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Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy

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Abstract

BACKGROUND—The use of fixed-dose combination nucleoside reverse-transcriptase inhibitors (NRTIs) with a nonnucleoside reverse-transcriptase inhibitor or a ritonavir-boosted protease inhibitor is recommended as initial therapy in patients with human immunodeficiency virus type 1 (HIV-1) infection, but which NRTI combination has greater efficacy and safety is not known.

METHODS—In a randomized, blinded equivalence study involving 1858 eligible patients, we compared four once-daily anti retroviral regimens as initial therapy for HIV-1 infection: abacavir–lamivudine or tenofovir disoproxil fumarate (DF)–emtricitabine plus efavirenz or ritonavir-boosted atazanavir. The primary efficacy end point was the time from randomization to virologic failure (defined as a confirmed HIV-1 RNA level ≥1000 copies per milliliter at or after 16 weeks and before 24 weeks, or ≥200 copies per milliliter at or after 24 weeks).

RESULTS—A scheduled interim review by an independent data and safety monitoring board showed significant differences in virologic efficacy, according to the NRTI combination, among patients with screening HIV-1 RNA levels of 100,000 copies per milliliter or more. At a median follow-up of 60 weeks, among the 797 patients with screening HIV-1 RNA levels of 100,000 copies per milliliter or more, the time to virologic failure was significantly shorter in the abacavir–

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lamivudine group than in the tenofovir DF–emtricitabine group (hazard ratio, 2.33; 95% confidence interval, 1.46 to 3.72; P<0.001), with 57 virologic failures (14%) in the abacavir–lamivudine group versus 26 (7%) in the tenofovir DF–emtricitabine group. The time to the first adverse event was also shorter in the abacavir–lamivudine group (P<0.001). There was no significant difference between the study groups in the change from the baseline CD4 cell count at week 48.

CONCLUSIONS—In patients with screening HIV-1 RNA levels of 100,000 copies per milliliter or more, the times to virologic failure and the first adverse event were both significantly shorter in patients randomly assigned to abacavir–lamivudine than in those assigned to tenofovir DF–emtricitabine. (ClinicalTrials.gov number, NCT00118898.)

Treatment guidelines for initial therapy for human immunodeficiency virus type 1 (HIV-1) infection recommend the use of two nucleoside reverse-transcriptase inhibitors (NRTIs) with a nonnucleoside reverse-transcriptase inhibitor or a ritonavir-boosted protease inhibitor.[1,2] The NRTIs abacavir–lamivudine and tenofovir disoproxil fumarate (DF)–emtricitabine can be given once daily, provide potent antiviral activity, and are infrequently associated with mitochondrial toxic effects, lipoatrophy, or neuropathy.[3-5]

We conducted a multicenter, randomized, blinded equivalence study comparing the antiviral activity, safety, and tolerability of abacavir–lamivudine and tenofovir DF–emtricitabine given with efavirenz or ritonavir-boosted atazanavir. After a scheduled interim review, the data and safety monitoring board of the National Institute of Allergy and Infectious Diseases noted the inferior virologic efficacy of abacavir–lamivudine among participants with a screening HIV-1 RNA level of 100,000 copies per milliliter or more. We report here on the data released as a consequence of this review by the data and safety monitoring board.

METHODS

STUDY PATIENTS

The study population included HIV-1–infected patients who were at least 16 years of age, who had received at most 7 days of antiretroviral therapy previously, and who had acceptable laboratory values. Further details about the entry criteria are described in the study protocol (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The human subjects committee at each participating center approved the study protocol, and written informed consent was obtained from all participants in compliance with the human experimentation guidelines of the U.S. Department of Health and Human Services.

STUDY DESIGN

The AIDS Clinical Trials Group Study A5202 is an ongoing phase 3B, randomized, partially blinded study comparing four antiretroviral regimens for the initial treatment of HIV-1 infection. The planned study duration was 96 weeks after enrollment of the last patient. Baseline evaluations included a medical history, physical examination, CD4 cell count, and HIV-1 RNA level. At screening, a genotypic resistance test was required in patients with recent HIV-1 acquisition. Testing for the HLA-B*5701 allele was permitted but not required. Patients were randomly assigned to receive one of four oral once-daily regimens: 600 mg of efavirenz (Sustiva, Bristol-Myers Squibb) or 300 mg of atazanavir (Reyataz, Bristol-Myers Squibb) plus 100 mg of ritonavir (Norvir, Abbott Laboratories) given with either 600 mg of abacavir plus 300 mg of lamivudine (Epzicom, GlaxoSmithKline) or 300 mg of tenofovir DF plus 200 mg of emtricitabine (Truvada, Gilead Sciences). The study was double-blinded with regard to the NRTIs.

