Longitudinal Analysis of Clinical Markers following Antiretroviral Therapy Initiated during Acute or Early HIV Type 1 Infection

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Background. Treatment of acute human immunodeficiency virus type 1 (HIV-1) infection may have unique immunologic, virological, and clinical benefits. However, the timing of treatment, optimal starting regimens, and expected response to therapy have not been defined.

Methods. One hundred two subjects treated during acute and early HIV-1 infection were observed prospectively to determine the effect of time elapsed before initiation of therapy on time to virological suppression and absolute CD4+ cell count. Subjects were divided into pre- and postseroconversion groups on the basis of HIV-1 antibody status at the time of initiation of treatment. Absolute CD4+ cell counts were compared between these groups and with those of historical untreated persons who had experienced seroconversion. Potential predictors of time to virological suppression and CD4+ cell count at 12 months were assessed.

Results. Ninety-nine (97%) of 102 subjects achieved virological suppression. The median time to suppression was 11.1 weeks (95% confidence interval, 9.4–14.9) and was independent of initial regimen. The mean CD4+ cell count at 12 months was 702 cells/mm3 (95% confidence interval, 654–750 cells/mm3) and showed an increasing trend over 60 months. Treated subjects demonstrated a statistically significant gain in the CD4+ cell count, compared with untreated historical control subjects, at 12 months. Comparable virological and immunologic outcomes were seen in the pre- and postseroconversion groups. Baseline virus load and nadir CD4+ cell count predicted time to virological suppression and CD4+ cell count at 12 months, respectively.

Conclusions. Early treatment of HIV-1 infection is well tolerated and results in rapid and sustained virological suppression. Preservation of CD4+ cell counts may be achieved with early therapy, independent of seroconversion status. Protease inhibitor–based and nonnucleoside reverse-transcriptase inhibitor–based regimens show comparable performance in tolerability, time to virological suppression, and CD4+ cell count when used as a first regimen.

Treatment of acute and early HIV-1 infection potentially confers a unique immunologic benefit, with preservation of HIV-specific CD4+ cell responses [1–4], a more homogenous virus population [5], and decreased seeding of reservoirs of latent virus [6]. In addition to the potential immunologic and virologic benefits of early therapy, there may be important public health considerations in reduction of disease transmission [7–9]. However, there is still considerable debate surrounding the advantages and disadvantages of treatment initiated during acute or early HIV-1 infection [10, 11].

In the United States, early treatment is often considered when the diagnosis is made within 6 months after seroconversion [12]. However, several unresolved questions remain involving the use and anticipated outcomes of antiretroviral therapy in acute and early HIV-1 infection. The efficacy of different starting regimens and the duration of the “window of opportunity” for early intervention are not known. Expected time to virological suppression is not well characterized in acute infection and is largely based on clinical experience with chronically infected subjects, despite recognized differences in viral dynamics and immunologic function in these 2 distinct phases of infection [13]. In addition,
differential outcomes in restoration of CD4+ cell counts have not been characterized on the basis of time elapsed before therapy or seroconversion status at the time of initiation of treatment, and which of these 2 factors has greater relative significance is also unknown.

Acute HIV-1 infection is seldom recognized in clinical practice, and data related to persons whose infection is diagnosed during this unique stage are therefore limited. Prior studies of acute infection often assess seroconversion status at baseline but not at the time of initiation of treatment and may therefore be less suited to discriminate between the effects of pre- versus postseroconversion therapy. The objective of this study was to provide long-term follow-up of a cohort of 102 treated subjects with acute and early HIV-1 infection and to characterize the effect of antiretroviral therapy in terms of time to virological suppression and absolute CD4+ cell count at ≥12 months.

METHODS

Definitions. Preseroconversion (acute) status was defined by positive results of HIV-1 nucleic acid tests and negative results of HIV-1 antibody tests, including negative results of HIV-1/2 ELISA or positive results of HIV-1/2 ELISA and negative or indeterminate results of HIV-1 Western blot. Postseroconversion (early) status was defined by positive results of HIV-1 antibody tests and evidence of seroconversion occurring within the previous 12 months. Recent seroconversion was confirmed by a nonreactive result of detuned HIV-1 ELISA [14] or a documented negative result of an HIV antibody test 12 months previously. Time to treatment was defined as the number of days elapsed between date of first positive HIV-1 test result (antibody or virus load, whichever was obtained first) and initiation of antiretroviral therapy.

