

# Simplification of Antiretroviral Therapy to a Single-Tablet Regimen Consisting of Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate Versus Unmodified Antiretroviral Therapy in Virologically Suppressed HIV-1–Infected Patients

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**Objective:** To evaluate a simplification strategy for HIV-1–infected patients virologically suppressed on antiretroviral therapy (ART) by switching to a single-tablet regimen consisting of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF).

**Design:** Prospective, randomized, controlled, open-label, multicenter study.

**Methods:** Patients on stable ART with HIV-1 RNA <200 copies per milliliter for  $\geq 3$  months were stratified by prior nonnucleoside reverse transcriptase inhibitor–based or protease inhibitor–based therapy and randomized (2:1) to simplify treatment to EFV/FTC/TDF or to stay on their baseline regimen (SBR). Efficacy and safety assessments were performed at baseline and at weeks 4, 12, 24, 36, and 48. Additional patient-reported outcomes included the following: adherence by visual analog scale, quality of life by SF-36 (v2) survey, HIV Symptom Index, and the Preference of Medication and Perceived Ease of the Regimen for Condition questionnaires.

**Results:** Three hundred patients (EFV/FTC/TDF 203, SBR 97) were evaluated (prior protease inhibitor–based ART, 53%; non-nucleoside reverse transcriptase inhibitor–based ART, 47%). The arms were well balanced at baseline with 88% males, 29% blacks, and a mean age of 43 years; CD4 was 540 cells per cubic millimeter, 96% had HIV-1 RNA <50 copies per milliliter, and 88% were on their first ART regimen. Through 48 weeks, 89% vs. 88% in the EFV/FTC/TDF vs. SBR arms, respectively, maintained HIV-1 RNA <200 copies per milliliter by time to loss of virologic response algorithm (intent to treat, noncompleters = failures) with the difference (95%

confidence interval) between arms of 1.1% (–6.7% to 8.8%), indicating noninferiority of EFV/FTC/TDF vs. SBR. Similarly, maintenance of HIV-1 RNA <50 copies per milliliter by time to loss of virologic response algorithm was 87% vs. 85% for EFV/FTC/TDF vs. SBR, respectively [difference (95% confidence interval) 2.6% (–5.9% to 11.1%)]. Discontinuation rates were similar (EFV/FTC/TDF 11%, SBR 12%); more discontinuations for adverse events occurred in the EFV/FTC/TDF arm vs. SBR (5% vs. 1%), most commonly for nervous system symptoms. More patients withdrew consent in the SBR arm vs. EFV/FTC/TDF (7% vs. 2%). Estimated glomerular filtration rate (by Modification of Diet in Renal Disease) remained unchanged over 48 weeks in both arms (median change <1 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>). A decrease in fasting triglycerides was observed at 48 weeks in the EFV/FTC/TDF vs. SBR arm (–20 vs. –3.0 mg/dL;  $P = 0.035$ ). Adherence of  $\geq 96\%$  was reported by visual analog scale in both arms at baseline and at all study visits.

**Conclusion:** Simplification to EFV/FTC/TDF maintained high and comparable rates of virologic suppression vs. SBR through 48 weeks.

**Key Words:** EFV/FTC/TDF single-tablet regimen, once-daily antiretroviral regimens, treatment simplification

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## INTRODUCTION

Combination antiretroviral therapy (ART) has evolved considerably over the past 12 years leading to better control of HIV replication; preservation of the immune system; and decreased incidence of opportunistic infections, malignancies, and deaths. However, successful ART has been hampered by complicated regimens, high pill burden, drug–drug interactions, and frequent short- and long-term adverse effects, leading to decreased adherence to prescribed regimens. Studies suggest that high adherence rates are necessary to achieve optimal outcomes and to minimize the emergence of HIV drug resistance.<sup>1</sup> Hence, there is a need for simplified regimens that provide a lower pill burden, reduced dosing frequency, and a favorable safety profile.<sup>2</sup>

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The standard of care for treatment of HIV infection involves the use of a combination of antiretroviral drugs from multiple classes. Since October 2004, the Department of Health and Human Services treatment guidelines have recommended use of efavirenz (EFV) with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) as one of the preferred options for nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens in HIV-infected treatment-naive patients (except in pregnancy or women of high pregnancy potential).<sup>3</sup> Approval of a single-tablet regimen containing EFV, FTC, and TDF (EFV/FTC/TDF, Atripla; Bristol Myers Squibb & Gilead Sciences, LLC) has afforded clinicians the opportunity to provide patients with a potent and convenient one-pill once-daily treatment option. The components of EFV/FTC/TDF have demonstrated efficacy and safety in randomized comparative trials in treatment-naive patients,<sup>4,5</sup> and pharmacokinetic studies in healthy volunteers have demonstrated bioequivalence of EFV/FTC/TDF compared with its components administered separately.<sup>6</sup>

In an effort to potentially reduce adverse effects and to improve adherence and/or lower pill burden, attention has been focused on changing the protease inhibitor (PI) component in PI-based antiretroviral regimens in virologically suppressed patients to an NNRTI. Several studies have demonstrated that changing from a PI to an NNRTI, while keeping the nucleoside reverse transcriptase inhibitor (NRTI) backbone unaltered, can be successfully accomplished while maintaining virologic suppression after the switch.<sup>7-9</sup> Virologic suppression has also been successfully maintained in EFV-treated patients who have had their thymidine analogue-containing NRTI backbone switched to a nonthymidine analogue [eg, switching zidovudine (ZDV)/lamivudine (3TC) to FTC/TDF].<sup>10,11</sup> To date, few randomized controlled trials have evaluated the strategy of simplifying an entire treatment regimen in virologically suppressed patients.<sup>12</sup>

The purpose of this study was to evaluate a simplification strategy for HIV-1-infected patients suppressed on ART by switching to a single-tablet regimen consisting of EFV/FTC/TDF. This was a 48-week randomized, prospective, multicenter, open-label study comparing the effectiveness (efficacy, safety, and tolerability) in subjects switched to EFV/FTC/TDF with that of subjects continuing unmodified ART as measured by the proportion of patients who maintain HIV-1 RNA <200 copies per milliliter at week 48 using the time to loss of virologic response (TLOVR) algorithm. Other end points included evaluation of maintenance of HIV-1 RNA <50 copies per milliliter by TLOVR, change from baseline in CD4 cell count, change in estimated glomerular filtration rate (GFR) by calculated creatinine clearance (Cockcroft-Gault method<sup>13</sup>) and the Modification of Diet in Renal Disease (MDRD) method,<sup>14</sup> and change in hemoglobin and lipid profile through 48 weeks. Assessments were also included to evaluate change in HIV Symptom Index, quality of life, medication preference, and adherence.

## METHODS

An institutional review board or ethics committee approved the study protocol and the informed consent form

that was given to each participant. A total of 296 patients were initially targeted for enrollment with equal stratification by the use of PI (including ritonavir-boosted PI) or NNRTI in the treatment regimen. Patients entering the study were randomized (2:1) to either simplify treatment to EFV/FTC/TDF or stay on their baseline regimen (SBR). Entry criteria included male or nonpregnant female patients 18 years or older with adequate renal function defined as having a calculated creatinine clearance  $\geq 60$  mL/min by the Cockcroft-Gault formula.<sup>13</sup> Patients were required to have documented HIV-1 seropositivity and demonstrated maintenance of virologic suppression for at least 3 months on their current regimen defined as having 2 consecutive plasma HIV-1 RNA values <200 copies per milliliter using the Amplicor HIV-1 Monitor test (version 1.5; Roche Diagnostic Systems, Inc, Branchburg, NJ). The initial or "qualifying" HIV-1 RNA value was obtained within 3 months of study entry, and the second or "confirmatory" HIV-1 RNA was performed at screening. For the qualifying HIV-1 RNA determination, a value <200 copies per milliliter if measured by branched chain DNA assay (bDNA, Chiron 3.0) was allowed for entry; however, the confirmatory HIV-1 RNA was performed using the Amplicor HIV-1 Monitor test, v1.5, ultrasensitive assay. Patients were not permitted to have an HIV-1 RNA value  $\geq 200$  copies per milliliter between the qualifying and confirmatory measurements. No CD4 criterion was mandated for entry, and patients were required to have a life expectancy of greater than or equal to 1 year.

