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Simplification of Antiretroviral Therapy with Efavirenz/Emtricitabine/Tenofovir DF Single Tablet Regimen vs. Continued Unmodified Antiretroviral Therapy in Virologically-Suppressed, HIV-1-Infected Patients

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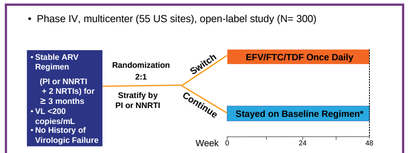
Background / Objective

- Co-formulated EFV/FTC/TDF is the first once daily single tablet antiretroviral (ARV) regimen approved in the United States, Canada, and the EU
- The components have demonstrated long-term efficacy and safety in treatment naive patients (Arribas JR et al. JAIDS 2008;47:74-78)
- The objective of this study was to evaluate whether virologically-suppressed patients who simplified their current ARV regimen to a single tablet regimen of EFV/FTC/TDF would have similar effectiveness (efficacy, safety and tolerability) compared to patients who remained on their unmodified ARV regimen through 48 weeks

Figure 1. Study Design



Methods

Key Inclusion / Exclusion Criteria

- HIV-1 RNA < 200 copies/mL for ≥ 3 months on current ARV regimen
- Receiving first ARV regimen, or documented suppression on a previous PI-based regimen at time of prior change in therapy
- Calculated CrCL ≥ 60 mL/min (by Cockcroft-Gault formula)
- Patients with known resistance to study agents at any time in the past, and those receiving the individual components of the single tablet regimen (EFV+FTC+TDF) were excluded

Study Assessments

- HIV-1 RNA, CD4 count, chemistries, CBC performed at baseline and Weeks 4, 12, 24, 36, and 48
- GFR estimated by calculated CrCL (Cockcroft-Gault) and Modified Diet in Renal Disease (MDRD)
- Select patient-reported outcomes:
  - Adherence by visual analog scale
  - Preference of Medication questionnaire (EFV/FTC/TDF arm only)
  - Perceived Ease of Regimen for Condition survey

Statistical Methods

- Assessments were based on intent-to-treat (ITT) analysis*
- Primary endpoint was maintenance of virologic suppression defined as the proportion of patients with HIV-1 RNA < 200 copies/mL on their original assigned regimen through 48 Weeks based on TLOVR algorithm and assuming that non-completers = failures (NC=F)
  - Responders defined as those with HIV-1 RNA < 200 copies/mL at Week 48 without an HIV-1 RNA value ≥ 200 copies/mL on 2 successive occasions, or without having the last HIV-1 RNA value ≥ 200 copies/mL while on-study followed by discontinuation
  - The EFV/FTC/TDF arm was declared to be non-inferior to the SBR arm if the lower confidence boundary of the responder difference (EFV/FTC/TDF - SBR) was greater than –0.15. Sample size was estimated using a non-inferiority margin (Δ) of 15% at 80% power

*ITT population included all patients randomized and who received at least one dose of study medication

Results

Figure 2. Patient Disposition

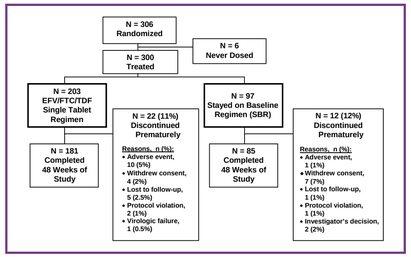


Table 1. Baseline Characteristics

	EFV/FTC/TDF (N = 203)	SBR (N = 97)	Total (N = 300)
Males, n (%)	181 (89%)	83 (86%)	264 (88%)
Age (mean; years)	42	44	43
Race			
Caucasian, n (%)	140 (69%)	64 (66%)	204 (68%)
African American, n (%)	56 (28%)	30 (31%)	86 (29%)
Ethnicity			
Hispanic / Latino, n (%)	46 (23%)	24 (25%)	70 (23%)
HIV-1 RNA (copies/mL)			
<50	194 (96%)	95 (98%)	289 (96%)
50 - <200	7 (3%)	2 (2%)	9 (3%)
≥200[a]	2 (<1%)	0 (0%)	2 (<1%)
CD4 cell count (mean; cells/μL)	536	548	540
Current ARV as first regimen (%)	88	88	-
Duration of current ARV (median [IQR]; years)	2.6 (1.3, 4.9)	3.1 (1.3, 5.2)	-

