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Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1:

A Randomized Trial

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Abstract

Background—Limited data compare once-daily options for initial therapy for HIV-1.

Objective—To compare time to virologic failure; first grade-3 or -4 sign, symptom, or laboratory abnormality (safety); and change or discontinuation of regimen (tolerability) for atazanavir plus ritonavir with efavirenz-containing initial therapy for HIV-1.

Design—A randomized equivalence trial accrued from September 2005 to November 2007, with median follow-up of 138 weeks. Regimens were assigned by using a central computer, stratified by screening HIV-1 RNA level less than 100 000 copies/mL or 100 000 copies/mL or greater; blinding was known only to the site pharmacist. (ClinicalTrials.gov registration number: NCT00118898)

Setting—59 AIDS Clinical Trials Group sites in the United States and Puerto Rico.

Patients—Antiretroviral-naive patients.

Intervention—Open-label atazanavir plus ritonavir or efavirenz, each given with with placebo-controlled abacavir–lamivudine or tenofovir disoproxil fumarate (DF)–emtricitabine.

Measurements—Primary outcomes were time to virologic failure, safety, and tolerability events. Secondary end points included proportion of patients with HIV-1 RNA level less than 50 copies/mL, emergence of drug resistance, changes in CD4 cell counts, calculated creatinine clearance, and lipid levels.

Results—463 eligible patients were randomly assigned to receive atazanavir plus ritonavir and 465 were assigned to receive efavirenz, both with abacavir–lamivudine; 322 (70%) and 324 (70%), respectively, completed follow-up. The respective numbers of participants in each group who received tenofovir DF–emtricitabine were 465 and 464; 342 (74%) and 343 (74%) completed follow-up. Primary efficacy was similar in the group that received atazanavir plus ritonavir and and the group that received efavirenz and did not differ according to whether abacavir–lamivudine or tenofovir DF–emtricitabine was also given. Hazard ratios for time to virologic failure were 1.13 (95% CI, 0.82 to 1.56) and 1.01 (CI, 0.70 to 1.46), respectively, although CIs did not meet prespecified criteria for equivalence. The time to safety ($P = 0.048$) and tolerability ($P < 0.001$) events was longer in persons given atazanavir plus ritonavir than in those given efavirenz with abacavir–lamivudine but not with tenofovir DF–emtricitabine.

Limitations—Neither HLA-B*5701 nor resistance testing was the standard of care when A5202 enrolled patients. The third drugs, atazanavir plus ritonavir and efavirenz, were open-label; the nucleoside reverse transcriptase inhibitors were prematurely unblinded in the high viral load stratum; and 32% of patients modified or discontinued treatment with their third drug.

Conclusion—Atazanavir plus ritonavir and efavirenz have similar antiviral activity when used with abacavir–lamivudine or tenofovir DF–emtricitabine.

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Treatment guidelines for initial HIV-1 therapy recommend 2 nucleoside reverse transcriptase inhibitors (NRTIs) with a non-NRTI (NNRTI), ritonavir-boosted protease inhibitor, or integrase inhibitor (1, 2). Abacavir–lamivudine and tenofovir disoproxil fumarate (DF)–emtricitabine are efficacious, once-daily NRTIs (3–5). The preferred NNRTI is efavirenz, and atazanavir plus ritonavir is 1 of the preferred protease inhibitors (1, 6, 7).

AIDS Clinical Trials Group (ACTG) Study A5202 compared efficacy, safety, and tolerability of abacavir–lamivudine or tenofovir DF–emtricitabine with atazanavir plus ritonavir or efavirenz. After scheduled interim data review, the data and safety monitoring board noted inferior virologic efficacy of abacavir–lamivudine compared with tenofovir DF–emtricitabine among patients with HIV-1 RNA levels of 100 000 copies/mL or more at screening (8). We now report the final results of the primary study objectives comparing atazanavir plus ritonavir against efavirenz.

Methods

Design

Study A5202 was a phase 3b, randomized equivalence study of 4 regimens for initial treatment of HIV-1. The study enrolled participants from September 2005 to November 2007. Median (25th, 75th percentile) follow-up was 138 weeks (106 weeks, 169 weeks), with the last patients followed until November 2009. The protocol was amended in July 2006 to exclude patients with chronic hepatitis B infection because of new treatment guidelines. In February 2008, the data safety monitoring board of the National Institute of Allergy and Infectious Diseases Division of AIDS recommended that persons with screening HIV-1 RNA levels of 100 000 copies/mL or more be unblinded (8). Human subjects committees of all sites approved the protocol, and informed consent was obtained from all participants.

Setting and Participants

Fifty-nine ACTG sites in the United States and Puerto Rico enrolled patients aged 16 years or older with HIV-1 who had had, at most, 7 days of previous antiretroviral therapy. Patients were recruited from local clinics and excluded if they were pregnant or breastfeeding; were using immunomodulators; had any known allergies to the study drugs; abused substances that would interfere with the study; had a serious illness; had an important cardiac conduction disorder; required prohibited medications; showed evidence of major resistance mutations; were incarcerated; or, as of July 2006, had hepatitis B. Resistance testing was required for recently infected patients.

Randomization and Interventions

Patients were randomly assigned to receive openlabel 300-mg atazanavir (Bristol-Myers Squibb, Plainsboro, New Jersey) plus 100-mg ritonavir (Abbott Laboratories, Abbott Park, Illinois) or 600-mg efavirenz (Bristol-Myers Squibb), along with placebo-controlled 600-mg abacavir–300-mg lamivudine (GlaxoSmith-Kline, Research Triangle Park, North Carolina) or 300-mg tenofovir DF–200-mg emtricitabine (Gilead Sciences, Gilead Sciences, Foster City, California). Randomization was stratified by HIV-1 RNA level (<100 000 copies/mL or ≥100 000 copies/mL) at screening and intent to participate in a metabolic substudy. Participants were randomly assigned through permuted blocks in a 1:1:1:1 ratio. Allocation used a centralized computer system, with assignment dynamically balanced by site. Balance was achieved by monitoring the total number of patients assigned to each study group by site and overriding assignments when imbalance would exceed a preset maximum. The NRTI treatment assignment was blinded to everyone except the site pharmacist. Unblinding occurred for patients in the high-screening viral load stratum (as a result of data safety monitoring board recommendations) and in persons with NRTI-related toxicity (suspected by the investigator) who had protocol-defined virologic failure or were enrolled with hepatitis B.

Outcomes and Follow-up

The primary efficacy end point was time from randomization to virologic failure (confirmed HIV-1 RNA level ≥1000 copies/mL at or after 16 weeks and before 24 weeks or ≥200 copies/mL at or after 24 weeks). The primary safety end point was time from treatment dispensation to first grade-3 or -4 sign, symptom, or laboratory abnormality (graded according to a toxicity rating scale developed by the Division of AIDS [version 1.0, December 2004]) at least 1 grade higher than at baseline, excluding unconjugated hyperbilirubinemia and creatine kinase. The primary tolerability end point was originally defined as time to change in assigned antiretroviral drugs. Study evaluations were done before entry; at entry; at weeks 4, 8, 16, and 24; and every 12 weeks thereafter regardless of treatment modifications. Adverse event reporting was done by local investigators in an open-ended manner, including study drug causality, at each visit. After screening, HIV-1 RNA measurement (Cobas Amplicor HIV-1 Monitor Test, version 1.5, Roche, Basel, Switzerland) was done at Johns Hopkins University. Planned and actual study duration was 96 weeks after enrollment of the last patient.

The ACTG Data Management Center oversaw the quality of completion of case report forms and computerized data. Monitors contracted by the National Institutes of Health visited all sites to review data. The data safety monitoring board reviewed study conduct and safety data at 2 planned annual reviews. Efficacy data were reviewed at the second review, and an additional safety and efficacy review was requested for 4 months later. Early stopping guidelines stated that a regimen would be considered inferior if the 99.95% 2-sided CI for the hazard ratio (HR) for virologic failure did not include 1.0.

Secondary outcomes included HIV-1 RNA level less than 50 copies/mL and change in CD4 cell count, calculated creatinine clearance, and fasting lipid levels. Emergence of a resistant virus was assessed by genotypic testing at Stanford University for all patients who met protocol-specified criteria for virologic failure and on their baseline samples. Major mutations were defined by the International AIDS Society–USA (9), as well as T69D, L74I, G190C/E/Q/T/V for reverse transcriptase, and L24I, F53L, I54V/A/T/S, G73C/S/T/A and N88D for protease. An adherence questionnaire (10) was administered at weeks 8 and 24 and every 24 weeks thereafter.

