease in HIV infection even in patients with controlled viremia receiving ARV therapy [31–33]. As noted above, recent experience indicates that the circulating CD4 T-cell count in the setting of cytokine-based therapy of HIV disease may not be a valid predictor of clinical benefit [22]. Therefore, to confirm clinical utility, clinical trials will need to focus on clinical end points to determine whether the promising biologic effects of IL-7 can be translated into clinical benefit.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the authors that are published to benefit the reader. The posted materials are not copyrighted. The content of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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