A Randomized Trial of 2 Different 4-Drug Antiretroviral Regimens versus a 3-Drug Regimen, in Advanced Human Immunodeficiency Virus Disease

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To compare long-term virologic benefits of antiretroviral regimens in persons with advanced human immunodeficiency virus (HIV) disease, a randomized, open-label study was conducted of 517 subjects with no or limited previous experience with antiretroviral therapy. Subjects received lamivudine plus zidovudine and indinavir (indinavir group), efavirenz plus indinavir (efavirenz + indinavir group), or nelfinavir plus indinavir (nelfinavir + indinavir group) and were monitored for 2.1 years. Virologic failure was lower in the efavirenz + indinavir group (P = .04) and higher in the nelfinavir + indinavir group (P = .006), compared with that in the indinavir group. No difference in grade 3 or 4 adverse event rates in the efavirenz + indinavir group (P = .97) and a trend toward an increased rate in the nelfinavir + indinavir group (P = .07), compared with the indinavir group, were noted. A 4-drug regimen containing efavirenz plus indinavir resulted in a superior virologic response, whereas one containing nelfinavir plus indinavir resulted in an inferior response and a greater likelihood of toxicity.

Combination antiretroviral regimens containing human immunodeficiency virus (HIV) type 1 protease inhibitors (PIs) provide clinical benefits and can achieve long-term virus suppression with partial reconstitution of the immunologic perturbations associated with HIV infection [1, 2]. Although virologic response rates of 50%–90% have been described in some patient settings, patients with high HIV-1 RNA levels and low CD4 cell
counts (advanced HIV disease) can have blunted responses to 3-drug regimens [1, 3, 4].

The optimal combination antiretroviral regimens for the treatment of advanced HIV disease have not been well defined. At the time of the design of this study, preliminary data suggested that regimens with 2 PIs might provide additional virological and pharmacological advantages in the treatment of HIV infection [5]. The mechanism of pharmacologic enhancement during dual-PI therapy has been attributed to the inhibition of cytochrome P450 activity in intestinal epithelium and hepatocytes, as well as via P-glycoprotein inhibition [6, 7]. Previous data have suggested that nelfinavir, through its competitive inhibition of CYP3A4 activity, might allow for indinavir to be given every 12 h at a reduced dose of 1000 mg, providing an enhanced regimen that would facilitate the administration of indinavir [8]. In addition, nonnucleoside reverse-transcriptase inhibitors (NNRTIs) were recognized to be potent inhibitors of HIV-1 replication, and initial studies suggested that NNRTIs could enhance the efficacy of antiretroviral regimens [9, 10]. On the basis of this information, we evaluated 2 different 4-drug regimens containing indinavir with either efavirenz or nelfinavir for the treatment of patients with advanced HIV disease.

SUBJECTS, MATERIALS, AND METHODS

Study design. Adult AIDS Clinical Trials Group (AACTG) 388 was a randomized, open-label study that compared 2 different 4-drug regimens of lamivudine, zidovudine, and indinavir with either efavirenz or nelfinavir with a standard 3-drug regimen of lamivudine, zidovudine, and indinavir. The planned study duration was 72 weeks, which was subsequently increased to 96 weeks beyond the enrollment of the last subject. Subjects were recruited from 44 Adult AIDS Clinical Trials Unit sites in the United States and Italy. Institutional review boards or ethical committees at the participating institutions approved the study, and all subjects provided written informed consent.

The randomization used a permuted block design and was stratified according to CD4 cell count (≤50 cells/mm³ vs. >50 cells/mm³) and HIV-1 RNA level (≤40,000 copies/mL vs. >40,000 copies/mL) at screening, as well as previous antiretroviral experience (no therapy vs. limited therapy). Randomization was performed using an AACTG centralized-computer system, which required site personnel to enter subjects’ eligibility data to receive a treatment assignment.

Study population. Eligible subjects had a CD4 cell count ≤200 cells/mm³ or a plasma HIV-1 RNA level ≥80,000 copies/mL at screening and no or limited prior antiretroviral therapy. Prior antiretroviral therapy was restricted to nucleoside reverse-transcriptase inhibitors (NRTIs) zidovudine, stavudine, didanosine, and zalcitabine. Additional enrollment criteria included a hemoglobin level ≥9.1 g/dL for men or ≥8.9 g/dL for women, a neutrophil count ≥850 cells/mm³, a platelet count ≥65,000 platelets/mm³, a serum amylase level ≤1.5 times the upper limit of normal, and hepatic aminotransferase levels ≤5 times the upper limit of normal. Patients were ineligible if they were pregnant or breast-feeding.