Statistical Analysis

The primary efficacy hypothesis was that in each of the NRTI groups, atazanavir plus ritonavir was equivalent to efavirenz. Regimens were prespecified to be equivalent if the 2-sided 95% CI for the HR from a Cox proportional hazards model was between 0.71 and 1.40. Assessment of the proportional hazards assumption provided mixed results. Graphical methods (11, 12) did not indicate that the proportionality assumption was violated, whereas addition of a time-by-treatment interaction term to the model indicated a significant decrease in the HR for each third-drug comparison over time, with effect changing direction at about 2 years of follow-up. The HRs we report may be viewed as an average of the treatment effect over the range of observed times (13).

A sample size of 1800 patients (450 per group) provided 89.8% probability of declaring equivalence if 2 regimens were the same, assuming uniform accrual, exponential virologic failure, and time distributions, with assumed virologic failure probability of 31.9% by 96 weeks. This assumption regarding virologic failure rate was based on available data at the time of protocol development from another ACTG trial using zidovudine–lamivudine plus efavirenz (8, 14). On the basis of this event rate, an HR of 1.40 would represent a 96-week difference in probability of virologic failure of approximately 10%.

Primary efficacy data were analyzed on the basis of each patient's randomly assigned regimen. The protocol originally defined safety events as events that occurred while receiving the assigned regimen and the tolerability end point as any change in the randomized regimen. After the high screening viral load stratum was unblinded, the safety end point was modified to include events that occurred while patients were receiving the assigned third drug (censored at the time of the modification), and the tolerability end point was based on the first modification of the third drug (ignoring NRTI switches). Time-to-event survival distributions were estimated by using the Kaplan–Meier method and compared with log-rank tests stratified by a screening viral load less than 100 000 copies/mL or 100 000 copies/mL or more. The HRs were estimated with Cox proportional hazards models stratified by screening viral load. For patients without virologic failure, the time was censored at the scheduled visit week of measured HIV-1 RNA. Similarly, for patients without safety or tolerability events, the time was censored at the date of the last sign or symptom evaluation or laboratory measure (safety) or at the date of the last reported antiretroviral treatment evaluation (tolerability).

Binary end points were compared by using a Cochran–Mantel–Haenszel (stratified) or Fisher exact test (unstratified), as appropriate. Changes in continuous measures (for example, CD4 count, fasting lipid levels, and calculated creatinine clearance) from baseline were compared by using a stratified Mann–Whitney test. Calculated creatinine clearance change within treatment regimen was assessed by using the signed rank test.

Data analyses are based on all follow-up, including follow-up after unblinding to NRTIs. *P* values and CIs are 2-sided and nominal, with no adjustment for interim analyses. The significance level for assessing modification of treatment effect was prespecified at 0.10. Analyses were done by using SAS, version 9 (SAS Institute, Cary, North Carolina), and Splus, version 6 (Insightful, Seattle, Washington).

Role of the Funding Source

Study A5202 was funded by the National Institutes of Health. The funding source had no role in the design, data collection, analysis, manuscript preparation, interpretation, or decision to submit the manuscript for publication.

Results

Study Patients and Follow-up Disposition

Study A5202 enrolled 1857 eligible patients (7 others were ineligible and excluded from the analysis) from September 2005 to November 2007 (Table 1). Follow-up was 0 to 208 weeks (median [25th, 75th percentile], 138 weeks [106 weeks, 169 weeks]); there was no significant difference in time to premature discontinuation between study groups, censoring persons who died, completed the study, or stopped because their study site closed owing to loss of funding ($P = 0.48$). Figure 1 shows the flow of patients through the study. Nine patients who never started treatment with the study drug regimen were included in the primary efficacy analyses. A total of 83 patients switched from the assigned efavirenz regimen to atazanavir plus ritonavir: 6 before and 40 at or after virologic failure, and 37 without virologic failure. Forty-five patients switched from atazanavir plus ritonavir to efavirenz: 2 before and 16 at or after virologic failure, and 27 without virologic failure.

Primary Virologic Outcome

Among persons randomly assigned to receive atazanavir plus ritonavir or efavirenz with abacavir–lamivudine, the HR (efavirenz being the reference) for time to virologic failure was 1.13 (95% CI, 0.82 to 1.56), with no difference in treatment effect by viral load stratum

($P = 0.147$) (Figure 2; Table 2; and Appendix Table 1, available at www.annals.org). For atazanavir plus ritonavir or efavirenz with tenofovir DF–emtricitabine, the HR was 1.01 (CI, 0.70 to 1.46), with no difference by viral load strata ($P = 0.37$). Although both CIs include an HR of no difference (1.0), neither met prespecified equivalence boundaries. The probability of remaining free of virologic failure at week 96 for atazanavir plus ritonavir or efavirenz with abacavir–lamivudine was 83.4% and 85.3%, respectively (difference, −1.9 percentage points [CI, −6.8 to 2.9 percentage points]). Values for atazanavir plus ritonavir or efavirenz with tenofovir DF–emtricitabine were 89.0% and 89.8% (difference, −0.8 percentage point [CI, −4.9 to 3.3 percentage points]). Table 2 and Appendix Table 1 summarize results and the probability of virologic failure.

A prespecified sensitivity analysis included potential virologic failures without confirmation ($n = 34$) and suggested that third-drug treatment effect differed by screening viral load stratum (P for interaction = 0.096). In the high viral load stratum, persons assigned to receive abacavir–lamivudine with atazanavir plus ritonavir had a higher rate of virologic failure than persons assigned to receive efavirenz (HR, 1.68 [CI, 1.08 to 2.60]; $P = 0.019$), a difference not seen in the low viral load stratum (HR, 0.99 [CI, 0.64 to 1.54]; $P = 0.97$). For comparison of the third drugs with tenofovir DF–emtricitabine, this sensitivity analysis was similar to primary results. In another prespecified sensitivity analysis that classified unconfirmed virologic failure, death, and discontinued follow-up as failures, results were similar to those of the primary efficacy analysis. Additional prespecified sensitivity analyses included censoring at first modification of the third drug, censoring at first modification of any assigned drugs, and censoring persons in the high viral load stratum at the time of the data safety monitoring board action; all had similar results to those of the primary analyses (Appendix Table 2, available at www.annals.org).

Secondary Virologic End Point Analyses

A prespecified comparison of atazanavir plus ritonavir and efavirenz with NRTIs combined (factorial analysis) was done because there was no evidence that the treatment effect differed by NRTIs ($P = 0.65$). For atazanavir plus ritonavir versus efavirenz, the HR for time to virologic failure was 1.08 (CI, 0.85 to 1.38), with CIs within the prespecified equivalence boundaries. However, for this comparison, there was a significant interaction with screening viral load ($P = 0.080$), in which the HRs were 1.35 (CI, 0.96 to 1.92) and 0.88 (CI, 0.62 to 1.23) for the high and low viral load stratum, respectively.

A cross-sectional analysis that assessed the proportion of patients with HIV-1 RNA levels less than 50 copies/mL (regardless of previous virologic failure or regimen change) was done in 1642 (88%) and 1498 (81%) of patients with HIV-1 RNA results available at weeks 48 and 96, respectively. Data were missing primarily because of premature discontinuation of the study (for example, because the patient moved, was incarcerated, or was deported) or the patient was lost to follow-up. Patients with missing data were more likely than persons with results to be younger, to be a non-Hispanic black person, to report previous intravenous drug use, and to have hepatitis B or C infection. Among patients with available HIV-1 RNA data, 78% of those assigned to receive atazanavir plus ritonavir and 87% of those assigned to receive efavirenz combined with abacavir–lamivudine had an HIV-1 RNA level less than 50 copies/mL at week 48 (difference, −8 percentage points [CI, −13 to −3 percentage points]; $P = 0.03$); respective values at week 96 were 85% and 91% (difference, −6 percentage points [CI, −11 to −1 percentage point]; $P = 0.012$). Values for atazanavir plus ritonavir versus efavirenz with tenofovir DF–emtricitabine were 84% and 90% at week 48 (difference, −6 percentage points [CI, −11 to −1 percentage point]; $P = 0.012$) and 90% and 91% at week 96 (difference, −1 percentage point [CI, −5 to 3 percentage points]; $P = 0.58$). In a prespecified, worst-case sensitivity analysis, in which patients with missing data were assigned to the group with HIV-1 RNA levels of 50 copies/mL or more, 48-week results

were similar to primary analyses, and at 96 weeks, abacavir–lamivudine no longer favored efavirenz. Finally, in the analysis of time to regimen failure, with the end point defined as time to first confirmed virologic failure or discontinuation of assigned protease inhibitor or NNRTI, no significant treatment differences were found between atazanavir plus ritonavir and efavirenz with abacavir–lamivudine (HR, 0.87 [CI, 0.71 to 1.08]) or tenofovir DF–emtricitabine (HR, 0.93 [CI, 0.74 to 1.17]) (Appendix Figure, available at www.annals.org).