Randomization was stratified according to the screening HIV-1 RNA level obtained before study entry (≥100,000 vs. <100,000 copies per milliliter), with the use of a permuted-block

design with dynamic balancing according to the main institution. Screening of HIV-1 RNA levels was performed at any laboratory certified under the Clinical Laboratory Improvement Amendments. Study evaluations were completed before entry, at entry, at weeks 4, 8, 16, and 24, and every 12 weeks thereafter for the duration of the study in all patients, regardless of any treatment modification. After screening, the level of HIV-1 RNA was measured (Roche Amplicor Monitor assay, version 1.5) at Johns Hopkins University. At the time of protocol-defined virologic failure, geno-typing for drug resistance was performed at Stanford University; the baseline samples obtained from the patients were genotyped retrospectively.

Abbott Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline provided the study medications and had input into the protocol development and review of the manuscript. All the authors participated in the trial design, data analysis, and preparation of the manuscript, and all the authors vouch for the completeness and accuracy of the reported data.

HIV-1 DRUG-RESISTANCE TESTING

Since this is an ongoing study, the data and safety monitoring board recommended a resistance analysis that was restricted to the frequency of major mutations at baseline and at the time of virologic failure; the board also recommended that specific mutations not be disclosed. Major resistance mutations were defined as those listed by the International AIDS Society–USA,[6] as well as L74I and G190C/E/Q/T/V for reverse transcriptase, and L24I, F53L, I54V/A/T/S, and G73C/S/T/A for protease.

STATISTICAL ANALYSIS

The primary efficacy end point was the time from randomization to virologic failure (defined as a confirmed HIV-1 RNA level ≥1000 copies per milliliter at or after 16 weeks and before 24 weeks, or ≥200 copies per milliliter at or after 24 weeks). The primary hypotheses were that for each of the regimens that included ritonavir-boosted atazanavir and efavirenz, abacavir–lamivudine was equivalent to tenofovir DF–emtricitabine, and for each NRTI regimen, ritonavir-boosted atazanavir was equivalent to efavirenz. Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. A planned sample size of 1800 subjects (450 per group) would provide an 89.8% probability of declaring equivalence if two regimens were the same, assuming uniform accrual, exponential virologic failure, and lost-to-follow-up time distributions among the four groups, with event probabilities of 17.46% and 10.00%, respectively, at 48 weeks.

Study conduct and safety data were reviewed yearly by the data and safety monitoring board. Efficacy data were reviewed annually starting with the second review of study data. Early-stopping guidelines for inferiority were prespecified, with a regimen considered to be inferior if the 99.95% two-sided confidence interval for the hazard ratio for virologic failure did not include 1.0.

Analyses of efficacy data followed the intention-to-treat principle and were stratified according to the screening HIV-1 RNA level. Time-to-event distributions were estimated with the use of the Kaplan–Meier method and compared by means of two-sided log-rank tests. Hazard ratios were estimated with the use of Cox proportional-hazards models.

The primary safety end point was the time from the initiation of treatment to the first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than that at baseline, excluding isolated unconjugated hyper-bilirubinemia and elevations in the creatine kinase level, while the patient was receiving the randomly assigned treatment. Adverse events were graded ranging from 1 to 4, with 1 indicating mild events and 4 indicating potentially

life-threatening events, according to a severity scale as adopted in December 2004 by the Division of AIDS at the National Institutes of Health.

The data and safety monitoring board met on January 29, 2008, for the first efficacy review. Protocol prespecified time-to-event distributions were presented overall and within each screening HIV-1 RNA stratum. The data and safety monitoring board noted excess virologic failures in both groups of patients who received regimens containing abacavir–lamivudine; additional requested analyses showed that these excess failures associated with abacavir–lamivudine occurred within the higher screening HIV-1 RNA stratum. When data in the four groups were combined and analyzed as two groups (i.e., the group receiving regimens with abacavir–lamivudine and the group receiving regimens without abacavir–lamivudine), the difference between these two groups was determined to be highly statistically significant. The data and safety monitoring board found the strength and validity of these findings sufficient to warrant stopping the further study of abacavir–lamivudine among participants with a screening HIV-1 RNA level of at least 100,000 copies per milliliter. The board specified that the remainder of the study should continue without change. Further details of board's findings and recommendations are provided in the Supplementary Appendix

On release of these findings from the data and safety monitoring board, the study team completed additional analyses based on a previous analysis plan. Treatment-effect modification was assessed for six prespecified baseline covariates: sex, race or ethnic group, age, HIV-1 RNA level, CD4 cell count, and available or unavailable test results for HIV-1 genotype at screening.

For the safety end point, data were censored at the first discontinuation of a randomly assigned active NRTI. Changes in the CD4 count, fasting lipid level, and calculated creatinine clearance from baseline to week 48 were compared among patients for whom data were available with the use of a Wilcoxon–Mann–Whitney test. The binary end point of an HIV-1 RNA level of less than 50 copies per milliliter was compared at week 48 with the use of a chi-square test. Reported P values are two-sided.

Analyses were performed with the use of SAS software, version 9 (SAS) and with S-Plus software, version 6 (Insightful).