Patients were required to be on their first ART regimen or have documented viral suppression on a previous PI-based regimen at the time of prior change in therapy. ART was defined as a PI (with or without ritonavir boosting) plus at least 2 NRTIs or an NNRTI plus at least 2 NRTIs. Patients taking an NNRTI-based regimen consisting of EFV plus TDF and FTC were excluded; however, patients taking EFV plus TDF and 3TC were allowed entry. Patients taking a PI-based regimen, which included TDF and FTC, were allowed to participate. Also excluded were patients who had taken NRTI-only therapy for >7 days before their current therapy, individuals with known hypersensitivity to any of the components of EFV/FTC/TDF, or those known to have resistance to any of the study agents at any time in the past. Patients with a new AIDS-defining condition (with the exception of CD4 criteria) diagnosed within 30 days of baseline, those taking nephrotoxic medications (eg, aminoglycoside antibiotics, intravenous amphotericin B, cidofovir, cisplatin, foscarnet, intravenous pentamidine, and other agents with significant nephrotoxic potential) or agents known to interact with EFV, were also excluded from study participation.

## Efficacy End Points

The primary end point was the maintenance of virologic suppression as defined by proportion of patients with HIV-1 RNA <200 copies per milliliter on their original assigned regimen at 48 weeks based on TLOVR and based on the intent-to-treat (ITT) population, assuming that noncompleters were equal to failures (NC = F). The ITT population was defined as those receiving at least 1 dose of study medication. NCs were defined as the subjects who prematurely discontinued from the

study for any reason. Responders were those who maintained HIV-1 RNA <200 copies per milliliter at week 48 without intervening virologic rebound, which was defined as a confirmed HIV-1 RNA value of  $\geq 200$  copies per milliliter on 2 successive occasions or having the last HIV-1 RNA value to be  $\geq 200$  copies per milliliter, while on study followed by discontinuation. Patients having a screening HIV-1 RNA <200 copies per milliliter but with a baseline value  $\geq 200$  copies per milliliter and who were subsequently found to have HIV-1 RNA <200 copies per milliliter by week 12 without experiencing a confirmed virologic rebound were considered responders. The proportion of patients with HIV-1 RNA <50 copies per milliliter was also assessed at week 48 by TLOVR (ITT, NC = F) in a similar manner to the proportion with HIV-1 RNA <200 copies per milliliter.

Additional efficacy end points included assessments of the proportion of patients with HIV-1 RNA <200 and <50 copies per milliliter (by TLOVR, ITT, NC = F) within each treatment stratum (prior NNRTI and prior PI) and the change from baseline in CD4 cell count. Patients experiencing protocol-defined virologic failure had viral genotypic analysis performed at the time of virologic rebound.

### Clinical and Laboratory Assessments

Evaluations for safety and efficacy were performed at baseline (within 30 days of screening) and at weeks 4, 12, 24, 36, and 48 or at the early study withdrawal visit. Laboratory assessments included determination of CD4 cell count, plasma HIV-1 RNA (Amplicor Monitor test, v1.5, Ultrasensitive), complete blood count with differential analysis and platelet count, serum chemistry profile, and a fasting lipid panel (obtained only at baseline and at weeks 24 and 48). Adverse events (AEs) were mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA; International Federation of Pharmaceutical Manufacturers and Associations, Chantilly, VA), and the incidence of each preferred term event was tabulated. AEs were summarized by grade and the investigator's assessment of relationship to the study drug. AEs and clinically significant laboratory abnormalities were graded according to the Gilead Sciences grading scale for severity of AEs and laboratory abnormalities as previously described.<sup>4,5</sup> AEs were followed up through the end of the study or until the investigator and/or sponsors determined that the subject's condition was stable.

### Outcomes Research Assessments

Assessments at each visit included an HIV Symptom Index questionnaire,<sup>15</sup> a Preference of Medication (POM) questionnaire (included for the EFV/FTC/TDF arm only), assessment of adherence by visual analog scale (VAS),<sup>16</sup> and the Perceived Ease of Regimen for Condition (PERC) survey. The HIV Symptom Index is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment.<sup>15</sup> For each symptom, a 5-point scale was used to score responses; however, for the present study analysis, responses were dichotomized to "no symptom" and "with symptom." The POM questionnaire is a single-item measure that asks patients how the current medicine compares with the previous

antiretroviral medicines prescribed by their doctor. For POM, the response set is as follows: (1) *much better, I prefer this medication*; (2) *slightly better*; (3) *about the same*; (4) *slightly worse*; and (5) *much worse, I much prefer my previous medication*. Because of the stated comparison to the prior regimen, the POM questionnaire was administered only to patients randomized to the EFV/FTC/TDF arm. For the PERC survey, a questionnaire was specifically constructed for this trial, all patients were queried as to how easy they perceived it to be to follow their current HIV medication regimen. Possible responses were scored on a 4-point scale ranging from "very easy" to "very difficult"; however, for purposes of the analysis, responses were dichotomized to either "very easy" or "not very easy." In addition to these measures, quality of life was assessed by the Short Form 36, version 2 (SF-36 v2), at baseline and at weeks 4, 12, 24, and 48.<sup>17</sup>

### Statistical Analysis

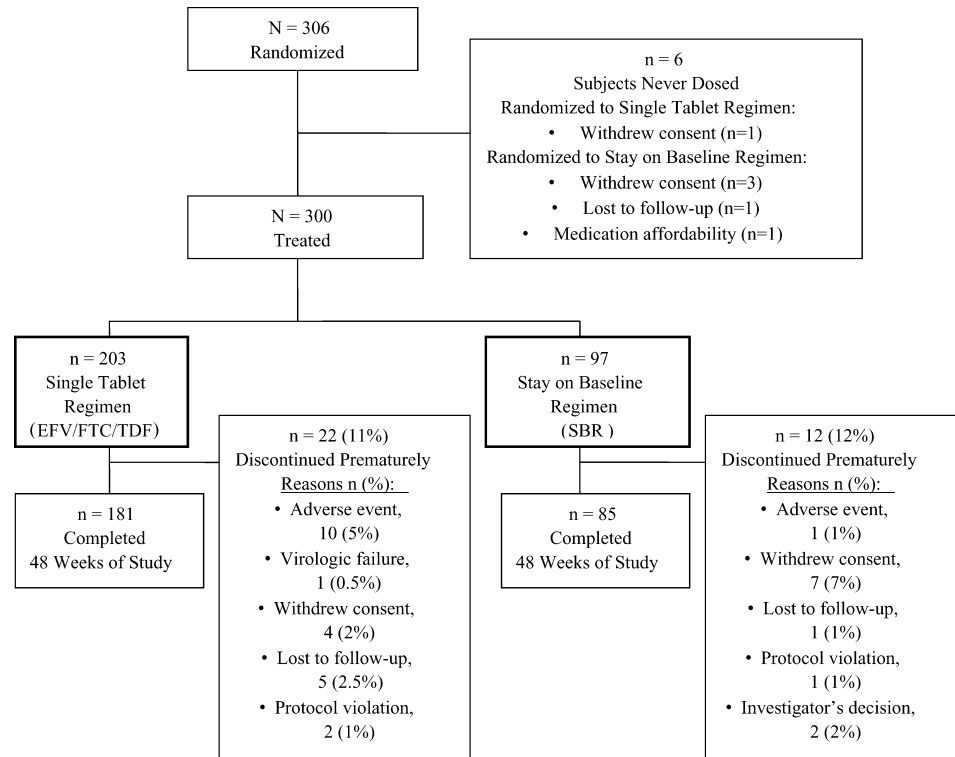
The ITT population included all patients who were randomized and received at least 1 dose of study medication. The safety population included all patients who received at least 1 dose of study medication. Sample size for the study was based on a noninferiority study design and an allocation of patients in a 2:1 ratio for efficacy based on the assumption that greater than 75% of the patients will remain on study and maintain HIV-1 RNA <200 copies per milliliter at 48 weeks after switch. Assuming 80% power, a delta of 15% and using a 2-sided alpha of 0.05, a minimum of 296 patients would be required [198 for arm 1 (EFV/FTC/TDF) and 98 for arm 2 (SBR)].