Safety End Point

Time to safety event was longer among persons who received atazanavir plus ritonavir than those who received efavirenz combined with abacavir–lamivudine (HR, 0.81 [CI, 0.66 to 1.00]; $P = 0.048$), with no significant difference in treatment effect by viral load stratum ($P = 0.71$) (Figure 2, Table 2, and Appendix Table 1). Table 3 summarizes the main differences in triggering safety events. No significant difference in rate of safety events was found between persons given atazanavir plus ritonavir versus those given efavirenz combined with tenofovir DF–emtricitabine (HR, 0.91 [CI, 0.72 to 1.15]; $P = 0.44$), and no significant difference in treatment effect by screening viral load stratum was found ($P = 0.85$). Sensitivity analyses included censoring at the time of the first modification of any part of the original assigned regimen and time to first safety end point, regardless of whether the original regimen had been modified. The results did not differ from those of the primary analyses (Appendix Table 2).

Tolerability End Point

The third drug in the regimen was modified in 596 patients who initiated treatment (Figure 1). Time to regimen change was longer with atazanavir plus ritonavir than with efavirenz with abacavir–lamivudine (HR 0.69 [CI, 0.55 to 0.86]; $P < 0.001$), without significant evidence that results differed by viral load stratum ($P = 0.63$) (Figure 2, Table 2, and Appendix Table 1). No significant difference in the time to tolerability end point was found in persons who received these drugs with tenofovir DF–emtricitabine (HR, 0.84 [CI, 0.66 to 1.07]; $P = 0.166$), and no significant evidence was found that rates differed by viral load stratum ($P = 0.90$). Figure 1 shows reasons for modification. When analyzed as originally specified by the protocol, in which the end point was time to first change in any part of the assigned regimen, time to regimen change was longer among persons who received atazanavir plus ritonavir than those who received efavirenz with abacavir–lamivudine ($P = 0.06$); this difference was not seen with tenofovir DF–emtricitabine ($P = 0.22$) (Appendix Table 2).

Immunologic Outcome

Change in CD4 cell counts from baseline to weeks 48 and 96 was examined in 1645 (89%) and 1493 (80%) of patients with results available, respectively. Reasons for missing CD4 values were similar to reasons noted for HIV-1 RNA. Change in CD4 cell counts did not differ between persons given atazanavir plus ritonavir or efavirenz with abacavir–lamivudine, with a median change of 0.178 versus 0.188×10^9 cells/L ($P = 0.94$) and 0.250 versus 0.251×10^9 cells/L ($P = 0.89$), respectively. Change in CD4 cell count was greater in persons given atazanavir plus ritonavir than those given efavirenz with tenofovir DF–emtricitabine at weeks 48 and 96, with a median change of 0.175 versus 0.163×10^9 cells/L ($P = 0.040$) and 0.252 versus 0.221×10^9 cells/L ($P = 0.002$), respectively.

Clinical Events and Laboratory Measures

Prespecified clinical and laboratory events were events of interest in persons with HIV-1 and events related to known toxicities of study drugs. These included 31 deaths (Figure 1) and 95 AIDS-defining events in 82 patients. No significant difference was found in time to

AIDS or death in persons assigned to receive atazanavir plus ritonavir and those assigned to receive efavirenz with abacavir–lamivudine (HR, 0.93 [CI, 0.56 to 1.54]; $P = 0.77$) or tenofovir DF–emtricitabine (HR, 1.23 [CI, 0.70 to 2.39]; $P = 0.42$). Other events of interest for patients assigned to receive atazanavir plus ritonavir and efavirenz with abacavir–lamivudine were vascular events (coronary artery disease, infarction, ischemia, angina, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease) in 2 (<1%) patients in each treatment group; renal diagnoses of the Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure in 4 (1%) and 5 (1%) patients; bone fractures in 16 (3%) and 22 (5%) patients; and suspected hypersensitivity reaction in 34 (7%) and 53 (11%) patients, respectively. Respective numbers for patients assigned to receive atazanavir plus ritonavir and efavirenz with tenofovir DF–emtricitabine were vascular events in 1 (<1%) and 6 (1%); renal diagnoses in 6 (1%) and 3 (1%); bone fractures in 21 (5%) and 21 (5%); and suspected hypersensitivity reaction in 27 (6%) and 25 (5%).

Analyses of change in lipid levels included persons with available fasting measurements at baseline and while receiving the originally assigned protease inhibitor or NNRTI at weeks 48 and 96. Data were available in 82% and 80% of these patients at weeks 48 and 96, respectively. Most patients with missing lipid values provided nonfasting samples. Patients with fasting lipid values did not seem to differ systematically from those with missing or nonfasting lipid values. Table 3 summarizes changes in fasting values from baseline. Persons who received efavirenz compared with atazanavir plus ritonavir with abacavir–lamivudine or tenofovir DF–emtricitabine had significantly greater increases in all cholesterol levels but not in total–high-density lipoprotein cholesterol ratios.

Table 3 summarizes changes from baseline in calculated creatinine clearance (among persons receiving an assigned protease inhibitor or NNRTI) at weeks 48 and 96. An increase from baseline in calculated creatinine clearance occurred in patients who received atazanavir plus ritonavir or efavirenz with abacavir–lamivudine ($P < 0.001$ for both), with no significant difference in the distribution of change at weeks 48 and 96. Calculated creatinine clearance was increased at weeks 48 and 96 in persons who received tenofovir DF–emtricitabine with efavirenz ($P < 0.001$ for both) but not in persons who received atazanavir plus ritonavir at week 48 ($P = 0.53$ for week 48 and $P = 0.38$ for week 96). The distribution of change in calculated creatinine clearance differed significantly at both weeks 48 and 96 between recipients of atazanavir plus ritonavir and recipients of efavirenz given with tenofovir DF–emtricitabine. Treatment with tenofovir DF–emtricitabine was discontinued or the dose was reduced because of changes in renal function in 6 patients receiving atazanavir plus ritonavir and 3 receiving efavirenz.

HIV-1 Drug Resistance

Of the 269 patients with protocol-defined virologic failure, 265 had resistance data available at failure and baseline; of these, 25 had major mutations at baseline. Among patients with virologic failure, emergent resistance mutations were less frequent in those assigned to received atazanavir plus ritonavir than in those assigned to receive efavirenz, combined with either NRTI ($P < 0.001$ for both) (Appendix Table 3, available at www.annals.org). There was also a lower frequency of NRTI-associated mutations among persons assigned to receive atazanavir plus ritonavir than those assigned to receive efavirenz with abacavir–lamivudine ($P < 0.001$) or tenofovir DF–emtricitabine ($P = 0.046$).

Adherence

Among persons with adherence data, no missed doses in the previous week were self-reported at weeks 8, 48, and 96 by 87% to 92% of those assigned to receive abacavir–lamivudine plus atazanavir plus ritonavir and by 89% to 90% of persons assigned the same

NRTIs with efavirenz ($P \geq 0.26$ for all comparisons). Among persons with adherence data, no missed doses in the previous week were self-reported at weeks 8, 48, and 96 by 91% to 93% of those assigned to receive tenofovir DF–emtricitabine with atazanavir plus ritonavir and by 92% of those assigned to receive the same NRTIs with efavirenz ($P \geq 0.60$ for all comparisons).

Discussion

Our analyses show, for the first time to our knowledge in a large, randomized study, that a ritonavir-boosted protease inhibitor had similar virologic efficacy as an efavirenz-based regimen with either abacavir–lamivudine or tenofovir DF–emtricitabine. Rates of safety and tolerability end points were lower among persons assigned to receive atazanavir plus ritonavir than among those who received efavirenz with abacavir–lamivudine; no differences were observed when these agents were combined with tenofovir DF–emtricitabine.

Review of MEDLINE through August 2010 and meeting abstracts from the past 3 years showed that the largest previous study to compare a ritonavir-boosted protease inhibitor with efavirenz was study A5142, which compared lopinavir plus ritonavir with efavirenz with nonrandomized NRTIs and showed that protocol-defined efficacy favored efavirenz (15). Our study differs from study A5142 in that randomized and blinded NRTIs and atazanavir plus ritonavir (6) was used. Several recent studies reported similar efficacy of ritonavir-boosted protease inhibitors and nevirapine-containing regimens (16, 17). Another study (219 participants) compared atazanavir plus ritonavir with efavirenz, both combined with tenofovir DF–emtricitabine, and showed virologic noninferiority of atazanavir at 48 weeks for a mean change from baseline in HIV-1 RNA level (18).