Study treatment. Subjects received 1 of 3 treatment regimens given orally: lamivudine (150 mg) and zidovudine (300 mg) as a fixed dose combination tablet (Combivir; GlaxoSmithKline) 2 times daily and indinavir (800 mg) 3 times daily (indinavir group); or Combivir 2 times daily, indinavir (1000 mg) 3 times daily, and efavirenz (600 mg) once daily (efavirenz + indinavir group); or Combivir 2 times daily, indinavir (1000 mg) 2 times daily and nelfinavir (1250 mg) 2 times daily (nelfinavir + indinavir group). Because efavirenz has been shown to induce CYP4503A activity, a higher dose of indinavir (1000 mg every 8 h) was used [8, 11]. The substitution of stavudine for zidovudine was permitted in the event of drug-associated toxicity. A protocol modification in February 1999 increased the dose of indinavir to 1200 mg 2 times daily when coadministered with nelfinavir because of new pharmacokinetic and safety data with the 1200-mg dose [12]. Subjects who had virologic failure were offered the option of alternative therapy based on antiretroviral phenotypic susceptibility of their virus at the time of virologic failure.

Outcome measurements. The primary outcome measures were antiretroviral activity, safety, and tolerability of the 2 different 4-drug regimens, compared with the 3-drug regimen. Antiretroviral activity was defined as the time to virologic failure. Virologic failure was defined as a confirmed increase in HIV-1 RNA level greater than baseline values or 1.0-log greater than the nadir values during the first 24 weeks of study treatment, an HIV-1 RNA level >200 copies/mL at week 24, or virologic relapse (2 consecutive HIV-1 levels >200 copies/mL after 2 consecutive HIV-1 RNA levels <200 copies/mL).

Secondary outcome measurements included changes in CD4 cell counts, the proportion of patients who had HIV-1 RNA levels <200 copies/mL or <50 copies/mL over time, and the time to treatment failure (defined as the development of virologic failure, an AIDS-defining event or death, whichever occurred first).

Study procedures. Clinical assessments, HIV-1 RNA measurements, CD4 cell counts, and routine laboratory tests were performed before study entry, at the time of study entry, at weeks 4 and 8, and every 8 weeks thereafter. HIV-1 RNA levels were measured by use of an ultrasensitive assay (Roche Diagnostic Systems), with a lower limit of detection of 50 copies/mL [13].

Study medication adherence was evaluated in 282 subjects as part of an adherence intervention substudy [14]. Adherence was assessed with a standardized adherence questionnaire during study treatment and at the time of confirmed virologic failure.
Eight- and 12-h indinavir and 12-h nelfinavir intensive pharmacokinetic studies were conducted in a subset of subjects in the indinavir group \((n = 8)\) and the nelfinavir + indinavir group \((n = 10)\). After the indinavir dose increase in the nelfinavir + indinavir group, intensive pharmacokinetic studies were repeated in an additional group of subjects \((n = 7)\). Intensive pharmacokinetic studies of the efavirenz + indinavir group were not included, because this interaction has been well described elsewhere \[15\]. Indinavir and nelfinavir concentrations were measured by high-performance liquid chromatography, with a lower limit of quantification of 10 and 200 ng/mL, respectively. Individual plasma samples were collected for efavirenz, indinavir, and nelfinavir population pharmacokinetic studies at weeks 16, 24, and 48. The analytical methods for these assays have been described elsewhere \[16, 17\].

Viral phenotype and viral genotype analyses were done at the time of virologic failure. Genotypic resistance testing was performed in 3 AACTG laboratories by use of the Applied Biosystems HIV-1 Genotyping System (version 1.0; Applied Biosystems) \[18\]. Mutations in the HIV-1 reverse-transcriptase and protease regions associated with antiretroviral resistance were defined according to the 2001 International AIDS Society–USA Update on Drug Resistance Mutations in HIV-1 \[19\]. Phenytoin resistance testing was done by use of a commercial recombinant virus assay (PhenoSense; ViroLogic) \[20\]. Phenotypic resistance was defined as an IC<sub>50</sub> ≥ 3-fold higher than that of a susceptible reference strain.

**Interim analyses.** A data and safety monitoring board reviewed the study on 2 separate occasions, according to the Lan and DeMets spending function with O’Brien-Fleming boundaries for efficacy comparisons \[21, 22\].

**Statistical analyses.** ACTG 388 was designed to have 90% power to detect a 30% reduction in the intent-to-treat rate of virologic failure for each 4-drug regimen, compared with the 3-drug regimen, over an expected median follow-up of 108 weeks in 2 pairwise 2-sided hypothesis tests at an 0.025 level, to give an overall nominal level of significance of \(P = .05\).