## RESULTS

### Patient Disposition

A total of 306 subjects were enrolled at 55 study sites in the United States (53 sites) and Puerto Rico (2 sites) from August 2006 through November 2006. Six patients who were never dosed were excluded from analysis (Fig. 1). Five of the 6 patients who were never dosed had been randomized to SBR, 3 of whom withdrew consent, 1 patient could not afford payment for ART, and 1 patient was lost to follow-up. One patient randomized to EFV/FTC/TDF withdrew consent before dosing.

Of 300 patients who received at least 1 dose of study drug, 203 were randomized to receive EFV/FTC/TDF, whereas 97 remained on SBR (Fig. 1). A total of 266 subjects completed the 48-week study; discontinuation rates were similar in the 2 treatment groups (11% in the EFV/FTC/TDF group and 12% in the SBR group). The most common reason for early discontinuation in the EFV/FTC/TDF group was for an AE (10 patients; 5%), whereas the most common reason for premature termination in the SBR group was withdrawal of consent (7 patients; 7%). Of the 10 patients in the EFV/FTC/TDF arm who discontinued for an AE, 5 patients (2%) experienced moderate (grade 2; n = 3 patients) or moderate to severe (grades 2 and 3; n = 2 patients) nervous system symptoms (NSSs) and/or psychiatric symptoms; all were on prior PI-based ART. Two patients discontinued for investigator-defined increase in serum creatinine. Each patient was



**FIGURE 1.** Disposition of patients participating in the study.

discontinued for acute hepatitis, elevated aminotransferase, and acute pancreatitis. The hepatitis and pancreatitis events were considered serious and attributed by the investigator to be study drug related. One patient (0.5%) in the EFV/FTC/TDF arm discontinued prematurely for virologic failure. Of the 7 patients in the SBR group who withdrew consent, the timing varied from 5 to 48 weeks (just before the final visit). Two of these patients received EFV/FTC/TDF after study discontinuation. Of the 4 patients in the EFV/FTC/TDF group who withdrew consent, the timing ranged from 4 days to 24 weeks.

### Demographic and Patient Characteristics

Demographic and other baseline patient characteristics were similar in the 2 treatment arms (Table 1). Subjects were predominantly male (88%) with a median [interquartile range (IQR)] age of 43 (38–48) years; 22% of subjects were 50 years and younger at entry. Whites comprised 68% of subjects; however, nearly one third of patients were black or African American, and 23% reported Hispanic or Latino ethnicity. The most common mode of acquisition of HIV was men who had sex with men.

The majority (96%) of subjects had HIV-1 RNA <50 copies per milliliter, 3% had HIV-1 RNA values between 50 and 200 copies per milliliter, and 2 (both in the EFV/FTC/TDF arm) had HIV-1 RNA  $\geq$ 200 copies per milliliter at baseline (Table 1). The latter 2 subjects had HIV-1 RNA levels <200 copies per milliliter at screening, and both patients had HIV-1 RNA values that subsequently remained <200 copies per milliliter at all post-baseline visits; none experienced virologic failure. Median CD4 cell count was 516 cells per cubic millimeter; less than 10% of subjects had a CD4 cell count

below 200 cells per cubic millimeter at baseline. Fifteen patients were coinfecting with hepatitis B virus or hepatitis C virus at baseline [14 patients (7%) in the EFV/FTC/TDF arm vs. 1 patient (1%) in the SBR arm ( $P = 0.043$ )]. When surveyed at study entry as to the reasons for study participation, 94% of subjects in each group cited simplification of their current regimen. Only 3% and 2% in the EFV/FTC/TDF and SBR groups, respectively, cited intolerability of their current regimen, whereas concern about long-term side effects was cited as a reason by 21% and 13% in the EFV/FTC/TDF and SBR arms, respectively.

### Prior ART

Overall, subjects had been receiving ART for a median of 3 years, and 88% were receiving their first regimen at baseline. Within the PI stratum, only 12 subjects (EFV/FTC/TDF—9 subjects, SBR—3 subjects) had previously received a PI that differed from the PI contained in their baseline regimen. Forty-seven percent of subjects were receiving an NNRTI-based regimen [36% EFV, 11% nevirapine (NVP)], and 53% were on a PI-based regimen [15% ritonavir-boosted atazanavir (ATV/r), 13% lopinavir/ritonavir (LPV/r), 9% ritonavir-boosted fosamprenavir (FPV/r), 7% nelfinavir, and 9% other PIs given alone or boosted with ritonavir]. The most common NNRTI-based regimens were EFV plus ZDV/3TC (16%), abacavir (ABC)/3TC (6%), TDF + 3TC (5%), or didanosine (ddI) + 3TC (3%) and NVP plus ZDV/3TC (4%). For patients in the PI stratum, the most common regimens were ATV/r plus TDF/FTC (13%), LPV/r plus TDF/FTC (6%), FPV/r plus ABC/3TC (4%), nelfinavir plus ZDV/3TC (4%), LPV/r plus ZDV/3TC (3%), or FPV/r plus TDF/FTC (3%).

**TABLE 1.** Baseline Demographics and Treatment Characteristics

Characteristic	EFV/FTC/TDF (n = 203)*	SBR (n = 97)†	Total (N = 300)
Male sex (%)	89	86	88
Age, median (IQR), yrs	43 (37–47)	43 (38–50)	43 (38–48)
Race (%)			
White	69	66	68
African American	28	31	29
Other	3	3	3
Ethnic origin (%)			
Hispanic/Latino	23	25	23
HIV risk factor (%)			
Men having sex with men	80	77	79
Heterosexual contact	16	21	17
HIV-1 RNA (copies/mL), %			
<50	96	98	96
50 to <200	3	2	3
≥200	1	0	<1
CD4 cell count, median (IQR), cells/mm <sup>3</sup>	517 (367–670)	515 (377–649)	516 (367–654)
CD4 ≤ 200 cells/mm <sup>3</sup> (%)	6	13	9
Duration of current ART, median (IQR), yrs	2.6 (1.3–4.9)	3.1 (1.3–5.2)	—
Current ART as first regimen (%)	88	88	—

\*EFV/FTC/TDF = patients randomized to the single-tablet regimen (EFV/FTC/TDF).  
 †SBR = patients randomized to continue their same baseline antiretroviral regimen.

Overall, TDF was included as a component of the baseline regimen in 38% (n = 113) of subjects with nearly equal balance between arms (37% EFV/FTC/TDF, 40% SBR). A greater proportion of patients received TDF as part of PI-based ART (74%) compared with NNRTI-based ART (26%). ZDV was a component of the prior regimens in 39% (n = 116) of subjects (42% EFV/FTC/TDF, 32% SBR), with approximately two thirds of ZDV use occurring in subjects on NNRTI-based regimens. ABC was included as a component of the baseline regimen in 23% (n = 68) of subjects with roughly equal proportions of patients receiving this agent in the 2 treatment strata.

