Three- vs Four-Drug Antiretroviral Regimens for the Initial Treatment of HIV-1 Infection
A Randomized Controlled Trial

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The current standard of care for initial treatment of human immunodeficiency virus 1 (HIV-1) infection is 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) combined with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Three-drug antiretroviral regimens suppress viremia, increase CD4 cell counts, delay clinical progression, and improve survival. However, in treated patients with suppressed viremia, ongoing viral replication is well described. Some investigators have suggested that adding additional drugs to standard 3-drug regimens could improve antiretroviral activity and be more effective than a 3-drug regimen.

Objective To compare the safety/efficacy of 3-drug vs 4-drug regimens for initial treatment of HIV-1 infection.

Design The AIDS Clinical Trials Group (ACTG) A5095 study, a randomized, double-blind, placebo-controlled study with enrollment and follow-up conducted from March 22, 2001, to March 1, 2005, and enrolling treatment-naïve, HIV-1–infected patients with HIV-1 RNA levels of 400 copies/mL or greater from US clinical trials units of the ACTG.

Interventions Zidovudine/lamivudine plus efavirenz (3-drug regimen) vs zidovudine/lamivudine/abacavir plus efavirenz (4-drug regimen).

Main Outcome Measures Time to virologic failure (defined as time to first of 2 successive HIV-1 RNA levels ≥200 copies/mL at or after week 16), CD4 cell count changes, and grade 3 or 4 adverse events. HIV-1 RNA data were intent-to-treat, regardless of treatment changes.

Results Seven hundred sixty-five patients with a baseline mean HIV-1 RNA level of 4.86 log₁₀ (72 444) copies/mL and CD4 cell count of 240 cells/mm³ were randomized. After a median 3-year follow-up, 99 (26%) of 382 and 94 (25%) of 383 patients receiving the 3-drug and 4-drug regimens, respectively, reached protocol-defined virologic failure; time to virologic failure was not significantly different (hazard ratio, 0.95; 97.5% confidence interval, 0.69-1.33; P=.73). In planned subgroup analyses, increased risk for virologic failure was seen in non-Hispanic black patients (adjusted hazard ratio, 1.66; 95% confidence interval, 1.18-2.34; P=.003). At 3 years, the HIV-1 RNA level was less than 200 copies/mL in 152 (90%) of 169 and 143 (92%) of 156 patients receiving the 3-drug and 4-drug regimens, respectively (P=.59), and less than 50 copies/mL in 144 (85%) of 169 and 137 (88%) of 156 patients (P=.39). CD4 cell count increases and grade 3 or 4 adverse events were not significantly different.

Conclusions In treatment-naïve patients, there were no significant differences between the 3-drug and 4-drug antiretroviral regimens; overall, at least approximately 80% of patients had HIV-1 RNA levels less than 50 copies/mL through 3 years. These results support current guidelines recommending 2 nucleosides plus efavirenz for initial treatment of HIV-1 infection; adding abacavir as a fourth drug provided no additional benefit.

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toxicity, and costs, and prior studies comparing 3- and 4-drug antiretrovi-
ral regimens have demonstrated inconsistent results.14-16

The AIDS Clinical Trials Group (ACTG) A5095 study was designed originally to compare 3 simple, well-
tolerated antiretroviral regimens for the initial treatment of HIV-1 infection: 3 coformulated NRTIs (triple-nucleo-
side regimen); 2 coformulated NRTIs plus efavirenz (3-drug, standard-of-
care regimen); and 3 coformulated NRTIs plus efavirenz (4-drug regimen).

The triple-nucleoside group was dis-
continued early for virologic inferiority with a median 32 weeks of follow-
up, and the results comparing the triple-
nucleoside group with the combined efavirenz-containing regimen groups were analyzed and published.17 Of con-
tinued interest was whether the 4-drug regimen would demonstrate better an-
tiretroviral activity than the standard 3-drug regimen. To address this ques-
tion, ACTG A5095 participants in the 3- and 4-drug efavirenz-containing regi-
men groups continued blinded fol-
low-up through a median of 3 years as previously planned, and we report these results here.

METHODS

Study Participants

Potential study participants were re-
cruited and screened by the 33 units of the ACTG. Patients self-reported race/ ethnicity as American Indian/Alaska Native; Asian/Pacific Islander; black, non-Hispanic; Hispanic (of any race); white, non-Hispanic; or other/ unknown. Eligible participants were adult patients with HIV-1 infection who had not taken prior antiretroviral therapy and with a plasma HIV-1 RNA level of 400 copies/mL or greater (Am-
plicor or UltraSensitive HIV-1 Moni-
tor Assay version 1.0; Roche Molecu-
lar Systems, Branchburg, NJ). Part-
icipants were excluded if they had re-
ceived immunomodulators, investiga-
tional agents, or vaccinations within 30 days prior to entry, if they were preg-
nant or breastfeeding, or if their weight was less than 40 kg.

