Efavirenz-Based Regimens in Treatment-Naive Patients with a Range of Pretreatment HIV-1 RNA Levels and CD4 Cell Counts

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The potency of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and efavirenz in patients with higher viral loads (VLs) or low CD4 cell counts remains uncertain. Virologic failure and changes in CD4 count in relation to pretreatment VL and CD4 count were evaluated in treatment-naive patients randomized to treatment groups that received 2 or 3 NRTIs with efavirenz. Over 3 years, the risk of virologic failure was not significantly different among subgroups categorized according to pretreatment VL or CD4 count. No significant differences among subgroups were observed for CD4 count changes, except in patients with high pretreatment VL. There were no significant differences among subgroups with respect to treatment responses. These results demonstrate the potency of efavirenz-containing regimens across a spectrum of pretreatment VLs and CD4 counts.

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Antiretroviral treatment with a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) and 2 nucleoside reverse transcriptase inhibitors (NRTIs) is a recommended first-line regimen for HIV-1–infected individuals worldwide [1, 2]. Although studies have shown favorable virologic and immunologic responses to such regimens in treatment-naive populations overall [3–6], uncertainty persists about the efficacy of such regimens in patients with very high HIV-1 RNA levels or very low CD4 cell counts [1]. Although previous studies have found no significant difference in the rates of virologic failure for patients who begin treatment with an HIV-1 RNA level above or below 100,000 copies/mL, data are limited over the full range of HIV-1 RNA levels [7]. The association of immunologic recovery with pretreatment HIV-1 RNA level and CD4 cell count has been reported from several cohort studies [8, 9], but prospective clinical trial data are more limited [10, 11]. Some have proposed the use of additional drugs to enhance potency [12–14], with the hope of improving virologic and/or immunologic responses. AIDS Clinical Trials Group (ACTG) study A5095 found no overall differences in virologic or immunologic responses in treatment-naive patients starting a standard 3-drug regimen of zidovudine, lamivudine, and efavirenz, or a 4-drug regimen that also included the NRTI abacavir [5]. Because this study enrolled a substantial number of patients with plasma HIV-1 RNA levels above 300,000 copies/mL or with CD4 counts below 50 cells/mm3, we conducted previously unplanned analyses to assess whether pretreatment HIV-1 RNA level or pretreatment CD4 cell count were associated with virologic or immunologic outcomes for patients receiving a 3-drug or 4-drug efavirenz-based regimen. We also assessed whether adding a third NRTI improved responses in any subgroup.

Patients and methods. ACTG A5095 has been described elsewhere [5]. In this study, HIV-1–infected adult patients who had plasma HIV-1 RNA levels ≥400 copies/mL and who had not received prior antiretroviral therapy were randomized to receive efavirenz with either coformulated zidovudine/lamivudine (3-drug regimen) or zidovudine/lamivudine/abacavir (4-drug regimen) in a double-blind protocol. The study protocol was submitted, reviewed, and approved by institutional review boards at all sites.

As described elsewhere [5], patients’ plasma HIV-1 RNA levels were measured using the Roche HIV-1 Monitor Assay (ver-
CD4 cell counts were determined locally by use of standard techniques.

The primary outcome measures for these analyses were time to virologic failure, which was defined as the time to the first of 2 successive HIV-1 RNA levels ≥200 copies/mL at or after week 16, and change in CD4 cell count from baseline to study weeks 48, 96, and 144 (hereafter, “CD4 count change”). Pretreatment HIV-1 RNA level and CD4 cell count were determined as the geometric mean and the mean, respectively, from 2 evaluations obtained ≥24 h apart and prior to starting randomized treatment. Patients were categorized into subgroups with respect to pretreatment HIV-1 RNA level and pretreatment CD4 cell count. HIV-1 RNA level subgroups were as follows: <30,000 copies/mL, 30,000–99,999 copies/mL, 100,000–299,999 copies/mL, 300,000–749,999 copies/mL, and ≥750,000 copies/mL. The CD4 cell count subgroups were as follows: <50 cells/mm³, 50–199 cells/mm³, 200–349 cells/mm³, 350–499 cells/mm³, and ≥500 cells/mm³. To reduce variability in CD4 cell count, cell count changes at week 96 and 144 were determined as the mean of all evaluations obtained within ±24 weeks of each of these weeks to provide a linear interpolation over multiple scheduled evaluations. Because CD4 cell count changes over the first year were expected to be nonlinear, particularly over the first 6 months, the change from baseline to week 48 used a linear interpolation over evaluations obtained within ±12 weeks of week 48.