RESULTS

STUDY PATIENTS

A total of 1858 eligible patients were enrolled in the study from September 2005 to November 2007. This analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more. Baseline characteristics of these patients are summarized in Table 1.

FOLLOW-UP OF STUDY PATIENTS

Patients were followed for a period of 0 to 112 weeks, with a median follow-up of 60 weeks (interquartile range, 28 to 84). A total of 718 patients (90%) remained in the study. Follow-up was discontinued in 41 patients assigned to abacavir–lamivudine and in 38 patients assigned to tenofovir DF–emtricitabine, with no significant difference in the distributions of time to discontinuation (P = 0.91). Reasons for study discontinuation and other details of follow-up are summarized in the Supplementary Appendix.

PRIMARY OUTCOME

Protocol-defined virologic failure occurred in 57 patients in the abacavir–lamivudine group and in 26 patients in the tenofovir DF–emtricitabine group. The abacavir–lamivudine group had a significantly shorter time to virologic failure than did the tenofovir DF–emtricitabine group (hazard ratio, 2.33; 99.95% confidence interval [CI], 1.01 to 5.36; 95% CI, 1.46 to 3.72; P<0.001) (Fig. 1A). The estimated probability of remaining free of virologic failure beyond 48 weeks was 0.84 (95% CI, 0.79 to 0.88) in the abacavir–lamivudine group and 0.93 (95% CI, 0.90 to 0.96) in the tenofovir DF–emtricitabine group. Virologic failures were less frequent in the tenofovir DF–emtricitabine group according to the protocol-defined criteria for both early and late virologic failure (Table 2). In a multivariable model adjusted for prespecified baseline factors as main effects, the estimated hazard ratio for virologic failure for abacavir–lamivudine versus tenofovir DF–emtricitabine was 2.08 (95% CI, 1.28 to 3.37).

The relative hazard of virologic failure between the NRTI groups according to the six baseline covariates, calculated by means of univariate analysis, are shown in Figure 2. There were significant treatment interactions with sex (P = 0.04), available or unavailable genotype information at screening (P = 0.02), and baseline CD4 cell count (P = 0.007). Tenofovir DF–emtricitabine treatment was associated with a lower rate of virologic failure than abacavir–lamivudine among men, patients with a screening genotype result, and patients with a lower baseline CD4 cell count. When a multivariable model was fitted with these baseline factors, the differences in the hazard ratios for failure remained significant for male sex (P = 0.05), available genotype information (P = 0.03), and lower CD4 cell count (P = 0.01). Protocol-specified sensitivity analyses in which data for patients with missing samples to confirm virologic failure, those who died, and those who discontinued follow-up were classified as virologic failures showed results that were similar to the results of the primary analysis.

SECONDARY ANALYSES

The first of either virologic failure or NRTI modification occurred in 114 patients in the abacavir–lamivudine group as compared with 68 patients in the tenofovir DF–emtricitabine group (hazard ratio, 1.87; 95% CI, 1.38 to 2.54; P<0.001) (Fig. 1B). Among patients for whom data were available at week 48, a cross-sectional analysis that included patients regardless of their status with respect to previous virologic failure or change in therapy revealed that the HIV-1 RNA level was less than 50 copies per milliliter in 75% of patients (95% CI, 69 to 80) randomly assigned to abacavir–lamivudine and in 80% of patients (95% CI, 74 to 85) randomly assigned to tenofovir DF–emtricitabine (P = 0.20) (Fig. 1C). The proportion of patients with less than 50 HIV-1 RNA copies per milliliter therefore represents the aggregate success of both initial (randomly assigned) and subsequent therapy.

A post hoc analysis was conducted to assess the risk of subsequent virologic failure according to NRTI group among 448 patients with at least two consecutive plasma HIV-1 RNA measurements of less than 50 copies per milliliter during follow-up. In these patients, virologic failure was infrequent (12 failures in the abacavir–lamivudine group and 9 failures in the tenofovir DF–emtricitabine group), with no significant difference between the groups (P = 0.25).

IMMUNOLOGIC OUTCOME

CD4 cell count distributions and the change from baseline were similar in the two groups. At week 48, the median increase from baseline was 194 cells per cubic millimeter (interquartile range, 126 to 305) in the 248 patients assigned to abacavir–lamivudine and 199 cells per cubic millimeter (interquartile range, 129 to 302) in the 248 patients assigned to tenofovir DF–emtricitabine (P = 0.78).

ADVERSE EVENTS

Of the 794 patients who received the assigned therapy, 130 who received abacavir–lamivudine and 78 who received tenofovir DF–emtricitabine had at least one grade 3 or 4 sign, symptom, or laboratory abnormality while receiving their initial regimen that was at least one grade higher than the baseline value. Overall, 24 patients in the abacavir–lamivudine group and 13 patients in the tenofovir DF–emtricitabine group had a grade 4 event. The time to the safety end point was significantly shorter for abacavir–lamivudine than for tenofovir DF–emtricitabine (hazard ratio, 1.89; 95% CI, 1.43 to 2.50; P<0.001) (Fig. 3).