Design of Study

The ACTG A5095 study was designed originally as a randomized, double-
blind, placebo-controlled study of 3 ini-
tial antiretroviral regimens for treat-
ment of HIV-1 infection. The study was designed to enroll 1125 HIV-1-
infected patients who were randomly assigned with equal probability to re-
ceive 3 treatment regimens given orally: a triple-nucleoside regimen (zidovu-
dine/lamivudine/abacavir [one 300/150/300-mg pill coformulated as Triz-
ivir; GlaxoSmithKline, Research Triangle Park, NC; taken twice daily]); a 3-drug, standard-of-care regimen (zidovudine/lamivudine, 150-mg pill coformulated as Comb-
ivir, GlaxoSmithKline, taken twice daily) plus efavirenz [three 200-mg pills, Sustiva; Bristol-Myers Squibb, New York, NY; taken once daily]]; or a 4-drug regimen (zidovudine/lamivudine/abacavir [one 300/150/300-mg pill, coformulated, taken twice daily] plus efavirenz [three 200-mg pills, taken once daily]). Initially the study regimen consisted of 7 pills (in-
cluding matching placebos), divided twice daily; when efavirenz became available as 600-mg pills, the study regi-
men was reduced to 5 pills, divided twice daily. Randomization was strati-
fied by screening HIV-1 RNA levels (<100 000 copies/mL or ≥100 000 copies/mL).

Study visits were scheduled at weeks 2, 4, 8, 12, 16, 20, and 24 and then ev-
every 8 weeks and continued regardless of treatment change or discontinua-
tion. Each visit included clinical as-
sessments and laboratory testing, in-
cluding measurement of plasma HIV-1 RNA levels (HIV-1 Monitor Assay ver-
sion 1.0 used through April 2003; ver-
sion 1.5 used thereafter), performed centrally at a reference laboratory at Johns Hopkins Hospital, Baltimore, Md. CD4 cell counts were conducted at study visits at weeks 4 and 8 and then every 8 weeks at a Clinical Laboratory Improvement Amendments–approved laboratory (or equivalent) as part of the ACTG Immunology Quality Assurance Program. At baseline, hepatitis B surface antigen and hepa-
titis C antibody serologic tests also were obtained. An adherence question-
naire18 was either self-administered by the patient or completed by the pa-
tient with the assistance of the study co-
ordinator at weeks 4, 12, and 24 and then every 24 weeks.

For study-drug toxicity considered treatment-limiting by the site investi-
gator, patients could substitute stavu-
dine (Zerit, Bristol-Myers Squibb) for zidovudine, didanosine (Videx EC, Bris-
tol-Myers Squibb) for abacavir, and/or nevirapine (Viramune; Boehringer-
Ingelheim, Ingelheim, Germany) for efavirenz and still be considered to be receiving their initial regimen. In the event of virologic failure, patients could change to other study-provided anti-
retroviral drugs selected following ge-
notypic drug resistance testing (HIV-1 TRUGENE; Bayer Healthcare Diagnos-
tics, Berkeley, Calif). Genotypic test-
ing was not attempted if the HIV-1 RNA level was less than 500 copies/mL be-
cause of the low likelihood of obtaining a result. Adverse events were as-
essed and graded by the site study team using the National Institute of Allergy and Infectious Diseases Division of AIDS toxicity scale.19

The study protocol and all amend-
ments were submitted, reviewed, and ap-
proved by institutional review boards at each of the sites. The site study team re-
viewed the study purpose, design, pro-
dedures, risks, potential benefits, and al-
ternatives to study participation with poten-
tial study participants who pro-
vided written informed consent prior to the conduct of any study-related pro-
cedures and with each amendment. Study participants were further informed that their confidentiality would be protected and that they would not be identi-
fied personally in any materials pub-
lished about the study.

Study History

The study first enrolled on March 22, 2001, and accrued by November 4, 2002. The second annual review by the Na-
tional Institute of Allergy and Infection-
ous Diseases data and safety monitor-
ing board took place on February 6, 2003. At this review, the board concluded that the triple-nucleoside regimen was virologically inferior to each of the 2 efavirenz-containing regimens, thus meeting protocol-specified stopping criteria. The board recommended that the triple-nucleoside group be discontinued and unblinded and that data be released comparing this group with pooled data from the other 2 groups; these results, with a median follow-up of 32 weeks, were analyzed and published.17

The 2 groups taking efavirenz-containing regimens continued blinded follow-up. Follow-up was originally planned to end 96 weeks after randomization of the last patient. At the third board review on February 3, 2004, it was observed that event rates were lower than anticipated. Consequently, the study was amended to allow 24 weeks of additional follow-up, closing on March 1, 2005, with a median follow-up of 144 weeks, and data analysis commenced thereafter.

Statistical Methods
The primary safety end point was time to first new grade 3 or 4 adverse event. The primary efficacy end point, time to virologic failure, was defined as the time to the first of 2 successive HIV-1 RNA levels of 200 copies/mL or greater at or after week 16; the distribution of time to virologic failure was compared for the treatment groups. The study was designed to have 80% power to detect a hazard ratio (HR) of 0.70 for virologic failure between the study regimens.