In study A5202, there were greater increases in CD4 cell counts, albeit of unknown clinical relevance, among persons assigned to atazanavir plus ritonavir compared with efavirenz when combined with tenofovir DF–emtricitabine. This is consistent with the lower immunologic responses in persons who were assigned to receive efavirenz compared with lopinavir plus ritonavir in study A5142 (15). In addition, the frequency of emergent resistance to protease inhibitors was very rare (Appendix Table 3), which is consistent with other studies (5, 6, 15). We also showed that NRTI resistance emerged more often among patients with virologic failure who were assigned to receive efavirenz than among those assigned to receive atazanavir plus ritonavir (Appendix Table 3). Mutations included those associated with NNRTI resistance in the efavirenz groups and the M184V/I mutations associated with lamivudine and emtricitabine resistance in all groups. Other NRTI mutations were only seen in persons who were assigned efavirenz. The L74I/V mutation that is associated with abacavir resistance (19, 20) emerged in 6 and 1 persons randomly assigned to receive abacavir–lamivudine and tenofovir DF–emtricitabine, respectively. Seven patients had emergent K65R: 3 had received abacavir–lamivudine (1 had switched to alternative NRTIs before the time of virologic failure), and 4 had received tenofovir DF–emtricitabine. This mutation is seen in patients who have virologic failure while receiving tenofovir DF plus lamivudine and efavirenz (4) and is rarely seen in patients with virologic failure who are receiving tenofovir DF–emtricitabine (5, 6) and abacavir-lamivudine–based regimens (20).

Renal toxicity has been reported with tenofovir DF (21), and data are conflicting on whether ritonavir-based regimens increase nephrotoxicity induced by tenofovir DF (22–24). We observed no significant change from baseline in calculated creatinine clearance in persons who received atazanavir plus ritonavir with tenofovir DF–emtricitabine, compared with small but statistically significant increases in this measure within the other 3 study groups

(Table 3). Change in calculated creatinine clearance from baseline at 48 and 96 weeks differed between persons who received tenofovir DF–emtricitabine with efavirenz and those who received atazanavir plus ritonavir. Nevertheless, few patients assigned to receive tenofovir DF–emtricitabine had a decrease of 25% or more in renal function from baseline (data not shown) or had NRTIs discontinued or dose reduced because of changes in renal function. Moreover, targeted renal events were not demonstrably different from the other study groups and were rare, as seen in other studies (7, 25).

Despite efficacy results in study A5202 being similar, we were unable to declare equivalence on the basis of pre-specified HR boundaries probably resulting from the low rate of virologic failure at week 96 (11% to 17%) rather than the projected rate (32%). Nevertheless, in a post hoc assessment, the difference in probability of remaining free of virologic failure at 96 weeks did not exceed the 10% to 12% threshold typically used for defining equivalence or noninferiority (5, 6, 26). Other limitations of this study included that atazanavir plus ritonavir and efavirenz were given on an open-label basis, tenofovir DF–emtricitabine with efavirenz was not provided as the single fixed-dose combination pill, the NRTIs were prematurely unblinded in the high-screening viral load stratum, and approximately 32% of participants modified or discontinued their third drug regimen. In addition, resistance testing before treatment initiation was done in only 40% to 50% of patients, and when study A5202 enrolled participants, it was not routine to do HLA-B*5701 testing before use of abacavir; the latter would probably have influenced rates of selected safety and tolerability end points.

Results from study A5202 provide useful information for clinicians and patients making decisions about the initial treatment of HIV-1 infection. Atazanavir plus ritonavir and efavirenz provide similar antiviral activity when used with either of the NRTI pairs. There were, however, differences between regimens in CD4 cell count increases, frequency of emergent resistance, rates of safety and tolerability events, and changes in fasting lipid levels and renal variables. These factors should be considered when selecting initial treatment of patients with HIV-1 infection.

Context

There are few comparisons of once-daily treatment regimens for HIV-1.

Contribution

This randomized trial in antiretroviral-naive patients with HIV-1 showed that a once-daily ritonavir-boosted protease inhibitor regimen had similar virologic efficacy to a once-daily efavirenz-based regimen when combined with either abacavir–lamivudine or tenofovir DF–emtricitabine. The ritonavir-boosted protease inhibitor regimen seemed to be safer and more tolerable than the efavirenz regimen when combined with abacavir–lamivudine but not when combined with tenofovir DF–emtricitabine.

Caution

Patients and their physicians knew who was receiving the ritonavir-boosted protease inhibitor and efavirenz-based regimens, and one third of the patients modified or discontinued their regimens.

—The Editors

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APPENDIX

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Appendix Table 1

Summary of Primary End Points at Baseline, 48 Weeks, 96 Weeks, and Full Follow-up, With Efavirenz as the Reference in All Comparisons

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir + Ritonavir	Efavirenz	Atazanavir + Ritonavir
Time to virologic failure *				
Baseline				
Persons at risk, *n*	465	463	464	465
48 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*†	52/373 (11.9)	54/381 (12.3)	27/406 (6.1)	36/403 (8.2)
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*†	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*	1.9 (−2.9 to 6.8)		0.8 (−3.3 to 4.9)	
Full follow-up				
Events/total person-years at risk, *n/n*	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI)‡	1.13 (0.82 to 1.56)		1.01 (0.70 to 1.46)	
Screening HIV RNA level <100 000 copies/mL				
Baseline				
Persons at risk, *n*	266	264	265	265
48 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*†	24/223 (9.6)	22/223 (8.8)	15/229 (6.0)	17/233 (6.7)
96 wk				

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir + Ritonavir	Efavirenz	Atazanavir + Ritonavir
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	31/195 (12.6)	29/205 (11.7)	26/205 (10.8)	24/212 (9.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*	−0.8 (−6.6 to 4.9)		−1.1 (−6.5 to 4.3)	
Full follow-up				
Events/total person-years at risk, *n/n*	39/588.4	35/603.2	33/623.5	29/629.3
Estimated HR (95% CI)[‡]	0.89 (0.56 to 1.41)		0.87 (0.52 to 1.43)	
Screening HIV RNA level ≥100 000 copies/mL				
Baseline				
Persons at risk, *n*	199	199	199	200
48 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	28/150 (15.2)	32/158 (16.8)	12/177 (6.3)	19/170 (10.1)
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	32/136 (17.5)	43/133 (23.1)	18/162 (9.5)	24/152 (12.8)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*	5.6 (−2.6 to 13.8)		3.3 (−3.1 to 9.7)	
Full follow-up				
Events/total person-years at risk, *n/n*	33/423.3	48/414.0	24/472.2	28/457.1
Estimated HR (95% CI)[‡]	1.43 (0.91 to 2.24)		1.22 (0.70 to 2.11)	
Time to primary safety end point[§]				
Baseline				
Persons at risk, *n*	461	462	461	464
48 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	155/240 (35.9)	125/287 (28.4)	96/308 (22.3)	96/324 (21.8)
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*; *P* value	−6.2 (−12.9 to 0.4); 0.066		−2.5 (−8.6 to 3.7); 0.43	
Full follow-up				
Events/total person-years at risk, *n/n*	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI)[‡]; *P* value[‖]	0.81 (0.66 to 1.00); 0.048		0.91 (0.72 to 1.15); 0.44	

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir + Ritonavir	Efavirenz	Atazanavir + Ritonavir
Time to primary tolerability end point[¶]				
Baseline				
Persons at risk, *n*	461	462	461	464
48 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	114/349 (24.7)	75/387 (16.2)	86/376 (18.7)	60/403 (12.9)
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)*[†]	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*; *P* value	−9.8 (−15.6 to −4.0); 0.001		−3.8 (−9.2 to 1.6); 0.170	
Full follow-up				
Events/total person-years at risk, *n/n*	186/943.7	142/1052.6	142/1032.1	126/1088.5
Estimated HR (95% CI)[‡]; *P* value[‖]	0.69 (0.56 to 0.86); <0.001		0.84 (0.66 to 1.07); 0.166	

DF = disoproxil fumarate; HR = hazard ratio.

[*] All participants were analyzed as randomly assigned, and follow-up was included regardless of treatment status.

[†] Kaplan–Meier estimates are presented as cumulative probabilities of having the event by the given week.

[‡] HRs were estimated with Cox proportional hazards models and stratified by screening viral load strata for overall comparisons.

[§] First grade-3 or -4 sign, symptom, or laboratory abnormality while receiving the originally assigned third drug (atazanavir + ritonavir or efavirenz) that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase.

[‖] *P* value from a log-rank test stratified by screening viral load group.

[¶] First change in therapy, ignoring nucleoside reverse transcriptase inhibitors.