a. All subjects had HIV-1 RNA < 200 copies/mL at screening

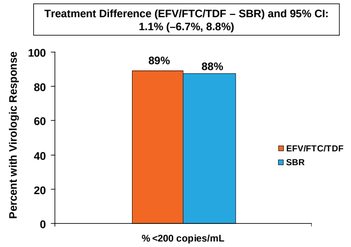
Table 2. Prior ARV Regimens

		EFV/FTC/TDF (N = 203)	SBR (N = 97)	Total (N = 300)
NNRTI-based, n (%)[a]		**95 (47%)**	**45 (46%)**	**140 (47%)**
Efavirenz		70 (34%)	41 (42%)	111 (37%)
Nevirapine		25 (12%)	4 (4%)	29 (10%)
PI-based, n (%)[a]		**108 (53%)**	**52 (54%)**	**160 (53%)**
Atazanavir/r		36 (18%)	10 (10%)	46 (15%)
Lopinavir/r		27 (13%)	12 (12%)	39 (13%)
Fosamprenavir/r		18 (9%)	10 (10%)	28 (9%)
Nelfinavir		12 (6%)	8 (8%)	20 (7%)
Other PI		15 (7%)	12 (12%)	27 (9%)
Most common regimens (%)[a]				
NNRTI-based	EFV + AZT/3TC			16%
	EFV + ABC/3TC			6%
	EFV + TDF + 3TC			5%
PI-based	ATV/r + TDF/FTC			13%
	LPV/r + TDF/FTC			6%
	FPV/r + ABC/3TC			4%

a. Percentage of total N for each column

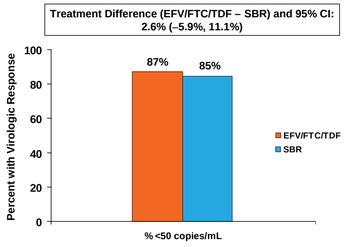
Figure 3. Efficacy Analysis Through 48 Weeks (TLOVR)

A) Percentage (%) of Patients with HIV-1 RNA <200 copies/mL



- The primary endpoint of non-inferiority of EFV/FTC/TDF to SBR was demonstrated

B) Percentage (%) of Patients with HIV-1 RNA <50 copies/mL



- Median change from baseline in CD4 cell count at Week 48 was 3 cells/μL and 9 cells/μL for EFV/FTC/TDF vs. SBR, respectively

Table 3. Efficacy Analysis by Prior Treatment Stratum: Week 48

Patients Below HIV-1 RNA Threshold (%)	Stratum at Baseline			
	Prior NNRTI		Prior PI	
	EFV/FTC/TDF (N = 95)	SBR (N = 45)	EFV/FTC/TDF (N = 108)	SBR (N = 52)
<200 copies/mL				
TLOVR[a]	92%	84%	87%	90%
M=E[b]	100%	100%	100%	100%
<50 copies/mL				
TLOVR	92%	82%	83%	87%
M=E	100%	97%	98%	98%

a. Time to loss of virologic response algorithm
b. Missing data (for any reason) was excluded in this analysis
P=NS for all comparisons in both strata

Virologic Failures

- 4 patients met virologic failure (VF) criteria and were genotyped
- 3 patients on the EFV/FTC/TDF arm had VF
  - 1 patient on prior FPV/r + TDF/FTC was discontinued for VF; Q151M multi-NRTI resistance and a Y188L EFV-R mutation were detected by more sensitive genotyping methods using patient-specific primers at screening and baseline and by conventional genotyping at discontinuation (DC). Additional RT mutations (K101E, M184V) developed at DC (Week 15; HIV-1 RNA = 77,300 c/mL)
  - 1 patient on prior LPV/r + TDF/FTC (DC for protocol violation) developed the K103N EFV-R mutation (Week 15, HIV-1 RNA = 307 c/mL)
  - 1 patient on prior EFV + AZT/3TC (DC with acute pancreatitis) had wild-type HIV-1 (Week 17, HIV-1 RNA = 286 c/mL)
- 1 patient (DC when consent withdrawn) on the SBR arm had VF (Week 19, HIV-1 RNA = 4810 c/mL)
  - Genotyping was unsuccessful (PCR amplification failure)

Table 4. Treatment-Related Adverse Events (All Grades)

Adverse Event by 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)
Dizziness	2%	0	18%[a]	2%	11%	1%
Abnormal Dreams	5%	0	8%	0	7%	0
Insomnia	3%	0	6%	0	4%	0
Somnolence	0	0	6%	0	3%	0
Nausea	1%	0	5%	4%	3%	2%
Diarrhea	2%	0	4%	0	3%	0
Fatigue	0	0	5%	0	2%	0
Depression	3%	0	1%	0	2%	0
Hyperlipidemia	0	2%	0	2%	0	2%
Anxiety	2%	0	1%	0	1%	0
Headache	1%	0	1%	2%	1%	1%
Creatinine increase	1%	0	2%	0	1%	0
Rash	1%	0	2%	0	1%	0

a. n = 20 patients. Severity: 16/20 Grade 1 (mild), 3/20 Grade 2 (moderate) , 1/20 Grade 3 (severe); 2 patients with Grade 2 and 1 patient with Grade 3 dizziness discontinued early for NSS