All P values and confidence intervals (CIs) presented were nominal, unadjusted for multiple interim analyses and comparisons. Since all pairwise comparisons between the 3 original study groups were planned, to protect the overall type I error rate the comparisons between the 3-drug and 4-drug groups and secondary treatment comparisons were evaluated at a 2.5% significance level with 97.5% CIs. Hazard ratios were presented with the 4-drug group as the numerator. Unless otherwise stated, efficacy analyses were intent-to-treat regardless of treatment discontinuation, and missing data were ignored; this assumption was evaluated using a logistic regression model for repeated-measurement data.20 As-treated analyses and sensitivity analyses that considered treatment discontinuation, missing data, or both as failure were used to examine the robustness of the study’s conclusions to these primary assumptions. All safety analyses were as-treated, including (as per ACTG convention) only patients who initiated study treatment with follow-up to 8 weeks after treatment discontinuation. Baseline HIV-1 RNA level and CD4 cell count were determined as the geometric and arithmetic means, respectively, of pre-entry and entry evaluations.

Failure-time methods were used to evaluate the safety and efficacy objectives. Failure-time distributions were estimated using the Kaplan-Meier method and compared with a stratified log-rank test. Cox proportional hazards models stratified by screening HIV-1 RNA levels were used for estimation of HRs and CIs. Interactions between covariates were evaluated within these models, and the validity of the proportional hazards assumption in these models was confirmed using the method of Grambsch and Therneau.21 Proportions of patients with HIV-1 RNA levels of less than 200 or less than 50 copies/mL were presented by treatment group over time. \( \chi^2 \) tests were used to compare groups at specific weeks.

CD4 cell counts were presented using estimated mean changes from baseline. \( t \) tests were used to compare groups at specific weeks. Fisher exact tests were used to compare new drug-resistance mutations between groups. Adherence was assessed as a dichotomous variable using a standard ACTG questionnaire18 in which participants were considered adherent if they reported no missed doses over the prior 4 days.

All comparisons between treatment groups were assessed at a nominal 2.5% significance level (\( P < .025 \)) (as indicated above). This was performed to achieve a study-wide 5% type I error rate for all comparisons between treatment groups. All other P values (for example, those assessing racial differences in responses) were assessed at a \( P < .05 \) level. SAS version 8 (SAS Institute Inc, Cary, NC) and S-plus version 6 (MathSoft Inc, Cambridge, Mass) were used for all analyses.

RESULTS

Baseline Characteristics
The table summarizes the baseline characteristics of the study participants. A total of 765 patients were randomly assigned to receive 1 of the 2 efavirenz-containing regimens. Patients included 145 women (19%), 164 Hispanics (21%), 271 non-Hispanic blacks (35%), and 314 non-Hispanic whites (41%). Mean baseline plasma HIV-1 RNA level was \( 4.86 \log_{10} \) (SD, 0.73 \( \log_{10} \)) copies/mL (72 444 copies/mL), and mean CD4 cell count was 240 cells/mm\(^3\) (SD, 192 cells/mm\(^3\)). Baseline characteristics were balanced between the 2 study treatment groups.

Patient Disposition
Figure 1 shows the disposition of patients in the study. Median follow-up time was 144 weeks (interquartile range, 120-168 weeks). Of the 765 patients randomized, a total of 594 (78%) completed the study, 157 (20%) prematurely discontinued, and 16 (2%) died (2 after premature study discontinuation). Time to premature study discontinuation was not significantly different between groups (\( \text{P} = .56 \)). Of 765 patients randomized, 7 (1%) did not start study treatment. At study completion, of 758 patients who started study treatment, 463 (61%) were taking initial study treatment, 70 (9%) had discontinued initial treatment and were taking another study-provided regimen, 61 (8%) had discontinued study treatment but remained in follow-up receiving or not receiving antiretroviral therapy, and 103 (14%) had discontinued study treatment due to premature study discontinuation, loss to follow-up, or death. Overall, of 295 treatment discontinuations, 79 (27%) were for virologic failure and 66 (23%) were for toxicity. Initial treatment discon-
Continuation rates were not significantly different between the 2 study treatment groups (P = .45).

**Virologic and Immunologic Responses**

More than 90% of data were available through week 192 in the 3-drug group and through week 144 in the 4-drug group. With the 4-drug group as the numerator, there was no apparent difference in the odds of missing data between the study groups (odds ratio, 1.05; 97.5% CI, 0.73-1.53; P = .51). If missing and off-study data are considered, then odds ratio, 1.14; 97.5% CI, 0.88-1.50; P = .31).

Overall, 99 (26%) of 382 patients receiving the 3-drug regimen and 94 (25%) of 383 receiving the 4-drug regimen reached protocol-defined virologic failure; time to first virologic failure was not significantly different between the 2 study treatment groups (P = .73) (FIGURE 2), with an estimated HR of 0.95 (97.5% CI, 0.69-1.33). Similar results were seen in subgroups: in 437 patients with screening HIV-1 RNA levels less than 100 000 copies/mL, 55 (25%) of 218 receiving the 3-drug regimen and 50 (23%) of 219 receiving the 4-drug regimen reached virologic failure, and in 328 patients with screening HIV-1 RNA levels of 100 000 copies/mL or greater, 44 (27%) of 164 receiving the 3-drug regimen and 44 (27%) of 164 receiving the 4-drug regimen reached virologic failure. An additional 14 patients (7 in each treatment group) had a single, unconfirmed HIV-1 RNA level of 200 copies/mL or greater at or after week 16 prior to loss to follow-up or study discontinuation. Including these patients in the analysis of virologic failure demonstrated similar results, as did both sensitivity analyses with alternative definitions of virologic failure (as described above) and as-treated analyses.