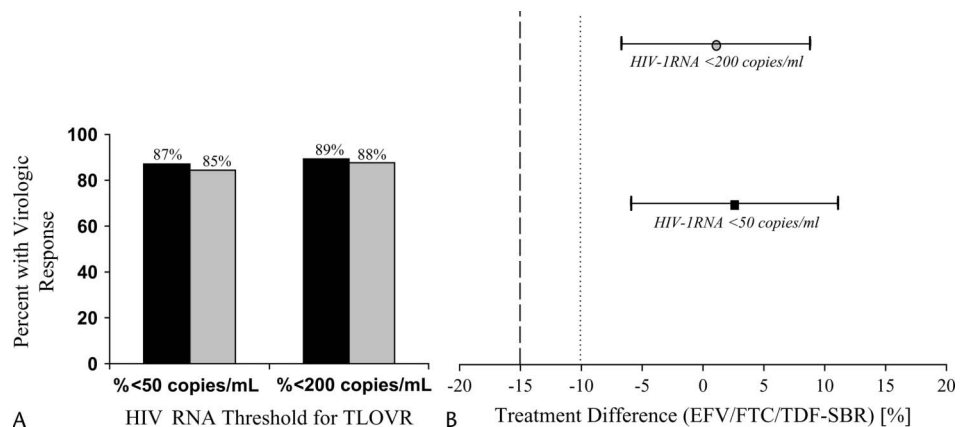
**Efficacy Results**

Rates of viral suppression in virologically suppressed patients who were switched to EFV/FTC/TDF compared with those who remained on their baseline ART regimen are displayed in Figure 2A and summarized in Table 2. The primary end point analysis (HIV-1 RNA < 200 copies/mL by TLOVR, ITT, NC = F) demonstrated that the proportion of responders was similar in the 2 treatment groups at week 48 (difference between groups for EFV/FTC/TDF minus SBR 1.1%, 95% confidence interval (CI) -6.7% to 8.8%; P = 0.823) (Fig. 2B, Table 2). Eighty-nine percent of patients in the EFV/FTC/TDF group were the responders compared with 88% of patients in the SBR group. Given that the lower confidence boundary for the responder difference (EFV/FTC/TDF minus SBR) was greater than -15%, the EFV/FTC/TDF arm was found to be noninferior to SBR. At 48 weeks, 87% of patients receiving EFV/FTC/TDF compared with 85% of patients on SBR maintained HIV-1 RNA <50 copies per milliliter (responder difference 2.6%, 95% CI -5.9% to 11.1%; P = 0.539) (Table 2; Figs. 2A, B]. Thus, for this lower cutoff, EFV/FTC/TDF was also found to be noninferior to SBR by TLOVR (ITT, NC = F) analysis.

When treatment responses were further evaluated by prior treatment strata (NNRTI or PI), similar responses between groups were observed (Table 3). At 48 weeks, 92% vs. 84% of patients on prior NNRTI-based ART maintained HIV-1 RNA <200 copies per milliliter when randomized to switch to EFV/FTC/TDF vs. continue SBR, respectively [treatment difference (95% CI) 7.4% (-4.8% to 19.1%), P = 0.245]. Similar responses were seen for the proportion of patients with HIV-1 RNA <50 copies per milliliter (Table 3). For patients on prior PI-based ART, 87% vs. 90% of patients achieved HIV-1 RNA <200 copies per milliliter when randomized to receive EFV/FTC/TDF vs. SBR, respectively [treatment difference (95% CI) -3.3% (-13.6% to 6.9%), P = 0.612]. Similar responses were observed in the prior PI stratum for the proportion of patients with HIV-1 RNA <50 copies per milliliter (Table 3).

Overall, 4 patients (1%) experienced virologic failure. Three of the patients with virologic failure were randomized to receive EFV/FTC/TDF and 1 to SBR. One of the patients who experienced virologic failure in the EFV/FTC/TDF arm

**FIGURE 2.** A, Percentage of patients with virologic response vs. HIV-1 RNA thresholds for the time to virologic response (TLOVR) analysis. Black-shaded columns are patients randomized to the single-tablet regimen of EFV/FTC/TDF; gray-shaded columns are patients randomized to SBR. B, Percentage of treatment differences between the EFV/FTC/TDF treatment arm minus the SBR arm for the TLOVR thresholds evaluated. Bars represent the lower and upper bounds of 95% CIs of the treatment differences.



**TABLE 2.** Primary Analysis of Response for HIV-1 RNA <200 Copies Per Milliliter and HIV-1 RNA <50 Copies Per Milliliter at 48 Weeks (ITT Population, NC = F)

HIV-1 RNA Threshold	Treatment Response (TLOVR), %*		
	EFV/FTC/TDF (n = 203)†	SBR (n = 97)‡	Difference (95% CI§) [P¶]
<200 copies/mL	89	88	1.1 (−6.7 to 8.8) [0.823]
<50 copies/mL	87	85	2.6 (−5.9 to 11.1) [0.539]

\*TLOVR algorithm.

†EFV/FTC/TDF = patients randomized to the single-tablet regimen (EFV/FTC/TDF).

‡SBR = patients randomized to continue their same baseline antiretroviral regimen.

§The CI difference in 2 proportions was calculated using a normal approximation and was weighted for baseline stratum.

¶P value is from Cochran–Mantel–Haenszel test stratified by baseline stratum.

discontinued early (week 15) with an HIV-1 RNA = 77,300 copies per milliliter. The patient had previously received FPV/r plus TDF/FTC as initial therapy for 1 year. Genotyping of the week 15 sample revealed a complex pattern of mutations, including reverse transcriptase (RT) mutations M184V, Q151M (multi-NRTI resistance genotype), K101E, and Y188L (EFV resistance genotype). Secondary PI resistance mutations were also noted, including M36I, F53L, and I64V. The patient was returned to his prior treatment regimen. Further genotyping studies were conducted on plasma samples from this patient using a more sensitive genotyping method that utilized patient-specific DNA primers to amplify the virus in the screening and baseline samples, both of which had <50 copies per milliliter of HIV-1 RNA. Both the Q151M and Y188L mutations were detected in both prestudy samples. Thus, this patient had evidence of preexisting NRTI and NNRTI resistance before the switch to EFV/FTC/TDF and additional RT mutations (K101E, M184V) that developed at the time of discontinuation. One patient in the EFV/FTC/TDF group was found to have HIV-1 RNA  $\geq$ 200 copies per milliliter (286 copies/mL) at the final (week 48) study visit; genotyping results revealed only wild-type virus. The third patient with virologic failure in the EFV/FTC/TDF arm experienced virologic rebound at the week 12 visit (HIV-1 RNA = 965 copies/mL), which was confirmed 2 weeks later (HIV-1 RNA = 307 copies/mL); the K103N mutation (EFV

resistance) was detected in the confirmatory viral load sample, whereas the initial week 12 sample showed only a wild-type viral genotype. The patient's ART regimen was subsequently changed to ATV/r plus TDF/FTC. One patient in the SBR arm experienced virologic rebound; genotyping could not be performed as a consequence of polymerase chain reaction amplification failure.

No significant changes in CD4 cell counts were observed within or between treatment arms during the study. At week 48, median (IQR) change from baseline in CD4 cell count in the EFV/FTC/TDF arm was 3 (−76, 94) cells per cubic millimeter compared with a change of 9 (−62, 87) cells per cubic millimeter in the SBR arm.

### Adverse Events

Treatment-emergent AEs occurring in at least 5% of subjects (all grades) are summarized by system and preferred term in Table 4. In general, AEs observed in the study were consistent with those previously reported in other trials evaluating EFV with TDF and FTC or 3TC.<sup>4,5,10,11</sup> There were no new or unexpected AEs reported in the study.

