Poster Number

# 483

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# Three Years of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Positive Patients (HBeAg+) With Chronic Hepatitis B (Study 103)


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## Background

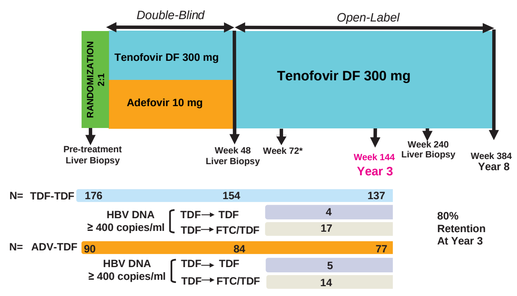
- Tenofovir DF (TDF) was approved for HIV-1 in 2001 and chronic hepatitis B (CHB) in 2008: ~ 2.4 million patient-years of experience
- Week 48 Phase 3 data showed TDF superior to adefovir dipivoxil (ADV):
  - 76% of HBeAg-positive TDF-treated patients (versus 13% ADV-treated patients) had HBV DNA <400 copies/mL
- TDF treatment in HBeAg-positive patients beyond Week 48 showed:
  - Both stable and viremic patients on ADV can effectively switch to TDF and achieve or maintain viral suppression (HBV DNA < 400 copies/mL), normal ALT and increasing HBeAg and HBsAg loss at Week 96
  - TDF patients treated for 96 weeks maintained HBV DNA < 400 copies/mL, normal ALT levels and experienced increasing HBeAg and HBsAg loss

## Objective

- Evaluate the safety and efficacy of up to 3 years of TDF therapy

## Methods

**Figure 1. HBeAg Positive Study 103 Design**




*Patients had the option to add FTC 200 mg at the discretion of the investigator if confirmedHBV DNA ≥400 copies/ml at week 72 or beyond

### Key Eligibility Criteria

- HBeAg-positive patients
- Age 18-69 years
- Compensated liver disease
- Nucleos(t)ide naive
- HBV DNA > $10^6$ copies/mL
- ALT ≥ 2 x ULN and <10 x ULN (females ULN=34 U/L; males ULN=43)
- Knodell necroinflammatory score ≥ 3
- HIV-1, HDV, HCV seronegative

### Assessments During Year 3

- HBV DNA and laboratory data every 12 weeks
- HBeAg and HBsAg every 12 weeks
- Resistance surveillance: patients with HBV DNA ≥ 400 copies/mL (69 IU/mL)

### Statistical Methods

**Long-Term Evaluation, TDF only analysis [LTE-TDF]**

- Patients discontinuing the study early and missing data due to death; safety, tolerability, or efficacy; loss to follow-up; or for any other reason who were failures for the endpoint or had an ongoing AE at the last on-study visit were considered failures.
- Patients missing data at random or who discontinued for administrative reasons with HBV DNA <400 copies/mL with no ongoing AEs were excluded for visits after discontinuation.
- Patients with HBsAg loss who discontinued the study for any reason and met the endpoint criteria at the last on-study visit had the last value carried forward (LOCF) and were included in the analysis as a success.
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

**Open-Label Extension, TDF only analysis [OLE-TDF]**

- Includes only those patients who entered the open label extension
- Employs an intent-to-treat missing=failure approach
- Patients who added emtricitabine were considered failures at all time points following the addition of emtricitabine

**On-Treatment Analysis [observed data, missing=excluded]**

- Excludes patients with missing data from both the numerator and denominator at each applicable time point for the analyses of HBV DNA, ALT, and HBeAg loss and seroconversion