Cox proportional hazards (for virologic failure) and generalized estimating equations with robust covariance estimates (for CD4 cell count change) were used for analysis. The associations between pretreatment HIV-1 RNA level and pretreatment CD4 cell count and the risk of virologic failure and CD4 count change were evaluated, along with treatment arm interactions with respect to HIV-1 RNA level and CD4 cell count subgroups. In analyses of CD4 count change, time (weeks 48, 96, and 144) was modeled as a factored covariate with contrasts defined such that the estimates for week 96 and 144 reflected the incremental change from week 48 to 96 and from week 96 to 144, respectively. Results are presented for an independence working correlation matrix, but were robust to the specific choice. Subgroup and randomized treatment main effects and interaction terms were all included in modeling; equality of subgroup and time effects, and interactions of subgroups with time (for CD4 count change) and treatment arm were tested with structured contrasts.

Analyses were performed intent-to-treat and as-treated. The only as-treated analyses presented are those that resulted in a substantive change in the intent-to-treat analysis results. For intent-to-treat analysis of virologic failure, event times were determined regardless of treatment discontinuation or change; for as-treated analyses, event times were censored at discontinuation of initial treatment. P values and confidence intervals (CIs) are presented unadjusted for multiple comparisons. Missing data were considered noninformative.

Results. Baseline characteristics and disposition of the cohort have been reported elsewhere [5]. In summary, 765 patients were randomized to receive a 3-drug (n = 382) or 4-drug (n = 383) efavirenz-based regimen; 81% of the patients were male; 41% were white non-Hispanic, 35% were black non-Hispanic, and 21% were Hispanic. The mean age was 37 years. Prior to starting treatment, 231 patients (30%) had HIV-1 RNA levels <30,000 copies/mL; 232 (30%) had levels from 30,000–99,999 copies/mL, 129 (17%) had levels from 100,000–299,999 copies/mL, 100 (13%) had levels from 300,000–749,999 copies/mL, and 73 (10%) had levels ≥750,000 copies/mL. A total of 155 patients (20%) had CD4 cell counts <50 cells/mm³, 206 (27%) had counts of 50–199 cells/mm³, 228 (30%) had counts of 200–349 cells/mm³, 105 (14%) had counts of 350–499 cells/mm³, and 71 (9%) patients had counts of ≥500 cells/mm³. A total of 75 patients had both pretreatment HIV-1 RNA levels ≥300,000 copies/mL and pretreatment CD4 cell counts <50 cells/mm³. Median study follow-up was 144 weeks; 79%, 70%, and 43% of patients received at least 48, 96, and 144 weeks of their initially randomized treatment, respectively. Although not statistically significant (P = .27), the estimated distribution of time to discontinuation of initial treatment suggested a shorter time to discontinuation for patients with pretreatment CD4 cell counts ≥500 cells/mm³.

A total of 193 patients (25%) reached protocol-defined virologic failure. Intent-to-treat analyses found no significant differences across subgroups categorized according to pretreatment HIV-1 RNA level and pretreatment CD4 cell count with respect to the distributions of time to virologic failure (P = .49 and P = .71, respectively; figure 1A and figure 1B). Although not statistically significant, patients with pretreatment CD4 cell counts ≥500 cells/mm³ tended to have the shortest time to virologic failure, compared with other pretreatment CD4 cell count subgroups; this trend was not observed in as-treated analysis (data not shown). There was no significant difference in the distributions of time to virologic failure for patients with pretreatment viral loads ≥300,000 copies/mL and CD4 cell count <50 cells/mm³, compared with all other patients (P = .91; hazard ratio [HR], 0.97; 95% CI, 0.61–1.56). There was no evidence of a difference in the relative hazard of failure between the 3- and 4-drug antiretroviral treatment regimens across pretreatment HIV-1 RNA level subgroups or pretreatment CD4 cell count subgroups (interaction test, P = .63 and P = .99, respectively; figure 1C and figure 1D).

Increases in CD4 cell count were seen across all pretreatment HIV-1 RNA level subgroups and all pretreatment CD4 cell count subgroups over successive years (figure 2A and figure 2B). A greater increase in CD4 cell count in year 1 was seen for patients with pretreatment HIV-1 RNA levels ≥300,000 copies/mL, compared with the remaining subgroups (P < .001); no significant differences were observed with respect to pretreatment.
HIV-1 RNA level over years 2 and 3 (P = .89 and P = .51, respectively; figure 2A).

No significant differences in CD4 count changes were observed with respect to pretreatment CD4 cell count subgroup (P = .33, P = .28, and P = .07, for years 1, 2, and 3, respectively) (figure 2B). Combined across all subgroups, smaller increases in CD4 cell count were estimated for year 3, compared with year 2 (+76 cells/mm³ [95% CI, 59–93 cells/mm³] vs. +40 cells/mm³ [95% CI, 32–48 cells/mm³]; P < .001). This was also observed in sensitivity analyses that included only patients with complete data over 3 years (n = 125). There was no evidence of differential 3- and 4-drug treatment effects across pretreatment HIV-1 RNA level subgroups or pretreatment CD4 cell count subgroups in each successive year of follow-up (interaction tests, P > .25; figure 2C and figure 2D).