Selected events that occurred in at least 5% of patients in each group are listed in Table 3; more adverse events occurred in the abacavir–lamivudine group than in the tenofovir DF–emtricitabine group. At week 48, fasting lipid levels had increased more in the patients who received abacavir–lamivudine than in the patients who received tenofovir DF–emtricitabine (median change in total cholesterol level: 34 vs. 26 mg per deciliter, P<0.001; high-density lipo-protein [HDL] cholesterol level: 9 vs. 7 mg per deciliter, P = 0.05; and triglyceride level: 25 vs. 3 mg per deciliter, P = 0.001). There was no significant difference between groups in the change in the ratio of total cholesterol to HDL cholesterol (median, −0.2 for both groups; P = 0.50).

Suspected study drug–related hypersensitivity occurred in 27 patients (7%) in each group. One patient who discontinued therapy because of a clinical syndrome not thought to be drug hypersensitivity died of a likely hypersensitivity reaction after restarting abacavir-containing study medication. Subsequent virologic failure among patients with suspected drug hypersensitivity occurred in four patients in the abacavir–lamivudine group and three patients in the tenofovir DF–emtricitabine group.

SELECTED CLINICAL AND LABORATORY EVENTS

AIDS events occurred in 26 patients assigned to abacavir–lamivudine (7%) and 17 patients assigned to tenofovir DF–emtricitabine (4%). HIV-related cancers occurred in 12 patients (8 who received abacavir–lamivudine and 4 who received tenofovir DF–emtricitabine). Bone fractures occurred in 7 patients who received abacavir–lamivudine and 10 patients who received tenofovir DF–emtricitabine. There were no myocardial infarctions. Two cases of renal failure occurred in each group. At week 48, the median change from baseline in the calculated creatinine clearance among patients assigned to NRTIs was 4 ml per minute (interquartile range, −7 to 16) in the 212 patients receiving abacavir–lamivudine and 2 ml per minute (interquartile range, −11 to 16) in the 241 patients receiving tenofovir DF–emtricitabine for whom data were available (P = 0.10).

HIV-1 DRUG RESISTANCE

Of the 83 patients with protocol-defined virologic failure, 2 randomly assigned to abacavir–lamivudine were excluded because of a wide genetic distance on neighbor-joining tree analysis between the viruses present at baseline and at the time of virologic failure, possibly consistent with sample contamination. Among the 81 patients with resistance data that could be evaluated, major reverse-transcriptase or protease resistance mutations at baseline were detected in 5 patients randomly assigned to abacavir–lamivudine and 4 randomly assigned to tenofovir DF–emtricitabine. Emergence of major drug-resistance mutations was noted in 25 patients in the abacavir–lamivudine group (6% of those randomly assigned to the group and 45% of group members with virologic failure) and in 10 patients in the tenofovir DF–emtricitabine group (3% and 38%, respectively). Among the 35 patients with the emergence of new major resistance mutations at the time of virologic failure, 3 in each group had other major mutations at baseline.

DISCUSSION

In this prospective, randomized, double-blind study of the initial treatment of HIV-1 infection, patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more were significantly less likely to have virologic failure if they were assigned to tenofovir DF–emtricitabine than if they were assigned to abacavir–lamivudine. The difference in virologic response between these two NRTI strategies prompted an independent data and safety monitoring board to recommend unblinding of the NRTI treatment assignments in patients in the high HIV-1 RNA stratum. This difference in virologic outcome favoring tenofovir DF–emtricitabine over abacavir–lamivudine was observed throughout the duration of the study and in multiple sensitivity analyses. The time to the primary safety end point was also significantly shorter among patients receiving abacavir–lamivudine than among those receiving tenofovir DF–emtricitabine.

One possible explanation for the results in the high screening HIV-1 RNA stratum is that abacavir–lamivudine is less potent than tenofovir DF–emtricitabine. Treatment of patients with high HIV-1 RNA levels may reveal differences between regimens that otherwise may not be seen when those with lower HIV-1 RNA levels receive treatment.[7-9] A detectable difference according to stage of disease is supported by our finding that the difference in virologic failure between the NRTI strategies significantly increased with a lower CD4 count.

The outcomes do not appear to be related to differences in baseline characteristics, since the study groups were well matched overall. Although there were minor imbalances between groups, the differences in virologic failure persisted after adjustment for multiple baseline covariates. The occurrence of suspected hypersensitivity reactions also did not appear to influence study outcomes: equal numbers of patients in both groups had suspected drug hypersensitivity, and virologic failure in these patients was infrequent. Other potential explanations for the study results include differences in the pharmacokinetics of the individual drugs,[10] in the types of emerging drug-resistance mutations at virologic failure, and in the influence of these mutations on the antiviral activity of the individual drugs.[11]

Smith et al. found that abacavir–lamivudine was virologically noninferior to tenofovir DF–emtricitabine when combined with lopinavir–ritonavir for the primary end point of an HIV-1 RNA level of less than 50 copies per milliliter at 48 weeks (missing values were counted as virologic failures), with similar results at 96 weeks of follow-up.[12] Differences between our study and the study by Smith et al. include baseline characteristics, definitions of study end points, and the third drug in the treatment regimen. Another notable difference is that 22% of patients in the study by Smith et al. discontinued the trial prematurely; the values for these patients were counted as virologic failures in the analysis of the primary efficacy end point at week 48, although the HIV-1 RNA levels in these patients at week 48 were not known.

