Immune Recovery after Autologous Stem Cell Transplantation Is Not Different for HIV-Infected versus HIV-Uninfected Patients with Relapsed or Refractory Lymphoma

Cecilia Simonelli, Stefania Zanussi, Chiara Pratesi, Maurizio Rupolo, Renato Talamini, Cristina Caffau, Maria Teresa Bortolin, Rosamaria Tedeschi, Giancarlo Basaglia, Mario Mazzucato, Rosa Manuele, Emanuela Vaccher, Michele Spina, Umberto Tirelli, Mariagrazia Michieli, and Paolo De Paoli

Division of Medical Oncology A, Microbiology, Immunology, and Virology Unit, Cellular Therapy and High-Dose Chemotherapy Unit, Epidemiology and Biostatistics Unit, Stem Cell Collection and Processing Unit, and Scientific Directorate, National Cancer Institute, Aviano, Italy

Background. High-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) are feasible and effective salvage treatments for human immunodeficiency virus (HIV)–related relapse or refractory lymphoma. Among the main concerns with ASCT in HIV-infected persons is the additional immune depletion caused by treatment, which could amplify the preexisting immune deficit. The aims of our study were to assess the impact of conventional chemotherapy before salvage treatment was administered, in this population, and to evaluate immune reconstitution dynamics during ASCT.

Methods. All 33 HIV-infected and HIV-uninfected patients who underwent comparable ASCT protocols at the National Cancer Institute (Aviano, Italy) who underwent ≥1 month of follow-up after transplantation were included in a prospective immunological study. Demographic, clinical, and immunovirological data were obtained before administration of induction therapy, during transplantation, and at 24 months of follow-up.

Results. Before HDC, no significant differences were observed in CD4+ cell subsets and signal joint T cell receptor excision circles (sjTRECs), although HIV-infected persons had inverted ratios of CD4+ cells to CD8+ cells because they had higher CD8+ T cell counts, compared with HIV-uninfected persons. After ASCT, this inversion was also observed in HIV-infected patients up to 24 months. CD4+ cell subsets had similar recoveries, with a temporary setback in HIV-infected persons 3 months after reinfusion, together with an increase in infections. sjTRECs demonstrated similar dynamics in both populations and serve as a useful predictive marker of recovery of CD4+ cell subsets. No significant changes emerged in HIV DNA levels during the follow-up period, with values at 24 months significantly lower than those at baseline.

Conclusions. Our study demonstrated that ASCT in HIV-infected persons with lymphoma does not worsen the initial immune impairment and does not enhance viral replication or the peripheral HIV reservoir in the long term.

Highly active antiretroviral therapy (HAART) has reduced the mortality and morbidity of human immunodeficiency virus (HIV)–infected patients [1, 2]. However, non-Hodgkin lymphoma (NHL) still remains one of the main causes of AIDS-associated death in these subjects [3, 4]. Moreover, the incidence of Hodgkin lymphoma has increased during the HAART era [5].

In the general population, high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) are the treatments of choice for relapse of non-Hodgkin lymphoma and Hodgkin lymphoma [6, 7]. Our research group and others have shown that ASCT is also feasible and effective in HIV-infected persons [8–14].

HIV infection causes a severe depletion of CD4+ T lymphocytes, which leads to a reduction in the heterogeneity of T cell receptor expression, a decrease in the
phenotypically defined naive CD4+ T cell count, and a decrease in thymic regeneration, which is measured as circular fragments of episomal DNA of the T cell receptor (signal joint T cell receptor rearrangement excision circles [sjTRECs]) [15–18]. Undoubtedly, HDC could exacerbate immunodepression that already affects HIV-infected patients and consequently facilitate the progression of infection. However, as with HIV-uninfected patients, conditioning regimens could also create an appropriate lymphoid space that is devoid of endogenous cellular populations competing for stimulatory cytokines; this may contribute to expansion of the transferred cells [19, 20]. Nevertheless, the dynamics of immune reconstitution, thymic regeneration, and viral replication have to be studied to optimize therapeutic strategies that target HIV-related lymphoma and HIV infection.