The primary measure of antiretroviral drug activity was the time to virologic failure. The time-to-event distributions were estimated by use of the Kaplan-Meier method and were compared with log-rank tests and proportional-hazards models stratified by screening CD4 cell count and HIV-1 RNA level, as well as previous antiretroviral experience. HIV-1 RNA data also were analyzed longitudinally, according to the proportions of subjects with HIV-1 RNA levels <200 copies/mL or <50 copies/mL, and were compared at weeks 24, 48, and 96 by use of the \(\chi^2\) test. Sensitivity analyses combining virologic outcome and treatment status and as-treated analyses also were performed. Because the results of these analyses were consistent with those of the primary analyses, they are not presented.

Changes in CD4 cell counts from baseline to weeks 24, 48, and 96 were compared by the Wilcoxon rank sum test.

In the analyses of adverse events (signs, symptoms, or laboratory abnormalities), the follow-up data were censored at the time of study discontinuation or 56 days after permanent treatment discontinuation and were restricted to subjects for whom the study treatment was dispensed. Adverse events were graded according to the rating scale of the AACTG \[23\].

Efficacy outcomes were analyzed on an intent-to-treat basis that included all available follow-up data (excluding 1 patient who did not meet study eligibility and discontinued the study after 34 days). Subjects who discontinued from the study before a virologic end point were considered as “censored” at the time of their last HIV-1 RNA evaluation. All failure and censoring times were grouped according to the study week of measurement. Because of a lack of assurance that early failure defined an inferior response to failure to respond by week 24, all events and censoring times before week 24 were assigned a failure time at week 24. Missing data were assumed to be noninformative; sensitivity analyses (data not shown) were performed to assess this assumption. Pairwise comparisons of each of the 4-drug regimens with the 3-drug regimen are presented; no comparisons between each of the 4-drug regimens were performed. Post hoc global \(\chi^2\) test was used to assess the evidence against the null hypothesis that the occurrence of specific adverse events was the same in the 3 treatment groups. All \(P\) values are 2-sided.

Descriptive methods were used to summarize observed resistance data in subjects with virologic failure. Pairwise \(\chi^2\) or Fisher’s exact test was used to compare resistance patterns between the 3-drug group and the efavirenz + indinavir and nelfinavir + indinavir groups. All \(P\) values are 2-sided.

Nonadherence was defined as taking <95% of study medication doses during a 4-day interval before study visits. Predictors of nonadherence over time were assessed by use of a generalized estimating equations logistic regression analysis, with an autoregressive order-1 working correlation structure \[24\]. Nonadherence as a predictor of virologic failure was assessed by use of the Cox proportional hazards model \[25\], with a time-dependent covariate for recent nonadherence.

**RESULTS**

*Enrollment and characteristics of the subjects.* There were 517 subjects randomly assigned to study treatment between 8 June 1998 and 8 January 1999. Of the 517 subjects, 168 were assigned to the indinavir group, 173 to the efavirenz + indinavir group, and 176 to the nelfinavir + indinavir group (figure 1). The 3 treatment groups had similar baseline characteristics (table 1). The study population was primarily naive to antiretroviral therapy (90%).

**Duration of follow-up and treatment status.** The median
Figure 1. Profile of subject enrollment and discontinuation from study. 3TC, lamivudine; EFV, efavirenz; IDV, indinavir; NFV, nelfinavir; ZDV, zidovudine.

duration of follow-up was 108 weeks. Thirteen subjects (2%) died. Of the remaining 504 subjects, 110 (22%) discontinued from the study. There were no significant differences in the rate of study discontinuation by treatment group ($P = .41$ [indinavir group vs. efavirenz + indinavir group]; $P = .38$ [indinavir group vs. nelfinavir + indinavir group]). Of those who discontinued, 66 (60%) discontinued before a primary study end point (virologic failure), which provided a rate of study discontinuation before virologic failure of 13%.