Abacavir–lamivudine was also associated with a shorter time to grade 3 or 4 adverse events than tenofovir DF–emtricitabine. Increases from baseline fasting lipids were significantly higher among patients who received abacavir–lamivudine than among patients who received tenofovir DF–emtricitabine, although the ratio of total cholesterol to HDL cholesterol did not differ significantly between the groups. This differential effect on lipids has been reported in studies comparing abacavir with tenofovir DF both in patients who had previously received treatment and those who had not.[12-14]

An unavoidable limitation of our analysis is that, with only the NRTI comparison in the high HIV-1 RNA stratum stopped, we cannot fully describe resistance data or the effect of the third drug (ritonavir-boosted atazanavir or efavirenz) on the outcome of NRTI treatment. In addition, in combining the four treatment groups into two groups on the basis of the recommendations

of the data and safety monitoring board, we are reporting a protocol-specified secondary analysis.

Nonetheless, the results of this double-blind, randomized, prospective study have important implications for clinical practice. Although treatment-success rates were high for both NRTI groups, patients in this study with high HIV-1 RNA levels who were randomly assigned to abacavir–lamivudine were more than twice as likely to have virologic failure as those who received tenofovir DF–emtricitabine. On the basis of this result, several treatment guidelines currently recommend that the data from our study be considered in selecting NRTIs for patients with high HIV-1 RNA levels who have not received antiretroviral treatment.[1,2,15]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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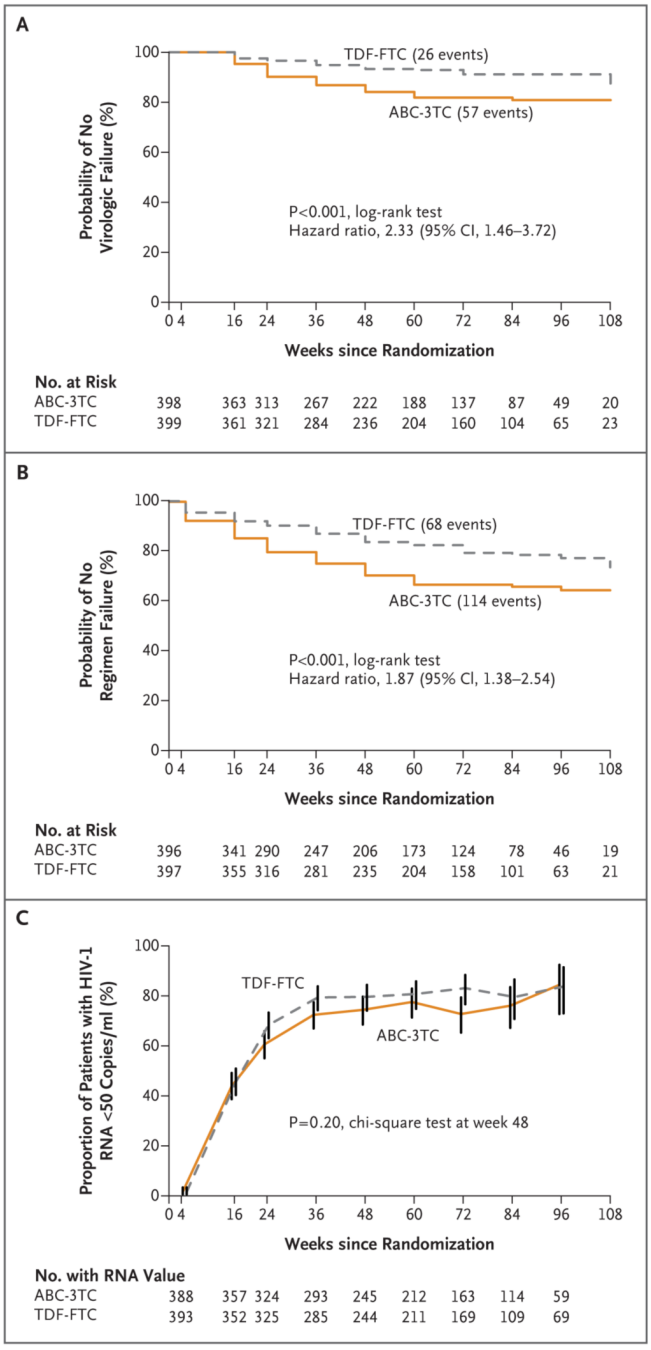

Figure 1. Time to Virologic Failure, Time to Regimen Failure, and Proportion of Patients with HIV-1 RNA of Less Than 50 Copies per Milliliter