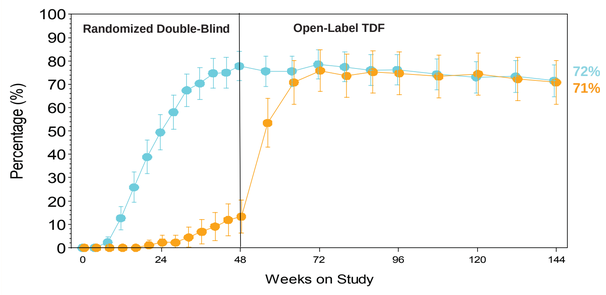
## Results

**Table 1. Baseline Characteristics of Patients Entering Year 3 Similar to Patients Randomized**

| | Randomized Treatment | | Patients Entering Year 3 | |
|---|---|---|---|---|
| | TDF (N=176) | ADV (N=90) | TDF-TDF (N=141) | ADV-TDF (N=82) |
| Mean Age (years) | 34 | 34 | 35 | 35 |
| Race<br>Caucasian<br>Asian | <br>52%<br>36% | <br>51%<br>36% | <br>55%<br>34% | <br>54%<br>34% |
| Male | 68% | 71% | 72% | 72% |
| Mean HBV DNA ($log_{10}$ copies/mL) | 8.64 | 8.88 | 8.66 | 8.84 |
| Mean ALT (U/L) | 142 | 155 | 142 | 159 |
| Mean Knodell necroinflammatory score<br>Mean Knodell fibrosis Score | 8.3<br>2.3 | 8.3<br>2.4 | 8.2<br>2.3 | 8.5<br>2.5 |
| Knodell fibrosis score = 4 (cirrhosis) | 20% | 20% | 22% | 20% |
| Viral Genotype<br>A<br>B<br>C<br>D | <br>23%<br>15%<br>25%<br>31% | <br>21%<br>11%<br>30%<br>35% | <br>25%<br>13%<br>24%<br>33% | <br>21%<br>8%<br>31%<br>36% |

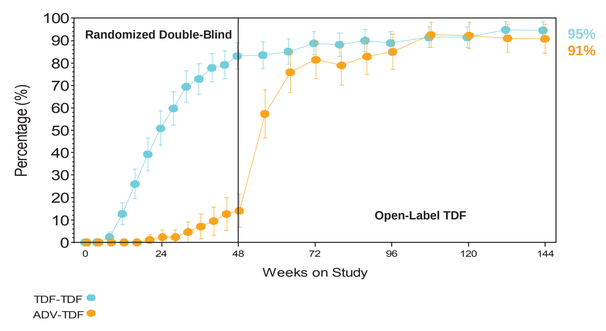
**Figure 2. HBV DNA Remains Suppressed with up to 3 Years of TDF Treatment (% Patients with HBV DNA < 400 copies/mL)**

**Figure 2a. LTE-TDF Analysis (Long-Term Evaluation, TDF only)**



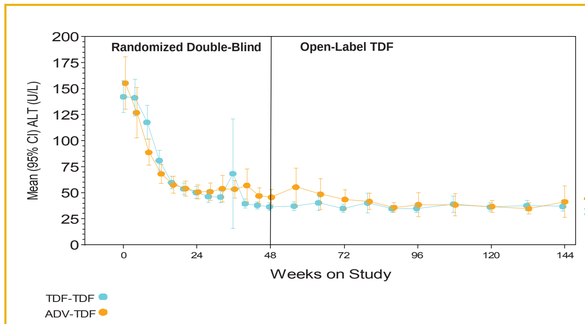

- OLE-TDF Analysis: % Patients with HBV DNA <400 copies/mL was 75% TDF-TDF and 74% ADV-TDF

**Figure 2b. On-Treatment Analysis**




- Includes 17 patients across both treatment groups who had HBV DNA <400 copies/mL at week 144 on FTC + TDF

**Figure 3. ALT (U/L) Over Time**




- Percent of Patients with Normalized ALT On-Treatment: 73% TDF-TDF; 76% ADV-TDF

**Figure 4. On-Treatment of Patients Initially Randomized to TDF with HBeAg Loss and Seroconversion at Years 1, 2 and 3**

