

# Characteristics of HBeAg-Positive Patients with HBsAg Loss/Seroconversion Following Treatment with Tenofovir Disoproxil Fumarate (TDF)



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## Introduction

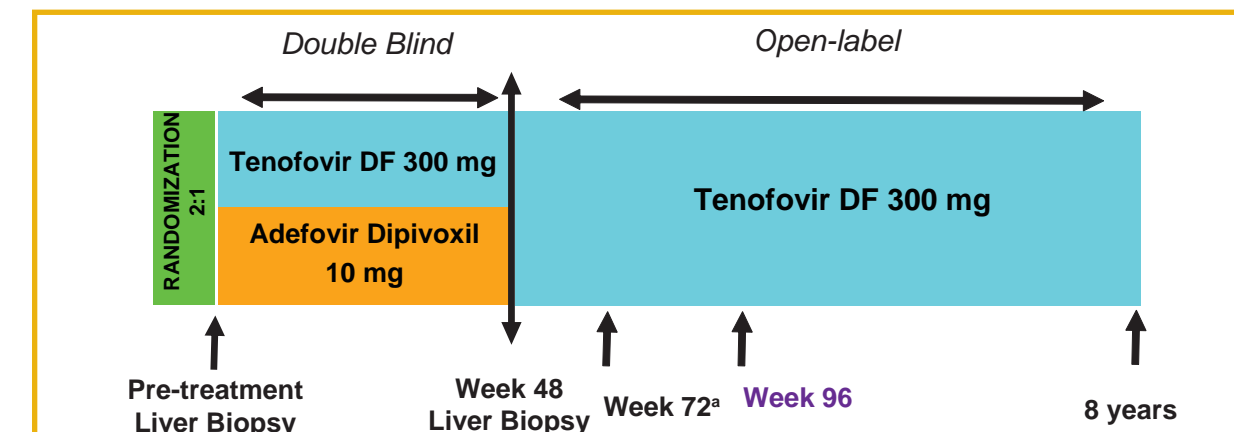
- Tenofovir DF (TDF) is a nucleotide analog and obligate chain terminator
- Approved for HIV-1 in 2001: over 2 million patient-years of experience
- Approved for chronic hepatitis B (CHB) in 2008
- Week 48 phase 3 data showed that TDF had superior antiviral efficacy to adefovir dipivoxil (ADV) in studies 102 (HBeAg negative patients) and 103 (HBeAg-positive patients)<sup>1</sup>:
  - 93% vs. 63% (HBeAg-negative) and 76% vs. 13% (HBeAg-positive) with HBV DNA <400 copies/mL (<69 IU/mL) (ITT)
  - 3% of patients treated with TDF for 48 weeks experienced HBsAg loss (vs. 0% ADV-treated patients)<sup>1</sup>
- Week 96 antiviral efficacy data demonstrates durable and potent activity in both HBeAg-negative and HBeAg-positive patients<sup>2,3</sup>:
  - 91% of HBeAg-negative and 78% of HBeAg-positive patients had HBV DNA <400 copies/mL (<69 IU/mL) (ITT)
  - Overall 6% of HBeAg positive patients lost HBsAg and 4.5% seroconverted to anti-HBs

## Objective

To evaluate the characteristics of the HBeAg+ patients treated with TDF who achieved HBsAg loss/seroconversion within the first 2 years of treatment