Subjects. One hundred two subjects (age, ≥18 years) with symptomatic acute or early HIV-1 infection were enrolled in an institutional review board–approved observational protocol based at the Massachusetts General Hospital (Boston) and collaborating regional centers during 1996–2003 (1996–2000, 44 subjects; 2000–2003, 58 subjects). Subjects were observed prospectively with serial clinical and immunologic assessments. Clinical and demographic data (including age, sex, HIV risk factor, baseline virus load, and seroconversion status) were collected at the time of enrollment; subsequent laboratory data (CD4+ cell count and virus load) were collected at monthly follow-up visits. Subjects were divided into 2 subgroups on the basis of phase of infection at the time of initiation of treatment (preseroconversion vs. postseroconversion). Most subjects were prescribed either a protease inhibitor– or nonnucleoside reverse-transcriptase inhibitor–based regimen, and all subjects were taking at least 3 antiretroviral drugs. The choice of therapy and changes in the regimen were determined by the treating clinicians throughout the study. Adherence, adverse events, and any change in regimen were monitored at each follow-up visit and were assessed by chart review. Patients were considered “compliant” if they adhered to ≥95% of their medication doses. This threshold was based on the significant decrement in virological control with <95% adherence documented by other groups [15–17]. Fourteen subjects who were treated during acute infection underwent structured treatment interruption and were excluded from during-treatment analyses from the time of treatment interruption. Subjects who experienced seroconversion while in the Multicenter AIDS Cohort Study (MACS) were used as historical control subjects. These untreated subjects were predominantly white (88%) and male (100%) and were seronegative at baseline. Seroconversion was observed during follow-up visits, with the last negative and first positive results <7 months apart. Participants were observed at routine intervals for CD4+ cell count determinations. Additional details of this cohort are described elsewhere [18–20].

Laboratory studies. HIV-1 antibody testing was performed using Abbott HIV-1/2 ELISA and the BioRad HIV-1 Western blot assay. The bioMérieux Vironostika LS assay for HIV-1 was used for the detuned ELISA testing. HIV-1 load was determined by commercially available methods (Abbott HIV-1/2 ELISA and the BioRad HIV-1 Western blot assay. Virological suppression was considered to be achieved when the plasma HIV-1 load decreased to less than the limit of detection for the assay used. Time to suppression was determined as the calendar time midpoint between the last positive and first undetectable virus load test result, with a maximum 6-week interval between these 2 measurements. Subjects for whom >6 weeks had elapsed between last detectable and first undetectable virus load measurements (n = 36) were analyzed separately to avoid inherent bias of longer time to virological suppression. The baseline virus load was titrated to its end point when initial quantification exceeded the upper limit of the assay used, when ever blood samples were available within 7 days of presentation, and before the initiation of antiretroviral therapy. CD4+ cell counts were assessed by standard flow cytometry methods. Nadir CD4+ cell counts were the lowest documented CD4+ cell count. Follow-up CD4+ cell data were drawn from recorded laboratory values within 3 months of the targeted time point, depending on sample availability, and were compared with those of historical untreated control subjects in the MACS cohort at equivalent follow-up intervals.

Statistical analyses. The primary end points of this study were time to virological suppression and absolute CD4+ cell count at ≥12 months. Time-to-event analyses included log rank tests and Cox proportional hazard modeling. Absolute CD4+ cell count at ≥12 months was compared between pre- and postseroconversion groups by 2-sample t tests. Time to treatment, seroconversion status, initial treatment regimen, calendar time, nadir and baseline CD4+ cell count, log of baseline virus load, and adherence were assessed as potential predictors of
CD4+ cell outcomes and time to virological suppression by linear regression and Cox proportional hazards regression, respectively. SAS, version 8.02 (SAS Institute), and GraphPad Prism, version 4.0 for Windows (GraphPad Software), were used for statistical analyses and figures, and all P values were 2-sided.

RESULTS

Baseline characteristics. One hundred two subjects were observed for a median of 40 months (interquartile range, 21–63 months). The median age was 36 years (interquartile range, 32–41 years), 94% of subjects were male, and 78% were white (table 1). Men who have sex with men was the most common HIV risk group (78 [83%] of 94 subjects with known risk factors). At presentation, 70 subjects (69%) had acute HIV-1 infection, and 32 (31%) had early HIV-1 infection. At the time of initiation of therapy, 41 (40%) were still negative for HIV-1 antibody, and 55 (54%) had experienced seroconversion. Test results were not available to distinguish between acute and early infection for 6 subjects. The mean baseline CD4+ cell count was 484 cells/mm3 (range, 42–1093 cells/mm3). At study entry, 41 (41%) of 100 subjects had CD4+ cell counts of >500 cells/mm3, and 4 (4%) had counts of <200 cells/mm3. CD4+ cell counts before antiretroviral therapy were not available for 2 subjects. The mean nadir CD4+ cell count was 422 cells/mm3 (range, 42–910 cells/mm3). The lowest documented CD4+ cell count was lower for subjects with acute infection (mean, 395 cells/mm3) than for those with early infection (mean, 469 cells/mm3; P < .05). The mean baseline virus load was 3,630,000 copies/mL (range, 2800–95,000,000 copies/mL) and varied significantly between subjects with acute infection (5,610,000 copies/mL; range, 11,000–95,000,000 copies/mL) and early infection (382,000 copies/mL; range 2800–2,950,000 copies/mL) (P < .0001).