Appendix Table 2

Summary of Sensitivity Analyses for Atazanavir Plus Ritonavir Versus Efavirenz, With Efavirenz as the Reference in All Comparisons

Outcome	End Point Description	Result Summary	Estimated Hazard Ratio (95% CI)[*]	
			Abacavir–Lamivudine	Tenofovir DF–Emtricitabine
Time to virologic failure	Primary efficacy end points plus potential virologic failures without confirmation sample (unconfirmed failures [*n* = 34]); all follow-up included, and patients were analyzed per originally assigned regimen	Suggestion that the third drug effect differed by screening viral load stratum in abacavir–lamivudine group (*P* = 0.096); this interaction was not detected with tenofovir DF–emtricitabine (*P* = 0.74)[†]	HIV RNA level: ≥100 000 copies/mL, 1.68 (1.08–2.60); <100 000 copies/mL, 0.99 (0.64–1.54)	HIV RNA level: ≥100 000 copies/mL, 1.11 (0.67–1.85); <100 000 copies/mLn, 0.99 (0.62–1.57)

Outcome	End Point Description	Result Summary	Estimated Hazard Ratio (95% CI)*	
			Abacavir–Lamivudine	Tenofovir DF–Emtricitabine
	Primary efficacy end points plus unconfirmed failures, premature study discontinuation, and deaths; all follow-up included, and patients were analyzed per originally assigned regimen	Similar to primary results	1.01 (0.81–1.26)	1.05 (0.82–1.35)
	Primary efficacy end points that occurred while receiving the originally assigned third drug; patients are censored from follow-up time at the first modification of the assigned third drug	Similar to primary results	1.28 (0.88–1.85)	1.15 (0.76–1.72)
	Primary efficacy end points that occurred while receiving the originally assigned regimen; patients are censored from follow-up time at the first modification of the assigned third drug or NRTI	Similar to primary results	1.28 (0.86–1.90)	1.21 (0.80–1.84)
	Primary efficacy end point, in which the high viral load stratum is censored at the time of the DSMB action; all follow-up is included for the low viral load stratum, and patients are analyzed per originally assigned regimen	Similar to primary results	1.02 (0.73–1.44)	1.04 (0.70–1.57)
Time to safety event‡	Primary safety end points that occurred while receiving the originally assigned regimen (third drug and NRTI); patients are censored from follow-up time at the first modification of the assigned third drug or NRTI; this was the primary safety end point before the DSMB decision	Similar to primary results	0.77 (0.62–0.95); $P = 0.015$§	0.90 (0.72–1.14); $P = 0.40$§
	Primary safety end points that occurred during the study; all follow-up included, and patients were analyzed per originally assigned regimen; signs or symptoms and laboratory data were collected throughout study follow-up regardless of regimen status; this end point was reviewed by the DSMB	Similar to primary results	0.79 (0.65–0.96); $P = 0.021$§	0.90 (0.72–1.12); $P = 0.33$§
Time to tolerability event	Time to the first change in regimen (third drug or NRTI); all follow-up included, and patients were analyzed per originally assigned regimen; this was the primary tolerability end point before the DSMB decision	Longer time to regimen change with atazanavir + ritonavir was less pronounced than in primary analysis; no change in results with tenofovir DF–emtricitabine	0.84 (0.70–1.01); $P = 0.060$§	0.87 (0.69–1.09); $P = 0.22$§

DF = disoproxil fumarate; DSMB = data and safety monitoring board; NRTI = nucleoside reverse transcriptase inhibitor.

*Hazard ratios were estimated with Cox proportional hazards models and stratified by screening viral load strata for overall comparisons.

†*P* value from likelihood ratio test for interaction between the third drug regimen assignment and viral load screening stratum.

‡First grade-3 or -4 sign, symptom, or laboratory abnormality that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase.

§*P* values from a log-rank test stratified by screening viral load group.

Appendix Table 3

Summary of Drug-Resistant Mutations, With Specific Major Mutations of Interest[*]

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz (*n* = 465)	Atazanavir + Ritonavir (*n* = 463)	Efavirenz (*n* = 464)	Atazanavir + Ritonavir (*n* = 465)
Virologic failure				
Events, *n (%)*	72 (15)	83 (18)	57 (12)	57 (12)
Genotype available at failure	71	83	55	57
Major mutations at baseline	8	7	7	3
Without mutations at baseline	63	76	48	54
Mutations, *n (%) [%]*[§]				
Any major[‡]	41 (9) [65][‖]	12 (3) [16][‖]	27 (6) [56][‖]	5 (1) [9][‖]
NRTI-associated[‡]	25 (5) [40][‖]	11 (2) [14][‖]	11 (2) [23][‖]	5 (1) [9][‖]
M184I/V	22	11	5	5
K65R	3	0	4	0
L74I/V	6	0	1	0
Other[¶]	6	0	1	0
NNRTI-associated[‡]	41 (9) [65]	1 (<1) [1]	27 (6) [56]	0 (0) [0]
K103N	30	0	19	0
Y181C	2	0	0	0
L100I	4	0	2	0
G190A/E/Q/S	9	0	6	0
Other[¶]	16	1	6	0
NRTI + NNRTI-associated[‡]	25 (5) [40]	0 (0) [0]	11 (2) [23]	0 (0) [0]
Protease-associated (N88N/S)[‡]	0 (0) [0]	1 (<1) [1]	0 (0) [0]	0 (0) [0]

DF = disoproxil fumarate; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

[*] Patients analyzed per assigned regimen; some patients switched from the originally assigned regimen before developing protocol-defined virologic failure.

[†] Results not available because the sample could not be amplified (*n* = 1) or quality control was unable to verify that there was no evidence of contamination (*n* = 2).

[‡] Major mutations were defined as those listed by the International AIDS Society-USA (9), as well as T69D, L74I, and G190C/E/Q/T/V for reverse transcriptase and L24I, F53L, I54V/A/T/S, G73C/S/T/A, and N88D for protease.

[§] Excludes patients with major resistance mutations present at baseline but includes 1 person who had resistance data available at virologic failure but not at baseline. Total may not add up to 100% because some patients had >1 mutation.

Values are total number (percentage of persons randomly assigned) [percentage of persons with a genotype and without baseline resistance].

‖New resistance at failure was tested for pairwise comparisons among virologic failures without baseline resistance by using the Cochran–Mantel–Haenszel test for stratified comparisons for efavirenz versus atazanavir plus ritonavir with abacavir–lamivudine for any major mutations ($P < 0.001$) and for NRTI-associated mutations ($P < 0.001$), and with tenofovir DF–emtricitabine with any major mutations ($P < 0.001$) and for NRTI-associated mutations ($P = 0.046$).

¶Other observed major NNRTI mutations include V106A/M, V108I, Y188C/H, P225H, and other observed major NRTI mutations were M41L, D67N, K70E, Y115F, and K219E. Other major mutations targeted but not observed in this study were K70R, Q151M, L210W, T215F/Y, A62V, V75I, F77L, F116Y, and T69D for NRTIs and G190C/T/V for NNRTIs.

