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Improvement in Fasting Lipids but Minimal Recovery of Limb Fat Were Seen 96 Weeks After Switching from Lamivudine/Zidovudine Plus Efavirenz to Fixed-Dose Efavirenz/Emtricitabine/Tenofovir DF in HIV-Infected Patients

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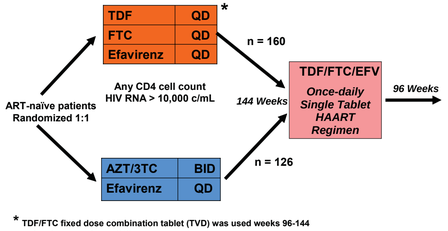
Introduction

- HIV disease treatment requires long-term highly active antiretroviral therapy (HAART)
- Metabolic abnormalities observed in HIV patients receiving HAART include:
  - Hyperlipidemia
  - Llimb fat and/or facial wasting, and/or central fat accumulation
  - Hyperglycemia
  - Insulin resistance with or without lipodystrophy
- Drugs within each antiretroviral class vary in their propensity to cause metabolic abnormalities
  - ACTG 5142 demonstrated a lower incidence of lipoatrophy among patients who received efavirenz (EFV)+ lopinavir/ritonavir (LPV/r) or LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) compared to EFV+2 NRTIs
    - Lipoatrophy occurred predominantly in the stavudine (d4T) or zidovudine (ZDV)-containing regimens in both the EFV + 2 NRTIs and LPV/r +2 NRTIs arms
- Identifying HAART regimens with a low propensity to cause metabolic abnormalities is a medically prudent goal

Background

Figure 1. Study Design



Methods

- Patients in both arms of Study 934 who completed 144 weeks were given the option to roll-over into an open-label extension phase of the study and switch their ARV regimen to the once-daily fixed-dose combination single tablet HAART regimen, EFV/FTC/TDF, and were followed for an additional 96 weeks (Weeks 145 → 240)
- Results presented focus on changes that occurred during the 96 weeks of follow-up post-switch to the once-daily single tablet HAART regimen, EFV/FTC/TDF, except for the adherence analysis
- An ad hoc adherence analysis was performed focusing only on patients taking once-daily regimens during Study 934:
  - 3 pills FTC + TDF + EFV — Baseline → Week 96
  - 2 pills FTC/TDF + EFV — Weeks 97 → 144
  - 1 pill EFV/FTC/TDF — Weeks 145 → 240

Methods (cont'd)

Adherence Definitions and Analyses

Adherence rates

- Calculated as (sum of maximum days whole treatment regimen taken) ÷ (sum of dosing duration)

Dosing duration was defined as

- Minimum of (last dosing date, pills returned date, next dispense date) minus (dispense date)
  - Dosing periods with any bottle not returned were excluded from the calculation

Adherence Analysis

- Analyzed by daily pill burden using mixed effect model (MITT subjects)

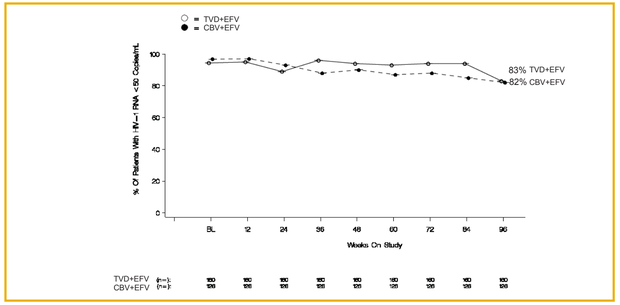
Results

Table 1. Patient Disposition Through 96 Wks After Switch to EFV/FTC/TDF

	FTC/TDF+EFV (N=160)	AZT/3TC+EFV (N=126)
Number of Patients Discontinued Study Regimen Prematurely	16 (10.0%)	18 (14.3%)
Reasons for Premature D/C		
Adverse Event	1 (0.6%)*	1 (0.8%)**
Suboptimal Virologic Response	0	1 (0.8%)
Non-Compliance	1 (0.6%)	0
Consent Withdrawn	5 (3.1%)	6 (4.8%)
Lost to Follow-up	5 (3.1%)	6 (4.8%)
Pregnancy	0	1 (0.8%)
Death	0	2 (1.6%)
Incarcerated	2 (1.2%)	0
Moved Out of State	2 (1.2%)	0
Research Unit Closed	0	1 (0.8%)

* Metastatic Anal CA, Week 39; ** Pulmonary MAC, Week 5

Figure 2. Percent of Subjects with HIV-RNA <50 (c/mL) (M=F) Through 96 Wks After Switch to EFV/FTC/TDF



Results (cont'd)

Figure 3. Mean (95% CI) Change in CD4 Counts (cells/mm³) Through 96 Wks After Switch to EFV/FTC/TDF