Results also remained consistent after adjusting for sex, age, race/ethnicity, hepatitis B/C serologic status, baseline HIV-1 RNA level, and baseline CD4 cell count (adjusted HR, 0.91;
97.5% CI, 0.65-1.28). Of 193 patients experiencing virologic failure, 136 (70%) were receiving initial treatment, 11 (6%) were temporarily holding initial treatment, 10 (5%) had discontinued study treatment but were taking other antiretroviral drugs (individually chosen by their primary care clinician), and 36 (19%) had discontinued all treatment. At the time of censoring, 515 (90%) of the remaining 572 patients not observed with virologic failure were receiving or temporarily holding initial treatment and 57 (10%) had permanently discontinued study treatment (34 had discontinued all antiretroviral drugs and 23 were receiving other antiretroviral drugs individually chosen by their primary care clinician).

In a multivariable Cox proportional hazards model adjusted for sex, age, race/ethnicity, hepatitis B/C serologic status, baseline HIV-1 RNA level, and baseline CD4 cell count and stratified

**Figure 1. Disposition of Patients—AIDS Clinical Trials Group Study A5095**

<table>
<thead>
<tr>
<th>Treatment Group Closed Early (Inferior Virologic Response)</th>
<th>1148 Patients Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>383 Assigned to Receive ZDV/3TC/ABC</td>
<td>377 Received Treatment as Assigned</td>
</tr>
<tr>
<td>377 Received Treatment as Assigned</td>
<td>6 Did Not Receive Treatment</td>
</tr>
<tr>
<td>1 Acute Illness</td>
<td>1 Ineligible</td>
</tr>
<tr>
<td>2 Lost to Follow-up</td>
<td>2 Subject Refusal</td>
</tr>
<tr>
<td>77 Received Initial Study Treatment But Did Not Complete Study</td>
<td>29 Discontinued Initial Study Treatment But Remained in Follow-up Before Discontinuing Study</td>
</tr>
<tr>
<td>6 Discontinued Study Before Virologic Failure</td>
<td>5 Patient Decision/Lost to Follow-up</td>
</tr>
<tr>
<td>1 Died</td>
<td>17 Discontinued Study After Virologic Failure</td>
</tr>
<tr>
<td>18 Patient Decision/Lost to Follow-up</td>
<td>2 Severe Debilitation/Clincal Event</td>
</tr>
<tr>
<td>3 Died</td>
<td>48 Discontinued Initial Study Treatment and Study Simultaneously</td>
</tr>
<tr>
<td>11 Discontinued Study After Virologic Failure</td>
<td>5 Died</td>
</tr>
<tr>
<td>5 Patient Decision/Lost to Follow-up</td>
<td>32 Patient Decision/Lost to Follow-up</td>
</tr>
<tr>
<td>11 Discontinued Study After Virologic Failure</td>
<td>10 Patient Decision/Lost to Follow-up</td>
</tr>
<tr>
<td>3 Discontinued Initial Treatment After Virologic Failure</td>
<td>1 Virologic Failure</td>
</tr>
<tr>
<td>22 Toxicity</td>
<td>31 Virologic Failure</td>
</tr>
<tr>
<td>27 Virologic Failure</td>
<td>27 Virologic Failure</td>
</tr>
<tr>
<td>382 Assigned to Receive ZDV/3TC/ABC + EFV</td>
<td>376 Received Treatment as Assigned</td>
</tr>
<tr>
<td>376 Received Treatment as Assigned</td>
<td>6 Did Not Receive Treatment</td>
</tr>
<tr>
<td>2 Lost to Follow-up</td>
<td>3 Refused</td>
</tr>
<tr>
<td>1 Unable to Obtain Baseline Specimens</td>
<td>87 Received Initial Study Treatment But Did Not Complete Study</td>
</tr>
<tr>
<td>32 Discontinued Initial Study Treatment But Remained in Follow-up Before Discontinuing Study</td>
<td>11 Discontinued Study Before Virologic Failure</td>
</tr>
<tr>
<td>10 Patient Decision/Lost to Follow-up</td>
<td>21 Discontinued Study After Virologic Failure</td>
</tr>
<tr>
<td>18 Patient Decision/Lost to Follow-up</td>
<td>3 Died</td>
</tr>
<tr>
<td>2 Died</td>
<td>55 Discontinued Initial Study Treatment and Study Simultaneously</td>
</tr>
<tr>
<td>51 Discontinued Study Before Virologic Failure</td>
<td>48 Patient Decision/Lost to Follow-up</td>
</tr>
<tr>
<td>3 Died</td>
<td>4 Discontinued Study After Virologic Failure</td>
</tr>
<tr>
<td>1 Severe Debilitation/Clincal Event</td>
<td>10 Patient Decision/Lost to Follow-up</td>
</tr>
<tr>
<td>27 Virologic Failure</td>
<td>27 Virologic Failure</td>
</tr>
<tr>
<td>383 Assigned to Receive ZDV/3TC/ABC + EFV</td>
<td>382 Received Treatment as Assigned</td>
</tr>
<tr>
<td>382 Received Treatment as Assigned</td>
<td>1 Did Not Receive Treatment (Refused)</td>
</tr>
</tbody>
</table>

ABC indicates abacavir; EFV, efavirenz; 3TC, lamivudine; ZDV, zidovudine.