Four subjects did not receive randomized treatment. Of the remaining 513 subjects, 207 (40%) discontinued the study treatment. There was a trend toward a lower treatment discontinuation rate for the efavirenz + indinavir group ($P = .07$) than the indinavir group, and no significant difference was observed between the nelfinavir + indinavir group and the indinavir group ($P = .25$). One hundred twenty-seven (25%) discontinued study treatment before developing virologic failure. Of the 207 subjects who discontinued treatment, 50 subjects (24%) discontinued because of protocol-defined events, and 1 patient was withdrawn because of ineligibility. The remaining

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects (n = 517)</th>
<th>Efavirenz + indinavir group (n = 173)</th>
<th>Nelfinavir + indinavir group (n = 176)</th>
<th>Indinavir group (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>421 (81)</td>
<td>143 (83)</td>
<td>149 (85)</td>
<td>129 (77)</td>
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<tr>
<td>Age, mean years</td>
<td>38.2</td>
<td>37.4</td>
<td>38.0</td>
<td>39.2</td>
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<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>248 (48)</td>
<td>81 (47)</td>
<td>88 (50)</td>
<td>79 (47)</td>
</tr>
<tr>
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<td>167 (32)</td>
<td>54 (31)</td>
<td>61 (35)</td>
<td>52 (31)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>88 (17)</td>
<td>35 (20)</td>
<td>24 (14)</td>
<td>29 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (3)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>9 (5)</td>
</tr>
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<td>CD4 cell count, mean cells/mm$^3$ (SD)</td>
<td>161 (166)</td>
<td>147 (151)</td>
<td>176 (190)</td>
<td>160 (154)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean $\log_{10}$ copies/mL (SD)</td>
<td>5.42 (0.60)</td>
<td>5.43 (0.63)</td>
<td>5.43 (0.57)</td>
<td>5.41 (0.60)</td>
</tr>
<tr>
<td>Median copies/mL</td>
<td>281,055</td>
<td>277,837</td>
<td>278,368</td>
<td>291,371</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. HIV-1, human immunodeficiency virus type 1.
Figure 2. Kaplan-Meier estimates of the time to virologic failure. Virologic failure was defined as an increase in human immunodeficiency virus type 1 (HIV-1) RNA level above baseline or nadir values, failure to achieve a HIV-1 RNA level <200 copies/mL by week 24, or relapse (2 consecutive HIV-1 RNA levels >200 copies/mL) after a confirmed virologic response (HIV-1 RNA level <200 copies/mL). All virologic failures that occurred before week 24 were assigned a failure time of 24 weeks. The stratified log-rank P values were for the comparison of efavirenz + indinavir with indinavir and \( P < 0.04 \) for the comparison of nelfinavir + indinavir with indinavir.

156 discontinuations (75%) were initiated by subjects; for the majority of these discontinuations, the reasons given included nonprotocol-defined, drug-associated toxicities or the number or timing of study medications.

Virologic failure study end points. One hundred seventy-two (33%) of 516 subjects developed virologic failure. Of these subjects, 3 had HIV-1 RNA levels increase above baseline values, 32 had increases of 1.0 log above nadir values, 56 failed to achieve an HIV-1 RNA level <200 copies/mL by week 24, and 81 had virologic relapse. Among those who had virologic failure, 52 were in the indinavir group, 39 in the efavirenz + indinavir group, and 81 in the nelfinavir + indinavir group.

A lower rate of virologic failure was seen in the efavirenz + indinavir group, compared with the indinavir group \( (P = 0.04; \text{estimated hazard ratio } [HR], 0.65; 95\% \text{ confidence interval } [CI], 0.42–0.99) \). In contrast, a higher rate of virologic failure was seen in the nelfinavir + indinavir group, compared with the indinavir group \( (P = 0.06; \text{estimated HR}, 1.64; 95\% \text{ CI}, 1.15–2.33) \) (figure 2).

Virologic responses. Three hundred seventy-one (72%) of 516 subjects had a confirmed virologic response (HIV-1 RNA level <200 copies/mL) by week 24. A longer time to a confirmed virologic response was seen in the nelfinavir + indinavir group, compared with the indinavir group \( (P = 0.06; \text{estimated HR}, 1.64; 95\% \text{ CI}, 1.15–2.33) \) (figure 2).

Genotypic resistance at virologic failure. Genotypic resistance data were obtained from 69 of 136 subjects who were receiving treatment at the time of virologic failure (15 in the indinavir group, 13 in the efavirenz + indinavir group, and 41 in the nelfinavir + indinavir group). Genotypic results were not obtained from 67 subjects because of failure of HIV-1 sequence amplification, thawed samples, or no available specimen.

HIV-1 with mutations at position 184 (M184V or M184I) were found in 35 subjects, including 12 subjects in the indinavir group, 5 in the efavirenz + indinavir group \( (P = 0.03, \text{Fisher’s exact test}) \), and 18 in the nelfinavir + indinavir group \( (P = 0.02, \text{Fisher’s exact test}) \). HIV-1 reverse-transcriptase mutations at positions 103 and/or 188 (associated with resistance to efavirenz) were found in 10 subjects, all of whom were in the efavirenz + indinavir group. In 5 of these 10 subjects, the efavirenz-resistant virus also was resistant to lamivudine (4 subjects) or zidovudine (1 subject). Major (primary) protease resistance mutations were not seen. Analysis of protease sequences at treatment failure showed minor (secondary) resistance mutations, many of which were present at baseline.

