Reduced Mobilization of CD34+ Stem Cells in Advanced Human Immunodeficiency Virus Type 1 Disease

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Granulocyte colony-stimulating factor (r-met Hu G-CSF; filgrastim; 10 μg/kg/day for 7 days) was used to mobilize CD34+ stem cells into the peripheral blood of human immunodeficiency virus type 1 (HIV-1)-infected individuals and a group of HIV-1-uninfected donors as a measure of immunologic reserve in HIV-1-infected people. G-CSF mobilized CD34+ cells of HIV-1-infected individuals with cell counts >500 CD4+ cells/mm3, as well as in HIV-1-uninfected donors. In contrast, CD34+ cell mobilization was significantly blunted in HIV-1-infected individuals with cell counts <500 CD4+ cells/mm3 (<200 cell days vs. >650 cell days, P < .0005, compared with the >500 CD4+ cell cohort). At least 1.75 x 10^6 CD34+ cells were harvested by leukapheresis from patients in each study cohort. CD34+ cell viability and the ability to differentiate precursor cells into myeloid and erythroid progenitor cells were not affected by HIV-1 infection.

Antiretroviral therapy suppresses viral replication, increases CD4+ cells in the peripheral blood, and provides clinical benefit for many patients with human immunodeficiency virus type 1 (HIV-1) infection [1, 2]. The extent of benefit is variable and is dependent primarily on the degree and durability of HIV-1 suppression. With the advent of HIV-1 protease inhibitors and a wider array of combination chemotherapeutic regimens, indefinite control of viral replication can be achieved for many patients. Unfortunately, viral replication cannot be controlled for prolonged periods of time in all patients, and even effective suppression of viral replication does not lead to viral eradication [3, 4]. The ultimate resumption of viral replication is due to a number of factors, including intolerance to and/or the emergence of viral strains with reduced susceptibility to antiretroviral drugs [5, 6]. Although a number of novel antiretroviral drugs that are likely to further improve the prognosis of HIV-1–infected individuals, antiviral chemotherapy is likely to be complicated by all the shortcomings noted in this article as well as by the cost and cumulative toxicity of lifelong administration. Treatment-limiting toxicity may develop even for patients in whom viral replication can be successfully suppressed for prolonged periods [7, 8].

Recently, there has been increasing interest in the development of genetic therapies that have as a goal the replacement of the HIV-1–infected reservoir with cells that are resistant to HIV-1 infection [9]. A number of novel strategies have been proposed, including antisense RNA, catalytic RNA, decoy RNAs, intracellular expression of single-chain antibody molecules, and cytotoxic gene products under the control of HIV-1 regulatory elements [10–22]. At present, although each of these approaches has theoretical merit, it is not clear which, if any, of these approaches will be of therapeutic benefit to HIV-1–infected individuals. All of these approaches, however, share...
the strategy of delivering the genetic therapy of interest to stem cells ex vivo, followed by the reinfusion of genetically modified cells into the HIV-1–infected donor.

Bone marrow stem cells can be mobilized into the peripheral blood by colony-stimulating factors, such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and stem-cell factor (SCF) [23, 24]. Stem cells can be mobilized into the peripheral blood of persons with malignancies, can be harvested, and can be reinfused after the delivery of cytotoxic chemotherapy that has been directed at the malignancy under treatment. The reinfusion of harvested stem cells accelerates resolution of neutropenia, allows the delivery of higher doses of chemotherapy, and lessens postchemotherapy infectious complications.

Substantial progress has been made in the optimization of regimens and harvesting schedules and in the characterization of cytokine-mobilized cells in HIV-1–uninfected individuals [25–33]. G-CSF has been useful clinically for the treatment of granulocytopenia associated with HIV-1 disease and/or therapeutic agents used in this patient population [34, 35]. Even in late stages of HIV-1 disease, continued administration of G-CSF mobilizes granulocytes and erythrocyte blast–forming units (BFU-E) into the peripheral blood. Although administration of G-CSF to HIV-1–infected individuals mobilizes bone marrow stem cells, little is known about the safety and optimal conditions for mobilization in this population, compared with HIV-1–uninfected individuals [36–39]. Furthermore, the yield, composition, and functional characteristics of mobilized cells at various stages of HIV-1 disease have not yet been fully delineated. AIDS Clinical Trials Group (ACTG) Study 285 was designed to determine whether adequate numbers of CD34+ cells could be safely mobilized from all stages of HIV-1 infection and to further characterize bone marrow stem cells harvested from the peripheral blood of HIV-1–infected subjects.