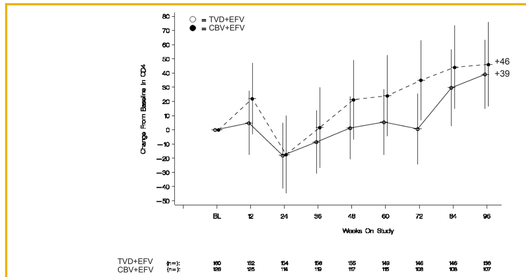
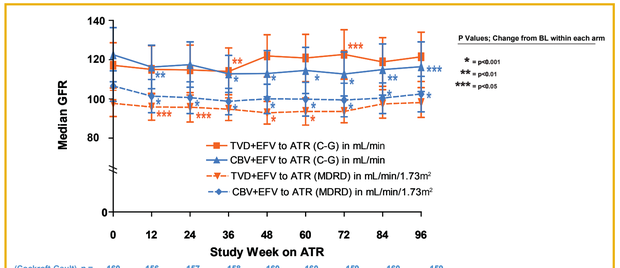


Figure 4. Median (IQR) Estimated GFR Through 96 Wks After Switch to EFV/FTC/TDF



Ad Hoc Adherence Analysis

Table 2. Summary of Three Once-daily HAART Regimens Taken During Study 934

Once-Daily Regimens	TDF + FTC + EFV (n=238)	FTC/TDF + EFV (n=162)	EFV/FTC/TDF (n=157)
Daily Pill Burden	3	2	1
Dose Duration (Study Weeks)	BL → 96	97 - 144	145 - 240
Mean Adherence Rate (%)	95.6	97.0	97.9

Table 3. Analysis of Three Once-daily HAART Regimens by Daily Pill Burden using the Mixed Effect Model (MITT subjects)

Daily Pill Burden Comparison	P Value
1 vs. 2	0.2304
1 vs. 3	0.0005
2 vs. 3	0.0262

Figure 5. Median Change (mg/dL) in Fasting Lipids Through 96 Wks After Switch to EFV/FTC/TDF

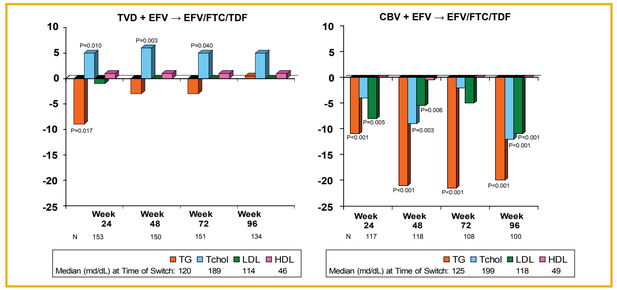
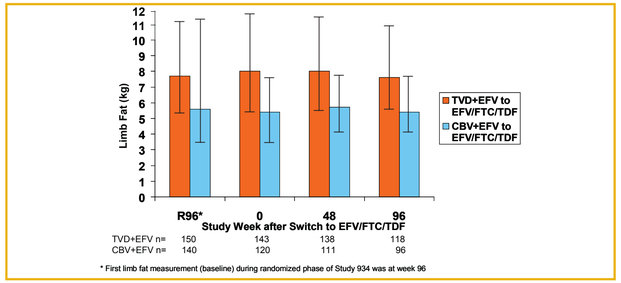


Figure 6. Median (IQR) Total Limb Fat (kg) Through 96 Wks After Switch to EFV/FTC/TDF



* First limb fat measurement (baseline) during randomized phase of Study 934 was at week 96

Conclusions

- In Study 934, patients who received HAART (either FTC/TDF + EFV or AZT/3TC + EFV) for 144 weeks and then switched therapy to the single tablet once-daily HAART regimen, EFV/FTC/TDF, for an additional 96 weeks of treatment demonstrated durable virologic suppression, continued immunologic recovery, and normal renal function
- In patients who received AZT/3TC + EFV for 144 weeks and switched to the single tablet once-daily HAART regimen, EFV/FTC/TDF, for an additional 96 weeks of treatment:
  - Statistically significant decreases were seen in fasting triglycerides, total cholesterol, and LDL
  - Minimal limb fat recovery occurred, however median total limb fat did not decrease further
    - Total limb fat continued to be lower than patients who received FTC/TDF + EFV for the first 144 weeks and then switched
- In an ad hoc analysis of adherence rates during the full 240 weeks of follow-up, adherence rates were statistically better when patients had smaller daily regimen pill burdens of 1 pill (EFV/FTC/TDF) (p=0.0005) or 2 pills (TVD+EFV) (p=0.026) each compared to 3 pills (FTC+TDF+EFV), respectively, despite mean adherence rates ≥ 95%