*Details reported in Gulick et al.*
by treatment group, there was an association between risk of virologic failure and race/ethnicity ($P = .03$). Specifically, there was an increased risk for virologic failure in non-Hispanic black patients compared with non-Hispanic white patients (adjusted HR, 1.66; 95% CI, 1.18-2.34; $P = .003$). Comparisons of time to virologic failure between patients of Hispanic or other race/ethnicity and non-Hispanic white patients were not significantly different ($P > .20$ for all comparisons). There was also a marginally increased risk of virologic failure for patients testing positive for hepatitis C antibody (estimated HR, 1.57; 95% CI, 1.02-2.41; $P = .04$). There were no significant associations with other baseline covariates and time to virologic failure ($P > .20$ for all).

Median time to virologic response (confirmed HIV-1 RNA levels less than 200 copies/mL) regardless of treatment change in both groups was 8 weeks ($P = .64$). Proportions of patients with HIV-1 RNA levels less than 200 copies/mL plateaued by week 16, remaining constant at 85% to 90% (Figure 3A). Proportions of patients with HIV-1 RNA levels less than 50 copies/mL began to plateau at week 24, remaining constant at 80% to 83% (Figure 3B). There were no significant differences between the groups at prespecified time points ($P > .05$). Additional analyses using intent-to-treat (missing data treated as failure; missing data or treatment discontinuation

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**Figure 2.** Time to First Virologic Failure (Intent-to-Treat Analysis)—3-Drug Group vs 4-Drug Group

![Time to First Virologic Failure](image)

The 4-drug group received zidovudine/lamivudine/abacavir plus efavirenz; 3-drug group, zidovudine/lamivudine plus efavirenz. The numbers at risk over time represent the number of patients in the study with-outh prior virologic failure (regardless of initial treatment status); patients previously discontinuing from the study prior to virologic failure are censored at the time of their last human immunodeficiency virus 1 RNA evaluation. The $P$ values and confidence intervals presented are nominal. CI indicates confidence interval; HR, hazard ratio.

**Figure 3.** Proportion of Patients With HIV-1 RNA Level Less Than 200 and Less Than 50 Copies/mL (Intent-to-Treat Analysis)—3-Drug Group vs 4-Drug Group

![Proportion of Patients](image)

The 4-drug group received zidovudine/lamivudine/abacavir plus efavirenz; 3-drug group, zidovudine/lamivudine plus efavirenz. The number of patients contributing data at each time point (the denominator for the proportion) represents the number of patients with a human immunodeficiency virus 1 (HIV-1) RNA evaluation for that study week; the numerator for the proportion is the number of patients with HIV-1 RNA levels less than 200 or less than 50 copies/mL (regardless of treatment status). Missing data (due to randomly missed evaluations, previous loss to follow-up, and administrative censoring) are ignored. Proportions are compared at weeks 24, 48, 72, 96, and 144 using $\chi^2$ tests. Error bars indicate 97.5% confidence intervals. All $P$ values and confidence intervals presented are nominal, unadjusted for multiple comparisons. Comparisons at prespecified time points were not significantly different ($P > .05$ for all).
treated as failure) or as-treated approaches demonstrated comparable findings (FIGURE 4).

CD4 cell counts increased from baseline in both treatment groups (overall mean increase at 144 weeks, 291 cells/mm³; 95% CI, 272-310) without significant differences between the groups (P > .05 at all time points) (FIGURE 5).

**Genotypic Resistance**

Genotypic testing was conducted retrospectively on baseline specimens and in real time on specimens with virologic failure from 193 patients who reached study-defined virologic failure. Of these, at baseline 175 (91%) had wild-type virus, and 18 (9%) had drug resistance–associated substitutions. Of the 18 with resistance-associated substitutions at baseline, 7 had substitutions associated with resistance to only 1 drug class (1 to lamivudine, 1 to another NRTI, 5 to NNRTIs), 9 had substitutions associated with resistance to 2 classes (4 to NRTIs and NNRTIs, 1 to NRTIs and PIs, 4 to NNRTIs and PIs), and 2 had substitutions associated with resistance to 3 classes. Among the 193 patients who experienced virologic fail-

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**Figure 4.** Proportion of Patients With HIV-1 RNA Levels Less Than 50 Copies/mL (4 Different Analyses)—3-Drug Group vs 4-Drug Group