Disease progression and treatment failure. Fifty-two subjects had a total of 59 AIDS-defining diagnoses, and 13 subjects died. The rates of these events were similar across the treatment groups. The incidence of AIDS-defining events was 5.7 cases/100 person-years of follow-up (95\% CI, 4.35–7.49). The incidence of AIDS or death was 6.9 cases/100 person-years of follow-up (95\% CI, 5.11–8.48).

The causes of death included end-stage HIV disease \( (n = \)
3), lymphoma (n = 2), and Pneumocystis carinii pneumonia, sepsis, disseminated varicella zoster, Kaposi sarcoma, progressive multifocal leukoencephalopathy, bacterial pneumonia, or cerebral aneurysm (n = 8). The cause of death was not known for 1 subject.

Compared with the indinavir group, a lower rate of treatment failure was seen in the efavirenz + indinavir group (P = .02), as well as a trend toward a higher rate in the nelfinavir + indinavir group (P = .06) (figure 3).

**CD4 cell count response.** There were consistent increases in mean CD4 cell counts during the study period in all 3 treatment groups. No significant differences were seen in the changes from baseline to weeks 24, 48, and 96 among the treatment groups (P > .4, for all comparisons). The mean increase in CD4 cell counts at week 96 was 250 cells/mm$^3$ (indinavir group), 265 cells/mm$^3$ (efavirenz + indinavir group), and 257 cells/mm$^3$ (nelfinavir + indinavir group).

**Adverse events.** There was no significant difference in the time to development of the first grade 3 (severe) or grade 4 (life-threatening) adverse events between the efavirenz + indinavir group and the indinavir group (P = .97) and a suggestion of an increased rate of adverse events in the nelfinavir + indinavir group, compared with the indinavir group (P = .07) (figure 4).

A total of 35 subjects (21%) in the indinavir group developed grade 3 or 4 signs or symptoms, compared with 41 (24%) in the efavirenz + indinavir group (P = .49) and with 50 (28%) in the nelfinavir + indinavir group (P = .12). The most frequent grade 3 or 4 signs or symptoms reported were aches or pains, fatigue, or gastrointestinal complaints (nausea, vomiting, and diarrhea; table 2).

A total of 57 subjects (34%) in the indinavir group developed grade 3 or 4 laboratory abnormalities, compared with 58 subjects (34%) in the efavirenz + indinavir group (P = .87) and with 63 (36%) subjects in the nelfinavir + indinavir group (P = .80). Grade 3 or 4 elevation in serum bilirubin levels occurred more frequently in the indinavir and nelfinavir + indinavir groups (global P < .001). Forty-one subjects developed grade 3 or 4 neutropenia; 21 were in the nelfinavir + indinavir group (global P = .05).

Nephrolithiasis occurred more frequently among subjects in the indinavir group (global P < .001). Peripheral neuropathy occurred in 12 subjects (6 of whom were receiving stavudine), and 4 subjects distributed across the 3 treatment groups developed Steven Johnson syndrome.

Seventy-two subjects (14%) had stavudine substituted for zidovudine, and for the majority of these subjects, the reason was drug-associated hematological toxicity. Of these 72 subjects, 22 (13%) were in the indinavir group, 20 (12%) in the efavirenz + indinavir group, and 30 (17%) in the nelfinavir + indinavir group.

**Pharmacologic studies.** Eight-hour pharmacokinetic studies for the indinavir group (800 mg every 8 h) in 8 subjects demonstrated that ranges in indinavir concentrations for time zero (predose) were <10–949 ng/mL; $C_{\text{max}}$, 3379–19,786 ng/mL; and $C_{\text{min}}$, <10–506 ng/dL.