Materials and Methods

Study participants. HIV-1–infected individuals at varying stages of HIV-1 infection and uninfected control donors were recruited into this study, which was done at 3 centers. HIV-1–infected study participants were stratified at study entry into 3 groups: cohort I—study participants with ≥500 CD4+ cells/mm3; cohort II—study participants with 200–500 CD4+ cells/mm3; and cohort III—study participants with <200 CD4+ cells/mm3. An HIV-1–uninfected control group was also recruited at one of the study sites.

Six study participants were recruited for each group. HIV-1 infection was determined by ELISA and confirmed by Western blot, viral culture, or the presence of HIV-1 RNA or p24 antigen in plasma. The HIV-1–uninfected control group consisted of healthy individuals who were seronegative for HIV-1 by ELISA. In addition, study participants were ≥18 years of age, had Karnofsky performance scores ≥70. They also had sufficient venous access to complete apheresis procedures, a hemoglobin ≥9.1 g/dL for men (>8.8 g/dL for women), an absolute neutrophil count ≥1000/mm3, and a platelet count ≥75,000/mm3. The serum glutamic-oxaloacetic transaminase (SGOT) was required to be ≤5 times the upper limit of normal, and the creatinine was required to be ≤1.5 times the upper limit of normal. Cohort I patients were not allowed to have taken antiretroviral drugs within 30 days of study entry. Cohort II and III patients were allowed to take any licensed antiretroviral drug or drug combination, provided that no changes had been made in the drug regimen during the 60 days preceding study entry. Patients with an active opportunistic infection within 14 days of study entry were excluded, as were patients who were actively abusing alcohol or illicit drugs.

Study design. After giving written informed consent and undergoing initial baseline evaluations, study participants initiated a regimen of r-met Hu G-CSF (filgrastim [Neupogen; Amgen, Thousand Oaks, CA]) at a dose of 10 μg/kg/day for 7 days by the subcutaneous route. HIV-1–infected study participants underwent leukapheresis on the 4th and 5th days of filgrastim administration. After the first 3 study participants in each group had completed the leukapheresis procedure and had been followed up for 3 weeks thereafter, the protocol team evaluated the safety and tolerability of the procedure and the yield of CD34+ cells. The protocol was designed to allow dose reduction of filgrastim for toxicity or dose escalation if the yield of CD34+ cells was insufficient and the 10 μg/kg dose had been well tolerated.

Leukapheresis. Study participants underwent leukapheresis at each site on days 4 and 5 with Cobe Spectra equipment (Cobe Instruments, Lakewood, CO) by means of bilateral peripheral venous access. The target amount of blood to be processed at each mononuclear cell collection was approximately 2 times the donor’s calculated blood volume and ranged between 10 and 12 L processed. Two leukapheresis bags (containing 60 and 140 mL of leukapheresis product, respectively) were collected from each study subject at each procedure. Samples were obtained from the 60-mL bag for functional studies and surface phenotypic characterization. The remaining 140-mL of leukapheresis product was frozen by controlled rate freezing for subsequent use. The larger sample of leukapheresis product was shipped on wet ice by overnight courier to the University of Colorado for recovery and characterization of CD34+ cells.

Flow cytometry. Surface phenotypic characterization of pe-
Figure 1. A, Peripheral blood CD4$^+$ cells/mm$^3$ vs. time, for individuals receiving filgrastim (granulocyte colony-stimulating factor [r-met Hu G-CSF]): top left, uninfected control donors; top right, human immunodeficiency virus type 1 (HIV-1)-infected participants with >500 CD4$^+$ cells/mm$^3$; bottom left, HIV-1–infected participants with 200–500 CD4$^+$ cells/mm$^3$; bottom right, HIV-1–infected participants with <200 CD4$^+$ cells/mm$^3$. Filgrastim increases the number of circulating CD4$^+$ cells in uninfected individuals and in HIV-1–infected individuals with >500 CD4$^+$ cells/mm$^3$ at baseline. B, Percentage peripheral blood CD4$^+$ cells vs. time, for individuals receiving filgrastim: top left, uninfected control donors; top right, HIV-1–infected participants with >500 CD4$^+$ cells/mm$^3$; bottom left, HIV-1–infected participants with 200–500 CD4$^+$ cells/mm$^3$; bottom right, HIV-1–infected participants with <200 CD4$^+$ cells/mm$^3$. Filgrastim has no effect on the percentage of circulating CD4$^+$ cells.
ripheral blood mononuclear cells (PBMC) and of apheresis product was performed by flow cytometry, using fresh cells, in ACTG certified flow cytometry laboratories located at each of the study sites.