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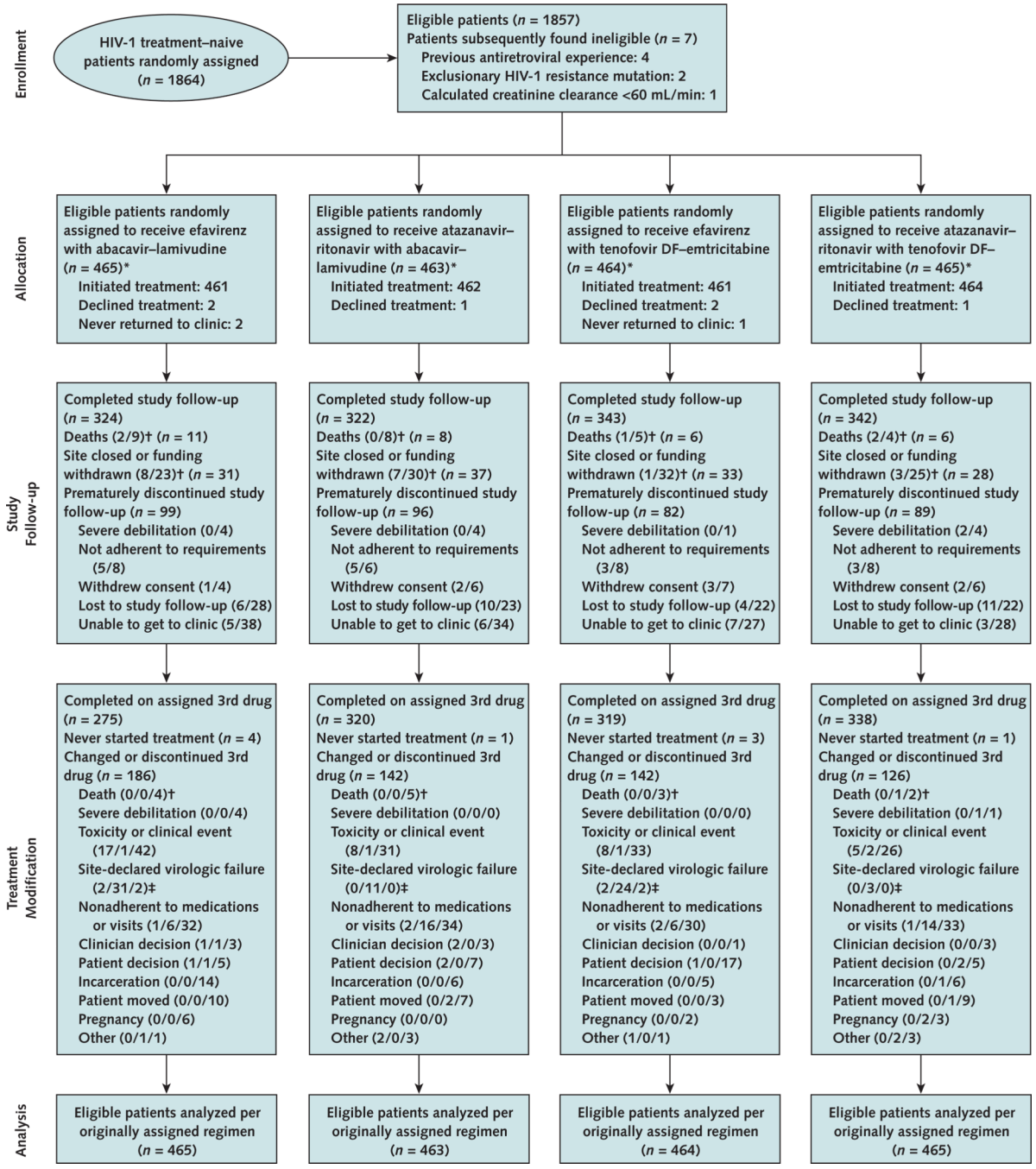


Figure 1. Study flow diagram

Patients were to remain in follow-up regardless of whether antiretroviral therapy was modified; therefore, study follow-up and treatment modification disposition are both presented. Reasons for discontinued study follow-up are split into (number after/number without protocol-defined virologic failure) to summarize the frequency of premature study discontinuation with regard to the primary efficacy end point; reasons for treatment modification are split into (number before/number after/number without protocol-defined virologic failure) to summarize the amount of censoring of primary efficacy end points in analyses limited to follow-up while patients were receiving the assigned treatment. “3rd drug” refers to atazanavir–ritonavir or efavirenz. DF = disoproxil fumarate. * Nucleoside

reverse transcriptase inhibitors were blinded through 25 February 2008 for persons with HIV-1 RNA levels of 100 000 copies/mL or more at screening and until final visits starting 1 July 2009 for those with HIV-1 RNA levels less than 100 000 copies/mL at screening. † Death was censored for premature study discontinuation and counted as a reason for treatment discontinuation if there was no previous modification to the third drug (number of treatment modifications due to death can be fewer than the number of deaths during the study follow-up owing to previous modifications for other reasons). Site closure was censored for premature study and treatment discontinuation. ‡ Site-declared virologic failure was by clinical determination of the site investigator, whereas protocol-defined virologic failure was determined strictly by the quantitative definition set forth in the protocol. Numbers may differ because not all patients who had protocol-defined virologic failure modified the third drug, or the drug modification may have been attributed to another reason, such as “nonadherent with medications or visits.”

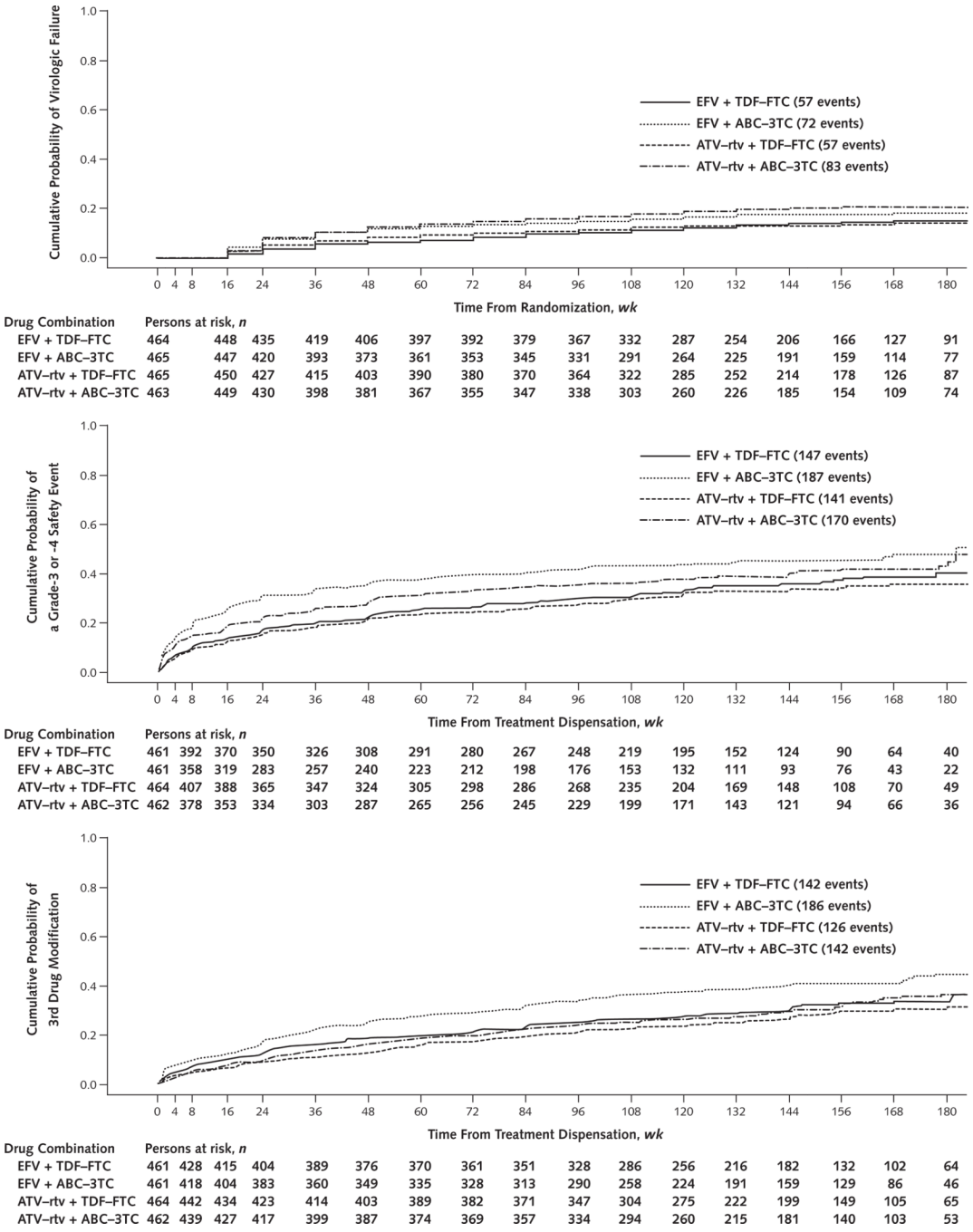
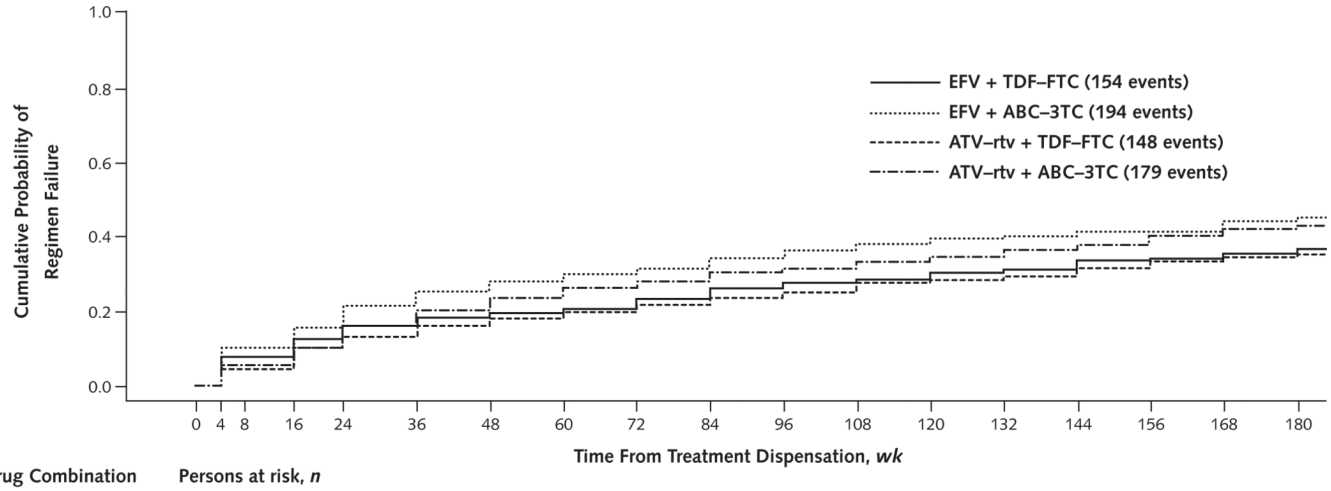


