Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function

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Objective: To characterize immune phenotype and thymic function in HIV-1-infected adults with excellent virologic and poor immunologic responses to highly active antiretroviral therapy (HAART).

Methods: Cross-sectional study of patients with CD4 T cell rises of ≥ 200 × 10^6 cells/l (CD4 responders; n = 10) or < 100 × 10^6 cells/l (poor responders; n = 12) in the first year of therapy.

Results: Poor responders were older than CD4 responders (46 versus 38 years; P < 0.01) and, before HAART, had higher CD4 cell counts (170 versus 35 × 10^6 cells/l; P = 0.11) and CD8 cell counts (780 versus 536 × 10^6 cells/l; P = 0.02). After a median of 160 weeks of therapy, CD4 responders had more circulating naive phenotype (CD45+CD62L+) CD4 cells (227 versus 44 × 10^6 cells/l; P = 0.001) and naive phenotype CD8 cells (487 versus 174 × 10^6 cells/l; P = 0.004) than did poor responders (after 130 weeks). Computed tomographic scans showed minimal thymic tissue in 11/12 poor responders and abundant tissue in 7/10 responders (P = 0.006). Poor responders had fewer CD4 cells containing T cell receptor excision circles (TREC) compared with CD4 responders (2.12 versus 27.5 × 10^6 cells/l; P = 0.004) and had shorter telomeres in CD4 cells (3.8 versus 5.3 kb; P = 0.05). Metabolic labeling studies with deuterated glucose indicated that the lower frequency of TREC-containing lymphocytes in poor responders was not caused by accelerated proliferation kinetics.

Conclusion: Poor CD4 T cell increases observed in some patients with good virologic response to HAART may be caused by failure of thymic T cell production.

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Keywords: AIDS, highly active antiretroviral therapy, HAART, CD4, thymus, T cell reconstitution

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**Introduction**

Suppression of viral replication after administration of potent antiretroviral therapy is associated with quantitative and qualitative immune enhancement [1,2], decreased rates of opportunistic infections [3,4] and decreased mortality [5–7]. In patients with relatively advanced disease, a biphasic pattern of CD4 and CD8 T cell recovery has been observed after the initiation of antiretroviral therapy. During the first 4 to 8 weeks, rises in CD4 and CD8 T lymphocytes of both naive and memory phenotypes have been observed [1,8–11]. This initial increase is likely a result, at least in part, of redistribution of sequestered cells into the circulation [12,13]. It is followed by a more gradual second-phase increase in CD4 T cells comprised mainly of naive phenotype cells [1,2,10,14].

In approximately 8–17% of patients, suppression of HIV-1 replication is not accompanied by an increase in circulating CD4 T cells [11,15–17]. Such patients may remain at increased risk for opportunistic infections [15] and have higher risk for progression to AIDS or death [17]. Although the factors responsible for these discordant responses are not well understood, the magnitude of CD4 T cell restoration after highly active antiretroviral therapy (HAART) has been correlated with the rate of pre-therapy CD4 T cell decline, baseline plasma viremia, total and naive-phenotype CD4 T cell counts, and the first-phase decay in plasma HIV-1 RNA levels [2,10,16,18].

We hypothesized that failure to restore circulating CD4 T cells after initiation of effective HAART may be caused in part by deficiencies in T cell production, particularly from the thymus. To explore this possibility, a cross-sectional study examined several indices of T cell production in patients with sustained virologic responses who had received at least 12 months of HAART, comparing those with a first year post-HAART CD4 T cell gain of \( \geq 200 \times 10^6 \) cells/l (CD4 responders) with those with a gain of \(< 100 \times 10^6 \) cells/l (poor responders).