The aims of this study are (1) to compare the pretreatment immune status of HIV-infected and HIV-uninfected individuals with relapsed or refractory lymphoma who underwent comparable ASCT protocols, to assess whether conventional chemotherapy has a different impact on the immune system of the 2 populations; (2) to describe the dynamics of immune reconstitution and thymic regeneration at up to 24 months of follow-up; and (3) to explain the dynamics of HIV replication during treatment and after ASCT.

**MATERIALS AND METHODS**

**Patients.** From October 2001 to March 2008, all HIV-infected patients (n = 24; 18 had high-grade non-Hodgkin lymphoma, and 6 had Hodgkin lymphoma) and HIV-uninfected patients (n = 9; all had high-grade non-Hodgkin lymphoma) with lymphoma that had relapsed or that was refractory to first-line chemotherapy, who received comparable HDC and ASCT protocols and showing at least 1-month follow-up after transplantation, were included in a prospective, immunovirologic study. The DCT for patients with high-grade non-Hodgkin lymphoma treated up to November 2002 consisted of 4 cycles of etoposide, cytarabine, cisplatinum, and methylprednisone; the regimen of dexamethasone, high-dose cytarabine and oxaliplatinum was used for patients treated thereafter. Before each cycle, rituximab was administered to all patients from the start of conditioning until aphaeresis, 15 days after reinfusion (aplasia), and 1, 3, 6, 12, and 24 months after ASCT. sjTRECs were not assessed at aphaeresis, 15 days after reinfusion, and at month 1 and 6 of follow-up; HIV DNA levels were also not determined at month 6.

All patients were monitored for the development of infectious complications. An infectious episode was assigned if there was clinically or microbiologically documented infection and/or fever without a localized source of infection or identified pathogen. Grading of the infections was scored according to Common Toxicity Criteria [23]. Antibacterial, antifungal, and (on the basis of individual history) antiviral prophylaxis were administered to all patients from the start of conditioning until neutrophil recovery. At enrollment, all HIV-infected patients were receiving HAART based on their clinical antiretroviral therapy histories and/or the HIV genotypic test result.

All patients agreed to participate in the study by signing an informed consent approved by our Institute Board of Ethics, in agreement with principles stated in the Declaration of Helsinki.

**Immunovirologic characterization.** The absolute lymphocyte subset counts were evaluated by a single platform, whole-blood lysing technique and with the EPICS XL flow cytometer (Beckman-Coulter), as described elsewhere [18]. Nave CD4+ T cells were defined by 3-color flow cytometry using monoclonal antibodies against CD4 (Dako), CD62L (Immunotech), and CD45RA (Beckman-Coulter) antigens [24].

Thymic regeneration was evaluated by assessing the number of sjTRECs per 10^6 peripheral blood mononuclear cells (PBMCs) using a real-time polymerase chain reaction (PCR) quantitative technique [18]. The HIV RNA level was quantified by using the Versant HIV-1 RNA 3.0 assay kit (b-DNA; Bayer Diagnostics). The HIV DNA level was measured by real-time PCR [22].