Antiretroviral treatment. The median time to treatment was 8 days (interquartile range, 5–24 days). A protease inhibitor–based treatment regimen was prescribed for 58 (57%) of 102 subjects (one-third received a boosted regimen); an non-nucleoside reverse-transcriptase inhibitor–based regimen was used for 41 (40%), and a triple–nucleoside reverse-transcriptase inhibitor regimen was prescribed for 2 subjects (2%). One subject was treated with a regimen including both a protease inhibitor and a nonnucleoside reverse-transcriptase inhibitor.

On the basis of chart review, 11% (95% CI, 6%–19%) of subjects reported gastrointestinal distress, 7% (95% CI, 3%–14%) developed hyperlipidemia, 4% (95% CI, 1%–10%) developed rash, and 4% (95% CI, 1%–10%) were given a diagnosis of nephrolithiasis. Adverse effects were appropriate to the agents prescribed. Fourteen subjects underwent structured treatment interruption; of the remaining 88 subjects, 42 (48%) continued their first prescribed antiretroviral regimen throughout the follow-up period, and 46 (52%) discontinued at least 1 drug from their initial antiretroviral regimen. Of these 46 subjects, 33 (72%) discontinued a nucleoside reverse transcriptase inhibitor, 14 (30%) discontinued a nonnucleoside reverse transcriptase inhibitor, and 29 (63%) discontinued a protease inhibitor (95% CI, 57%–84%, 18%–46%, and 48%–77%, respectively). After differences in exposure were adjusted for, there was no significant difference in the rate of discontinuation of a first medication between subjects receiving nonnucleoside reverse-transcriptase inhibitor–based regimens and those receiving protease inhibitor–based regimens (P = .10).

Table 1. Baseline characteristics of cohort in a study of the benefits of early treatment of HIV-1 infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with acute HIV-1 infection</th>
<th>Patients with early HIV-1 infection</th>
<th>Total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (interquartile range)</td>
<td>35 (31–39)</td>
<td>37 (34–43)</td>
<td>102</td>
</tr>
<tr>
<td>Male sex, % of patients</td>
<td>94</td>
<td>94</td>
<td>102</td>
</tr>
<tr>
<td>Men who have sex with men, % of patients</td>
<td>82</td>
<td>81</td>
<td>94</td>
</tr>
<tr>
<td>White race, % of patients</td>
<td>77</td>
<td>78</td>
<td>102</td>
</tr>
<tr>
<td>Time to treatment, median days (interquartile range)</td>
<td>8 (4–20)</td>
<td>15 (6–32)</td>
<td>100</td>
</tr>
<tr>
<td>Baseline CD4+ cell count, % of cohort &gt;500 cells/mm³</td>
<td>39</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up, median months (interquartile range)</td>
<td>38 (18–64)</td>
<td>44 (27–62)</td>
<td>102</td>
</tr>
<tr>
<td>Seroconversion status, % of cohort</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>69</td>
<td>31</td>
<td></td>
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<tr>
<td>At initiation of treatment</td>
<td>40</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Baseline virus load, mean copies/mL, (range)</td>
<td>5,610,000 (11,000–95,000,000)</td>
<td>382,000 (2800–2,950,000)</td>
<td>75</td>
</tr>
<tr>
<td>Baseline CD4+ cell count, mean cells/mm³, (range)</td>
<td>445 (42–1093)</td>
<td>567 (170–981)</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. Seroconversion status at the time of initiation of therapy was unknown for 6 subjects. MSM, men who have sex with men.
Virological suppression. Ninety-nine (97%) of 102 subjects achieved an undetectable virus load. Lack of documented virological suppression was the result of discontinuation of antiretroviral therapy before suppression in 3 subjects (3%). The median time to virological suppression was 11.1 weeks (95% CI, 9.4–14.9 weeks) (figure 1A), with no significant difference between subjects receiving protease inhibitor–based or nonnucleoside reverse-transcriptase inhibitor–based regimens (figure 1B). Subset analysis including subjects with virus load data >6 weeks apart showed no significant difference (median time to virological suppression, 14.4 weeks; 95% CI, 11.9–16.2 weeks). The percentage of subjects achieving an undetectable virus load at 16 and 24 weeks of follow-up was 78% (95% CI, 66%–88%) and 90% (95% CI, 79%–96%), respectively. There was no significant difference in either the rate of suppression or the median time to virological suppression between subjects who had not yet had seroconversion at the time of initiation of therapy (13.0 weeks; 95% CI, 7.7–16.5 weeks) and subjects positive for HIV-1 antibody at the start of therapy (11.1 weeks; 95% CI, 9.9–15.5 weeks) (figure 1C). Nonadherence was also not a significant predictor (median time to virological suppression for nonadherent subjects, 16.3 weeks [95% CI, 10.4–19.7 weeks], compared with 9.9 weeks [95% CI, 7.6–12.8 weeks] for adherent subjects) (figure 1D), but the small number of nonadherent subjects limits this comparison. Baseline virus load was the only significant predictor of the rate of virological suppression in a Cox proportional hazards regression model ($P = .03$).