**Methods**

**Patients**

Patients were attending the John T. Carey Special Immunology Unit at University Hospitals of Cleveland, Ohio and the San Francisco General Hospital, San Francisco, California. To be eligible for study participation, patients were HIV-1-infected adults who had received HAART for at least 12 months. Poor responders were those with a CD4 T cell rise of \(< 100 \times 10^6 \) cells/l over the first year of effective HAART; CD4 responders were those with increases of \( \geq 200 \times 10^6 \) cells/l during the same time period. All eligible subjects were invited to participate.

Informed consent was obtained from all study participants in accordance with policies of the institutional review boards of Case Western Reserve University, University Hospital of Cleveland and the University of California, San Francisco.

Demographic information, risk factors for HIV-1 infection, medical history, including current and past antiretroviral therapy, pre-therapy plasma HIV-1 RNA levels, CD4 and CD8 T cell counts were collected by review of databases and clinical charts. Venous blood samples and a non-contrast computed tomograph (CT) of the chest were obtained at study entry. Complete data were not collected on all patients, but all data collected are shown in the tables and figures.

**Isolation of peripheral blood mononuclear cells**

Samples (50 ml) of venous blood were drawn into heparinized tubes and processed within 6 h of collection. Peripheral blood mononuclear cells (PBMC) were separated by Ficoll-Hypaque density sedimentation, washed and resuspended in culture medium consisting of RPMI-1640 medium supplemented with 10% heat-inactivated pooled human serum (Gemini Bioproducts, Calabasas, California, USA). 2 mmol/l L-glutamine, 50 U/ml penicillin, 50 \( \mu \)g/ml streptomycin, and 10 mmol/l HEPES buffer.

**T cell subsets and plasma HIV-1 RNA**

Dual- and three-color flow cytometric studies were performed using a whole blood lysis method (http://actg.s+.com/immeth.htm) and fluorochrome-labeled murine monoclonal antibodies (Pharmigen, San Diego, California, USA). Plasma HIV-1 RNA levels were measured using a reverse transcriptase (RT) polymerase chain reaction (PCR) technique (Amplicor; Roche, Nutley, New Jersey, USA). The lower limit of detection for the assay was 400 copies/ml. Eight patients had plasma HIV-1 RNA levels measured by RT-PCR using the Roche ultrasensitive assay with a lower detection limit of 40 copies/ml (Amplicor; Roche).

**Chest computed tomographic scans**

Non-contrast chest CT scans were performed using contiguous 5 mm sections from the sternal notch through the xiphoid process. Scans were read by radiologists who were blinded to patient age and clinical data. The scans were scored on a scale of 0 to 5 [19], as follows: 0, no visible thymic tissue (i.e., entirely replaced by fat); 1, minimal tissue, barely recognizable; 2, minimal tissue, more obvious; 3, moderate tissue; 4, moderate tissue, greater extent; 5, thymic mass of...
concern for thymoma. Scores < 3 represented minimal thymic tissue while those ≥ 3 were interpreted to represent abundant thymic tissue [19].

Measurement of T cell receptor rearrangement excision circles
Quantification of T cell receptor rearrangement excision circles (TREC) in purified CD4 and CD8 cells was performed by real-time quantitative PCR using the 5’ nuclease (TaqMan) assay with an ABI7700 detection system (Perkin-Elmer, Norwalk, Connecticut, USA), as previously described [20]. PBMC were separated into CD4 cell- and CD8 cell-enriched populations by positive selection using MACS magnetic microbeads (Miltenyi-Biotech, Auburn, California, USA). Cells were lysed in 100 μg/ml proteinase K (Boehringer, Indianapolis, Indiana, USA) for 1 h at 56°C, and then lysates were incubated for 10 min at 95°C. Real-time quantitative PCR was performed on 5 μl of cell lysate (50 000 cells) with the following primers: cacatcctttcacaatgt and gccagctgagggttagg, and probe FAM–acactctttgaattgttggtct–TAMRA (MegaBases, Chicago, Illinois, USA). PCR reactions contained 0.5 U platinum taq polymerase (Gibco, Grand Island, New York, USA), 3.5 mmol/l MgCl2, 0.2 mmol/l dNTPs, 500 nmol/l of each primer, 150 nmol/l probe and Blue-636 (MegaBases). After incubation at 95°C for 5 min, the reactions were amplified through 40 cycles (at 95°C for 30 s and 60°C for 1 min). A standard curve was plotted and TREC values were calculated using the ABI7700 software. All samples were analyzed in duplicate.