**Statistical analysis.** Significant tests for proportions were computed using the Fisher exact test. We used the Mann Whitney U test to evaluate the differences between groups in continuous variables (HIV-infected vs HIV-uninfected patients, HIV-infected patients with infectious episodes vs HIV-infected patients without infectious episodes, and rituximab-treated vs rituximab-untreated patients) and the Wilcoxon rank sum test for longitudinal analysis of matched data. Correlations between the immunological covariates at baseline and 3 and 12 months after ASCT were analyzed using the Spearman coefficient. Except for CD56+ cells, the concentration of lymphocyte subsets in the aphaeric product correlated well with that found in peripheral blood at aphaeresis (12 observations; r = 0.77–0.90; P <.005). Considering these results, to increase the power of statistical analyses, we evaluated the associations between the peripheral T cell subsets at aphaeresis and the subset recoveries...
Table 1. Baseline Demographic and Clinical Characteristics of 33 Patients with Relapsed or Refractory Lymphoma, by Human Immunodeficiency Virus (HIV) Infection Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-infected patients (n = 24)</th>
<th>HIV-uninfected patients (n = 9)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (12.5)</td>
<td>3 (33.3)</td>
<td>.31</td>
</tr>
<tr>
<td>Male</td>
<td>21 (87.5)</td>
<td>6 (66.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>15 (62.5)</td>
<td>1 (11.1)</td>
<td>.02</td>
</tr>
<tr>
<td>≥45</td>
<td>9 (37.5)</td>
<td>8 (88.9)</td>
<td></td>
</tr>
<tr>
<td><strong>HCV infection status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>15 (62.5)</td>
<td>7 (77.8)</td>
<td>.68</td>
</tr>
<tr>
<td>Positive</td>
<td>9 (37.5)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td><strong>HBsAg status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>22 (91.7)</td>
<td>8 (88.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (8.3)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoma histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade non-Hodgkin lymphoma</td>
<td>18 (75.0)</td>
<td>9 (100.0)</td>
<td>.16</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>6 (25.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage (Ann Arbor)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>3–4</td>
<td>22 (91.7)</td>
<td>9 (100.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP-like</td>
<td>14 (58.3)</td>
<td>6 (66.7)</td>
<td>.71</td>
</tr>
<tr>
<td>Other</td>
<td>10 (41.7)</td>
<td>3 (33.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous rituximab chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (79.2)</td>
<td>7 (77.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (20.8)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of previous chemotherapy cycles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>18 (75.0)</td>
<td>6 (66.7)</td>
<td>.68</td>
</tr>
<tr>
<td>&gt;6</td>
<td>6 (25.0)</td>
<td>3 (33.3)</td>
<td></td>
</tr>
<tr>
<td><strong>TECT duration, months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>13 (54.2)</td>
<td>5 (65.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>&gt;5</td>
<td>11 (45.8)</td>
<td>4 (44.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoma status at enrolment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed lymphoma</td>
<td>19 (79.2)</td>
<td>7 (77.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Refractory lymphoma</td>
<td>5 (20.8)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; TECT, time elapsed from previous chemotherapy.  

*a Determined by the Fisher exact test.

RESULTS

Baseline characteristics. No differences were observed in demographic and clinical characteristics before DCT between HIV-infected and HIV-uninfected patients, except for age (Table 1). Table 2 shows median values and IQRs for some immunological characteristics of patients with lymphoma before DCT, by HIV infection status. HIV infection was associated with higher CD8<sup>+</sup> T cell counts (median for HIV-infected patients, 678 cells/μL [IQR, 423–1015 cells/μL]; median for HIV-uninfected patients, 265 cells/μL [IQR, 159–336 cells/μL]; P<.01) and an inverted ratio of CD4<sup>+</sup> cells to CD8<sup>+</sup> cells (median for HIV-infected patients, 0.24 [IQR, 0.17–0.51]; median for HIV-uninfected patients, 1.77 [IQR, 0.94–1.87]; P<.001). No significant differences between the groups were found for the other analyzed variables.