## Methods

Figure 1. Study Design of Phase 3 Pivotal Study 103

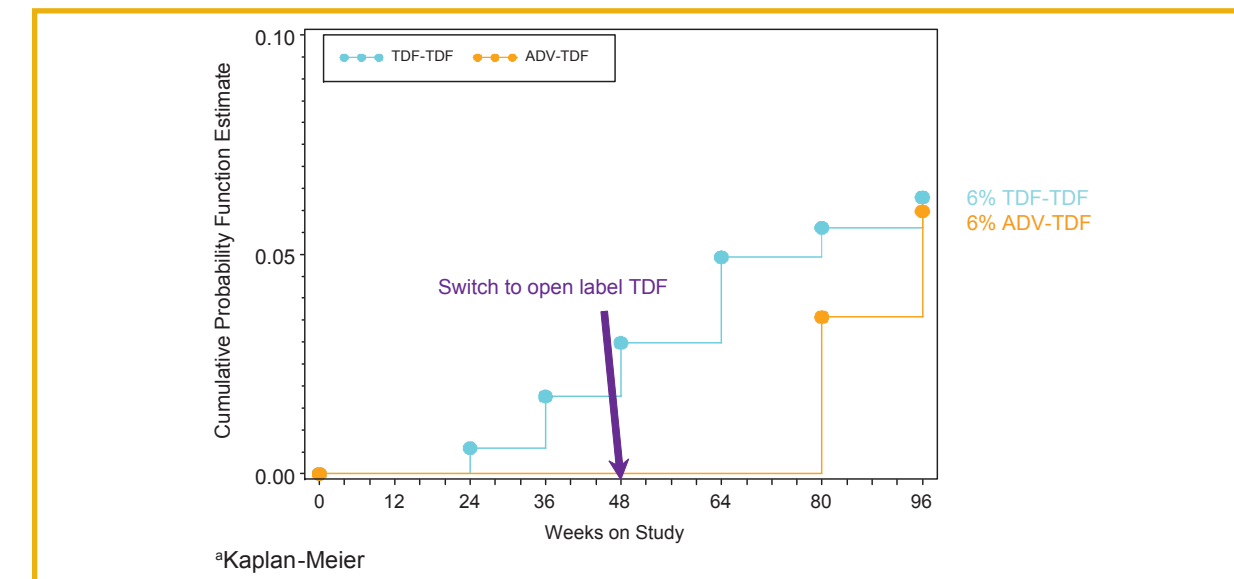


a. Week 72 HBV DNA  $\geq$  400 copies/mL option to add emtricitabine (FTC) to TDF as a fixed dose combination tablet

- HBV DNA and laboratory parameters were assessed every 4-8 weeks
- HBeAg and HBsAg assessed qualitatively every 12-16 weeks
- HBsAg measured quantitatively using the Abbott Architect Assay (sensitivity  $\leq$  0.05 IU/mL) every 12-16 weeks

## Results

Figure 2. Cumulative Probability\* of HBsAg Loss in Study 103 (HBeAg Positive Patients)



## Results (cont'd)

Table 1. Baseline Demographic and Disease Characteristics (HBeAg Positive Patients)