Measurement of T cell production
The FACS/stable isotope/mass spectrometric method for measuring cell proliferation was used as described previously [21,22]. Briefly, the method involves three steps: (a) administration of [6,6-2H2]-glucose by constant, 12 h intravenous infusion, accompanied by blood draws every 4 h during the infusion (to measure enrichment of plasma glucose) and at day 7 and day 14 after the initiation of the infusion (to measure the fraction of dividing cells labeled during the infusion period that had appeared in the circulation); (b) sort purification of relevant subpopulations of CD4 and CD8 T cells (at least one million each); and (c) determination of the enrichment of [2H2]-deoxyadenosine (dA) in the DNA of the purified cell subpopulations using gas chromatography-mass spectrometry (GC-MS). Deoxyadenosine was prepared from T cell DNA by enzymatic hydrolysis followed by separation on an LC18 SPE column (Supelco, Bellefonte, Pennsylvania, USA), as previously described [23]. Kinetic calculations were based on the precursor–product relationship [24,25] and carried out as described elsewhere [21].

Telomere restriction fragment length measurement by flow cytometry
Cryopreserved PBMC were washed and separated into CD4 cell- and CD8 cell-enriched populations using magnetic microbeads (Miltenyi-Biotech GmbH, Germany). Cells were resuspended in 100 μl Ortho PermeaFix (Johnson & Johnson, Raritan, New Jersey, USA) for 45 min at room temperature and washed with phosphate-buffered saline and 2× saline sodium citrate (SSC). The cell pellet was resuspended in tubes containing 100 μl hybridization buffer: 50% Ultra Pure formamide (ICN, Aurora, Ohio, USA), 5× SSC, 5× Denhardt’s solution, 1.0 mg/ml sonicated salmon sperm DNA (Canadian Life Technologies, Toronto, Canada), 0.1 mg/ml 5’-fluorescein-(CCCTAA)3 probe or 0.1 mg/ml 5’-fluorescein-(TAG-CAC-ACT-CAC-CAC-TAG) control probe (PerSeptive Biosystems, Framingham, Massachusetts, USA). All denaturation and hybridization steps were performed in a Progene Thermocycler (Thecne, Nutley New Jersey, USA) in one cycle comprising incubations: 80°C for 20 min, 36°C for 3 h, and 4°C hold. Cells were washed once in 2× SSC and analyzed by flow cytometry (Epics, Altra, Coulter, Hialeah, Florida, USA). HL60 cells, 293 cells, and Jurkat cells were used as control cell lines to generate a standard curve of telomere restriction fragment length (TRFL) (as measured by Southern blot hybridization) and mean channel fluorescence was determined by flow cytometry. The mean channel fluorescence was determined at least three times and the average values were plotted, r = 0.553. Mean TRFL of patient samples was extrapolated from the standard curve.

Statistical analysis
Quantitative data were summarized by use of median and interquartile range. Continuous data were analyzed by appropriate non-parametric methods comparing poor responders and CD4 responders. Categorical data were presented as absolute frequencies and compared using the chi-square test. The Spearman’s rank test was used to assess correlations between variables. All P values were two-tailed and not adjusted for multiple testing. All analyses were done using SPSS version 8.0 (SPSS, Chicago, Illinois, USA).