Figure 2. Time to primary virologic, safety, and tolerability end points

Each of these plots presents 1 minus the probability of remaining event-free, as estimated by the Kaplan–Meier method. The presented numbers of events are the total numbers of events during the entire follow-up (through 208 weeks). Presentation of time in figures was truncated because the numbers at risk declined after this point. By study design, follow-up was scheduled to be 96 weeks after the last participant enrolled. ATV–rtv + ABC–3TC = atazanavir + ritonavir with abacavir–lamivudine; ATV–rtv + TDF–FTC = atazanavir + ritonavir with tenofovir disoproxil fumarate–emtricitabine; EFV + ABC–3TC = efavirenz + abacavir–lamivudine; EFV + TDF–FTC = efavirenz plus tenofovir disoproxil fumarate–

emtricitabine. **Top**. Time to protocol-defined virologic failure (confirmed plasma HIV-1 RNA level ≥1000 copies/mL at or after 16 weeks and before 24 weeks or ≥200 copies/mL at or after 24 weeks). **Middle**. Time to first primary safety end point (first grade-3 or -4 sign, symptom, or laboratory abnormality while receiving the originally assigned third drug [atazanavir plus ritonavir or efavirenz] that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase). **Bottom**. Time to primary tolerability end point (first change in therapy, ignoring nucleoside reverse transcriptase inhibitors).



Drug Combination	Persons at risk, *n*															
EFV + TDF–FTC	461	424	402	386	375	369	363	348	335	299	261	226	189	151	113	81
EFV + ABC–3TC	461	413	388	361	342	329	319	312	299	262	233	202	171	145	104	69
ATV–rtv + TDF–FTC	464	441	415	401	388	376	368	358	349	310	271	238	201	165	118	79
ATV–rtv + ABC–3TC	462	435	413	385	366	349	338	328	318	284	239	211	175	145	103	71

Appendix Figure. Time to regimen failure

Time to regimen failure (first confirmed virologic failure or discontinuation of therapy with the assigned nonnucleoside reverse transcriptase inhibitor) is shown. The plot presents 1 minus the probability of remaining event-free, as estimated by the Kaplan–Meier method. The presented numbers of events are the total numbers of events during the entire follow-up (through 208 weeks). Presentation of time in figures was truncated because the numbers at risk declined after this point. By study design, follow-up was scheduled to be 96 weeks after the last participant enrolled. ATV–rtv + ABC–3TC = atazanavir plus ritonavir with abacavir–lamivudine; ATV–rtv + TDF–FTC = atazanavir + ritonavir with tenofovir disoproxil fumarate–emtricitabine; EFV + ABC–3TC = efavirenz plus abacavir–lamivudine; EFV + TDF–FTC = efavirenz plus tenofovir disoproxil fumarate–emtricitabine.

Table 1

Baseline Characteristics of the Patients in Study A5202

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine		Total (*n* = 1857)
	Efavirenz (*n* = 465)	Atazanavir + Ritonavir (*n* = 463)	Efavirenz (*n* = 464)	Atazanavir + Ritonavir (*n* = 465)	
Men, *n (%)*	367 (79)	388 (84)	393 (85)	387 (83)	1535 (83)
Women, *n (%)*	98 (21)	75 (16)	71 (15)	78 (17)	322 (17)
Median age (Q1–Q3), *y*	37 (31–45)	38 (30–45)	39 (31–44)	39 (31–46)	38 (31–45)
Age group, *n (%)*					
16–19 y	6 (1)	6 (1)	2 (<1)	3 (1)	17 (1)
20–29 y	95 (20)	94 (20)	98 (21)	100 (22)	387 (21)
30–39 y	169 (36)	166 (36)	148 (32)	142 (31)	625 (34)
40–49 y	135 (29)	138 (30)	154 (33)	146 (31)	573 (31)
50–59 y	43 (9)	55 (12)	56 (12)	60 (13)	214 (12)
>59 y	17 (4)	4 (1)	6 (1)	14 (3)	41 (2)
Race or ethnicity, *n (%)*[*†]					
White, non-Hispanic	174 (38)	189 (41)	197 (43)	186 (40)	746 (40)
Black, non-Hispanic	164 (35)	153 (33)	151 (33)	147 (32)	615 (33)
Hispanic	106 (23)	108 (23)	104 (22)	111 (24)	429 (23)
Asian or Pacific Islander	8 (2)	7 (2)	5 (1)	12 (3)	32 (2)
Native American or Alaskan Native	5 (1)	2 (<1)	4 (1)	3 (1)	14 (1)
>1 race	5 (1)	4 (1)	2 (<1)	5 (1)	16 (1)
Screening HIV RNA level, *n (%)*					

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine		Total (*n* = 1857)
	Efavirenz (*n* = 465)	**Atazanavir + Ritonavir (*n* = 463)**	**Efavirenz (*n* = 464)**	**Atazanavir + Ritonavir (*n* = 465)**	
<100 000 copies/mL	266 (57)	264 (57)	265 (57)	265 (57)	1060 (57)
≥100 000 copies/mL	199 (43)	199 (43)	199 (43)	200 (43)	797 (43)
Median HIV-1 RNA level (Q1–Q3), *log$_{10}$ copies/mL*‡	4.7 (4.3–5.0)	4.6 (4.3–5.1)	4.7 (4.4–4.9)	4.7 (4.3–5.1)	4.7 (4.3–5.0)
HIV-1 RNA level, *n (%)*					
<1000 copies/mL	5 (1)	4 (1)	3 (1)	4 (1)	16 (1)
1000–9999 copies/mL	51 (11)	54 (12)	54 (12)	48 (10)	207 (11)
10 000–49 999 copies/mL	183 (39)	195 (42)	197 (42)	202 (43)	777 (42)
50 000–99 999 copies/mL	119 (26)	77 (17)	108 (23)	87 (19)	391 (21)
100 000–249 999 copies/mL	44 (9)	52 (11)	35 (8)	55 (12)	186 (10)
250 000–499 999 copies/mL	24 (5)	24 (5)	17 (4)	24 (5)	89 (5)
500 000–999 999 copies/mL	17 (4)	35 (8)	23 (5)	28 (6)	103 (6)
>999 999 copies/mL	22 (5)	22 (5)	27 (6)	17 (4)	88 (5)
Median CD4 count (Q1–Q3), × *10^9 cells/L*†§	0.225 (0.103–0.324)	0.236 (0.072–0.346)	0.234 (0.103–0.334)	0.224 (0.087–0.327)	0.230 (0.090–0.334)
CD4 count, *n (%)*					
0–0.049 × 10^9 cells/L	82 (18)	94 (20)	81 (17)	82 (18)	339 (18)
0.050–0.099 × 10^9 cells/L	31 (7)	43 (9)	32 (7)	44 (9)	150 (8)
0.100–0.199 × 10^9 cells/L	87 (19)	72 (16)	78 (17)	74 (16)	311 (17)
0.200–0.349 × 10^9 cells/L	170 (37)	142 (31)	171 (37)	173 (37)	656 (35)
0.350–0.499 × 10^9 cells/L	73 (16)	79 (17)	70 (15)	71 (15)	293 (16)

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine		Total (*n* = 1857)
	Efavirenz (*n* = 465)	Atazanavir + Ritonavir (*n* = 463)	Efavirenz (*n* = 464)	Atazanavir + Ritonavir (*n* = 465)	
>0.499 × 10^9 cells/L	22 (5)	33 (7)	31 (7)	21 (5)	107 (6)
Hepatitis B surface antigen, *n (%)*[†]					
Positive	9 (2)	6 (1)	12 (3)	8 (2)	35 (2)
Negative	455 (98)	453 (99)	452 (97)	454 (98)	1814 (98)
Hepatitis C antibody, *n (%)*[†]					
Positive	27 (6)	33 (7)	41 (9)	31 (7)	132 (7)
Negative	437 (94)	426 (93)	419 (91)	427 (93)	1709 (93)
Indeterminate	1 (<1)	0 (0)	2 (<1)	2 (<1)	5 (<1)
Genotype before entry, *n (%)*	202 (43)	221 (48)	219 (47)	188 (40)	830 (45)
Reported history of AIDS, *n (%)*	88 (19)	84 (18)	71 (15)	69 (15)	312 (17)

Q = quartile.