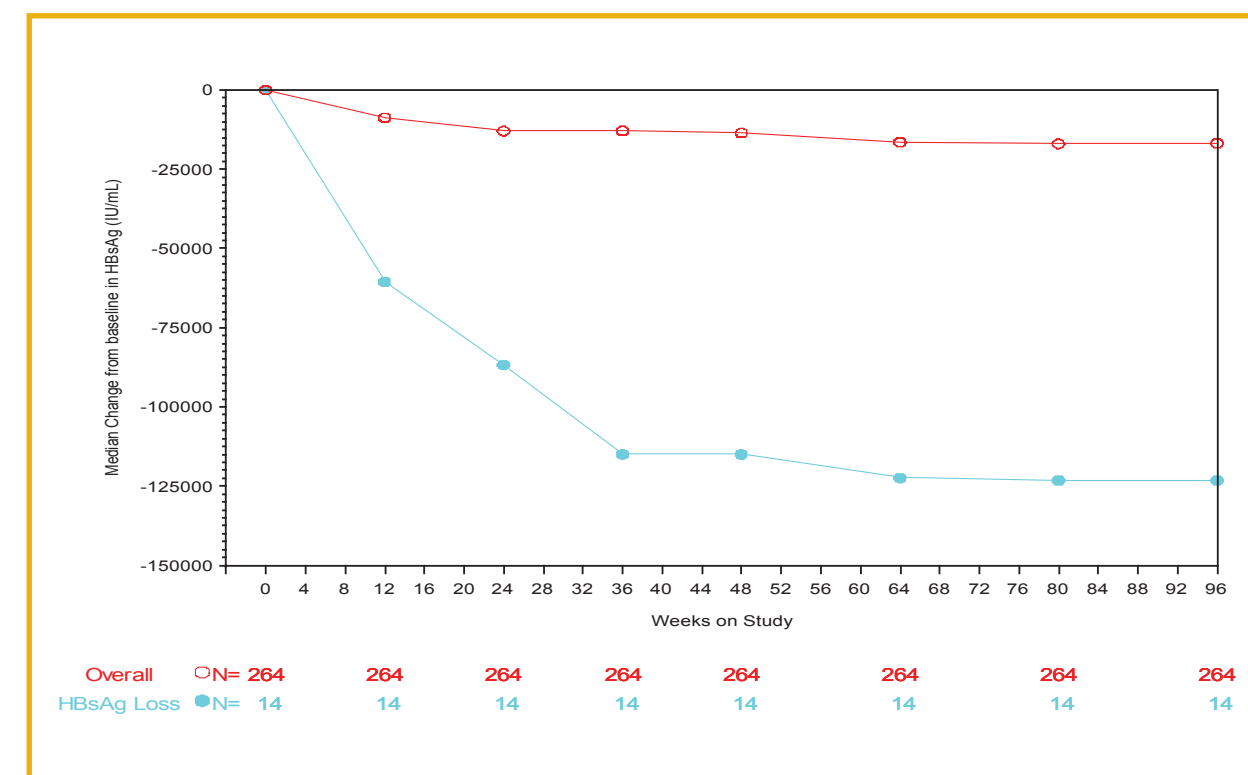
Characteristic <sup>a</sup>	Patients with HBsAg Loss (N=14)	Overall Population (N=266)
Mean Age (years)	34	34
Caucasian	14 (100%)	138 (52%)
Male	11 (79%)	183 (69%)
Mean HBsAg (log <sub>10</sub> IU/mL)	5.09 (4.62, 5.38)	4.47 (1.01, 5.40)
Mean HBV DNA (log <sub>10</sub> c/mL)	9.49 (8.47, 9.64)	8.72 (4.67, 10.92)
Mean ALT (U/L)	163	147
Previous Interferon experience	0%	43 (16%)
Mean Knodell necroinflammatory Score	9.0	8.3
Mean Knodell fibrosis Score	3.0	2.3
Viral Genotype		
A	8 (57%)	58 (22%)
B	0	35 (14%)
C	0	69 (27%)
D	6 (43%)	84 (32%)