Results
Twenty-two patients (21 males) were studied: 12 were poor responders and 10 were CD4 responders (Table 1). The median [interquartile range (IQR)] duration of HAART was 160 weeks (103–195) for poor responders and 130 weeks (97–161) for CD4 responders at the time the blood was drawn and the study was performed. Poor responders were older than CD4 responders (46 versus 38 years; P = 0.01); they also
tended to have lower pre-therapy HIV-1 RNA levels and higher pre-therapy CD4 T cell counts, but these differences were not statistically significant. Poor responders had higher median CD8 T cell counts before therapy than CD4 responders did (780 versus 536 × 10^6 cells/l; \( P = 0.02\)). The median CD4 T cell change after 12 months of HAART was 37 × 10^6 cells/l in the poor responders compared with 270 × 10^6 cells/l in the CD4 responders. Despite having fewer CD4 T cells at baseline, CD4 responders had a significantly higher absolute number of CD4 T cells after 1 year of therapy (median 355 × 10^6 cells/l) than did poor responders (median 216 × 10^6 cells/l) (\( P = 0.006\)).

**Table 1.** Baseline characteristics of the study subjects and peripheral blood lymphocyte phenotypes after highly active antiretroviral therapy.

<table>
<thead>
<tr>
<th></th>
<th>Poor responders</th>
<th>Responders</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Age [median (IQR) years]</strong></td>
<td>46 (45–51)</td>
<td>38 (35–42)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Duration of HAART [median (IQR) weeks]</strong></td>
<td>160 (103–195)</td>
<td>130 (97–161)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Plasma HIV-1 viral load before HAART [median (IQR) log_{10} RNA copies/ml]</strong></td>
<td>4.0 (3.9–4.6)</td>
<td>4.9 (3.7–5.6)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>CD4 T cells [median (IQR) × 10^6 cells/l]</strong></td>
<td>170 (90–276)</td>
<td>35 (10–260)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Before HAART</strong></td>
<td>216 (120–301)</td>
<td>355 (270–538)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>After 1 year of HAART</strong></td>
<td>37 (3–58)</td>
<td>270 (235–330)</td>
<td></td>
</tr>
<tr>
<td><strong>At the time of analysis</strong></td>
<td>285 (151–323)</td>
<td>585 (435–661)</td>
<td></td>
</tr>
<tr>
<td><strong>CD8 T cells [median (IQR) × 10^6 cells/l]</strong></td>
<td>780 (690–1030)</td>
<td>536 (372–710)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Before HAART</strong></td>
<td>592 (538–902)</td>
<td>1147 (658–1430)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>At the time of analysis</strong></td>
<td>780 (690–1030)</td>
<td>536 (372–710)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**CD8^{+}/CD45RA^{+}/CD62L^{+}** |

<table>
<thead>
<tr>
<th></th>
<th>Poor responders</th>
<th>Responders</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4^{+}/CD45RA^{+}/CD62L^{+}</strong></td>
<td>44 (33–107)</td>
<td>227 (153–343)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>CD4^{+}/CD45RA^{+}/CD45RO^{+}</strong></td>
<td>171 (111–234)</td>
<td>304 (188–353)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>CD8^{+}/CD45RA^{+}/CD62L^{+}</strong></td>
<td>174 (85–264)</td>
<td>487 (326–616)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>CD8^{+}/CD45RA^{+}/CD45RO^{+}</strong></td>
<td>182 (169–256)</td>
<td>273 (192–414)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**HAART, highly active antiretroviral therapy; IQR, interquartile range.**

**T cell receptor rearrangement excision circles**

As non-replicating episomal products of T cell receptor gene rearrangements, TRECs may be used, with some caveats, to estimate the numbers of naive T cells recently emigrated from the thymus [27–30]. CD4 cells with HIV-1 infection both before [19] and after [26] HAART. Almost all (11 of 12) poor responders had thymic indices < 3, consistent with minimal thymic tissue. In contrast, 7 of 10 CD4 responders had thymic indices ≥ 3, consistent with abundant thymic tissue (\( P = 0.006\)) (Fig. 1).

