Six Year Safety and Efficacy of Tenofovir DF (TDF) in Combination with Lamivudine (3TC) and Efavirenz (EFV) in Antiretroviral-Naïve Patients

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Background

- Study 903 is a Phase III trial with an ongoing 336-week open-label extension phase and a completed 144-week randomized, double-blind phase designed to evaluate TDF compared to stavudine (d4T) in combination with 3TC and EFV in antiretroviral-naïve patients

Methods

- Study 903 inclusion/exclusion criteria:
  - HIV-infected patients naïve to antiretroviral treatment, 18-65 years of age, with plasma HIV RNA > 5,000 copies/mL (c/mL)
  - No significant laboratory or clinical abnormalities
  - No CD4+ cell count criteria
- Patients in select sites (Argentina, Brazil, and Dominican Republic) rolled-over into a 7-year (336-week) open-label extension phase (903E)
- Data obtained from patients originally randomized to TDF and participating in 903E were analyzed

Results

Figure 1. Study Design

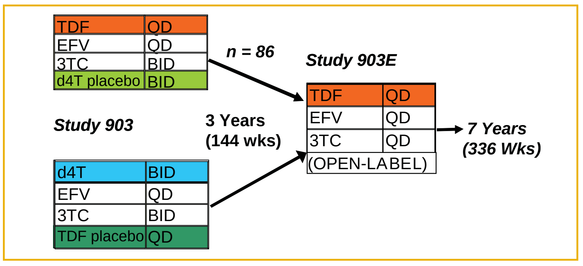


Table 1. Baseline Demographic and HIV Characteristics

	TDF+3TC+EFV (n = 86)
Mean ± SD Age in yrs (Range)	33 ± 7 (19 to 51)
Male	62%
Race	
White	70%
Black	12%
Other	18%
Mean ± SD HIV-RNA in $\log_{10}$ c/mL (Range)	4.86 ± 0.6 (3.12 to 6.45)
Mean ± SD CD4 count in cells/mm^3 (Range)	299 ± 188 (6 to 838)

- Median duration on TDF (Range): 296 weeks (156 to 307)

Patient Disposition Through 6 Years:

- 86 patients enrolled in Study 903 open-label extension phase and continued treatment with TDF
- 12 patients discontinued from the study prior to Year 6 (Week 288)
  - 1 patient discontinued due to adverse event (asymptomatic increase in serum amylase/lipase)
  - 3 patients had virologic failure
  - 2 patients discontinued due to pregnancy
  - 6 patients either withdrew consent, were non-compliant or lost to follow-up
- No patient developed Fanconi syndrome
- No patient discontinued due to renal abnormalities

Figure 2. Proportion with HIV-1 RNA < 400 c/mL Through 6 Years (M=F)

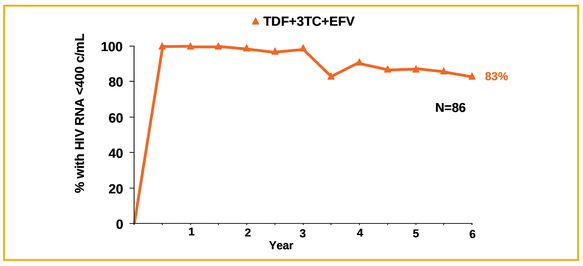


Figure 3. Proportion with HIV-1 RNA < 50 c/mL Through 6 Years (M=F)

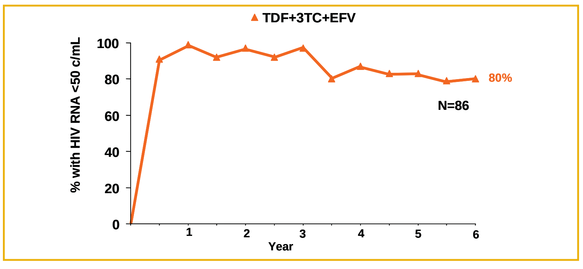
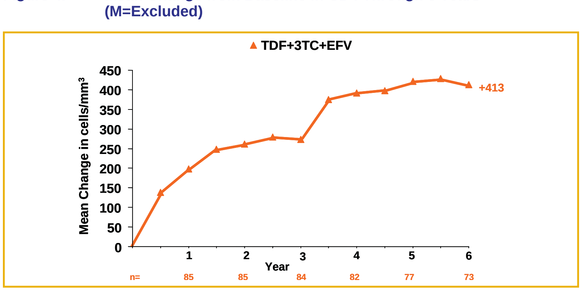