Panel A shows the time to protocol-defined virologic failure, and Panel B shows the time to the first occurrence of either virologic failure or modification of a nucleoside reverse-transcriptase inhibitor (NRTI). Panel C shows the proportions of patients with an HIV-1 RNA level below 50 copies per milliliter in an analysis involving patients with available data, regardless of whether they had previously discontinued their assigned NRTI or had virologic failure. The vertical bars denote 95% binomial confidence intervals at each study week. All three analyses were restricted to patients with a screening HIV-1 RNA level of 100,000 copies

per milliliter or more and compared abacavir–lamivudine (ABC-3TC) with tenofovir DF–emtricitabine (TDF-FTC), both combined with efavirenz or with ritonavir-boosted atazanavir.

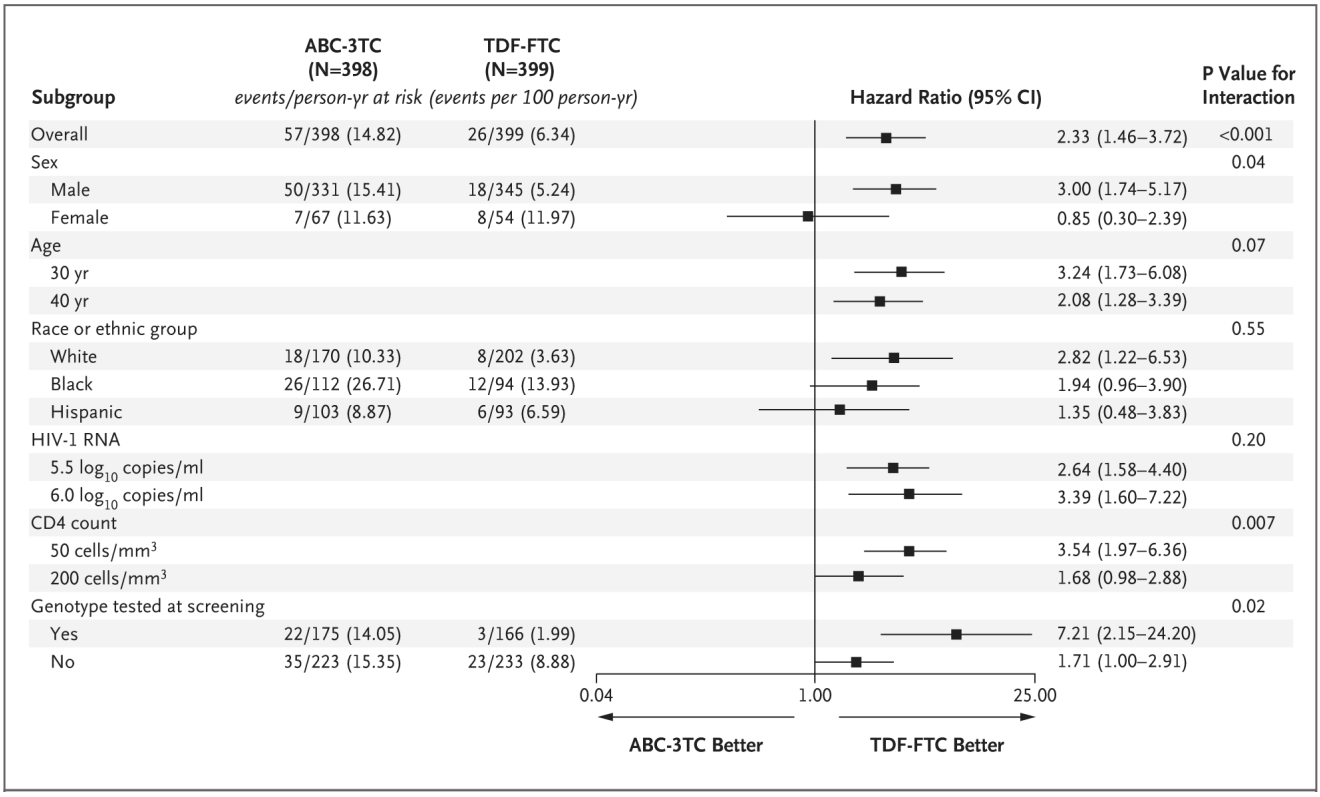

Figure 2. Estimated Effect of Abacavir–Lamivudine (ABC-3TC) versus Tenofovir DF–Emtricitabine (TDF-FTC) on the Hazard of Virologic Failure, According to Baseline Characteristics

In the univariate analysis, modeling for treatment-effect modification used the continuous form for age, CD4 cell count, and HIV-1 RNA level. Estimated treatment effects are shown as example values for these continuous variables. Multivariate analysis showed similar results.