**Fig. 1.** Thymic index by chest computed tomographic scan. A thymic index ≥ 3 represents abundant thymic tissue.

**Lymphocyte subsets**

At the time of evaluation, the median number of circulating naive-phenotype (CD45RA^{+}/CD62L^{+}) T cells was significantly higher in CD4 responders than in poor responders: 227 versus 44 × 10^6 cells/l for CD4 cells (\( P = 0.001\)) and 487 versus 174 × 10^6 cells/l for CD8 T cells (\( P = 0.004\)) (Table 1). CD4 responders also displayed a trend toward higher median numbers of memory (CD45RO^{+}/CD45RA^{−}) phenotype CD4 cells (304 versus 171 × 10^6 cells/l; \( P = 0.07\)) and CD8 cells (273 versus 182 × 10^6 cells/l; \( P = 0.13\)).

The median (IQR) proportion of lymphocytes with the natural killer phenotype (CD16 or CD56) was higher in poor responders than in CD4 responders: 10% (8.5–17.5) versus 6% (3.7–8.0) (\( P = 0.005\)).

**Thymic index**

As measured by chest CT, thymus size has been found to correlate with naive CD4 T cell counts in persons with HIV-1 infection both before [19] and after [26] HAART. Almost all (11 of 12) poor responders had thymic indices < 3, consistent with minimal thymic tissue. In contrast, 7 of 10 CD4 responders had thymic indices ≥ 3, consistent with abundant thymic tissue (\( P = 0.006\)) (Fig. 1).
responders had increased numbers of circulating TREC-positive CD4 cells (median 27.5 × 10^6 cells/l; IQR, 21.2–54.5) compared with poor responders (median 2.12 × 10^6 cells/l; IQR, 0.47–4.46) \((P = 0.004)\) (Fig. 2). CD4 responders also had more TREC-positive CD8 T cells in peripheral blood than poor responders \([25.9 \text{ (IQR, 14.7–41.8)} \text{ versus 1.9 \times 10}^6 \text{ cells/l (IQR, 0.8–8.5); } P = 0.01]\).

**Telomere restriction fragment length**

Since telomeres shorten progressively as a function of repeated cell divisions [31,32], TRFL was examined as a marker for cellular replicative history. Median length was significantly shorter in the CD4 T cells of poor responders compared with CD4 responders: 3.8 kb (IQR, 2.8–4.7) versus 5.3 kb (IQR, 4.2–7.0) \((P = 0.05)\) (Fig. 3). In contrast, telomere lengths of CD8 T cells were comparable in both groups (data not shown).

**T lymphocyte production rates**

Since the proportion of TREC-containing lymphocytes can be affected both by thymic production and by peripheral replication and dilution, CD4 and CD8 cell production rates were measured using a metabolic label incorporated during cellular division. Uptake of deuterium-labeled glucose and measurement of labeled deoxyadenosine in cellular DNA has been used to quantify the production and decay of lymphocytes in health and in HIV-1 infection [21–23]. Two poor responders (TREC-positive CD4 cells of 0.07 and 1.98 × 10^6 cells/l) and three CD4 responders (TREC-positive CD4 cells of 72.6, 20.5, and 27.5 × 10^6 cells/l) were studied using this technique. The production of CD4 T cells per day averaged 2.5 \((\pm 1.3)\) × 10^6 cells/l in CD4 responders and 0.9 \((\pm 1.3)\) × 10^6 cells/l in poor responders \((P = 0.25)\). Similar results were found for CD8 T cells production, where the CD4 responders averaged 2.8 \((\pm 0.6)\) × 10^6 cells/l per day and the poor responders averaged 1.1 \((\pm 1.6)\) × 10^6 cells/l per day \((P = 0.25)\). Mean fractional replacement rates \((\pm SD)\) for CD4 and CD8 cells were also not significantly different between the CD4 responders \((0.0045 \pm 0.0016 \text{ and 0.0040 \pm 0.0024, respectively})\) and poor responders \((0.0065 \pm 0.0092 \text{ and 0.0020 \pm 0.0008, respectively})\).