### NSSs and Psychiatric Symptoms

Of the treatment-emergent AEs, NSSs and psychiatric symptoms were among the AEs reported with the highest frequencies overall and were more common in the EFV/FTC/TDF arm (Table 4). Patients receiving prior PI-based ART compared with prior NNRTI-based ART were more likely to experience NSSs and psychiatric symptoms when switched to EFV/FTC/TDF. The overall prevalence of NSS was 22% in patients randomized to EFV/FTC/TDF and 13% in SBR patients, whereas psychiatric symptoms were reported in 28% and 8% of patients in the EFV/FTC/TDF and SBR arms, respectively. The most frequently reported treatment-emergent NSSs for the EFV/FTC/TDF vs. SBR arms were dizziness (12% vs. 2%), headache (5% vs. 7%), and somnolence (3% vs. 0%). Of the psychiatric symptoms, abnormal dreams (7% vs. 0%), insomnia (4% vs. 0%), anxiety (4% vs. 1%), and depression (8% vs. 4%) were most commonly reported. Importantly, NSSs and psychiatric symptoms tended occur early (ie, within hours to days); most events were mild in intensity and transient in nature; symptoms usually persisted for a few days to a few weeks. For 5 patients (2%) in the

**TABLE 3.** Analysis of Response by Prior Treatment Stratum for HIV-1 RNA <200 Copies Per Milliliter and HIV-1 RNA <50 Copies Per Milliliter at 48 Weeks (ITT Population, NC = F)

HIV-1 RNA threshold	Treatment Response (TLOVR), %*			Treatment Response (TLOVR), %		
	Prior NNRTI			Prior PI		
	EFV/FTC/TDF (n = 95)†	SBR (n = 45)‡	Difference (95% CI§) [P¶]	EFV/FTC/TDF (n = 108)	SBR (n = 52)	Difference (95% CI) [P]
<200 copies/mL	92	84	7.1 (−4.8 to 19.1) [0.245]	87	90	−3.3 (−13.6 to 6.9) [0.612]
<50 copies/mL	92	82	9.4 (−3.1 to 21.8) [0.153]	83	87	−3.2 (−14.8 to 8.4) [0.651]

\*TLOVR algorithm.

†EFV/FTC/TDF = patients randomized to the single-tablet regimen (EFV/FTC/TDF).

‡SBR = patients randomized to continue their same baseline antiretroviral regimen.

§The CI difference in 2 proportions was calculated using a normal approximation.

¶P value is from Cochran–Mantel–Haenszel test.

**TABLE 4.** Treatment-Emergent AEs (All Grades) Reported for at Least 5% of Patients

Subjects (%) With AEs by System and Preferred Term*	Prior NNRTI		Prior PI		Total	
	EFV/FTC/TDF (n = 95)†	SBR (n = 45)‡	EFV/FTC/TDF (n = 108)	SBR (n = 52)	EFV/FTC/TDF (n = 203)	SBR (n = 97)
Gastrointestinal disorders and administration site conditions	25	18	26	27	26	23
Diarrhea	8	9	8	8	8	8
Nausea	2	4	6	8	4	6
General disorders	14	9	19	25	17	17
Fatigue	4	0	9	8	7	4
Pyrexia	2	2	2	8	2	5
Infections and infestations	47	51	37	36	42	43
Bronchitis	8	2	5	6	6	4
Nasopharyngitis	6	7	2	2	4	4
Sinusitis	5	4	5	8	5	6
Metabolism and nutrition	5	9	7	11	6	10
Hyperlipidemia	1	4	1	6	1	5
NSS disorders	15	18	29	10	22	13
Somnolence	0	0	6	0	3	0
Headache	4	11	6	4	5	7
Dizziness	5	2	18	2	12	2
Psychiatric disorders	22	9	32	8	28	8
Anxiety	3	0	6	2	4	1
Depression	7	4	8	4	8	4
Insomnia	3	0	6	0	4	0
Abnormal dreams	5	0	9	0	7	0
Respiratory, thoracic, and mediastinal disorders	10	27	18	23	14	25
Cough	6	9	8	10	7	9
Nasal congestion	2	9	0	2	1	5
Pharyngolaryngeal pain	1	0	2	11	1	6
Sinus congestion	2	0	6	8	4	4
Skin and subcutaneous tissue disorders	18	13	20	6	19	9
Rash	5	2	6	2	5	2

\*Preferred terms were mapped according to the Medical Dictionary for Regulatory Activities (MedDRA).

†EFV/FTC/TDF = single-tablet regimen (EFV/FTC/TDF).

‡SBR = patients randomized to stay on their baseline antiretroviral regimen.

EFV/FTC/TDF group, moderate to severe NSSs and psychiatric symptoms led to study drug discontinuation. All 5 patients were in the prior PI stratum. In these patients, symptoms began in the first week after initiation of EFV/FTC/TDF for 4 subjects and 1 month after initiation of EFV/FTC/TDF for the fifth subject.

**Renal AEs**

For 2 patients (1%) in the EFV/FTC/TDF arm, increase in serum creatinine resulted in study drug discontinuation. One patient, an obese 48-year-old African American male weighing 122 kg (body mass index, 39 kg/m<sup>2</sup>) at screening and having a medical history that included diabetes mellitus, hypertension, stroke, congestive heart failure, and renal insufficiency, had a moderate (grade 2) serum creatinine elevation (2.3 mg/dL) at both the screening and baseline visits. Because the patient’s calculated creatinine clearance was 70 mL/min when based on actual body weight, he met inclusion criteria. However, when GFR was estimated by creatinine clearance calculated using ideal body weight (40 mL/min) or by MDRD (39 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>), renal function was well below the

entry cutoff. This patient’s serum creatinine was 2.4 mg/dL at week 4 and 2.3 mg/dL when discontinued from study at week 6. The other patient, a 41-year-old white male with a history of chronic depression and low back pain managed with opiate/acetaminophen combination products, had a serum creatinine of 1.4 mg/dL at baseline, which was unchanged at week 4 and subsequently found to be 1.3 mg/dL when discontinued from study at week 21.

Mild (grade 1) treatment-emergent serum creatinine elevations were reported for similar proportions of subjects in each arm (EFV/FTC/TDF 2%, SBR 3%). Aside from the previously mentioned patient who was enrolled with a preexisting grade 2 serum creatinine value, there were no grade 2 or greater treatment-emergent serum creatinine elevations reported. In addition, there was no statistically significant difference within or between treatment groups for median (IQR) change in calculated creatinine clearance from baseline to week 48 [−1.2 (−4.0 to 1.3) mL/min for the EFV/FTC/TDF group vs. −0.6 (−4.0 to 2.6) mL/min for the SBR group]. By the MDRD method, no statistically significant difference was observed between or within groups in median (IQR) results from

baseline to week 48 [−0.44 (−1.9 to 2.7) mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> for the EFV/FTC/TDF group vs. −0.41 (−4.0 to 1.9) mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> for the SBR group] (Fig. 3A). In the prior PI stratum, median (IQR) change from baseline in MDRD was similar to the overall population (−0.37 vs. −0.40 mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> for EFV/FTC/TDF vs. SBR; *P* = 0.682).

Given that 38% of patients had TDF as a component of their baseline ART (or conversely, 62% were naive to TDF), estimated GFR changes were evaluated in patients with and without prior use of TDF. When GFR was estimated by MDRD in patients not receiving TDF at baseline (Fig. 3B), no differences were observed between arms in median change at week 48 (−0.50 mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> for EFV/FTC/TDF vs. −0.46 mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> for SBR), and for patients on prior TDF-containing regimens, the median change at week 48 was <0.4 mL·min<sup>−1</sup>·1.73 m<sup>−2</sup> in both arms (data not shown). Similarly, median change in creatinine clearance from baseline to week 48 for patients naive to TDF at baseline did not differ among treatment arms [−3 mL/min for both the EFV/FTC/TDF arm (*n* = 129) and the SBR arm (*n* = 58)]. For patients treated with an antiretroviral regimen that did contain TDF at baseline, median change in creatinine clearance from baseline to week 48 was +3 mL/min for EFV/FTC/TDF (*n* = 74) vs. +1 mL/min for SBR (*n* = 39).