Viral quantitation. Plasma HIV-1 RNA was quantified by use of the Roche Amplicor HIV-1 Monitor assay (Roche Molecular Systems, Nutley, NJ) performed in a laboratory certified by the Virology Quality Assurance Program of the Division of AIDS. The lower limit of assay quantitivity was 400 copies/mL. Plasma samples with values \( \leq \) 400 copy/mL, the limit of the Amplicor assay, were reassayed by use of the ultrasensitive Monitor assay (Roche Molecular Systems), which provides a lower limit of quantitation of 50 copies/mL. HIV-1 DNA in PBMC was quantified as described elsewhere by a polymerase chain reaction (PCR) assay with an internal quantification standard, by use of gag primers [40].

Infectious HIV-1 was isolated from purified CD34+ products obtained on study days 4 and 5 according to the ACTG consensus protocol [41]. Approximately \( 10^7 \) purified CD34+ cells were cocultured with an equal number of 3- to 4-day-old phytohemagglutinin-stimulated lymphoblasts obtained from random HIV-1-seronegative donors. Fresh 3- to 4-day-old phytohemagglutinin-stimulated lymphoblasts were added weekly, and the culture supernatants were monitored for HIV-1 p24 antigen (Coulter Diagnostics, Hialeah, FL) twice weekly. Cultures were considered to be negative if p24 antigen was not detected after 30 days of culture. The presence of HIV-1 DNA in CD34+ cell preparations was determined by PCR amplification. Total cell DNA was extracted and purified from 2 \( \times \) \( 10^6 \) purified CD34+ cells (Qiamp; Qiagen, Valencia, CA). DNA from \( \sim \) 5 \( \times \) \( 10^5 \) cells was used in a PCR assay according to the manufacturers’ instructions (Amplicor HIV-1 Test; Roche Diagnostic Systems). The sensitivity of the DNA PCR assay was confirmed with a 5-copy HIV-1 DNA standard.

CD34+ cell separation. CD34+ cells were purified from leukapheresis product by use of the Miltenyi SuperMACS (Miltenyi Biotech, Auburn, CA), as described elsewhere and modified as follows [42, 43]. Approximately \( 10^7 \) cells were incubated with anti-CD34 antibody (Miltenyi), washed, and resuspended in 400 \( \mu \)L of Hanks’ balanced salt solution (HBSS). One hundred microliters of magnetic beads were then added to the cells, mixed, and incubated at 20°C. After incubation, the cells were washed twice in cold HBSS, passed through 30-micron filters, and applied to a prewashed SuperMACS column positioned within the magnetic field. Unlabeled cells were washed through 3 times with HBSS, the column removed from the field, and then the CD34+ cells were eluted. The column was then washed and the procedure was repeated until the entire leukapheresis was separated. The total number of CD34+ cells was then enumerated, the viability determined by trypan blue exclusion, and the purity determined by flow cytometry using anti-CD34 antibodies (HCPA2; BDIS, San Jose, CA). Proliferative capacity was analyzed in standard colony assays with the following modifications. Five hundred CD34+ cells were cultured in 1 mL Methocult H4320 (Stem Cell Technologies, Inc., Vancouver, British Columbia) in the presence of the following human growth factors (each at 10 \( \mu \)g/mL): interleukin (IL)-1, IL-3, IL-6, recombinant human (rh) G-CSF, and rhSCF. Erythropoietin was also added at 3 U/mL (R&D Systems, Minneapolis). Cultures were incubated at 37°C in 5% \( \text{CO}_2 \), and colonies (granulocyte-macrophage colony-forming units [CFU-GM], BFU-E, and mixed CFU) were enumerated on day 14.

Statistical methods. The Kruskal-Wallis rank sum test, followed by the method of multiple comparisons, was used to compare the 4 cohorts on areas under the curve constructed for observed rises in CD34+ cells between baseline and day 10. Plasma HIV-1 RNA levels at baseline and day 27 were compared by the Wilcoxon signed rank test. Spearman rank correlation coefficients were calculated to examine the correlations of baseline CD4+ cell counts with peak CD34+ and CD4+ cell counts. The Kruskal-Wallis rank sum test was used to compare CD34+ cell recoveries.