Twelve-hour pharmacokinetic studies for the nelfinavir + indinavir group (1000 mg every 12 h) in 10 subjects demonstrated that ranges in indinavir concentrations for time zero were <10–3740 ng/mL; $C_{\text{max}}$, 3379–18,210 ng/mL; and $C_{\text{min}}$, 10–4236 ng/mL. Overall, 5 of 10 subjects in this group had undetectable
Figure 4. Kaplan-Meier estimates of the time to a first grade 3 (severe) or grade 4 (life-threatening) adverse event. The stratified log-rank $P$ values were $P = .97$ for the comparison of efavirenz + indinavir with indinavir and $P = .07$ for the comparison of nelfinavir + indinavir with indinavir.

indinavir concentrations at 12 h, compared with 1 of 8 subjects in the indinavir group. Ranges in nelfinavir concentrations for time zero were <200–4610 ng/mL; $C_{\text{min}}$, 2437–9336 ng/mL; and $C_{\text{max}}, 155–6262$ ng/mL. After the indinavir dose increase (1200 mg every 12 h), ranges in indinavir concentrations in 7 subjects for time zero were 58–5215 ng/mL; $C_{\text{max}}, 6154–16,658$ ng/mL; and $C_{\text{min}}, <10–1684$ ng/mL. Ranges in nelfinavir concentrations for time zero were 611–8307 ng/mL; $C_{\text{max}}, 1869–9973$ ng/mL; and $C_{\text{min}}, <200–4270$ ng/mL.

Overall, nelfinavir showed a relatively flat concentration profile in 4 subjects and concentration values $>1500$ ng/mL at the end of the observed dosing interval in 5 subjects, when coadministered with indinavir at either dose.

The single-point efavirenz plasma concentrations obtained at week 24 were representative of the efavirenz concentrations at other weeks. Because each point represented a different subject, the data indicate that efavirenz concentrations were sustained throughout the 24-h dosing interval.

Adherence assessment. A total of 282 (54%) subjects were enrolled in the adherence substudy. No difference was noted in baseline characteristics between the main study and substudy populations. At week 24, 20%, 22%, and 26% of subjects reported nonadherence in the indinavir, efavirenz + indinavir, and nelfinavir + indinavir groups respectively; at week 48, these proportions were 17%, 18%, and 32%, respectively. In repeated measurement analysis, subjects in the nelfinavir + indinavir group were more likely to report nonadherence, compared with the indinavir group ($P = .008$; odds ratio, 2.13; 95% CI, 1.22–3.72). In survival models, nonadherence also was associated with an increased risk of virologic failure ($P = .002$; HR, 12.37; 95% CI, 1.38–4.08).

DISCUSSION

This study demonstrated that, in subjects with advanced HIV disease, treatment with a 4-drug regimen of efavirenz, indinavir, lamivudine, and zidovudine provided long-term virologic benefit, compared with a standard 3-drug regimen containing indinavir. A prolonged period of virus suppression characterized this superior response which resulted in a significant decrease in the risk for viral rebound. This advantage occurred without adverse implications for toxicity or tolerability. A possible contributing factor to this observed virologic benefit is the sustained efavirenz plasma concentrations during long-term dosing. In treatment-naive subjects, the efavirenz inhibitory quotient (trough/IC$_{50}$) is high and sustained throughout the dosing interval, which may be beneficial when efavirenz is combined with a “nonboosted” PI, such as indinavir.

In contrast, the 4-drug regimen with nelfinavir, indinavir, lamivudine, and zidovudine did not provide additional virologic benefit, compared with the 3-drug regimen. An inferior short-term virologic response was observed, which was accompanied by a trend toward a greater likelihood of serious drug-associated toxicity. This observation may be partially attributed to a pharmacologic factor, because the anticipated elevation in indinavir plasma concentrations may not have been realized during combination with nelfinavir. The higher rate of serious adverse events was characterized by primarily grade 3 or 4 gastrointestinal complaints of nausea, vomiting, and diarrhea, and neutropenia and may have resulted in decreased exposure to the treatment regimen.

Despite the open-label nature of the study, the objective virologic end points on which these conclusions are based make
Table 2. Grade 3 (severe) or grade 4 (life threatening) adverse events, according to treatment group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Efavirenz + indinavir (n = 173)</th>
<th>Nelfinavir + indinavir (n = 176)</th>
<th>Indinavir (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea with or without vomiting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nephrolithiasis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin level, &gt;2.5× upper limit of normal</td>
<td>0</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Absolute neutrophil count, &lt;750 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>12</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Hepatic aminotransferase level, &gt;5× upper limit of normal</td>
<td>11</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Serum triglycerides, &gt;750 mg/dL</td>
<td>12</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

**NOTE.** Patients with >1 episode of the same adverse event were counted only once.

<sup>a</sup> Comparing the 3 treatment groups; 
<sup>b</sup> Comparing the 3 treatment groups.

The primary study end point less susceptible to study subject and investigator bias. All the virologic efficacy results were robust to adjustment by baseline characteristics. There was no evidence of interactions between treatment and sex or race.