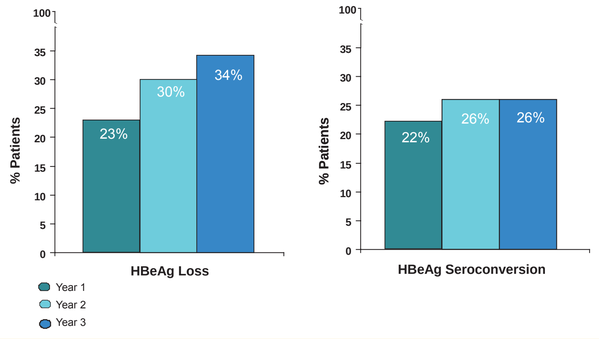
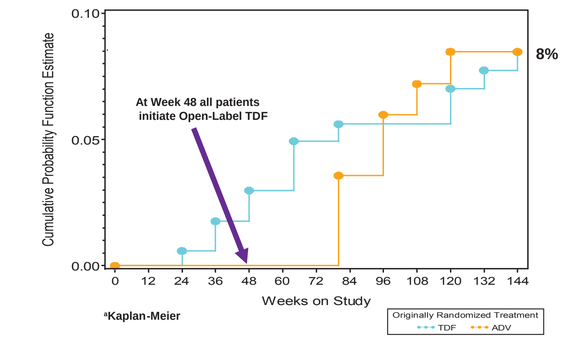



**Figure 5. Cumulative Probability[a] of HBsAg Loss**




[a]Kaplan-Meier

- 14/20 patients with HBsAg loss discontinued treatment and entered treatment-free follow-up (mean 171 days off treatment)
- 2/20 patients who seroconverted to anti-HBs have discontinued from the study

### Surveillance for Resistance Results

Overall HBV DNA from 18 viremic patients were genotypically evaluated and 5 patients had amino acid substitutions in conserved site region:

Patients originally randomized to TDF:
TDF: rtR51K
FTC + TDF: rtR192H
FTC + TDF: rtL180L/M ± rtM204M/V ± rtA181T

Patients originally randomized to ADV:
ADV-TDF: rtN236N/T ± rtR274Q/R
ADV-TDF: rtG152E

Phenotypically these conserved site changes were evaluated in vitro in HepG2 cells. No HBV pol/RT amino acid substitutions associated with TDF resistance developed through 144 weeks of treatment

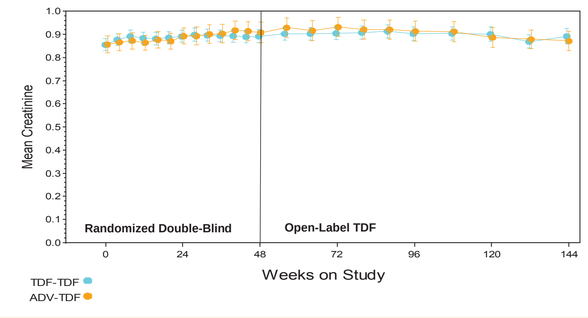
For complete details see Poster # 480 by Snow-Lampart et al. Resistance Surveillance for up to 144 Weeks in HBeAg+ and HBeAg- Hepatitis B Patients Treated with Tenofovir DF Showed No Relationship Between Virologic Breakthrough and Emergence of Genotypic Changes in HBV Polymerase

**Table 2. Summary of Cumulative Open Label Safety Data Through Week 144**

| | TDF-TDF (N=154)[a] | ADV-TDF (N=84)[a] |
|---|---|---|
| Study Drug-Related SAE | 2 (1.3%) | 2 (2.4%) |
| Deaths | 0 | 0 |
| Grade 3 or Grade 4 Laboratory Abnormality | 19 (12.3%) | 13 (15.5%) |
| Discontinued due to an AE<br>creatinine increase | 1 (<1%)<br>1 (<1%) | 0<br>0 |
| Confirmed phosphorus < 2mg/dL | 0 | 1 (1%) |
| Confirmed 0.5 mg/dL increase from baseline in creatinine | 0 | 2 (2%) |
| Confirmed creatinine clearance < 50 mL/min | 0 | 0 |

a. N's reflect the number of patients who entered the open-label extension

**Figure 6. Creatinine Over Time**




## Conclusions

**At Year 3, 80% of patients remained on treatment demonstrating**

- **durable and potent antiviral activity, i.e., 93% of patients had HBV DNA <400 copies/mL**
- **an 8% cumulative probability of HBsAg loss**
- **no resistance to TDF**
- **a favorable tolerability profile**

## Acknowledgements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