a. Given the small sample size, median rather than mean values are reported for patients with HBsAg loss

Table 2. HBsAg Clearance by Genotype

Genotype	HBsAg Clearance at Year 2 n/N (%)
A	8/67 (12%)
B	0/35 (0%)
C	0/69 (0%)
D	6/90 (7%)

Figure 3. Median Change From Baseline in HBsAg Levels Over Time: HBeAg-Positive Patients with HBsAg Loss vs. Overall Population<sup>a</sup>



a. LOCF (last observation carried forward)

Figure 4. HBsAg Levels Over Time for the HBeAg-Positive Patients with HBsAg Loss

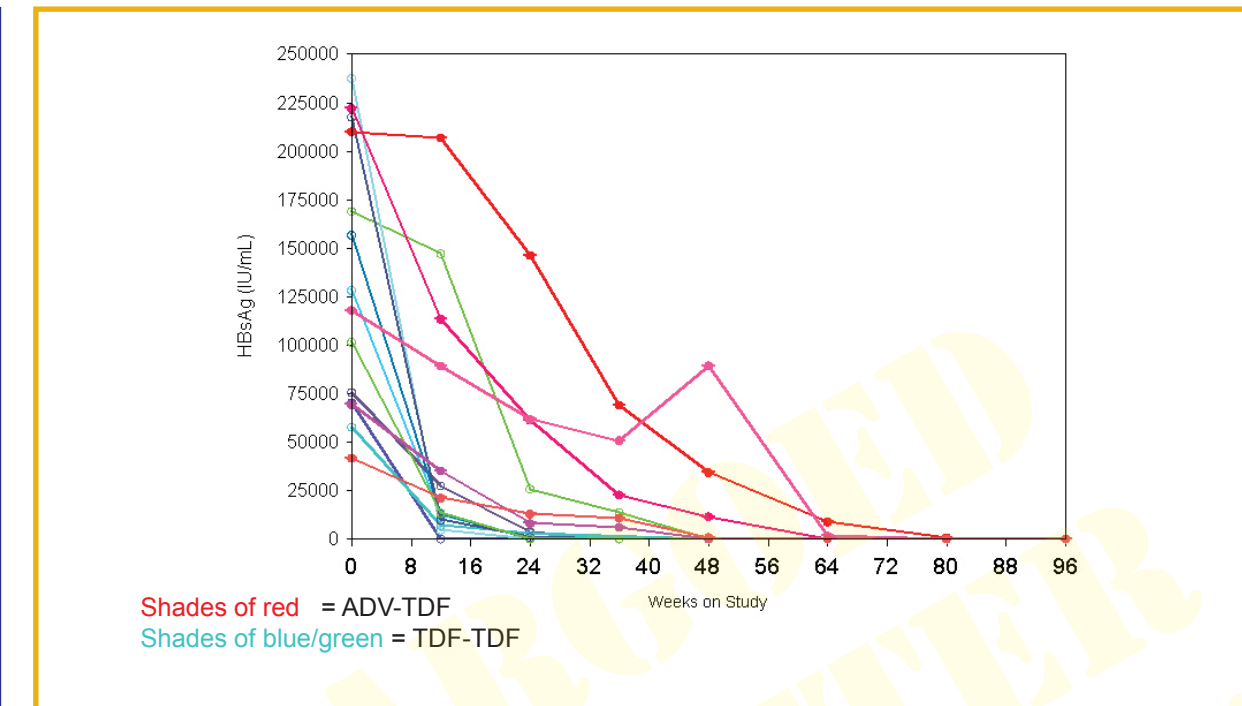


Figure 5. Median Change from Baseline in HBV DNA Levels Over Time: HBeAg-Positive Patients with HBsAg Loss vs. Overall Population

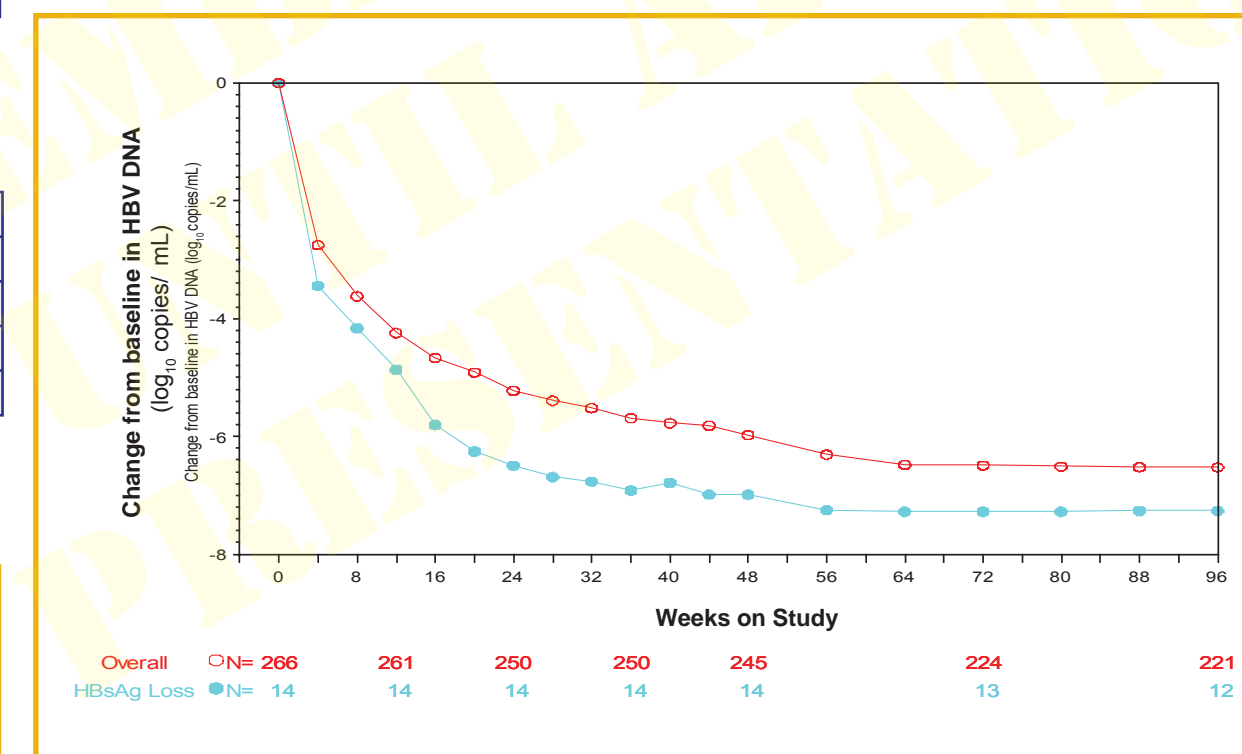


Figure 6. HBV DNA Levels Over Time for the HBeAg-Positive Patients with HBsAg Loss