Results

Study participants. Baseline characteristics of study participants are outlined in table 1. The population consisted primarily of white men between the ages of 30 and 60 years.

Safety and tolerability. Administration of filgrastim to this patient population was well tolerated. Pheresis times were 3-4.4 h (mean, 3.7 h) and did not vary significantly among the cohorts. A single study participant in cohort III experienced transient grade 3 bone pain; no grade 3 or 4 adverse symptoms were observed during the course of the trial in any other study participants. Grade 3 or 4 laboratory toxicities included a single patient in cohort III who experienced granulocytopenia 2-4 months after the course of filgrastim. This study participant

### Table 3. Mean CD4+ cell count (cells/mm³).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Baseline</th>
<th>Day 65</th>
<th>Day 167</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>815</td>
<td>556</td>
<td>718</td>
</tr>
<tr>
<td>II</td>
<td>307</td>
<td>268</td>
<td>305</td>
</tr>
<tr>
<td>III</td>
<td>110</td>
<td>133</td>
<td>108</td>
</tr>
<tr>
<td>HIV-1 uninfected</td>
<td>738</td>
<td>608</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** HIV-1, human immunodeficiency virus type 1.

### Table 4. Recovery, viability, and functional analysis of purified CD34+ cell preparations.

<table>
<thead>
<tr>
<th>CD4+ cells/mm³ at baseline</th>
<th>Total CD34+ cells</th>
<th>% CD34+</th>
<th>Viability</th>
<th>Plating efficiency</th>
<th>Total colonies</th>
<th>CFU-GM (CFUs/500 CD34+ cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>9.55</td>
<td>91.7</td>
<td>96.2</td>
<td>0.2374</td>
<td>118.7</td>
<td>62.8</td>
</tr>
<tr>
<td>200-500</td>
<td>8.15</td>
<td>88.5</td>
<td>95.9</td>
<td>0.258</td>
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</tr>
<tr>
<td>&gt;500</td>
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<td>93.3</td>
<td>0.3236</td>
<td>161.8</td>
<td>73.4</td>
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<tr>
<td>HIV-1 uninfected</td>
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<td>95.3</td>
<td>95.3</td>
<td>0.2269</td>
<td>113.5</td>
<td>69.3</td>
</tr>
</tbody>
</table>

**NOTE.** CFU-GM, granulocyte-macrophage colony-forming units; HIV-1, human immunodeficiency virus type 1.

a Plating efficiency, colonies observed/CD34+ cells plated.

b Expressed as colonies/500 CD34+ cells plated.
Figure 2.  

A. Peripheral blood CD34+ cells/mm³ vs. time, for individuals receiving filgrastim (granulocyte colony-stimulating factor [r-met Hu G-CSF]): top left, uninfected control donors; top right, human immunodeficiency virus type 1 (HIV-1)-infected participants with >500 CD4+ cells/mm³; bottom left, HIV-1-infected participants with 200–500 CD4+ cells/mm³; bottom right, HIV-1-infected participants with <200 CD4+ cells/mm³. Filgrastim increases the number of circulating CD34+ cells in uninfected individuals and in HIV-1-infected individuals with >500 CD4+ cells/mm³ at baseline. 

B. Percentage peripheral blood CD34+ cells vs. time, for individuals receiving filgrastim: top left, uninfected control donors; top right, HIV-1–infected participants with >500 CD4+ cells/mm³; bottom left, HIV-1–infected participants with 200–500 CD4+ cells/mm³; bottom right, HIV-1–infected participants with <200 CD4+ cells/mm³. Filgrastim increases the percentage of circulating CD4+ cells in uninfected individuals and in HIV-1–infected individuals with >500 CD4+ cells/mm³ at baseline.

was also granulocytopenic at study entry. Nine of 24 study participants experienced reversible thrombocytopenia (platelet counts of 51,000–90,000/mm³) during days 6–10 in association with the leukapheresis procedure.
levels in the groups as a whole were unchanged (table 2). Rises in plasma HIV-1 RNA were independent of study cohort, baseline plasma HIV-1 RNA levels, and antiretroviral drug regimens. These short-term changes in plasma HIV-1 RNA are described in more detail elsewhere [44]. In all but 1 study participant, plasma HIV-1 RNA levels returned to baseline levels by day 30. In this study participant, antiretroviral chemotherapy was initiated and plasma HIV-1 RNA levels became undetectable. PBMC HIV-1 DNA levels fell transiently by day 6 but returned to baseline levels by day 30 (data not shown). Thus, although an early small increase in plasma HIV-1 RNA level and an early small decrease in PBMC HIV-1 DNA level were noted, each of these parameters returned to baseline values by day 30.

