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Tenofovir Disoproxil Fumarate and Lamivudine Combination Therapy Compared to Lamivudine Alone for HBV in Therapy- Naïve HIV/HBV Co-infected Patients: 48 Week Interim Results

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Introduction

- Tenofovir disoproxil fumarate (TDF) is an acyclic nucleotide reverse transcriptase inhibitor that has shown durable activity against most wild-type and nucleoside-resistant HIV
- TDF has potent activity *in vivo* and *in vitro* against wild-type and lamivudine (LAM)-resistant Hepatitis B virus (HBV) (Table 1)
- After one to two years of LAM therapy, LAM resistance has been shown to develop in approximately 25% to 52% of HIV/HBV co-infected patients, respectively.

Table 1. *In Vitro* Activity of Tenofovir Against Wild-type and Lamivudine-resistant HBV

	IC_{50} (µM)	
Cell Type	Tenofovir	Lamivudine
HepAD38 (wild-type)	0.17	0.016
HepAD79 (LAM-R)	0.17	3.6
Fold Change:	None	225-fold

Ying et al., J. Viral Hepatitis (2000)

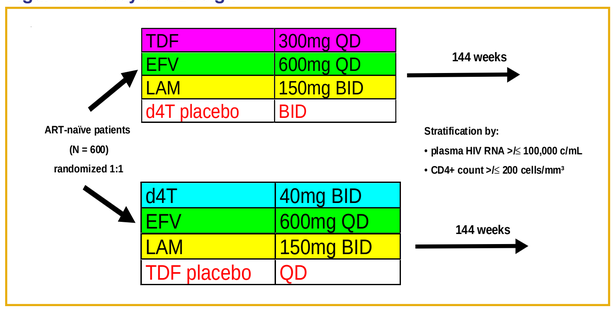
Objective

- To explore the antiviral efficacy of TDF 300mg QD + LAM 150mg BID vs. LAM 150mg BID alone on Hepatitis B virus in treatment-naive patients co-infected with HIV/HBV

Methods

- Study 903 is an ongoing Phase 3, randomized, double-blind, 144 week study comparing the safety and efficacy of TDF vs. d4T when used in combination with EFV and LAM in 600 HIV treatment-naïve patients.
- EFV and d4T have no reported anti-HBV activity
- All patients evaluated for HBsAg at Baseline
- Inclusion criteria for exploratory analysis, HBsAg positive
  - HBV DNA value >10^6 copies/mL at Baseline
  - Baseline and Week 48 HBV DNA samples available
- For patients HBsAg positive at Baseline, HBV DNA and serologies measured every 12 weeks prospectively throughout the trial
- Safety labs and clinical adverse events collected at Weeks 2, 4, and then every 4 weeks through Week 48
- Wilcoxon rank sum test used for comparison of HBV DNA change from Baseline for TDF+LAM vs. LAM alone

Figure 1. Study 903 Design



Viral Measurements

- Plasma HIV RNA: PCR assay (Roche Amplicor® HIV-1 Monitor Test, version 1.0 or 1.5; Standard and Ultrasensitive methods)
- Serum HBsAg: EIA (Abbott Auszyme® Monoclonal EIA in Indianapolis and Abbott AxSYM in Geneva)
- Serum HBV DNA: PCR assay (Roche Amplicor® HBV Monitor Test)
- HBeAb: Competitive EIA (Diasorin ETI-EBK Kit)
- HBeAg: Direct noncompetitive EIA (Diasorin ETI-EBK Kit)

Genotypic Analysis Methods

- Population based sequencing
  Serum HBV DNA → PCR → Sequencing
- Serum samples with ≥1000 copies/mL of HBV DNA at Week 48 analyzed
- Region sequenced: rt 1 to 344 (1032 nucleotides) of HBV pol
- Compared the baseline and post-treatment sequences to identify any amino acid substitutions that developed

Results

Table 2. Baseline Characteristics for HIV/HBV Co-infected Patients

	TDF+LAM (n=5)	LAM (n=6)
Mean Age (yrs)	42	36
% Male	100%	83%
Mean HBV DNA (log_{10} c/mL)	8.30	8.86
Mean HIV-1 RNA (log_{10} c/mL)	4.89	4.77
Mean CD4+ count (cells/mm³)	151	249
Mean ALT (U/L)	97	78
HBeAg+	4	6

p>0.05 for all comparisons

Table 3. Week 48 Efficacy Summary

	TDF+LAM (n=5)	LAM (n=6)
Mean change HBV DNA (log_{10} c/mL)	-4.70	-2.95
HBV DNA < 1000 c/mL	4	1
LAM^R (YMDD mutant)	0/1	4/5*
HBeAg seroconversion	1	1
Mean change ALT level (U/L)	-55	-22
ALT > 5 x ULN (Weeks 0-48)	2	4

*M204V + L180M (n=3); M204I (n=1)

The 4 patients who developed the LAM^R showed a mean increase in HBV DNA of 2.3 log_{10} from their respective nadir.

Figure 2. Mean Change from Baseline in HBV DNA (95% CI)

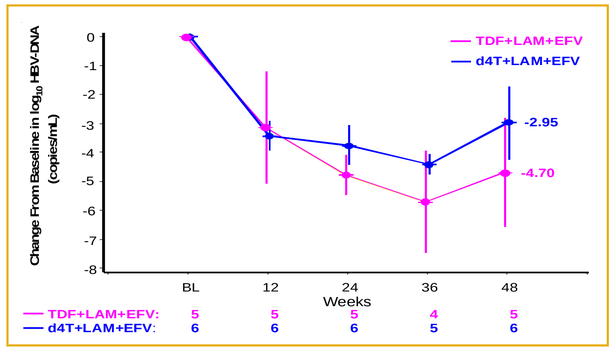
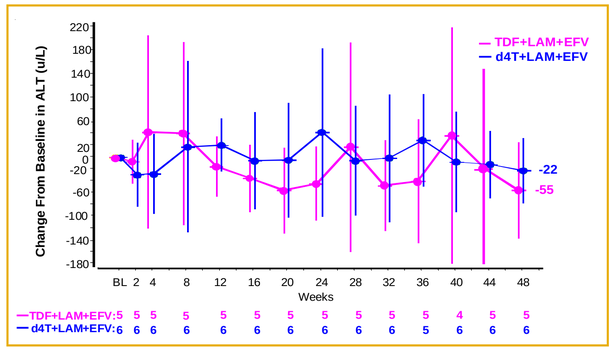


Figure 3. Mean Change from Baseline in ALT (95% CI)



Conclusions

- The combination of TDF + LAM appears to more effectively suppress both HBV replication and LAM resistance development compared to LAM alone.
- Further study will be needed to clarify the role of TDF + LAM combination anti-HBV therapy in HIV/HBV co-infected patients.