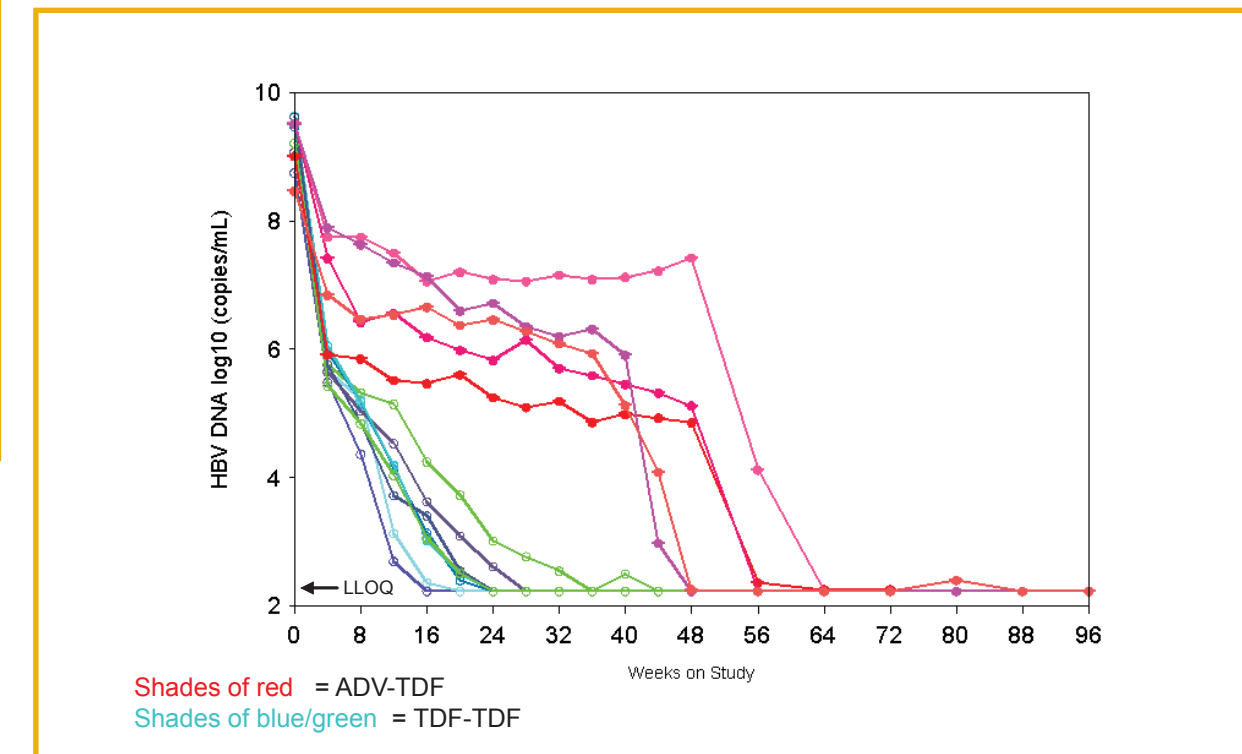


Figure 7. Temporal Relationship between HBeAg loss and HBsAg Loss

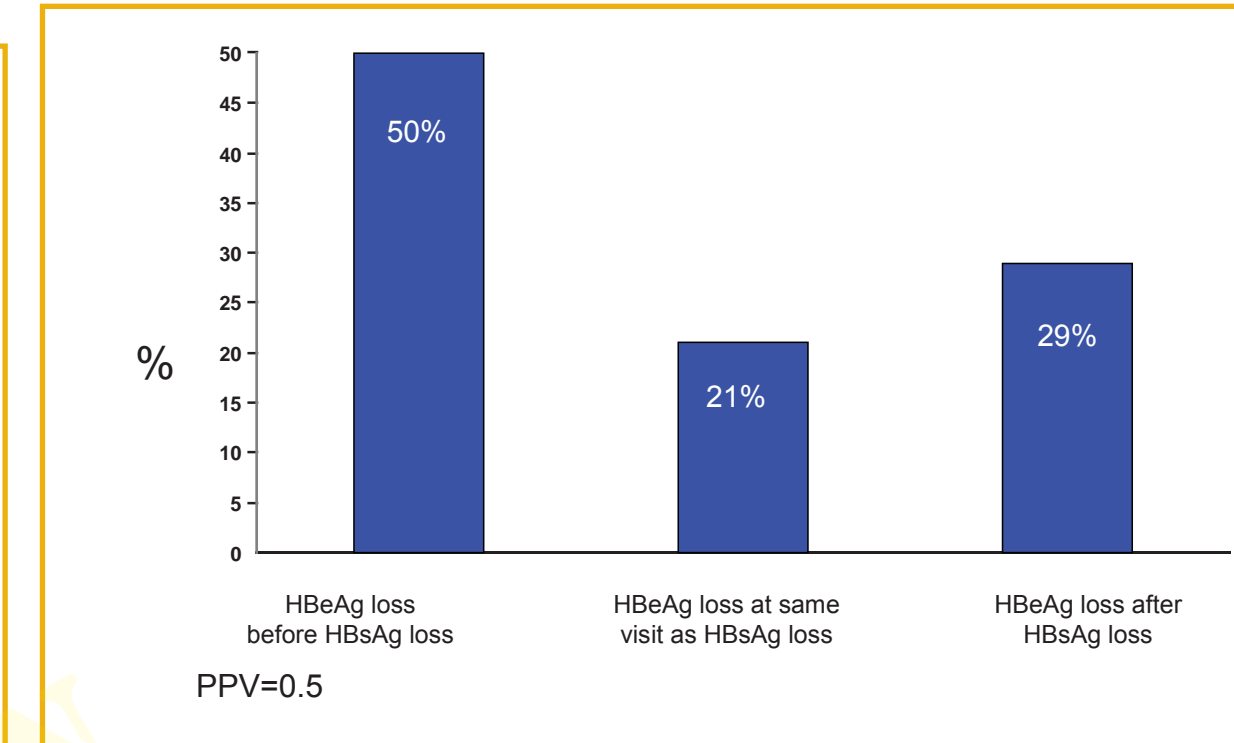


Table 3. Predictors of HBsAg Loss: Univariate Model Results

Characteristic	Odds Ratio	95% CI for OR	P-value
Baseline Log <sub>10</sub> HBV DNA	2.273	(1.071, 4.821)	0.0324
Baseline Log <sub>10</sub> HBsAg	15.762	(3.123, 79.560)	0.0008
Genotype A/D vs. Other	11.250	(1.441, 87.839)	0.021
Non-Asian vs Asian	7.881	(1.015, 61.196)	0.0484
Reduction from Baseline in Log <sub>10</sub> HBsAg at Week 24	5.128	(2.674, 9.804)	<0.0001
0.5 log decrease in HBsAg at Week 12 (y/n)	4.020	(1.347, 11.998)	0.0126
Gender M/F	1.641	(0.445, 6.051)	0.4565
Baseline Age	1.002	(0.957, 1.050)	0.9251
Baseline ALT	1.002	(0.999, 1.006)	0.1702
Baseline Knodell necroinflammatory score	1.368	(0.956, 1.957)	0.0869
Baseline Ishak fibrosis score	1.139	(0.810, 1.602)	0.4546
Reduction from Baseline in Log <sub>10</sub> HBV DNA at Week 4	1.529	(0.825, 2.833)	0.1774
Reduction from Baseline in Log <sub>10</sub> HBV DNA at Week 24	1.337	(0.907, 1.972)	0.1432
Baseline ALT 0-2xULN y/n	0.271	(0.035, 2.120)	0.2137
Baseline ALT 2-5xULN y/n	1.188	(0.387, 3.649)	0.7635
Baseline ALT >5xULN y/n	1.864	(0.559, 6.215)	0.3110

Table 4. Predictors of HBsAg Loss: Multivariate Model Results

In a Multivariate stepwise model considering baseline factors only, the only characteristics to remain in the model:			