**Discussion.** In this large prospective study of treatment-naive patients, we found that a standard efavirenz-based regimen demonstrated potent activity across a wide range of pretreatment HIV-1 RNA levels and pretreatment CD4 cell counts; adding a third NRTI did not improve responses. Neither pretreatment HIV-1 RNA level nor pretreatment CD4 cell count were found to be associated with an increased risk of virologic failure, even in patients with high HIV-1 RNA levels (≥300,000 copies/mL) and the lowest CD4 cell counts (<50 cells/mm³).
Although not statistically significant, one notable observation was that patients who started the study with CD4 cell counts $\geq 500$ cells/mm$^3$ tended to have the worst and most variable outcome in intent-to-treat analyses. This outcome was not seen in as-treated analysis and seems to be explained by a higher, but not significantly different, rate of treatment discontinuation observed in this group. The most likely explanation for this observation is the change in treatment guidelines in 2001 during the course of the A5095 study that decreased the CD4 cell count threshold for starting therapy to 350 cells/mm$^3$ [2]. As a consequence, patients who entered A5095 with CD4 cell counts $\geq 500$ cells/mm$^3$ may have chosen to discontinue antiretroviral therapy, although they continued to be followed in the study.

Long-term data on CD4 cell count increases in patients who start antiretroviral treatment are relatively scarce. In this study, although we found a larger increase in CD4 cell counts over the first year of treatment that tended to be greater among patients who started treatment with higher HIV-1 RNA levels, significant

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**Figure 2.** Estimated change in CD4 cell count (CD4 count change) and estimated difference in CD4 count change from baseline, with 95% confidence intervals (whiskers). Estimated change in CD4 cell count from baseline over years 1-3 is shown according to pretreatment HIV-1 RNA level (A) and pretreatment CD4 cell count (B). Estimated difference in CD4 count change from baseline for 2 regimens, 3 nucleoside reverse transcriptase inhibitors [NRTIs] with efavirenz versus 2 NRTIs with efavirenz) is also shown according to pretreatment HIV-1 RNA level (C) and CD4 cell count (D). Estimates were obtained from a full linear model containing pretreatment subgroup, treatment arm, and time main effects, and 2- and 3-way interaction terms, as appropriate. $P$-values are from a robust score test against the null hypothesis of equivalent CD4 count changes across all pretreatment subgroups (panels A and B) and against the null hypothesis of equivalent treatment differences across all pretreatment subgroups (no interaction) (panels C and D).
differences between pretreatment HIV-1 RNA level subgroups or pretreatment CD4 cell count subgroups were not detected later in follow-up. Although increases in CD4 cell count were detected for each of the 3 years of follow-up that were analyzed, the magnitude of the increases lessened over each subsequent year.

There are several limitations to this study. This was an unplanned analysis of A5095 and as such, it was not powered specifically to examine these pretreatment HIV-1 RNA level and CD4 cell count subgroup differences, or their interactions with treatment. Although our results are convincing, as they do not show any consistent trends across the subgroups, it is possible that modest differences do exist that the present study was not powered to detect. Additionally, there may be HIV-1 RNA levels at which these findings do not apply. Although patients enrolled in A5095 across a spectrum HIV-1 RNA levels—the maximum pretreatment HIV-1 RNA level observed in the study was more than 7 million copies/mL—patients with very high HIV-1 RNA levels accounted for only 10% of our study population. We also did not thoroughly examine the impact of additional patient characteristics on treatment outcome and their interaction with these pretreatment markers, as has been described elsewhere [8]. Because we previously reported an association between black race and an increased risk of virologic failure in A5095 [5], as part of the present analysis we explored this association in the context of pretreatment HIV-1 RNA level and pretreatment CD4 cell count. However, because of our limited sample size across subgroups, our data set did not allow us to draw any reliable conclusions regarding the issue. We also noted that, although pretreatment differences in CD4 cell count were maintained over 3 years in this study at a subgroup level, there was extensive intersubject variation in responses within each subgroup, such that many patients who started antiretroviral therapy with very low CD4 cell counts completed 3 years of treatment with a CD4 cell count comparable to or greater than that of some patients who started treatment with a much higher CD4 cell count. A key future study would be to carefully examine factors associated with this variability.

In summary, we found that efavirenz-based regimens were associated with potent virologic and immunologic responses over 3 years in patients across a wide spectrum of pretreatment HIV-1 RNA levels and pretreatment CD4 cell counts and that 4-drug therapy offered no additional benefit, compared with standard 3-drug therapy. We conclude that efavirenz-based regimens can be used in treatment-naive patients across the spectrum of HIV disease and that the addition of antiretroviral agents to a standard 3-drug regimen is unnecessary, regardless of pretreatment HIV-1 RNA level or CD4 cell count.

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