Immunological recovery during ASCT. In studying the dynamics of immunological recovery, differences in CD4<sup>+</sup> T cell counts between HIV-infected and HIV-uninfected patients were
### Table 2. Baseline Immunological Characteristics in Human Immunodeficiency Virus (HIV)–Infected Patients and HIV-Uninfected Patients with Relapsed or Refractory Lymphoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-infected patients</th>
<th>HIV-uninfected patients</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with data</td>
<td>22</td>
<td>8</td>
<td>.10</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>190 (90–289)</td>
<td>288 (165–615)</td>
<td></td>
</tr>
<tr>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>17</td>
<td>5</td>
<td>.88</td>
</tr>
<tr>
<td>Naive CD4&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>33 (5–59)</td>
<td>26 (14–160)</td>
<td></td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>678 (423–1015)</td>
<td>265 (159–336)</td>
<td>.004</td>
</tr>
<tr>
<td>Ratio of CD4&lt;sup&gt;+&lt;/sup&gt; cells to CD8&lt;sup&gt;+&lt;/sup&gt; cells</td>
<td>22</td>
<td>8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.24 (0.17–0.51)</td>
<td>1.77 (0.94–1.87)</td>
<td></td>
</tr>
<tr>
<td>CD56&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>22</td>
<td>8</td>
<td>.36</td>
</tr>
<tr>
<td>Naive CD56&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>57 (47–121)</td>
<td>87 (59–151)</td>
<td></td>
</tr>
<tr>
<td>CD19&lt;sup&gt;+&lt;/sup&gt; cell count, cells/µL</td>
<td>79 (30–141)</td>
<td>106 (30–173)</td>
<td>.73</td>
</tr>
<tr>
<td>sjTREC level, sjTRECs/10&lt;sup&gt;6&lt;/sup&gt; PBMCs</td>
<td>21</td>
<td>7</td>
<td>.16</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>391 (86–587)</td>
<td>496 (268–1063)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** The sum does not add up to the total because of missing values. PBMCs, peripheral blood mononuclear cells; sjTRECs, signal joint T cell receptor excision circles.

**a** Determined by Mann-Whitney U test.

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Figure 1. Lymphocyte count recovery dynamics for absolute CD4<sup>+</sup> count (A), absolute naive CD4<sup>+</sup> count (B), absolute CD8<sup>+</sup> cell count (C), ratio of CD4<sup>+</sup> cells to CD8<sup>+</sup> cells (D), absolute CD56<sup>+</sup> cell count (E), and absolute CD19<sup>+</sup> cell count (F) at baseline, apheresis, prior to high-dose chemotherapy (HDC), and at day 15 and month 1, 3, 6, 12, and 24 after autologous stem cell transplantation, according to human immunodeficiency virus (HIV) infection. In each panel, notched solid (HIV-infected patients) and open boxes (HIV-uninfected patients) represent 25th and 75th percentile values; the middle line and vertical lines correspond to the median value and both the 10th and 90th percentiles, respectively. Statistically significant differences between baseline values and their matched values at subsequent steps of the treatment were calculated by Wilcoxon rank sum test and reported above as continuous lines for HIV-infected patients and as dotted lines for HIV-uninfected patients. *P<.05, by Mann Whitney U test, for comparison between groups.
HIV-uninfected patients attained the initial median values 12 absolute numbers was observed until year 2 after transplantation, reached the normal range [25] by 6 months after transplantation, and median values in the aplastic period; the CD19+ cell count had recovered somewhat by 3 months after transplantation, and median values reached the normal range [25] by 6 months after transplantation (Figure 1F). Subsequently, a marked enhancement in absolute numbers was observed until year 2 after transplantation (median in HIV-infected patients, 446 cells/μL [IQR, 240–690 cells/μL]; median in HIV-uninfected patients, 495 cells/μL [IQR, 335–704 cells/μL]; P = .70). Twelve (50%) of 24 HIV-infected patients and 6 (66.7%) of 9 HIV-uninfected patients were treated with rituximab during DCT. The recovery in the CD19+ cell count occurred 3 months later in rituximab-treated patients than in rituximab-untreated patients: the median values for rituximab-treated and rituximab-untreated patients were 2 cells/μL (IQR, 0–77 cells/μL) and 132 cells/μL (IQR, 43–198 cells/μL; P = .03), respectively, at month 3 and 128 cells/μL (IQR, 59–265 cells/μL) and 197 cells/μL (IQR, 127–339 cells/μL; P = .39), respectively, at month 6.