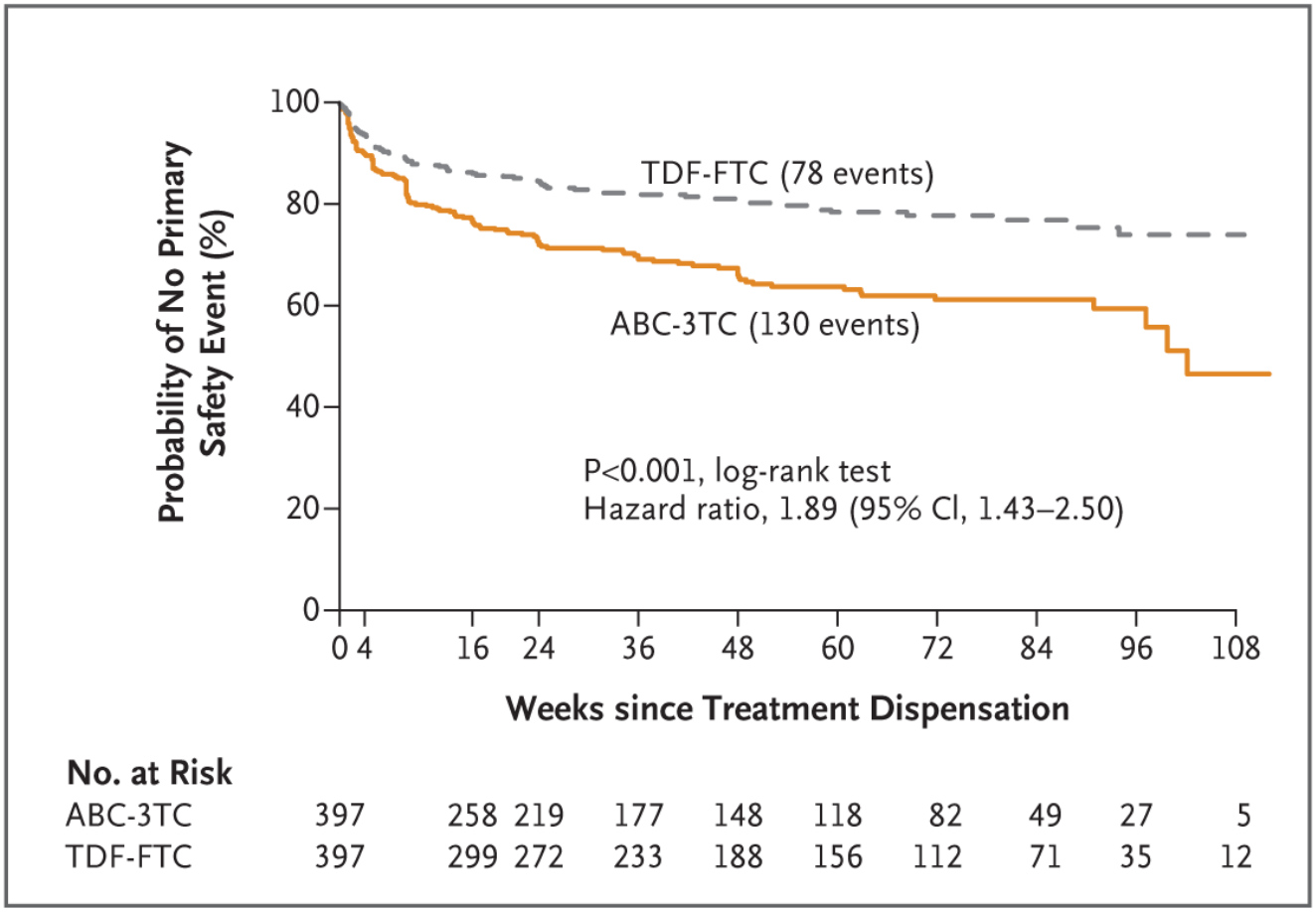

Figure 3. Time to Safety End Point

Shown is the probability of not having a first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than the grade at baseline (excluding hyperbilirubinemia and elevation in the creatine kinase level) among patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more who were initially assigned to a regimen containing either abacavir–lamivudine (ABC-3TC) or tenofovir DF–emtricitabine (TDF-FTC). This was an as-treated analysis involving patients receiving the randomly assigned nucleoside reverse-transcriptase inhibitor regimen.