After 12 months of treatment, 83 (91%) of 91 evaluable subjects maintained an undetectable virus load; 65 (72%) of 90 continued to receive the same antiretroviral regimen initially prescribed at study entry. At 18 months of follow-up, 66 (92%) of 72 evaluable subjects maintained virus loads that were less than the limit of detection; 50 (69%) continued the initial regimen. After 3 years of follow-up, 49 (86%) of 57 subjects continued taking antiretroviral therapy, had an undetectable virus load, and had a CD4+ cell count of >500 cells/mm$^3$.

CD4+ cell outcomes. The mean CD4+ cell count at 12 months of follow-up was 702 cells/mm$^3$ (95% CI, 654–750 cells/mm$^3$), representing an increase of 218 cells/mm$^3$ from baseline (figure 2A) over the first year of treatment. The percentage of subjects with a CD4+ cell count of >500 cells/mm$^3$ increased from 41% at baseline to 84% at 12 months of follow-up (OR, 7.4; 95% CI, 3.6–14.3). At the end of the study (4387.8 person-months of follow-up) only 1 (1%) of 94 evaluable subjects had a CD4+ cell count of <200 cells/mm$^3$. This subject had a nadir

Figure 1. A, Time to virological suppression from the initiation of treatment for the study cohort (median time to virological suppression, 11.1 weeks). B–D, Comparison of time to virological suppression for subjects prescribed a protease inhibitor–based regimen (PI; median time to virological suppression, 13.1 weeks) versus a nonnucleoside reverse-transcriptase inhibitor–based regimen (NNRTI; median time to virological suppression, 9.1 weeks) (B), acute (median time to virological suppression, 13.0 weeks) versus early (median time to virological suppression, 11.1 weeks) seroconversion status at the time of treatment initiation (C), and >95% adherence to antiretroviral therapy (median time to virological suppression, 9.9 weeks) versus <95% adherence to therapy (median time to virological suppression, 16.3 weeks) (D). VL, virus load.
CD4+ cell count of 283 cells/mm³ and had self-discontinued therapy ∼28 months before AIDS was diagnosed. Overall, there was a continued incremental increase in CD4+ cell counts over 60 months for subjects who continued taking antiretroviral therapy (figure 2B), and this trend was independent of seroconversion status at the time of initiation of treatment (figure 3). In a univariate analysis, baseline and nadir CD4+ cell counts were statistically significant predictors of 12-month CD4+ cell count (P<.001); time to treatment, seroconversion status, and initial regimen were not. When multiple covariates were assessed in a multivariable model, only nadir CD4+ cell count was a statistically significant predictor (P = .002). Comparison of CD4+ cell outcomes in the study group with those of untreated controls in the MACS cohort (table 2) showed a consistent statistically significant difference starting at 12 months of therapy (P = .01) and increasing over 36 months (P<.001) (figure 4).

**DISCUSSION**

Whether initiation of early therapy should be standard of care for those with acute or early HIV-1 infection is unknown, and although this nonrandomized study is not designed to answer that question directly, the long-term follow-up of this relatively large cohort provides a useful framework on which to base clinical expectations when early therapy is initiated.

The majority of patients who initiate antiretroviral therapy during acute or early infection can be expected to tolerate therapy and to demonstrate clinical markers of disease control. The proportion of subjects achieving an undetectable virus load at
24 weeks was slightly higher in our study (90%) than in prior reports of chronically infected subjects with first exposure to protease inhibitors (53%) [21] or in treatment-naive persons (84%) [22], but differences in methodology limit this comparison. More than 90% of subjects in our cohort with available virus load measurements were able to maintain virological suppression at 12 and 18 months of follow-up, similar to the results of other studies of treatment-naive subjects [23]. The longer follow-up period in this study afforded evaluation of durability of virological control; virus loads were undetectable in 86% of subjects after 3 years of follow-up and in 100% of subjects who continued to undergo therapy.