The rate of study discontinuation before the primary study end point of virologic failure was 13%. The overall rate of treatment discontinuation was high (40%), with a treatment discontinuation rate before virologic failure of 24%. Sensitivity analyses (data not shown) that considered composite end points combining treatment discontinuation and virologic outcomes confirmed that the higher rates of premature treatment discontinuation did not alter the conclusions of the study. In addition, similar results were seen with the as-treated analyses.

No unexpected drug-associated adverse events were noted. A significantly higher rate of nephrolithiasis and grade 3 and 4 elevation in serum bilirubin were noted for the 3-drug regimen. These findings suggest a decreased overall drug exposure to indinavir for both 4-drug regimens, which possibly contributed to pharmacologic mechanisms, as described above.

The higher rate of adverse events observed in the nelfinavir + indinavir group may have contributed to the inferior response seen with this regimen. Similar findings have been noted in other studies evaluating 4-drug regimens [26]. Analysis of an adherence substudy showed worse study medication adherence for the nelfinavir + indinavir group, which was associated with virologic failure. Because subjects received combination therapy with lamivudine, zidovudine, and nelfinavir at recommended doses in addition to indinavir, we a priori expected a virologic effect similar to that of the 3-drug regimen. The inferior virologic response seen in the nelfinavir + indinavir group probably was related to multiple factors, including a higher adverse event rate, worse study medication adherence, and an overall inability to tolerate and maintain the regimen. In addition, trough nelfinavir plasma concentrations may not have been sustained over time, further impacting the potential efficacy.

The pharmacokinetic data from this study and another study of nelfinavir + indinavir regimens [17] have more clearly defined the pharmacokinetic interaction potential between these PIs. Although nelfinavir is a substrate for CYP4503A and can result in significant drug-drug interactions, additional isoforms involved in nelfinavir metabolism have been identified (e.g., CYP 2C9 and CYP4502C19) [27, 28]. These additional metabolic pathways may explain the variable pharmacologic results observed when these 2 PIs are taken together.

We chose PI-based regimens for this study, to provide a high genetic barrier to the development of viral resistance in the setting of advanced HIV disease. A 3-drug regimen with efavirenz was not chosen because of the unavailability of data about its effectiveness in advanced HIV disease when the study was designed, as well as the potential risk for the emergence of viral resistance with NNRTIs [29, 30]. To address concerns about potential multidrug resistance during the study, HIV-1 RNA levels were closely monitored. Subjects who had virologic failure were promptly offered the option of alternative therapy based on antiretroviral phenotypic susceptibility of their virus at the time of confirmed failure. Recent studies whose designs allowed for early recognition of virologic failure have shown limited viral resistance in the setting of virologic failure, despite potent antiretroviral regimens [31–34]. Because of the early recognition of virologic failure in this study, breakthrough viruses were not anticipated to have resistance to all drugs in the 4-drug regimens. In fact, resistance studies in subjects with virologic failure found limited viral resistance, with lamivudine resistance being the most common finding across all treatment groups [35]. Dual resistance to la-
mivudine and efavirenz was infrequent and major (primary) protease resistance was not seen.

Since the design of this study, other strategies to enhance the potency of combination antiretroviral therapy have been evaluated. Such strategies include the pharmacological use of low doses of the HIV-1 PI ritonavir to boost the drug exposure of a second HIV-1 PI, such as indinavir or lopinavir [36–37]. At the time of design of this study, the equivalence of efavirenz and PI regimens as part of 3-drug regimens had not been demonstrated and was not studied as part of AACTG 388 [38]. Therefore, we cannot comment on the potential utility of a standard 3-drug regimen using efavirenz in advanced HIV disease. Switching to alternative potent regimens after prolonged periods of virus suppression has been shown to result in persistent virologic suppression [39, 40]. The strategy of switching to simplified potent regimens after successful long-term viral suppression in the setting of advanced HIV disease currently is under investigation in a follow-up study.

This study highlights the continued need for improved antiretroviral regimens for the treatment of HIV infection and the need for long-term studies, because the relative merits and toxicities of the studied regimens would not have been appreciated in a short-term study. The study further emphasizes the benefit of an efavirenz-based regimen as a strategy for increasing the potency of a regimen. In contrast, the strategy of a dual-PI–based regimen with nelfinavir and indinavir was found not to be useful. The study also highlights the need to explore alternative strategies and emphasizes the need to balance the potency of regimens with their side effects. On the basis of these findings, more potent, but simplified, regimens should and are being explored.