The absolute number of CD4⁺ cells/mm³ in the peripheral blood rose acutely from days 3–7 after administration of filgrastim in many study participants (figure 1A). CD4⁺ cell rises were most pronounced in the HIV-1–seronegative cohort and in cohort I study participants. Less pronounced rises were observed in HIV-1–infected study participants with <500 CD4⁺ cells/mm³. CD4⁺ cells returned to baseline levels within 30 days of filgrastim administration (table 3). Although the number of CD4⁺ cells/mm³ in the peripheral blood rose, there was no increase in the percentage of circulating CD4⁺ cells (figure 1B). There was no evidence of a downward trend in CD4⁺ cells in study participants through the 180-day postleukapheresis follow-up period (table 3).

CD34 cell mobilization and characterization. The number and percentage of CD34⁺ cells rose in the peripheral blood in response to filgrastim administration (figure 2A, 2B). Greater rises were observed in HIV-1–seronegative control donors and in HIV-1–infected study participants with >500 CD4⁺ cells/mm³ than in individuals with more advanced disease. A median area under the curve analysis comparing CD34⁺ cell change from baseline to day 10 showed significant differences among the cohorts (Kruskal-Wallis test, P = .006; figure 3). The method of multiple comparisons demonstrated no difference between the uninfected control group and cohort I. Cohort I patients exhibited a significantly greater rise in CD34⁺ cells than either cohort II patients (P = .015) or cohort III patients (P = .029). There was no difference between cohorts II and III (P = .807). Direct correlations were observed between baseline CD4⁺ cell count and the peak number of CD34⁺ cells after G-CSF filgrastim administration (Spearman’s rank correlation, ρ = .709; P = .0007) and between baseline CD4⁺ cell count and the peak

**Figure 3.** Area under the curve (AUC) analysis for CD34⁺ cell increase over baseline after filgrastim administration, by study stratum. HIV, human immunodeficiency virus.

**Figure 4.** Elevations in CD4⁺ cell and CD34⁺ cell counts correlate with baseline CD4⁺ cell number. Top, Peak CD34⁺ cell count/mm³ after filgrastim (granulocyte colony-stimulating factor [r-met Hu G-CSF]) vs. baseline CD4⁺ cell count. Bottom, Peak CD4⁺ cell count/mm³ after filgrastim vs. baseline CD4⁺ cell count. Patient cohorts are as indicated by the symbols in the figure.
CD4⁺ cell count after G-CSF filgrastim mobilization (Spearman rank correlation, 0.933; P < .0001; figure 4A, 4B). In addition, there was a trend toward a delayed rise in CD34⁺ cells in the peripheral blood in individuals with more advanced disease and a somewhat slower return to baseline. Despite the blunted rise in CD34⁺ cells in individuals with more advanced disease, there was not a significant difference in the number of CD34⁺ cells purified from these individuals, compared with the HIV-1–seronegative cohort and those with less advanced disease (table 4).

Recovery and purification of CD34⁺ cells were unaffected by HIV-1 serologic status, disease stage, baseline plasma HIV-1 RNA levels, CD4⁺ cell count, or antiretroviral regimen. Roughly 50% of the CD34⁺ population was recovered from leukapheresis packs after fractionation by Miltenyi columns without regard to disease stage. The number of CD34⁺ cells recovered ranged from $7.25 \times 10^6$ to $1.75 \times 10^6$ cells per leukapheresis in the 4 study participant cohorts (table 4). Cell viability and CD34⁺ cell purity were also similar among the 4 study participant cohorts. CD34⁺ cells from HIV-1–infected study participants, regardless of disease stage, formed colony-forming units with the same degree of efficiency as did cells from HIV-1–seronegative control donors. Although HIV-1 could occasionally be isolated from purified CD34⁺ cell populations, and although HIV-1 DNA could be identified in the enriched CD34⁺ cell product, this cell population did not contain large amounts of HIV-1 (table 5).