A. As-Treated, Missing Data Treated as Failure

B. Intent-to-Treat, Missing Data Ignored

C. Intent-to-Treat, Missing Data Treated as Failure

D. Intent-to-Treat, Missing Data or Off-Treatment Treated as Failure

The 4-drug group received zidovudine/lamivudine/abacavir plus efavirenz; 3-drug group, zidovudine/lamivudine plus efavirenz. For each panel, the number of patients contributing data at each week (the denominator for the proportion) represents the number of patients: A, With a human immunodeficiency virus 1 (HIV-1) RNA evaluation for that study week while receiving initial treatment; B, With an HIV-1 RNA evaluation regardless of treatment status; and C and D, Expected to have an HIV-1 RNA evaluation based on their randomization date. The numerator for the proportion is the number of patients with: A, HIV-1 RNA levels < 50 copies/mL (missing data treated as failure); B, HIV-1 RNA levels < 50 copies/mL (regardless of treatment status, missing data ignored); C, HIV-1 RNA levels < 50 copies/mL (regardless of treatment status, missing data treated as failure); and D, HIV-1 RNA levels < 50 copies/mL (missing data treated as failure, off-initial treatment treated as failure). Error bars indicate 97.5% confidence intervals. All P values and confidence intervals presented are nominal, unadjusted for multiple comparisons. Comparisons at prespecified time points were not significantly different (P > .05 for all).
ure, 15 (8%) had NNRTI-resistant virus at baseline. At virologic failure, of 175 patients without preexisting resistance, 143 (82%) had genotypic results available, 27 (15%) did not have genotypic testing conducted because their HIV-1 RNA levels at virologic failure were less than 500 copies/mL, and 5 (3%) could not be sequenced because of failure of the assay to generate a result despite at least 2 attempts. Of the 143 with genotypic information available at virologic failure, 72 (50%) had wild-type virus (37 receiving 3 drugs, 35 receiving 4 drugs), and the other 71 (50%) had new resistance mutations (34 receiving 3 drugs, 37 receiving 4 drugs): NNRTI resistance only (15 receiving 3 drugs, 22 receiving 4 drugs); M184I/V only (4 receiving 3 drugs, 2 receiving 4 drugs); both M184I/V and NNRTI resistance (13 receiving 3 drugs, 7 receiving 4 drugs); M184I/V, other NRTI-associated mutations, and NNRTI resistance (1 receiving 3 drugs, 3 receiving 4 drugs); M184I/V and other NRTI-associated mutations (1 receiving 3 drugs); and M184I/V, other NRTI-associated mutations, or NNRTI resistance together with PI-associated mutations (3 receiving 4 drugs).

Among the treatment-emergent nucleoside mutations, significant zidovudine-associated mutations were uncommon (*<2%); the K65R and L74V substitutions that confer resistance to abacavir occurred once, or not at all, respectively. Thus, resistance to lamivudine, NNRTI, or both was selected commonly at virologic failure with both the 3- and 4-drug regimens, but resistance to zidovudine (or stavudine) and abacavir (or didanosine) was uncommon.

**Assessment of Adherence**

More than 88% of expected adherence assessments were available. Ignoring missing evaluations, 82% to 85% of patients reported not missing a dose over the prior 4 days at each prespecified time point, without significant differences between groups ($P > .05$ at all time points) (FIGURE 6). Similar results were seen when missing data were considered missed doses: 76% to 80% of patients reported not missing a dose over the prior 4 days at each prespecified time point, without significant differences between groups ($P > .10$ at all time points).
Occurrence of Adverse Events
In total, 166 (22%) of 758 patients reported a new grade 4 event; of those remaining, 257 (34%) of 758 reported a new grade 3 event. There were no significant differences in time to first grade 3 or 4 toxicity between the 2 study groups (P = .39). For treatment-limiting toxicity in patients receiving the active drug assignment, 69 (9%) of 758 substituted stavudine for zidovudine, 25 (7%) of 382 substituted didanosine for abacavir, and 75 (10%) of 758 substituted nevirapine for efavirenz.

Hypersensitivity reactions suspected to be drug-related were reported for 28 (7%) of 376 patients receiving the 3-drug regimen (receiving abacavir placebo) and 37 (10%) of 382 patients receiving the 4-drug regimen. Most (58/65 [89%]) suspected hypersensitivity reactions were attributed by the site investigators to abacavir. There was 1 reported case of Stevens-Johnson syndrome in the 4-drug group.

Among all 765 patients randomized, 29 (4%) experienced at least 1 Centers for Disease Control and Prevention category C AIDS-defining event, and 100 (13%) (53 [14%] of 382 in the 3-drug group and 47 [12%] of 383 in the 4-drug group) reported at least 1 HIV-1–associated adverse event (most commonly, localized varicella zoster [28], oropharyngeal candidiasis [25], mucocutaneous herpes simplex virus [24], and single-episode bacterial pneumonia [15]). There were 2 deaths among those receiving treatment in the 3-drug group (motor vehicle incident [1] and laryngeal carcinoma [1]) and 3 deaths in the 4-drug group (HIV encephalopathy [1] and suicide [2]).

Race/Ethnicity Differences
To understand the differences in virologic failure by race/ethnicity, we undertook a series of post hoc analyses. All treatment groups had high rates of virologic suppression; for example, the proportions of patients with HIV-1 RNA levels less than 50 copies/mL at 144 weeks were 60 (91%) of 66 Hispanics, 85 (80%) of 106 non-Hispanic blacks, and 130 (89%) of 146 non-Hispanic whites. Non-Hispanic black patients, compared with non-Hispanic whites, had significantly lower median baseline CD4 cell counts (184 vs 246 cells/mm³, respectively; P = .007) and absolute neutrophil counts (1890 vs 2312 cells/mm³, P < .001). Among those who would go on to experience virologic failure, non-Hispanic blacks, compared with non-Hispanic whites, had significantly fewer baseline NRTI substitutions (0/83 [0%] vs 5/67 [7%], respectively) and NNRTI substitutions (5/83 [6%] vs 9/67 [13%]).