AIDS CLINICAL TRIALS GROUP 388 STUDY

The following institutions and investigators participated in the AIDS Clinical Trials Group 388 Study: James Horton (Carolina Medical Center); Cheryl Marcus (University of North Carolina at Chapel Hill); Jennifer Graham and Robert Hill (University of Alabama at Birmingham); Leslie Thompson and Miguel Castro (University of Miami AIDS Clinical Research Unit); Joseph Pulvirenti (Cook County Hospital); Harold Kessler (Rush-Presbyterian St. Luke’s Medical Center); Michael Para and Kathy Watson (Ohio State University College of Medicine and Public Health); Diane Daria and Pamela Daniel (University of Cincinnati); Debra Johnson and Virgilio Clemente (University of Southern California); James Richardson (Indiana University); Scott Hamilton (Wishard Memorial Hospital, Indiana University); Cindy Rohde and Gail Rudberg (University of Minnesota); Jorge Santana and Santiago Marrero (University of Puerto Rico); Gidon Beall (Harbor–University of California Los Angeles); Margrit Carlson (University of California Los Angeles Medical Center); Beverly Putnam and Sally Canmann (University of Colorado); Richard Pollard and Monica Pickthall (University of Texas Medical Branch–Galveston); Pablo Tebas and Thomas Stüffler (Washington University, St. Louis); Karen Cavanagh and Marina Queen (New York University Medical Center/Bellevue); Joanne Frederick and Scott Souza (University of Hawaii); Sherri Swan and Margaret McDaniel (Duke University); Rebecca Clark and Jeanne Dumestre (Tulane–Louisiana State University); Ann Conrad and Ron Johnson (Case Western Reserve University); Susan Cahill and Bruce Coon (University of California San Diego); Janet Hines and Keith Mickelberg (University of Pennsylvania); Robert Delpenha and Lisa Alexis (Howard University); Jane Reid and Tammy O’Hara (University of Rochester Medical Center); Todd Stroberg and Roy Gulic (Weil Medical College at Cornell University); Jeffrey Jacobson and Mary Sarah Dolan (Mount Sinai School of Medicine); Dorcas Baker and Ilene Wiggins (Johns Hopkins University); Joanne Stekler and N. Jeanne Conley (University of Washington School of Medicine); Jane Norris and Debbie Slamovitz (Stanford University); Francesco Mazzotta and Massimo Di Pietro (Ospedale S.M. Annunziata, Italy); Giampiero Cadeo and Roberto Stellini (Spedali Civili Brescia, Italy); Francesco Meneghetti and Anna Maria Cattelan (Azienda Ospedaliera Padova, Italy); Giampiero Carosi and Francesco Castelli (University of Brescia, Italy); Francesco Milazzo and Giuseppe Rizzardini (Ospedale L. Sacco, Italy); Mauro Moroni and Salvatore Sollima (University of Milan, Italy); Vincenzo Vullo and Angela Corpolongo (University of Rome, Italy); A. Lisa Mukherjee (Harvard School of Public Health); Brooks Jackson (Johns Hopkins Medical Laboratories); Maria Franca Pirillo, Clementina Galluzzo, and Liliana Weimer (Instituto Superiore di Sanità, Italy); Anne Knack and Marlene Cooper (Frontier Science and Technology Research Foundation, New York); Dawn Bell, Kellye Maxwell, and Barbara Brizz (ACTG Operations Center, Maryland); Ana Martinez (Division of AIDS, National Institute of Allergy and Infectious Diseases).

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References


In an article in the 1 September 2003 issue of the Journal (Fischl MA, Ribaudo HJ, Collier AC, et al. A Randomized Trial of 2 Different 4-Drug Antiretroviral Regimens versus 3-Drug Regimen, in Advanced Human Immunodeficiency Virus Disease (J Infect Dis 2003;188:625–34), the list of authors should have included the following 2 individuals: Lisa M. Demeter and Susan H. Eshleman. Dr. Demeter’s affiliation is Division of Infectious Diseases, University of Rochester, Rochester, New York; Dr. Eshleman’s affiliation is Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, Maryland. The authors regret this error.

In an article in the 15 June 2003 issue of the Journal (Bonacorsi S, Clermont O, Houdouin V, et al. Molecular Analysis and Experimental Virulence of French and North American Escherichia coli Neonatal Meningitis Isolates: Identification of a New Virulent Clone. J Infect Dis 2003;187:1895–1906), there is an error in line 12 of the right-hand column on page 1896; the numeral should be 6 (rather than 9), so that the “which” clause beginning on line 11 reads as “which belong to the outer membrane protein pattern (OMP) 6 subclone.” The authors regret this error.