**Other Safety Results**

In the EFV/FTC/TDF arm, treatment was discontinued for serious AEs in 3 additional subjects. One patient, a 46-year-old male on EFV + ZDV/3TC for 5 years before entry, was discontinued from study at week 16 for acute pancreatitis (grade 3) considered related to study drug. Another patient, a 44-year-old male on EFV + ZDV/3TC for 2 years before enrollment, had treatment discontinued at week 25 for alanine aminotransferase (grade 2) and aspartate aminotransferase (grade 1) elevations not considered related to study drug. The third subject, a 42-year-old male on LPV/r + TDF/FTC for 1 year before entry, experienced acute hepatitis (grade 3) at week 22 considered related to study drug and was discontinued at that time from study.

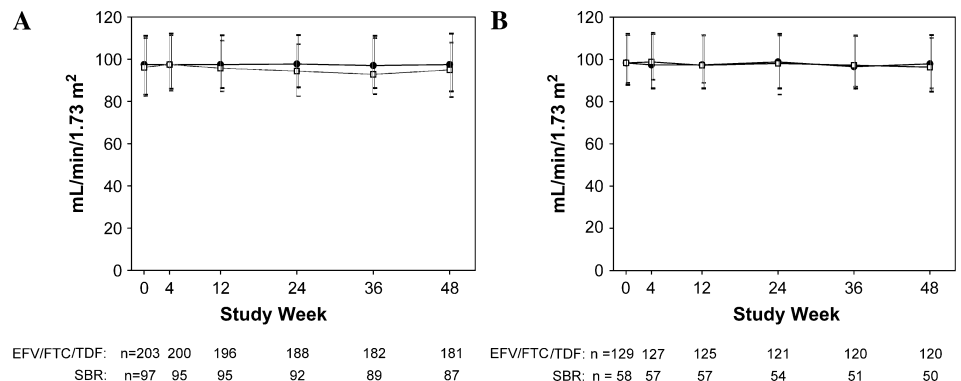
Results for fasting lipid parameters at baseline and change from baseline at week 48 are summarized in Table 5 for each treatment arm and by prior NNRTI or PI strata. Overall, no significant differences were seen between treatment arms for fasting total cholesterol and low-density lipoprotein

cholesterol. Although there was no change from baseline observed in fasting high-density lipoprotein (HDL) cholesterol overall or in the prior NNRTI stratum, there was a significant increase in HDL cholesterol observed in the EFV/FTC/TDF arm vs. SBR arm for patients in the prior PI stratum (median change: EFV/FTC/TDF group 5.0 mg/dL vs. SBR group 0.0 mg/dL; *P* = 0.044).

For fasting triglycerides, significant differences were observed between groups for the change from baseline at week 48 (EFV/FTC/TDF −20 mg/dL vs. SBR −3.0 mg/dL; *P* = 0.035). The change in triglycerides was greatest in the prior PI stratum (median change from baseline to week 48: EFV/FTC/TDF −29.0 mg/dL vs. SBR 1.0 mg/dL; *P* = 0.007). In addition, the impact on fasting triglycerides of prior use of ABC (*n* = 68) and ZDV (*n* = 116) and for patients whose prior regimens contained TDF (*n* = 113) or did not contain TDF (*n* = 187) was also examined. In the subgroup of patients receiving prior ABC-containing regimens who were switched to EFV/FTC/TDF, a trend toward a greater decline in fasting triglycerides was seen at week 48 compared with patients receiving ABC in the SBR arm [median (IQR) change from baseline: −24.0 (−92 to 5) mg/dL vs. 4.5 (−41 to 80) mg/dL; *P* = 0.074], whereas prior use of ZDV did not significantly affect fasting triglyceride levels at week 48. For patients on a TDF-containing regimen at baseline, no differences were observed between arms at 48 weeks, whereas for patients on a regimen that did not include TDF, there was a greater reduction in median fasting triglycerides at 48 weeks in the EFV/FTC/TDF arm vs. SBR arm (−20 vs. 2 mg/dL; *P* = 0.056).

A statistically significant increase was noted in median (IQR) hemoglobin in the EFV/FTC/TDF arm from baseline to week 48 [0.5 (1.0) g/dL, *P* < 0.001] compared with no statistically significant change from baseline in the SBR arm [0.1 (−0.2 to 0.3) g/dL, *P* = 0.279]. The difference between groups was also statistically significant at week 48 (*P* < 0.001); however, median (IQR) values were in the normal range at baseline [14.3 (13.3–14.9) g/dL] and remained so throughout the study. When patients receiving ZDV as a component of their baseline regimen were switched to EFV/FTC/TDF [85 of 203 patients (42%)], median (IQR) change from baseline at week 48 in hemoglobin was 0.8 (0.5–0.9) g/dL compared with 0.3 (−0.1 to 0.6) g/dL for patients who continued their ZDV-containing baseline regimen [31 of 97 patients (32%), *P* = 0.009].

**FIGURE 3.** A, Median and IQR values for GFR as estimated by the MDRD method. B, Median (IQR) GFR as estimated by the MDRD method for the subset of patients receiving an antiretroviral regimen that did not include TDF at baseline. For both panels, squares represent patients randomized to the single-tablet regimen of EFV/FTC/TDF and ovals represent patients randomized to SBR.



**TABLE 5.** Fasting Lipid Results at Baseline and Change from Baseline Values at Week 48

	Prior NNRTI		Prior PI		Total	
	EFV/FTC/TDF (n = 95)*	SBR (n = 45)†	EFV/FTC/TDF (n = 108)	SBR (n = 52)	EFV/FTC/TDF (n = 203)	SBR (n = 97)
Total cholesterol (mg/dL)						
Baseline	195 (169–224)	185 (168–206)	185 (167–215)	191 (164–225)	191 (168–218)	189 (164–218)
Change at week 48	−6.0 (−14 to 0.1)	2.0 (−11 to 13)	4.0 (−4.9 to 9.1)	0.0 (−9.8 to 9.0)	−1.5 (−7.3 to 2.6)	1.0 (−7.0 to 7.7)
LDL cholesterol (mg/dL)						
Baseline	113 (90–135)	98 (85–116)	111 (92–138)	118 (92–135)	112 (91–136)	108 (89–127)
Change at week 48	−5 (−12 to 1)	−3 (−11 to 2)	0 (−6 to 4)	−4.0 (−10 to 3)	−2.0 (−7 to 1)	−4.0 (−9 to 1)
HDL cholesterol (mg/dL)						
Baseline	45 (38–55)	45 (36–57)	41 (36–48)	44 (38–50)	43 (37–50)	44 (36–53)
Change at week 48	−1.0 (−3 to 0.5)	0.5 (−2 to 3.0)	5.0 (3–7)‡	0 (−1 to 5)	1.5 (1–3)	0 (−1 to 3)
Total cholesterol to HDL ratio						
Baseline	4.1 (3.6–5.1)	3.8 (3.3–4.9)	4.6 (3.6–5.4)	4.3 (3.6–5.5)	4.3 (3.6–5.3)	4.3 (3.4–5.3)
Change at week 48	−0.02 (−0.3 to 0.2)	0.08 (−0.6 to 0.5)	−0.3 (−0.6 to −0.2)	−0.06 (−0.4 to 0.3)	−0.2 (−0.4 to −0.1)	0.05 (−0.4 to 0.2)
Triglycerides (mg/dL)						
Baseline	150 (104–218)	149 (92–288)	153 (104–206)	173 (87–204)	152 (104–211)	170 (87–260)
Change at week 48	−9.0 (−48 to 10)	−8.0 (−56 to 83)	−29 (−65 to −26)§	1.0 (−29 to 25)	−20 (−50 to −15)¶	−3 (−29 to 39)

Results expressed as median (IQR).  
 LDL, low-density lipoprotein.  
 \*EFV/FTC/TDF = patients randomized to single-tablet regimen (EFV/FTC/TDF).  
 †SBR = patients randomized to continue their same baseline antiretroviral regimen.  
 ‡P = 0.044 for EFV/FTC/TDF vs. SBR.  
 §P = 0.007 for EFV/FTC/TDF vs. SBR.  
 ¶P = 0.035 for EFV/FTC/TDF vs. SBR.