**Thymic regeneration.** Before HDC, the HIV-uninfected patients experienced a 65% decrease in the initial sjTREC value and reached slightly lower values than did HIV-infected patients (median for HIV-infected patients, 457 sjTRECs/10^6 PBMCs [IQR, 379–1075 sjTRECs/10^6 PBMCs]; median for HIV-uninfected patients, 173 sjTRECs/10^6 PBMCs [IQR, 110–4222 sjTRECs/10^6 PBMCs]; P = .41). After ASCT, the slow but steady reconstitution of sjTRECs demonstrated similar kinetics in the 2 cohorts, with median values surpassing baseline levels at month 12 in both groups, although this reconstitution attained statistical significance only for HIV-infected patients (median for HIV-infected patients at baseline, 391 sjTRECs/10^6 PBMCs; median at month 12, 786 sjTRECs/10^6 PBMCs [IQR, 34–3897 sjTRECs/10^6 PBMCs]; P = .04) (Figure 2). By month 24, sjTREC values had increased additionally in both groups.

**Determinants of immunological recovery.** We investigated whether the recovery of immunological parameters up to 12 months from ASCT could be associated with the concentration of cell subtypes at baseline and at the time of apheresis and/or with the amount of reinfused CD34+ stem cells. We found that naive CD4+ T cell counts at baseline were correlated with

![Figure 2. Thymic function recovery. Notched solid (human immunodeficiency virus [HIV]–infected patients) and open boxes (HIV-uninfected patients) represent 25th and 75th percentile values; the middle and vertical lines correspond to the median value and both the 10th and 90th percentiles, respectively. Statistically significant differences between baseline values and their matched values at subsequent steps of the treatment were reported (Wilcoxon rank sum test). HDC, high-dose chemotherapy; PBMC, peripheral blood mononuclear cell; sjTREC, signal joint T cell receptor excision circle.](cid:2010:50(15 June) HIV/AIDS)

![Figure 3. Human immunodeficiency virus [HIV] DNA dynamics. Notched boxes represent 25th and 75th percentile values; the middle and vertical lines correspond to the median value and both the 10th and 90th percentiles, respectively. Statistically significant differences between baseline values and their matched values at subsequent steps of the treatment were reported (Wilcoxon rank sum test). HDC, high-dose chemotherapy; PBMC, peripheral blood mononuclear cell.](cid:2010:50(15 June) HIV/AIDS)
recovery of the same T cell subset at month 3 after ASCT ($r = 0.62; P = .02$). A very good association of sjTREC level at baseline with the same parameter at 12 months from ASCT was found ($r = 0.82; P = .0002$). Moreover, the sjTREC value strongly correlated with recovery of CD4$^+$ and naive CD4$^+$ T cell counts at 12 months ($r = 0.63 \ [P = .006]$ and $r = 0.73 \ [P = .005]$, respectively).

The subset concentration at the time of apheresis influenced the corresponding recovery of all T cell subsets at 3 months after ASCT ($r = 0.55–0.61; P = .002–.02$). This influence was slightly less evident for CD4$^+$ and CD8$^+$ T subsets at month 12 after ASCT, with the correlation model assessment being less fit ($r = 0.48–0.55; P \leq .05$). On the contrary, CD34$^+$ cells correlated well with the recovery in B cells ($r = 0.50, P < .05$), NK cells ($r = 0.46, P < .05$), and sjTRECs ($r = 0.45, P = .05$) at month 12 after ASCT.