Time to virological suppression in subjects with acute HIV-1 infection is comparable to that expected in chronically infected persons, despite the fact that persons with acute infection typically have a higher initial virus load. The findings of this study also suggest that ~25% of persons may require a change of at least 1 drug over the first 12 months of therapy, and 30% may require a change by 18 months of therapy, irrespective of initial regimen.

The mean quantitative increase in the CD4+ cell count over the first year of therapy in our study was 218 cells/mm³, exceeding overall consensus statement expectations (~150 cells/mm³) [24]; this increase was likely attributable to both treatment effect and natural recovery from the nadir CD4+ cell count observed during acute infection. The gain in the CD4+ cell count in treated subjects, compared with historical control subjects, at all time points after ≥12 months suggests that early intervention may preserve CD4+ cells even before there is clinical evidence of immunologic deterioration.

There were no statistically significant differences in absolute CD4+ cell counts or times to virological suppression for the pre- and postseroconversion groups, suggesting that treatment responses are similar between the 2 groups. This is consistent with the findings of other studies of acute and early infection [4, 25]. The role of nadir CD4+ cell count as a predictor of CD4+ cell response to therapy, as demonstrated in this study, has also been previously described in patients with chronic HIV infection [26].

The findings of this study are encouraging with respect to overall tolerability of antiretrovirals, effective virological suppression, and restoration of CD4+ cells and suggest that there are significant increases in CD4+ cell counts, compared with untreated persons with recent seroconversion, beginning at 12 months of therapy. However, the results must be viewed in context of the relative risks of antiretroviral exposure and lack of proven long-term clinical benefit. Initiation of early therapy years before a patient would otherwise meet treatment criteria

Table 2. Comparison of baseline characteristics and mean CD4+ T cell outcomes over 36 months of follow-up in treated study subjects versus untreated historical control subjects with recent seroconversion.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present study</th>
<th>MACS cohort</th>
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<tbody>
<tr>
<td></td>
<td>Value</td>
<td>No. of</td>
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<tr>
<td></td>
<td></td>
<td>subjects with</td>
</tr>
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<td></td>
<td></td>
<td>available data</td>
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<tr>
<td>Age, median years (range)</td>
<td>36 (21–63)</td>
<td>102</td>
</tr>
<tr>
<td>White race, %</td>
<td>78</td>
<td>102</td>
</tr>
<tr>
<td>Geographic origin</td>
<td>MA</td>
<td>102</td>
</tr>
<tr>
<td>Male sex, % of subjects</td>
<td>94</td>
<td>102</td>
</tr>
<tr>
<td>Men who have sex with men, % of subjects</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>CD4+ cell count, mean cells/mm³ (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>484 (441–527)</td>
<td>100</td>
</tr>
<tr>
<td>6 months</td>
<td>618 (574–662)</td>
<td>85</td>
</tr>
<tr>
<td>12 months</td>
<td>702 (654–750)</td>
<td>80</td>
</tr>
<tr>
<td>24 months</td>
<td>704 (643–766)</td>
<td>58</td>
</tr>
<tr>
<td>30–36 months</td>
<td>698 (618–778)</td>
<td>44</td>
</tr>
</tbody>
</table>

NOTE. Untreated control subjects were part of the Multicenter AIDS Cohort Study (MACS); MACS data are from [18]. CA, California; IL, Illinois; MA, Massachusetts; MD, Maryland; NR, not reported; PA, Pennsylvania.
results in significantly prolonged exposure to antiretroviral drugs and the risks inherent to these drugs. As all-cause mortality shifts to non–HIV-related causes in the era of HAART [27], the relative advantages of early therapy must be carefully weighed against the disadvantages.

Protease inhibitor–based and nonnucleoside reverse-transcriptase inhibitor–based regimens showed comparable performance with respect to tolerability, efficacy of virological suppression, and preservation of CD4+ cells in the treatment of acute and early HIV-1 infection. Although this study was not designed to determine the window of opportunity for potential immunologic benefit with early therapy, it suggests that quantitative preservation of CD4+ cells can be achieved with treatment initiated even after HIV-1 antibody seroconversion during the early phase of infection. Efforts to elucidate predictors of a favorable response to early therapy may help target specific populations for this intervention in the future. Larger randomized studies are necessary to determine the long-term clinical consequences of early antiretroviral therapy and merit further investigation.

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