**Outcomes Research Results**  
**Quality of Life**

Baseline values for the SF-36 physical and mental composite scores were similar in patients enrolled in the study compared with those for the general population. Median scores were approximately 50 at baseline, and overall, there were no marked changes from baseline in SF-36 scores for either treatment group during the study. For the physical component summary, differences between treatment groups (EFV/FTC/TDF vs. SBR) for the change from baseline were statistically significant at week 48 (mean difference 2.0, 95% CI 0.5 to 3.5, P = 0.010). For the mental component summary and health domains, no significant differences were observed between treatment arms.

**Adherence**

Self-reported adherence using a VAS was high in both treatment groups at baseline and during the study (≥96% in both treatment groups at all visits). When based on pill counts over the duration of treatment (EFV/FTC/TDF arm only), an adherence rate of ≥95% was observed for 89% of patients.

**Preference of Medication**

At all post-baseline study visits, for the overall population and by prior stratum (NNRTI or PI), patients randomized to EFV/FTC/TDF preferred this treatment over the previous regimen (P < 0.001). The proportion of patients reporting that EFV/FTC/TDF was “much better” than their previous regimen increased from 64% at week 4 to 85% at week 48. However, there were 10 patients (5%) who reported that they

much preferred their previous regimen to EFV/FTC/TDF on at least 1 occasion; 5 of the 10 patients discontinued early due to an AE, 3 patients completed the study, whereas 2 patients withdrew consent. Four of the 5 patients discontinuing for an AE had received a prior PI-based therapy.

**Perceived Ease of Regimen for Condition**

At baseline, the percentage of patients who considered their regimen “very easy to take” was lower in the EFV/FTC/TDF group (68%) compared with the SBR group (75%). For all subsequent visits, significantly more subjects who received EFV/FTC/TDF considered it an easier regimen to take than their previous regimen (P < 0.001), whereas over time, there were no significant changes in the ease of taking the regimen. At week 48, 97% of patients found EFV/FTC/TDF “very easy to take” compared with 81% of patients in the SBR group (P < 0.001).

**HIV Symptom Index**

Questionnaire results revealed 2 categories of responses: a transient worsening of symptoms of dizziness or light-headedness in patients switching treatment to EFV/FTC/TDF and sustained improvements of other symptoms in patients switching treatment to EFV/FTC/TDF compared with either no change or a slight worsening in symptoms in patients who continued SBR.

Subjects in the EFV/FTC/TDF arm had more symptoms of dizziness or light-headedness compared with the SBR arm at week 4 (39% vs. 25%, respectively, P = 0.018). This difference was primarily due to changes in subjects who had received a prior PI-based regimen (27% with symptoms at

baseline to 46% with symptoms at week 4,  $P = 0.002$ ). The worsening in symptoms of dizziness and light-headedness was a transient change through week 4; no significant differences were found between groups at any other time points during the study.

Significant reductions in the following 4 symptoms of HIV were noted at all study visits (with noted exceptions) for patients randomized to the EFV/FTC/TDF arm: (1) diarrhea or loose bowel movements; (2) bloating, pain, or gas in the stomach; (3) changes in the way their body looked (all visits except weeks 12 and 24); and (4) problems having sex (all visits except week 24). For diarrhea or loose bowel movements, there was a statistically significant reduction in the proportions of patients with symptoms in the EFV/FTC/TDF arm who had received a prior PI-based regimen [from 52% at baseline to 32% of patients with symptoms at week 48 ( $P = 0.002$ )].

## DISCUSSION

Simplification of antiretroviral regimens is an important and achievable aim of contemporary ART. This report represents the first controlled clinical trial conducted in HIV-infected patients using the approved formulation of a single-tablet regimen of EFV/FTC/TDF. The components have been shown to be well tolerated and effective in randomized controlled trials conducted in treatment-naïve patients.<sup>4,5</sup> In this study, high rates of virologic suppression were maintained in virologically suppressed patients who simplified therapy to EFV/FTC/TDF or continued their unmodified baseline antiretroviral regimen, and EFV/FTC/TDF was found to be noninferior to SBR.

For the primary analysis end point, a threshold of HIV-1 RNA <200 copies per milliliter was chosen. This suppression threshold has been used by others, including the Adult AIDS Clinical Trials Group (AACTG).<sup>18</sup> Importantly, at baseline, 96% of patients in both arms had HIV-1 RNA <50 copies per milliliter, and at 48 weeks, the proportion of patients who maintained HIV-1 RNA <50 copies per milliliter (by TLOVR algorithm) was similar to the proportion below 200 copies per milliliter (Table 2; Figs. 2A, B). Treatment with EFV/FTC/TDF was found to be noninferior to SBR at the HIV-1 RNA <50 copies per milliliter end point as well. Thus, by either end point, HIV suppression was maintained in a high percentage of patients in both treatment arms through 48 weeks. When treatment responses were evaluated by prior strata (NNRTI or PI) in an exploratory TLOVR analysis, responses were lower in the prior PI stratum compared with SBR, whereas with prior NNRTI treatment, responses in the EFV/FTC/TDF arm were higher than those observed in the SBR arm. For both treatment strata, responses between arms did not differ significantly (Table 3). The lower response rates observed in the prior PI stratum for patients switched to EFV/FTC/TDF vs. SBR are likely driven by a higher percentage of subjects in the EFV/FTC/TDF arm who discontinued early for an AE, particularly for NSSs and/or psychiatric symptoms. Thus, although noninferiority was achieved between treatments overall, patients switched to EFV/FTC/TDF should always be closely monitored for safety/tolerability and for virologic control.

Results from this study add to and extend existing data from earlier switch studies in virologically suppressed patients.<sup>7-11</sup> Few studies have evaluated the strategy of simplifying an entire treatment regimen in virologically suppressed patients. In the Alize study, comparable rates of virologic suppression were observed at 48 weeks in patients randomized to switch to a once-daily regimen of EFV + FTC + ddI vs. continued PI-based ART given multiple times daily.<sup>12</sup> The present study is the first to demonstrate that virologically suppressed patients receiving a wide array of NRTI backbones given with NNRTI- or PI-based therapies can be safely switched to a single-tablet regimen, taken once daily. Importantly, the majority of patients (88%) enrolled in this study were receiving their initial treatment regimen for a median of 3 years; none had previously experienced virologic failure.

There were 2 patients (both in the EFV/FTC/TDF arm) in whom resistance mutations were present upon genotype testing. One patient discontinued EFV/FTC/TDF early (week 15) for virologic failure, showing a complex pattern with multiple RT mutations and several secondary PI resistance mutations. The multi-NRTI (Q151M) mutation and the EFV resistance mutation Y188L were detected in samples obtained before starting EFV/FTC/TDF when analyzed by a more sensitive genotyping method. Because neither TDF nor FTC has been shown to select for the Q151M resistance genotype either in vitro or in vivo, this may reflect transmission of a resistant virus that was suppressed by the patient's prior antiretroviral regimen (FPV/r + TDF/FTC). Nonetheless, for this patient, the M184V and K101E mutations seem to have been selected during treatment with EFV/FTC/TDF, consistent with the known resistance profiles of FTC and EFV, respectively. For another patient who experienced virologic rebound, the K103N RT mutation (EFV resistance) was observed in the confirmed virologic failure sample. Pre-switch genotype data were not available for this patient; however, the K103N mutation was not observed in the viral genotype generated from an earlier EFV/FTC/TDF treatment sample (week 12) from this patient. Thus, the K103N mutation seems to have developed during therapy with EFV/FTC/TDF.