Table 5. Discontinuations Due to Adverse Events

N (%)	EFV/FTC/TDF (N = 203)	SBR (N = 97)
Any Adverse Event	10 (5%)	1 (1%)
Nervous system symptoms (NSS)[a]	5 (2%)	0
Increased creatinine[b]	2 (<1%)	0
Acute hepatitis	1 (<1%)	0
AST/ALT elevation	1 (<1%)	0
Acute pancreatitis	1 (<1%)	0
Gastritis	0	1 (1%)

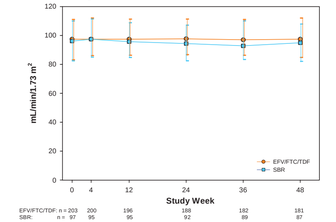
a. All patients were in the PI stratum. 4/5 patients experienced >1 NSS AE; NSS AE (number of patients) were: headache (1), dizziness (3), insomnia (2), somnolence (1), personality change (1), mood disturbance (2). 8/10 NSS AE were Grade 2 (moderate), 2/10 (dizziness, headache) were Grade 3 (severe)

b. 1 patient had baseline Scr = 2.4 mg/dL and discontinued at Week 6 with Scr = 2.3 mg/dL; 1 patient had baseline Scr = 1.4 mg/dL and discontinued at Week 21 with Scr = 1.3 mg/dL. Neither patient experienced a Scr elevation while on study in excess of their baseline value

Figure 4. Median (IQR) Glomerular Filtration Rates Estimated by MDRD

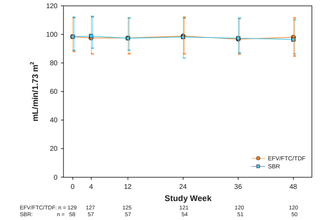
A) All Patients (N = 300)

- Median change from baseline at Week 48 was <1mL/min/1.73m² for both arms



B) Subset of Patients not Receiving TDF in Their Baseline Regimen (n = 187)

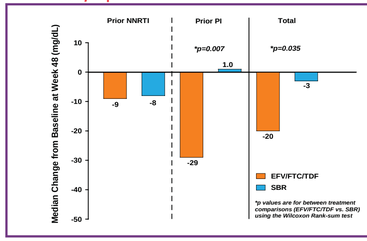
- Median change from baseline at Week 48 was <1mL/min/1.73m² for both arms



Fasting Lipid Results

- For the overall study population, no differences were observed between arms at Week 48 in median change from baseline in total cholesterol, LDL-cholesterol, or total cholesterol/HDL ratio
- The median (IQR) change from baseline in HDL-cholesterol at Week 48 for patients in the prior PI stratum was 5.0 (3, 7) mg/dL for EFV/FTC/TDF vs. 0 (-1, 5) mg/dL for SBR (p = 0.044); for this stratum there was also a trend toward improvement in total cholesterol/HDL ratio (p = 0.092)

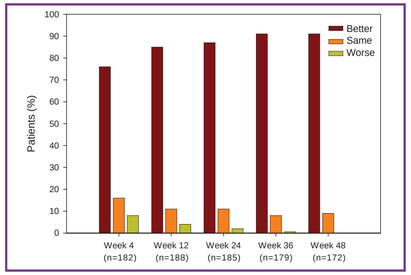
Figure 5. Median Change from Baseline at Week 48 in Fasting Triglycerides by Prior Treatment Stratum and for the Overall Study Population



Patient-Reported Outcomes

- Adherence
  - Adherence by visual analog scale was ≥ 96% for both treatments at baseline and all post-baseline visits
- Perceived Ease of Regimen for the Condition survey
  - At Week 48, the proportion of patients reporting their regimen as "easy to take" was 97% for EFV/FTC/TDF vs. 81% for SBR (p < 0.001)
- Preference of Medication questionnaire
  - At all post-baseline visits, patients in the EFV/FTC/TDF arm preferred this treatment over their previous ARV regimen (p < 0.001)
  - At Week 48, 85% of patients reported EFV/FTC/TDF to be "*much better*" than their previous regimen; 6% reported it to be "*slightly better*"; 9% reported EFV/FTC/TDF as "*about the same*"

Figure 6. Preference of Medication (POM) Questionnaire Results: Patients Randomized to EFV/FTC/TDF Arm (Both Strata)



Conclusions

In this study of virologically suppressed patients, through 48 weeks:

- **High rates of virologic suppression were maintained in both treatment arms**
- **Simplification to EFV/FTC/TDF was well tolerated with low rates of discontinuations observed in both treatment arms**
- **Consistent with previous reports, the most frequently reported AEs in the EFV/FTC/TDF arm were nervous system symptoms primarily in patients naïve to EFV**
  - **These were transient, generally mild, and resulted in few treatment discontinuations**
- **Renal function remained stable through 48 weeks, including patients naïve to TDF at baseline**
- **Baseline adherence was high and remained high in both treatment arms**
- **Among patients randomized to EFV/FTC/TDF, 91% indicated a preference for the single tablet regimen compared to prior therapy, and 97% found EFV/FTC/TDF easy to take**