Figure 4. Mean Change from Baseline in CD4 Through 6 Years (M=Excluded)



Results (cont'd)

Resistance:

- 3 patients discontinued due to virologic failure
  - 2 Wild type genotypes
  - 1 T69N, M184V, K103N at Week 240
  - No K65R

Table 2. Serum Creatinine Through 6 Years

Maximum Confirmed Toxicity Grade (mg/dL)[a]	TDF+3TC+EFV (n = 86)
1 (>1.5 - 2.0)	2
2 (2.1 - 3.0)	0
3 (3.1 - 6.0)	0
4 (> 6.0)	0

a. Confirmed toxicity grade = two consecutive visits

Table 3. Serum Phosphorus Through 6 Years

Maximum Confirmed Toxicity Grade (mg/dL)[a]	TDF+3TC+EFV (n = 86)
1 (2.0-<2.2)	0
2 (1.5-1.9)	0
3 (1.0-1.4)	0
4 (<1.0)	0

a. Confirmed toxicity grade = two consecutive visits

Figure 5. Median Glomerular Filtration Rate (IQR) by Cockcroft-Gault (mL/min) and MDRD (mL/min/1.73m^2) through 6 Years

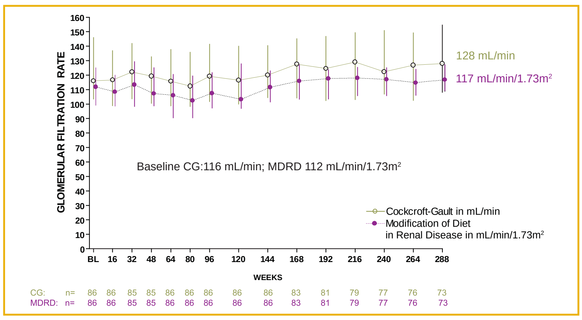
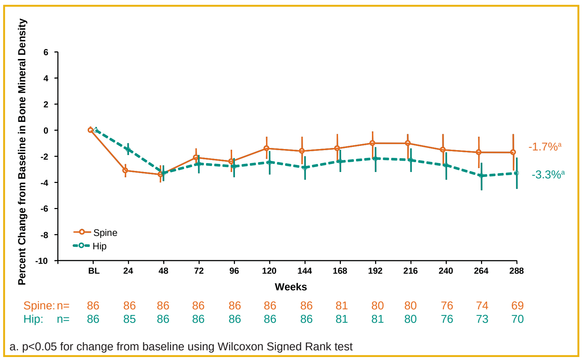


Figure 6. Mean % Change from Baseline in Spine and Hip BMD (95% CI) Through 6 Years

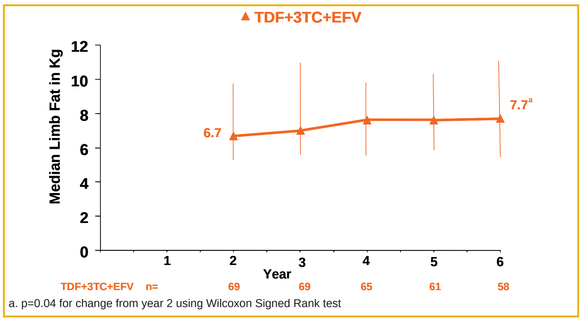


a. p<0.05 for change from baseline using Wilcoxon Signed Rank test

Bone Factures Through 6 Years:

- Through 6 years, 5 patients experienced bone fractures; all were trauma related and none were considered related to TDF

Figure 7. Median Total Limb Fat (IQR) Years 2-6



a. p=0.04 for change from year 2 using Wilcoxon Signed Rank test

Conclusions

Through 6 years of therapy in antiretroviral naïve patients, TDF+3TC+EFV demonstrated the following:

- **Sustained, durable antiretroviral efficacy**
- **Continued CD4 cell count increases**
- **No discontinuations due to renal adverse events**
- **Significant increases in limb fat from years 2 through 6**
- **No evidence of clinically relevant bone effects**