[*] Race or ethnicity was self-reported.

[†] Missing values for race or ethnicity (*n* = 5), $CD4^+$ cell count (*n* = 1), hepatitis B surface antigen (*n* = 8), and hepatitis C antibody (*n* = 11).

[‡] Baseline HIV-1 RNA level is calculated as the geometric mean of preentry and entry values.

[§] Baseline CD4 cell count is calculated as the mean of preentry and entry values.

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Table 2

Summary of Primary End Points at Baseline, 96 Weeks, and Full Follow-up, With Efavirenz as the Reference in All Comparisons

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir + Ritonavir	Efavirenz	Atazanavir + Ritonavir
Time to virologic failure [*]				
Baseline				
Persons at risk, *n*	465	463	464	465
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)* [†]	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*	1.9 (−2.9 to 6.8)		0.8 (−3.3 to 4.9)	
Full follow-up				
Events/total person-years at risk, *n/n*	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI) [‡]	1.13 (0.82 to 1.56)		1.01 (0.70 to 1.46)	
Time to primary safety end point [§]				
Baseline				
Persons at risk, *n*	461	462	461	464
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)* [†]	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*; *P* value	−6.2 (−12.9 to 0.4); 0.066		−2.5 (−8.6 to 3.7); 0.43	
Full follow-up				
Events/total person-years at risk, *n/n*	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI) [‡]; *P* value [‖]	0.81 (0.66 to 1.00); 0.048		0.91 (0.72 to 1.15); 0.44	
Time to primary tolerability end point [¶]				
Baseline				
Persons at risk, *n*	461	462	461	464
96 wk				
Events/persons at risk (Kaplan–Meier estimate), *n/n (%)* [†]	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), *percentage points*; *P* value	−9.8 (−15.6 to −4.0); 0.001		−3.8 (−9.2 to 1.6); 0.170	
Full follow-up				
Events/total person-years at risk, *n/n*	186/943.7	142/1052.6	142/1032.1	126/1088.5

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir + Ritonavir	Efavirenz	Atazanavir + Ritonavir
Estimated HR (95% CI)[‡]; *P* value[‖]	0.69 (0.56 to 0.86); <0.001		0.84 (0.66 to 1.07); 0.166	

DF = disoproxil fumarate; HR = hazard ratio.

[*] All participants were analyzed as randomly assigned, and follow-up was included regardless of treatment status.

[†] Kaplan–Meier estimates are presented as cumulative probabilities of having the event by the given week.

[‡] HRs were estimated with Cox proportional hazards models and stratified by screening viral load strata for overall comparisons.

[§] First grade-3 or -4 sign, symptom, or laboratory abnormality while receiving the originally assigned third drug (atazanavir + ritonavir or efavirenz) that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase.

[‖] *P* value from a log-rank test stratified by screening viral load.

[¶] First change in therapy, ignoring nucleoside reverse transcriptase inhibitors.

Table 3

Selected Safety Events, Median Change in Lipid Levels, and Median Change in Calculated Creatinine Clearance

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine		Total (*n* = 1848)
	Efavirenz (*n* = 461)	Atazanavir + Ritonavir (*n* = 462)	Efavirenz (*n* = 461)	Atazanavir + Ritonavir (*n* = 464)	
Death, *n* [*]	11	8	6	6	31
Prematurely discontinued follow-up, *n* [*]					
Severe debilitation	4	4	0	6	14
Unable to get to clinic	42	40	33	31	146
Prematurely modified third drug, *n*					
Toxicity or clinical event	60	40	42	33	175
Selected primary safety end point event, *n* (%) [†]					
Overall	187 (41)	170 (37)	147 (32)	141 (30)	645 (35)
Grade 3	167 (36)	149 (32)	126 (27)	128 (28)	570 (31)
Grade 4	20 (4)	21 (5)	21 (5)	13 (3)	75 (4)
Metabolic[‡]	55 (12)	49 (11)	25 (5)	26 (6)	155 (8)
Fasting total cholesterol level	21	11	7	2	41
Fasting LDL cholesterol level	29	14	15	7	65
Fasting triglycerides level	17	16	5	7	45
Blood glucose level	4	7	2	4	17
Gastrointestinal[‡]	23 (5)	38 (8)	22 (5)	25 (5)	108 (6)
AST	6	14	6	6	32
ALT	5	13	9	5	32

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	Efavirenz (*n* = 461)	Atazanavir + Ritonavir (*n* = 462)	Efavirenz (*n* = 461)	Atazanavir + Ritonavir (*n* = 464)	
Diarrhea or loose stools	11	7	6	6	30
Nausea, vomiting, or both	5	8	2	3	18
Neuropsychological‡	28 (6)	14 (3)	28 (6)	10 (2)	80 (4)
Depression	6	4	13	5	28
Dizzy or lightheaded	6	0	2	2	10
Insomnia, dreams, or sleep	6	0	5	0	11
General‡	71 (15)	64 (14)	46 (10)	59 (13)	240 (13)
Ache, pain, or discomfort	25	35	23	21	104
Fever	10	16	4	12	42
Asthenia, fatigue, or malaise	8	5	7	8	28
Headache	10	7	3	6	26
Rash or allergic rash	9	3	4	6	22

	Week		Week		Week		Week	
	48	96	48	96	48	96	48	96
Change in fasting lipid levels								
Persons assigned third drug, *n*	349	285	388	331	378	324	405	344
With missing data//	12	16	12	14	16	16	13	8
With nonfasting data	47	44	50	52	62	48	66	57
With fasting data¶	290	225	326	265	300	260	326	279

	Week		Week		Week		Week		
	48	**96**	**48**	**96**	**48**	**96**	**48**	**96**	
Median change from baseline, *mg/dL* (*P* value)[§]									
Total cholesterol level	40	39	29 (<0.001)	27 (0.002)	22	26	10 (<0.001)	13 (<0.001)	
LDL cholesterol level	20.5	19	13 (<0.001)	13 (0.006)	10	12	2 (0.002)	7 (0.026)	NA
HDL cholesterol level	12	13	8 (<0.001)	7 (<0.001)	8	9	4.8 (<0.001)	4 (<0.001)	NA
Triglyceride level	15	15	24 (0.070)	33 (0.005)	13	13	14 (0.26)	11 (0.77)	NA
Total–HDL cholesterol ratio	−0.2	−0.3	−0.2 (0.29)	0 (0.030)	−0.3	−0.3	−0.1 (0.022)	−0.1 (0.015)	NA
Change in calculated creatinine clearance									
Persons assigned third drug, *n*	348	303	386	347	376	341	406	363	
With missing data	10	16	9	17	16	14	12	11	
With available data	338	287	377	330	360	327	394	352	
Median change from baseline, *mL/min* (*P* value)[§]	4.3	7.8	3.1 (0.174)	6.1 (0.33)	4.1	4.9	−0.9 (0.001)	−2.6 (<0.001)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DF = disoproxil fumarate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable.

[*] Of the 1857 randomly assigned patients.

[†] Events that triggered a primary safety end point (first grade-3 or -4 sign, symptom, or laboratory abnormality while patients were receiving the originally assigned third drug [atazanavir + ritonavir or efavirenz] that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase). Only major categories in which ≥3% of patients experienced events in any study group are listed, along with the frequency of variables within each major category limited to those that occurred in >5 individuals in any study group. Because categories in which few events occurred are not included, the numbers do not add up to the total.

[‡] Major categories represent the number with ≥1 event in any of the subcategories. In contrast, the numbers in the subcategories represent the number with the specified grade-3 or -4 laboratory abnormality that triggered a safety event, recognizing that a single individual can have >1 of these at the time the safety end point was triggered.

[§] *P* values compare atazanavir + ritonavir with efavirenz when combined with either abacavir–lamivudine or tenofovir DF–emtricitabine at 48 and 96 wk. To convert total, LDL, and HDL cholesterol levels to mmol/L, multiply by 0.0259; to convert triglyceride levels, multiply by 0.0113.

[‖] Patients were considered to have missing data if no value was available within the time window for analysis and the patient received the third drug throughout the time window.

[¶] For patients with available data. For lipids, the sample size noted is for fasting total cholesterol level; other measures had 1 to 7 fewer observations, except for LDL cholesterol level, for which there were 13 to 26 fewer observations owing to the inability to derive calculated values from patients with high fasting triglyceride levels.

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