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Table 1

Baseline Characteristics of the Patients.*

Variable	Abacavir–Lamivudine (N = 398)	Tenofovir DF–Emtricitabine (N = 399)	Total (N = 797)
Sex — no. (%)			
Male	331(83)	345(86)	676 (85)
Female	67 (17)	54 (14)	121 (15)
Age — yr			
Median	38	40	39
Interquartile range	32–45	32–46	32–45
Age group — no. (%)			
16–19 yr	3 (1)	2 (1)	5 (1)
20–29 yr	77 (19)	68 (17)	145 (18)
30–39 yr	143 (36)	121 (30)	264 (33)
40–49 yr	121 (30)	142 (36)	263 (33)
50–59 yr	41 (10)	54 (14)	95 (12)
>59 yr	13 (3)	12 (3)	25 (3)
Race or ethnic group — no. (%)†‡			
White	170 (43)	202 (51)	372 (47)
Black	112 (28)	94 (24)	206 (26)
Hispanic	103 (26)	93 (23)	196 (25)
Asian or Pacific Islander	5 (1)	5 (1)	10 (1)
Native American or Alaskan Native	1 (<1)	1 (<1)	2 (<1)
Mixed race	7 (2)	3 (1)	10 (1)
HIV-1 RNA — $\log_{10}$ copies/ml‡§			
Median	5.0	5.0	5.0
Interquartile range	4.7–5.6	4.7–5.6	4.7–5.6
HIV-1 RNA level — no. (%)			
<1000 copies/ml	0	1 (<1)	1 (<1)
1000–9999 copies/ml	4 (1)	4 (1)	8 (1)
10,000–49,999 copies/ml	81 (20)	87 (22)	168 (21)
50,000–99,999 copies/ml	118 (30)	107 (27)	225 (28)

Variable	Abacavir–Lamivudine (N = 398)	Tenofovir DF–Emtricitabine (N = 399)	Total (N = 797)
100,000–249,999 copies/ml	77 (19)	75 (19)	152 (19)
250,000–499,999 copies/ml	36 (9)	39 (10)	75 (9)
500,000–999,999 copies/ml	41 (10)	46 (12)	87 (11)
>999,999 copies/ml	41 (10)	39 (10)	80 (10)
CD4 count — cells/mm^3[¶]			
Median	138	146	145
Interquartile range	36–282	45–294	41–285
CD4 count — no. (%)			
0–49 cells/mm^3	123 (31)	113 (28)	236 (30)
50–99 cells/mm^3	42 (11)	48 (12)	90 (11)
100–199 cells/mm^3	79 (20)	69 (17)	148 (19)
200–349 cells/mm^3	97 (24)	113 (28)	210 (26)
350–499 cells/mm^3	37 (9)	40 (10)	77 (10)
>499 cells/mm^3	20 (5)	16 (4)	36 (5)
Hepatitis B or C — no. (%)[‡//]	34 (9)	30 (8)	64 (8)
Genotype tested at screening — no. (%)[**]	175 (44)	166 (42)	341 (43)
Reported history of AIDS — no. (%)	102 (26)	87 (22)	189 (24)

[*] AIDS denotes acquired immunodeficiency syndrome.

[†] Race or ethnic group was self-reported.

[‡] There were missing values for 1 patient in the race or ethnic group category and the baseline RNA level category and for 18 patients in the hepatitis category.

[§] The baseline HIV-1 RNA level was calculated as the geometric mean of two measurements, one obtained before study entry and one at entry.

[¶] The baseline CD4 cell count was calculated as the mean of two measurements obtained at visits before study entry and at entry.

[//] The presence of hepatitis B or C was determined by the identification of hepatitis B surface antigen with or without DNA positivity or hepatitis C antibodies with or without RNA positivity.

[**] A total of 11% of study subjects underwent genotyping as mandated by the protocol, since HIV infection was recently acquired; in 32%, the strategy of obtaining the genotype at screening was the standard of care at that study site for patients who had not received treatment; 57% did not undergo genotype resistance testing.

Table 2

Timing of Virologic Failure According to Treatment Group.

Virologic Failure	Abacavir–Lamivudine (N = 57)	Tenofovir DF–Emtricitabine (N = 26)
		no. of patients
≥1000 copies/ml at 16 to <24 wk without previous level of <200 copies/ml	19	9
≥200 copies/ml at ≥24 wk without previous level of <200 copies/ml	9	2
≥200 copies/ml at ≥24 wk with previous level of <200 copies/ml	29	15

Table 3

Laboratory Abnormalities and Clinical Signs and Symptoms.*

Variable	Abacavir–Lamivudine (N = 397)	Tenofovir DF–Emtricitabine (N = 397)
Any laboratory abnormality or clinical adverse event — no. (%)	130 (33)	78 (20)
Selected laboratory abnormalities		
Metabolic — no. (%)	41 (10)	11 (3)
Triglycerides — no.	15	3
Cholesterol — no.		
Total	20	2
LDL (calculated)	13	4
ALT — no.	7	5
AST — no.	12	4
Selected signs and symptoms		
Diarrhea or loose stool — no.	7	7
Nausea or vomiting — no.	3	3
General signs or symptoms — no. (%)	58 (15)	38 (10)
Pain or discomfort — no.	24	14
Rash — no.	8	8
Pruritus — no.	9	2
Fever — no.	10	8
Asthenia — no.	6	10
Headache — no.	8	6

* This table includes all patients with at least one grade 3 or 4 sign, symptom, or laboratory abnormality during the initial regimen that was at least one grade higher than the grade at baseline. Selected individual adverse events occurring in 5% or more of patients in either study group during the initial treatment with the assigned nucleoside reverse-transcriptase inhibitors are shown. The numbers within major categories do not necessarily sum to the total of the major category because they are selected. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and LDL low-density lipoprotein.