Characteristic	Odds Ratio	95% CI for OR	P-value
Baseline log <sub>10</sub> HBsAg	58.612	(5.778, 594.562)	<0.001
Baseline Knodell Necroinflammation	1.762	(1.074, 2.775)	0.024
In a Multivariate stepwise model considering baseline and on-treatment factors, the only characteristic to remain in the model:			
Characteristic	Odds Ratio	95% CI for OR	P-value
Reduction from Baseline in Log <sub>10</sub> HBsAg at Week 24	5.649	(2.278, 13.889)	0.0002

## Conclusions

- 6% of patients with up to 2 years of TDF treatment lost HBsAg
- HBeAg-positive patients who lost HBsAg:
  - were Caucasians chronically infected with genotypes A and D HBV
  - had high baseline HBsAg and HBV DNA levels
- In a multivariate model of baseline and on treatment factors, only the change in HBsAg levels at week 24 was significantly predictive of HBsAg loss

## References

- Marcellin P, Heathcote J, Buti M et al. Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B. NEJM 2008, Vol 359, pg 2442-2455.
- Marcellin P, Buti M, Krastev Z et al. Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102) presented at AASLD 2008 (#146).
- Heathcote J, Gane E, DeMan R et al. Two Year Tenofovir Disoproxil Fumarate (TDF) Treatment and Adefovir Dipivoxil (ADV) Switch Data in HBeAg-Positive Patients with Chronic Hepatitis B (Study 103) presented at AASLD 2008 (#158).

## Acknowledgements

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