**Dynamics of viral replication.** At enrollment, 16 patients had undetectable viral loads, 4 had viral loads of 204–1272 copies/mL, 1 had a viral load of 36,896 copies/mL, 1 had a viral load of 305,426 copies/mL, and 2 had missing data. Before transplantation, 23 of 24 patients had HIV RNA levels that were less than the detection limit. The 1 patient with detectable viremia had a multidrug-resistant HIV-1 genotype. Ten patients discontinued HAART during HDC because of hepatic and/or gastroenteric toxicity. Among these patients, 8 had a viral load rebound during the aplastic period and 1 had a viral load rebound 1 month from ASCT. However, after HAART re-introduction, 7 patients showed a virologic response in 4 weeks (reduction in the HIV RNA level, 0.5–3 log$_{10}$ copies/mL). Only 2 of 14 patients, who were consistently receiving HAART, presented with sporadic viral load “blips,” which did not exceed 200 copies/mL (1 month after transplantation in one subject and 12 months after transplantation in the other).

At the time of enrolment, HIV DNA levels were very low (median, 75 copies/10$^6$ PBMCs; IQR, 41–165 copies/10$^6$ PBMCs). Slight, transient, and nonsignificant fluctuations were observed until month 12 after transplantation, whereas HIV DNA values at month 24 after transplantation were significantly lower than those at baseline (median, 8 copies/10$^6$ PBMCs; IQR, 5–58 copies/10$^6$ PBMCs; $P = .04$) (Figure 3).

**Infectious complications after ASCT.** Infectious complications during the first 3 months after ASCT were rare among HIV-uninfected patients and more frequent among HIV-infected patients (44.4% vs 91.7%; $P = .01$): 1 patient died of sepsis, and 1 patient died of multiorgan failure associated with cytomegalovirus pneumonia ≤2 months after transplantation. The grading of the infectious complications ranged from 2 to 4, with comparable frequency of severe events (grade, 3–4) in the 2 groups (HIV-infected vs HIV-uninfected patients, 77% vs. 75%; $P = .92$). HIV-infected patients with infective episodes had a significant lower CD4$^+$ T cell count during the third month after reinfusion, compared with HIV-infected patients without infections (median for HIV-infected patients with infection, 108 cells/μL [IQR, 74–159 cells/μL]; median for HIV-infected patients without infection, 227 cells/μL [IQR, 183–270 cells/μL]; $P = .03$). Finally, no statistically significant differences in the occurrence of infectious episodes were observed 3 months after ASCT in the 2 groups (HIV-infected vs HIV-uninfected patients, 29.2% vs 11.1%; $P = .39$).

**DISCUSSION**

One of the main concerns with ASCT in HIV-infected patients is the additional immune depletion caused by the transplantation treatment. This could amplify the preexisting immune deficit due to the underlying HIV infection and, thus, undermine control over viral replication ensured by HAART. To date, studies of ASCT in HIV-infected patients have clarified the issues concerning feasibility and effectiveness, but the immunological status and/or the viral dynamics have been analyzed in detail only in few articles [18, 26, 27], and the data comparing the dynamics of immunological recovery between HIV-infected and HIV-uninfected individuals are scanty.

Our study compared the immunological baseline characteristics in 2 groups of HIV-infected and HIV-uninfected patients with relapsed or refractory lymphoma who began comparable ASCT protocols at our institute. Our data confirmed that front-line chemotherapy produced immunodepression in the general population [28], although immune impairment is qualitatively different from that observed in HIV-infected patients. In fact, HIV-infected patients had higher CD8$^+$ T cell counts and inverted ratios of CD4$^+$ cells to CD8$^+$, compared with HIV-uninfected patients. Surprisingly, we did not find major differences in the CD4$^+$ cell compartment and thymic reservoir. This result might be because the HIV-infected patients in our study demonstrated good control of HIV RNA levels thanks to previous and ongoing antiretroviral regimens, leading to a reduction of cell activation, proliferation, and apoptosis [16, 29].