### Discussion

Prior studies of CD34⁺ cell mobilization have indicated that it is feasible to harvest such cells from HIV-1–infected persons by use of filgrastim [37–39]. However, these studies were composed of fewer individuals and focused primarily on individuals with >200 CD4⁺ cells/mm³. The study reported here extends these observations by demonstrating that harvesting of CD34⁺ cells can be safely performed in HIV-1–infected individuals regardless of disease stage. Although there are slight differences in the day of peak response in patients with more advanced disease, the kinetics of changes in CD4⁺ and CD34⁺ cells in the peripheral blood in response to filgrastim administration are similar to those observed in uninfected individuals [25–28, 30, 31]. Although both plasma HIV-1 RNA and CD4⁺ cells rise acutely in association with filgrastim administration and leukapheresis, these parameters return to baseline values by day 30 in almost all cases. Furthermore, there is no evidence of an acceleration in the rate of CD4⁺ cell loss or of an increase in plasma HIV-1 RNA over a 6-month period after filgrastim mobilization. We have noted a significant decline in the ability of the same dose of filgrastim to mobilize CD34⁺ cells with advancing disease. In uninfected individuals, an increase in CD34⁺ cell mobilization has been demonstrated as filgrastim doses are increased from 3 to 10 μg/kg/day [31]. We did not attempt to determine whether doses of filgrastim >10 μg/kg/day might have overcome the lower rates of mobilization in patients with more advanced HIV-1 infection, because satisfactory recovery of CD34⁺ cells was achieved in later stages of illness despite the decreased degree of mobilization by filgrastim. The decreased mobilization of CD34⁺ cells in more advanced disease in response to filgrastim is compatible with observations that the number of CD34⁺ cells and CFU-GM progenitor cells are decreased in bone marrow aspirates obtained from simian immunodeficiency virus (SIV)–infected rhesus macaques in more advanced stages of SIV infection [45]. In a prior study, a decreased number of circulating granulocyte/macrophage progenitors has been observed under baseline conditions in HIV-1–infected individuals [46]. The decrease was more pronounced in individuals with fewer CD4⁺ cells and in
individuals with more evidence of viral replication in vivo. Although several study participants with more advanced disease were receiving protease inhibitors as part of their antiviral regimen in our study, the combinations of drugs taken by these particular patients reduced plasma HIV-1 RNA levels to <500 copies/mL in only 2 of 6 cohort II and 2 of 6 cohort III study participants. Thus, we cannot determine whether more effective antiretroviral therapy might restore the deficiency in CD34+ cell mobilization in parallel with other immunological improvements. Indeed, a recently published study indicates that treatment of HIV-1-infected individuals with highly active antiretroviral chemotherapy is associated with both an increase in the number of colony-forming units per milliliter in the peripheral blood and in the cloning efficiency of CD34+ cells obtained after control of viral replication is achieved [47]. It would be of interest to determine whether mobilization of CD34+ or CD34+ cells by filgrastim administration might improve with better control of viral replication or might be a predictor of the degree of immunological recovery in response to potent antiretroviral chemotherapy.

One difficulty in assessing both our study and the recently completed observational study of the effects of highly active antiretroviral therapy on the function of progenitor cells is the potential effect of antiretroviral chemotherapeutic agents on the bone marrow microenvironment. Because nucleoside analogs and, in particular, zidovudine have been shown to exhibit inhibitory effects on the bone marrow, future studies will need to be designed with this potential mitigating factor in mind. In our study, it is possible that the use of antiretroviral drugs might have affected the degree of mobilization in the more advanced 2 cohorts of patients. In analyzing such studies, differences that might be attributed to antiretroviral drugs might well be complex in their interpretation if there are counterbalancing effects of the antiretroviral therapy on the bone marrow microenvironment and of the potentially myelosuppressive effects of the drugs utilized. For example, in our study we observed a decrease in CD34+ cell mobilization in the 2 cohorts composed of individuals who were primarily receiving antiretroviral chemotherapy. However, we observed no differences in the cloning efficiency of CD34+ cells obtained from these patients, compared with the cohorts who were not receiving antiretroviral chemotherapy. In the Nielsen experience, cloning efficiency increased markedly after institution of antiviral therapy, but in this case patients were placed on fully suppressive regimens [47]. In that study, patients placed on zidovudine as part of the regimen had an increase in cloning efficiency, but there was a trend toward a lower increase in patients who were suppressed without zidovudine in the regimen. Because most of our treated patients received zidovudine and because most were not receiving fully suppressive regimens at the time of the trial, a similar analysis was not possible for our study.

As in prior studies, we found little evidence of HIV-1 infec-
stored as other parameters suggestive of immune reconstitution are achieved in these patients [65].

References