**Relationship frequencies for thymic index, phenotype and T cell receptor rearrangement excision circles**

A significant positive correlation was observed between the thymic index and the absolute number of CD4 T cells \((P = 0.004; \text{ Table 2})\), the absolute number of naive CD4 T cells \((P = 0.001)\), and the numbers of TREC-positive CD4 cells \((P = 0.01)\), but not between the frequency of TREC-positive CD8 cells \((P = 0.06)\) or the telomere lengths in CD4 or CD8 T cells (data not shown). Thymic index was inversely correlated with age \((P = 0.0001)\).

**Discussion**

HIV-1-infected patients with poor CD4T cell increases despite suppression of viral replication in response to...
HAART had fewer circulating naive CD4 T cells, smaller thymuses, fewer circulating CD4 T cells containing TREC-positive CD8 T cells with shorter telomeres. These findings suggest that in poor responders, thymic production is impaired or that recent thymic emigrants are sequestered, selectively deleted and/or rapidly diluted by peripheral expansion. With this in mind, cell kinetics were measured using a new, non-radioactive, metabolic labeling technique [21,22]. Although only five subjects were studied, there was no increase in incorporation of deuterium into the DNA of either CD4 or CD8 T cells in poor responders, suggesting that dilution of TREC-positive lymphocytes as a result of increased replication is not occurring in these patients.

The dramatic absence of thymic tissue in the poor responders compared with that in the CD4 responders suggests that failure of thymic function is a likely explanation for the poor CD4 T cell increases in these patients. Nonetheless, enhanced sequestration of newly produced lymphocytes also might contribute to the failure of cellular increases in the periphery. In this regard, we found increased expression of activation antigens (CD38 and HLA-DR) on both CD4 and CD8 T cells in poor responders (not shown). This may reflect heightened cellular activation, adhesion and cell death in lymphoid tissues of these patients [13].

Telomeres, consisting of TTAGGG repeats, are at the extreme ends of chromosomes and shorten progressively during cell division in vitro and with aging [34,35]. Telomerase, a ribonucleoprotein enzyme that synthesizes telomeric DNA repeats onto chromosomal ends, can compensate for telomere shortening [43]. Therefore, longer telomeres are seen in younger cells with a shorter replicative history but also may be seen in cells with altered telomerase activity. The shorter telomeres seen in the CD4 T cells of poor responders suggest that these cells have undergone more cellular divisions than the CD4 T cells of CD4 responders, as would be expected in populations enriched for memory/effector phenotype cells [23]. Although we cannot exclude the possibility that CD4 T cells of poor responders have altered telomerase activity, the results of our studies taken together are most consistent with a failure of thymic naive cell production in poor responders that results in a relative enrichment of memory cells with shorter telomeres.

If, as our data suggest, thymic potential determines the magnitude of cellular restoration seen after HAART, a more brisk CD4 T cell response might be expected after application of HAART in HIV-1-infected children. This appears to be the case as children, particularly younger children, tend to have more dramatic CD4 T cell increases after HAART [44,45] and these increases appear to be related to increases in thymic size [46]. Moreover, in contrast to findings among adults,
much of the CD4 T cell increase in children is seen among cells with a ‘naïve’ phenotype [44–47].

Although this small study was cross-sectional and retrospective, our findings suggest that the failure of immune restoration after suppression of HIV replication may in some instances be caused by impaired thymic output. If so, it is likely that patients manifesting such failure will have a restricted T cell receptor repertoire and will remain immunocompromised. It will be important in the future to clearly identify the predictors of poor CD4 responses. Given such information, it may then be possible to design studies aimed at augmenting intrathymic T cell production.

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