When comparing the dynamics of immunological recovery between the 2 populations, some evident differences at the beginning of the therapeutic program disappeared in the long term. We showed that the CD8$^+$ cell subpopulation, together with CD56$^+$ NK cells, recovered very rapidly in both HIV-infected and HIV-uninfected patients, leading, in the latter group, to a reversal of the ratio of CD4$^+$ cells to CD8$^+$ cells up to 2 years after transplantation. This is a known fact [30–32], but with respect to the HIV-infected population in this context, it demonstrated that HDC produced a quite different immune incompetence compared with the former conventional chemotherapy, which mainly affected the CD4$^+$ T subset without a significant impact on the ratio of CD4$^+$ cells to CD8$^+$ cells.

With regard to CD4$^+$ T lymphocyte recovery, we observed a temporary setback after the first 3 months after reinfusion in
HIV-infected patients; this was followed by a constant increase, which was comparable to that observed in HIV-uninfected patients. The naive CD4+ T lymphocyte count recovered similar to the overall CD4+ T cell subset, but with the relevant increase starting at the 12th month after transplantation. It is worth noting that, in the first 3 months after ASCT, infective episodes occurred significantly more frequently in our HIV-infected cohort. We showed that HIV-infected patients with infections in the early post-ASCT period had significant lower CD4+ T cell counts during the third month after reinfusion, compared with HIV-infected patients who do not have infection. Meanwhile, no correlation emerged between infective episodes and HAART interruptions, lymphoma relapses, or rituximab treatment (data not shown). Moreover, it is relevant to emphasize that no differences either in the frequency of infection or in the dynamics of CD4+ T cell improvement were seen after 3 months after ASCT.

The dynamics of B lymphocyte recovery were comparable in the 2 populations reaching normal values within 6 months. Our results and those of others [33] suggest that rituximab might have had an impact on virtual and persistent depletion of the B compartment.

sjTRECs demonstrated similar kinetics in the 2 cohorts, with median values surpassing the baseline values at 12 months after reinfusion; an additional increase was seen at 2 years in both populations. Only baseline sjTRECs levels were strongly associated with CD4+ cell count and newly generated T cell count at month 12 after ASCT. Overall, the present data indicate, for the first time, that HIV-infected subjects have an efficient thymus-dependent pathway of T cell reconstitution after ASCT as well as in HIV-uninfected individuals. As expected [34, 35], the number of reinfused CD34+ cells per kilogram did correlate with the recovery in B cell, NK cell, and sjTREC counts at month 12 after reinfusion. We confirm that the increase in lymphocyte count, early after engraftment, is mediated by the rapid expansion of preexisting mature cells, whereas the recovery of naïve cells starts later because of de novo thymic output [34–37].

Therefore, the data on immune reconstitution appeared to be encouraging. Just as reassuring were the data regarding viral control. Altogether, earlier [22] and present evidence suggest that HAART is capable of maintaining viral control even if immune depletion reaches its nadir; reinfusion of HIV-infected autologous cells does not amplify the peripheral HIV reservoir; only the total magnitude of peripheral preexisting HIV reservoir, probably established in the earliest stage of infection, might predict clinical outcome.

In conclusion, the present study demonstrates that HDC and ASCT in HIV-infected patients affected by relapsed or refractory lymphoma do not worsen initial immune impairment or enhance viral replication or peripheral HIV reservoir in the long term. However, in agreement with Diez-Martín et al [14], we found a transient increase in the incidence of early infective episodes in the HIV-infected cohort versus the general population. In our experience, early infections in HIV-infected patients might be associated with a setback in the CD4+ T cell count increase during the first 3 months after reinfusion. On the whole, these observations indicate that HIV-infected subjects require intensive infection prophylaxis and careful monitoring of immune reconstitution in the early posttransplantation period. In the end, we believe that it might be interesting to explore new immune adjuvant approaches (eg, use of interleukin-2 or interleukin-7) to promote an early CD4+ T cell expansion in the first interval after ASCT, to improve the clinical outcome of HIV-infected patients undergoing autologous transplantation.

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