Both treatment arms were generally well tolerated, and no new or unexpected safety findings were reported for patients participating in the trial. Five percent of subjects (10 patients) in the EFV/FTC/TDF arm were discontinued for an AE compared with 1% in the control arm. Five of the 10 patients (2%) in the EFV/FTC/TDF arm, who discontinued early, experienced NSSs and/or psychiatric symptoms, all of whom were in the prior PI stratum. This is not a surprising result given that a small percentage of patients switched from non-EFV-containing regimens to EFV/FTC/TDF would be expected to experience moderate or severe NSSs and/or psychiatric symptoms; similar findings have been reported by others and are contained in the EFV product label.<sup>8,12</sup> Overall, a higher percentage of patients in the EFV/FTC/TDF arm (particularly those in the PI stratum) reported NSSs and psychiatric symptoms (Table 4). As reported in other studies and observed in clinical practice, these symptoms tend to occur early, are generally transient, and are typically mild in severity.<sup>3,8,12</sup> This trial confirms this AE profile as the patient-reported symptoms on the HIV Symptom Survey, dizziness

and light-headedness, showed a transient worsening only during the first 4 weeks. No significant differences were noted between treatment arms beyond the 4-week time point for patients remaining on study. Thus, clinicians should continue to advise patients as to the potential to experience NSSs and psychiatric symptoms, in particular individuals switched to EFV/FTC/TDF from PI-based regimens or NNRTI-based regimens that contain NVP.

Renal AEs have been previously reported in association with use of TDF.<sup>19</sup> In this study, 2 patients were discontinued for elevated serum creatinine attributed by the investigator to be related to EFV/FTC/TDF. Overall, mild (grade 1) elevations in serum creatinine were seen in 2%–3% of patients and occurred with equal frequency in each arm. No clinically important changes from baseline were seen in GFR, estimated by calculated creatinine clearance and MDRD within or between treatment arms over 48 weeks (Fig. 3A). For patients who were naive to TDF at entry, the change in estimated GFR was not different in the EFV/FTC/TDF arm vs. SBR arm at 48 weeks (Fig. 3B). Overall, with the exception of a single patient enrolled with a preexisting moderate serum creatinine elevation, renal events reported in this study were not judged to be clinically important and are consistent with other trials utilizing a regimen of EFV plus TDF/FTC or TDF/3TC.<sup>4,5,20</sup>

Several studies have shown improvements in fasting lipid profile when suppressed patients have their PI switched to either an NNRTI or ABC.<sup>7,9</sup> Other studies have shown improvements in fasting lipids in patients receiving EFV-based regimens who have their thymidine analogue NRTI (ie, ZDV or stavudine) switched to TDF.<sup>10,11,21</sup> In this study, which involved treatment with a wide variety of ART regimens at entry, fasting HDL cholesterol (PI stratum only) and fasting triglycerides significantly improved from baseline in the EFV/FTC/TDF arm compared with control at 48 weeks. These changes in triglycerides were most pronounced in the prior PI stratum; improvements were also observed in the subgroup of patients receiving prior ABC-containing regimens and those naive to TDF, who switched therapy to EFV/FTC/TDF. No changes were found in low-density lipoprotein cholesterol or total cholesterol to HDL cholesterol ratio. Thus, although the changes observed in certain fasting lipid parameters were modest at best, switching to EFV/FTC/TDF from either a prior PI- or NNRTI-based regimen did not result in a worsening of lipid parameters, and in some patients, improvements were seen.

An increase from baseline in hemoglobin was observed when patients were switched to EFV/FTC/TDF, whereas this parameter remained essentially unchanged in patients on SBR. This effect was more pronounced for patients on prior ZDV-containing regimens who were switched to EFV/FTC/TDF. Increases in hemoglobin of a similar magnitude have been consistently observed in other trials, involving virologically suppressed patients, in which ZDV is switched to an alternative NRTI (eg, ddI or TDF) that is not typically associated with reductions in serum hemoglobin.<sup>10,11,22</sup>

The ability to simplify therapy to a single tablet taken once daily would be expected to positively impact adherence.<sup>2,23</sup> In this study, a difference between arms in adherence was not observed when assessed by VAS. This can be explained by the excellent adherence ( $\geq 96\%$ ) that was

observed at baseline. Thus, there was little room for improved adherence during the study for patients randomized to the EFV/FTC/TDF arm. Indeed, patients enrolled in the study were virologically suppressed at entry (96% had HIV-1 RNA  $< 50$  copies/mL) and had been receiving ART for a median duration of 3 years; therefore, the study population represents patients who are successful pill takers, whereas poorly adherent patients and those with treatment-limiting adverse reactions were implicitly excluded.

When asked about regimen preference by the POM survey, 85% of patients at week 48 stated that EFV/FTC/TDF was “much better” than their prior treatment regimen. Only 5% of subjects stated a preference for their prior regimen, most of whom discontinued EFV/FTC/TDF for an AE. Thus, the majority of patients who switched to EFV/FTC/TDF and tolerated this treatment indicated a preference for this regimen over prior ART. Similarly, at baseline, approximately 70% of patients considered their regimen easy to take when assessed by PERC questionnaire, whereas by the first study visit (week 4), more than 90% of patients in the EFV/FTC/TDF arm considered the single-tablet regimen easier to take than their previous regimen, and at week 48, 97% of patients considered the EFV/FTC/TDF regimen easier to take than prior therapy. However, given that the PERC survey was specifically developed for this study and has not yet been validated, these results must be interpreted within this context.

There are certain limitations to this study. In general, studies that involve switching therapy tend to attract patients motivated to make a change in treatment, and such studies can have an intrinsic bias toward favoring the switch strategy under evaluation. More than 90% of subjects cited regimen simplification as a reason for participation. This is not surprising given that the median duration of prior ART was 3 years, and individuals showing poor regimen tolerability would be much less likely to be receiving such long-term therapy. Thus, the motivation to simplify therapy in this stable population could have affected patients reporting of AEs, adherence, and/or medication preference. Randomization to the control arm could have been a disincentive for study participation for some patients. Of the 6 patients randomized but never treated, 3 of 5 patients randomized to SBR withdrew consent. Among the treated population, more patients randomized to the SBR arm withdrew consent compared with the EFV/FTC/TDF arm. However, given that only 2 of 7 patients in the SBR group had their post-study regimen changed to EFV/FTC/TDF, this would suggest that staying on the same baseline regimen was not an important disincentive. An open-label design was deemed appropriate given that the components of the single-tablet regimen were well characterized in earlier trials and the impracticality of adequately blinding for the multiple regimens taken by patients in the SBR arm. Furthermore, this type of design allowed for certain outcome measures (ie, POM and PERC) to be included that specifically addressed unique aspects associated with taking a single-tablet regimen. The majority of subjects enrolled were white males whose primary risk factor for HIV was men who had sex with men. The median age of our population was 43 years with less than 25% of subjects older than 50 years, and the median CD4 cell count at baseline was greater than 500

cells per cubic millimeter. Given this, it is conceivable that the clinical and laboratory tolerability of simplification to EFV/FTC/TDF may differ in other types of patients, particularly older individuals, females, non-whites; those with more advanced HIV disease; and individuals with multiple comorbidities requiring various concomitant therapies.

In summary, patients who were stable and virologically suppressed while receiving a wide array of NNRTI- and PI-based antiretroviral regimens and had their treatment simplified to a single-tablet regimen of EFV/FTC/TDF maintained high rates of virologic suppression compared with those who continued their regimen unmodified. Patients generally well tolerated simplification to EFV/FTC/TDF. Individuals on prior PI-based therapy were more likely to experience transient NSSs and psychiatric symptoms; for 2% of patients, these AEs were treatment limiting.

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