Non-Hispanic blacks had a significantly shorter time to discontinuation of their initial efavirenz-containing regimen than non-Hispanic whites (HR, 1.37; 95% CI, 1.03-1.84; P = .03). The most common reason for treatment discontinuation (in 43 [36%] of 118 non-Hispanic blacks and 24 [23%] of 105 non-Hispanic whites) was virologic failure. There was no significant difference in time to study discontinuation (P = .22). Non-Hispanic blacks had a significantly shorter time to grade 3 or 4 toxicity than non-Hispanic whites (HR, 1.38; 95% CI, 1.09-1.73; P = .007), driven primarily by neutropenia. Hispanics had no significant differences compared with non-Hispanic whites in times to regimen discontinuation (P = .55), study discontinuation (P = .61), or grade 3 or 4 toxicity (P = .92).

Non-Hispanic black patients reported missing at least 1 dose of medication over the prior 4 days significantly more often than non-Hispanic whites at week 4 (46 [20%] of 231 vs 28 [11%] of 255, respectively; P = .01) and week 12 (50 [22%] of 226 vs 32 [12%] of 267, P = .01). However, at weeks 24 and 48, there were no significant differences in self-reported adherence rates among racial/ethnic groups (P > .20 for all comparisons). In addition, using a Cox proportional hazards model, we found evidence of an interaction between race and adherence at week 12 (P = .05) but not week 4 (P = .34), in which non-Hispanic blacks who reported missing at least 1 dose of their efavirenz-containing regimen in the prior 4 days had a significantly shorter time to virologic failure than similarly adherent non-Hispanic whites (P = .001 by log-rank test); there were no differences in rates of virologic failure by race/ethnicity in the larger group of patients reporting not missing doses at week 12 (P = .18) (FIGURE 7). Repeating this analysis using data from the 3 original treatment groups, including the triple-nucleoside group but restricted to non-Hispanic blacks and non-Hispanic whites, suggested a 3-way interaction between treatment, adherence, and race/ethnicity (P = .04); although there was some evidence of interaction between race and week-12 adherence in the groups receiving an efavirenz-containing regimen (P = .06), no significant interaction was seen with the 3-nucleoside regimen (P = .41).

COMMENT
We found no significant differences over 3 years between the standard 3-drug regimen of zidovudine/lamivudine plus efavirenz and the 4-drug regimen of zidovudine/lamivudine/abacavir plus efavirenz for the initial treatment of HIV-1 infection with regard to initial virologic response, time to virologic failure, CD4 cell count, adverse events, adherence, resistance mutations at virologic failure, or treatment or study discontinuation rates. Previously, we reported that a triple-nucleoside regimen was virologically inferior to the pooled results from these 2 efavirenz-containing regimens over a median 32 weeks of follow-up. Overall, patients taking the efavirenz-containing regimens did well, with at least approximately 80% having an HIV-1 RNA level suppressed to less than 50 copies/mL at 3 years (144 weeks) of follow-up. Over 3 years, 155 patients (20%) were lost to follow-up (including 104 [14%] prior to reaching the primary study end point); this follow-up rate is similar to comparable HIV clinical trials in treatment-naive patients. Although the addition of a fourth drug to a standard 3-drug regimen has
been suggested to improve outcome for initial treatment of HIV-1 infection,8-13 prior results have been inconsistent, often due to inconvenient, toxic regimens that contained combinations of NNRTIs and PIs.14,16 For example, the ACTG 388 study randomized patients to receive a 3-drug regimen (zidovudine/lamivudine plus indinavir) or one of two 4-drug regimens (zidovudine/lamivudine plus indinavir and efavirenz; zidovudine/lamivudine plus indinavir and nelfinavir). In that study, the 4-drug regimen with efavirenz had a superior virologic response to the 3-drug regimen, but the 4-drug regimen with nelfinavir had a significantly worse virologic response and more toxicity.14 The ACTG 384 study randomized patients to receive either of two 3-drug regimens (stavudine and didanosine plus either efavirenz or nelfinavir) or a 4-drug regimen (stavudine and didanosine plus nelfinavir and efavirenz) and found superior virologic responses in the 3-drug, efavirenz-containing regimen without differences in toxicities. Our study used convenient, well-tolerated regimens but demonstrated no additional benefit to the 4-drug regimen over a standard 3-drug regimen.

In our study, although virologic response rates were high in all race/ethnicity groups, there was a significantly shorter time to virologic failure in non-Hispanic black (but not Hispanic) patients compared with non-Hispanic whites. Phase 3 clinical trials of efavirenz-containing regimens initially did not describe differences in virologic responses by racial/ethnic groups but had limited representation of black and Hispanic patients.23,25 A post hoc analysis of 411 patients (22% black, 17% Hispanic) taking zidovudine/lamivudine plus efavirenz from one of these studies found a shorter time to virologic failure in Hispanics compared with whites.26 The ACTG 384 study had greater representation from blacks and Hispanics but reported no racial/ethnic differences in responses to efavirenz-containing treatment.15,27 However, at least 2 previous reports noted racial/ethnic differences in virologic responses: a retrospective study of 450 patients (the majority of whom were black) found a significantly shorter time to virologic failure among blacks taking efavirenz-containing regimens compared with whites but no differences with indinavir- or nelfinavir-based regimens.28 In addition, investigators at Johns Hopkins reported that of 283 clinic patients receiving efavirenz-containing regimens (77% African American, 23% non-Hispanic white), the probability of treatment discontinuation by 1 year was significantly higher in African Americans (32%) than in whites (16%) (P = .002) and rates of HIV-1 RNA suppression to levels less than 400 copies/mL were lower (66% vs 82%, respectively [P = .01]).29 In contrast, although only 85 patients (81% African American, 19% white/non-Hispanic) received PI-based regimens in this cohort, there were no significant differences in treatment discontinuation or virologic suppression rates.

Our large study enrolled 35% non-Hispanic blacks and 21% Hispanics. At baseline, non-Hispanic blacks had significantly lower absolute neutrophil counts than non-Hispanic whites and a consequently shorter time to first grade 3 or 4 toxicity, driven by neutropenia. Benign neutropenia in black individuals is well described.30 Importantly, rates of study discontinuation were not different among racial/ethnic groups, and self-reported adherence was not different at weeks 24 and 48, although we found the rate of self-

![Figure 7. Time to First Virologic Failure by Race/Ethnicity and Self-Reported Adherence at Week 12](image-url)
reported adherence to be decreased by approximately 10% at weeks 4 and 12 in non-Hispanic blacks compared with non-Hispanic whites. We also found a significant interaction between race and adherence in which non-Hispanic blacks who self-reported missing at least 1 dose of their efavirenz-containing regimen over the prior 4 days at week 12 had a shorter time to virologic failure than did nonadherent non-Hispanic whites. No racial/ethnic differences were observed between patients reporting adherence at the week 12 visit. However, it should be noted that sample sizes were small for some groups, limiting inferences. No interaction between nonadherence and race was seen in patients taking the triple-nucleoside regimen, albeit with a shorter follow-up time. Of note, patients testing positive for hepatitis C antibody also had marginally significantly higher virologic failure rates than those without hepatitis C antibody, but this finding did not explain the racial/ethnic differences.

We previously reported that the presence of the T/T genetic polymorphism at position 516—which occurs more commonly in blacks and which codes for CYP2B6, the hepatic enzyme responsible for efavirenz metabolism—was associated with significantly higher efavirenz plasma exposures and early central nervous system symptoms, but we found no differences in treatment discontinuation, tolerability, or virologic response rates in that subanalysis. It is reasonable to hypothesize that the current findings might be explained by the presence of this genetic polymorphism, resulting in higher efavirenz levels and greater toxicity leading to incomplete adherence, development of drug resistance, and, ultimately, virologic failure. Other potential explanations include racial/ethnic differences in patterns of adherence due to factors such as selective drug taking, low-level toxicities, or social support. A limitation of these data is the fact that adherence is self-reported and the interaction of race/ethnicity, adherence, and treatment was seen at the week-12, but not the week-4, time point. Racial/ethnic and genetic differences in antiretroviral treatment responses and toxicities are critical to understand, because antiretroviral drugs are recommended and used in diverse populations worldwide. The efavirenz-containing regimens in this study were associated with a nearly 300-cells/mm³ increase in CD4 cell count over baseline over 3 years. Although some have suggested that NNRTI-based regimens are inferior to PI-based regimens in CD4 cell count recovery, our results appear comparable with results from long-term PI studies.

Genotypic evidence of resistance to NNRTIs was detected in stored samples from 8% of patients at baseline who would start an efavirenz-containing regimen and ultimately experience virologic failure. In contrast, NNRTI resistance was detected in only a single baseline sample from 81 participants who experienced virologic failure while receiving the triple-nucleoside regimen. Although these data suggest that primary drug resistance may have played a role in a small proportion of treatment failures, analysis of baseline samples from participants without treatment failure is required before conclusions can be made. Because resistance testing was not conducted routinely at baseline and results are therefore unavailable at present from participants who did not go on to experience treatment failure, we cannot draw definite conclusions from these data; nevertheless, they suggest that baseline genotypic resistance confers a risk for failure for those receiving an efavirenz-containing regimen and may support newer guidelines that recommend baseline resistance testing.

Study adverse events were the same as those previously associated with the individual drugs, and adding abacavir to the 3-drug regimen did not increase the adverse events. Hypersensitivity reactions are associated with both efavirenz and abacavir. Determining which of these drugs is causative when both are initiated together poses a challenge to clinicians. In this placebo-controlled study, 24 cases of abacavir-associated hypersensitivity reaction were ascribed to the 3-drug regimen that included abacavir placebo. Occurrence of abacavir hypersensitivity reactions in whites is associated with the presence of the HLA-B*5701 allele. Prospective screening to identify patients carrying this allele has been proposed.

**CONCLUSIONS**

The results of the ACTG A3095 study demonstrate no significant differences in safety or efficacy between zidovudine/lamivudine plus efavirenz and zidovudine/lamivudine/abacavir plus efavirenz over 3 years of follow-up. High rates of virologic suppression achieved in this study support current guidelines that recommend 2 nucleosides plus efavirenz among preferred regimens for the initial treatment of HIV-1 infection. Adding abacavir as a fourth drug to the standard initial 3-drug regimen did not change toxicity or adherence but provided no additional benefit.
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THREE- VS FOUR-DRUG REGIMEN FOR HIV-1 INFECTION


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