

## Background

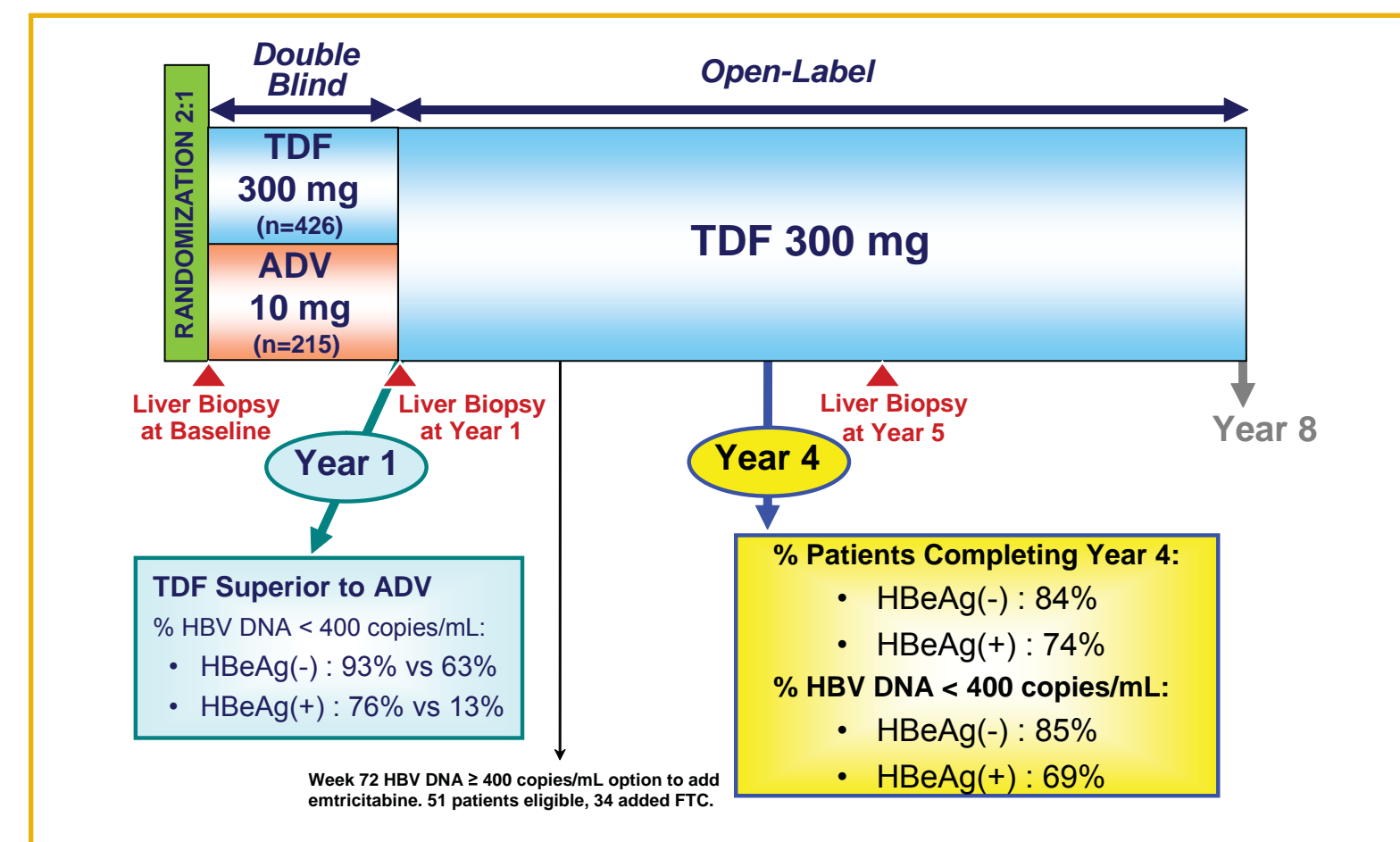
- TDF has potent antiviral activity and good safety in patients with HBeAg(-) or HBeAg(+) CHB
- In two registration studies (studies 102 and 103) with 375 HBeAg(-) and 266 HBeAg(+) patients, 0 HBeAg(-) and 23 HBeAg(+) patients experienced loss of HBsAg with up to 4 years of TDF treatment<sup>1</sup>
- Preliminary analysis showed baseline characteristics of HBeAg(+) patients who experienced HBsAg loss included genotype A or D, HBsAg  $\geq 4.5 \log_{10}$  IU/mL, HBV DNA  $\geq 9 \log_{10}$  copies/mL, and Knodell Necroinflammatory Score  $\geq 9$ <sup>2</sup>

## Objectives

- To compare the change in HBsAg levels during TDF treatment across genotypes in HBeAg(-) and HBeAg(+) patients
- To further define characteristics and outcome markers associated with HBsAg loss

## Methods

Figure 1. Study Design: HBeAg(-) and HBeAg(+) Patients



- HBsAg was quantified every 12 weeks using Abbott Architect assay (LLOQ=1 IU/mL). Loss of HBsAg was defined as a negative test result by qualitative serology test
- Baseline and on-treatment factors were evaluated using univariate tests for the TDF-TDF groups of HBeAg(+) and HBeAg(-) patients
- Factors determined to be associated with HBsAg loss were included in a stepwise multivariate logistic model for two subgroups of the data, HBeAg(+) patients with genotypes A to D with and without HBsAg loss, and HBeAg(+) patients with genotypes A and D with and without HBsAg loss

Table 1. Baseline Characteristics of Patients WITH vs. WITHOUT HBsAg Loss

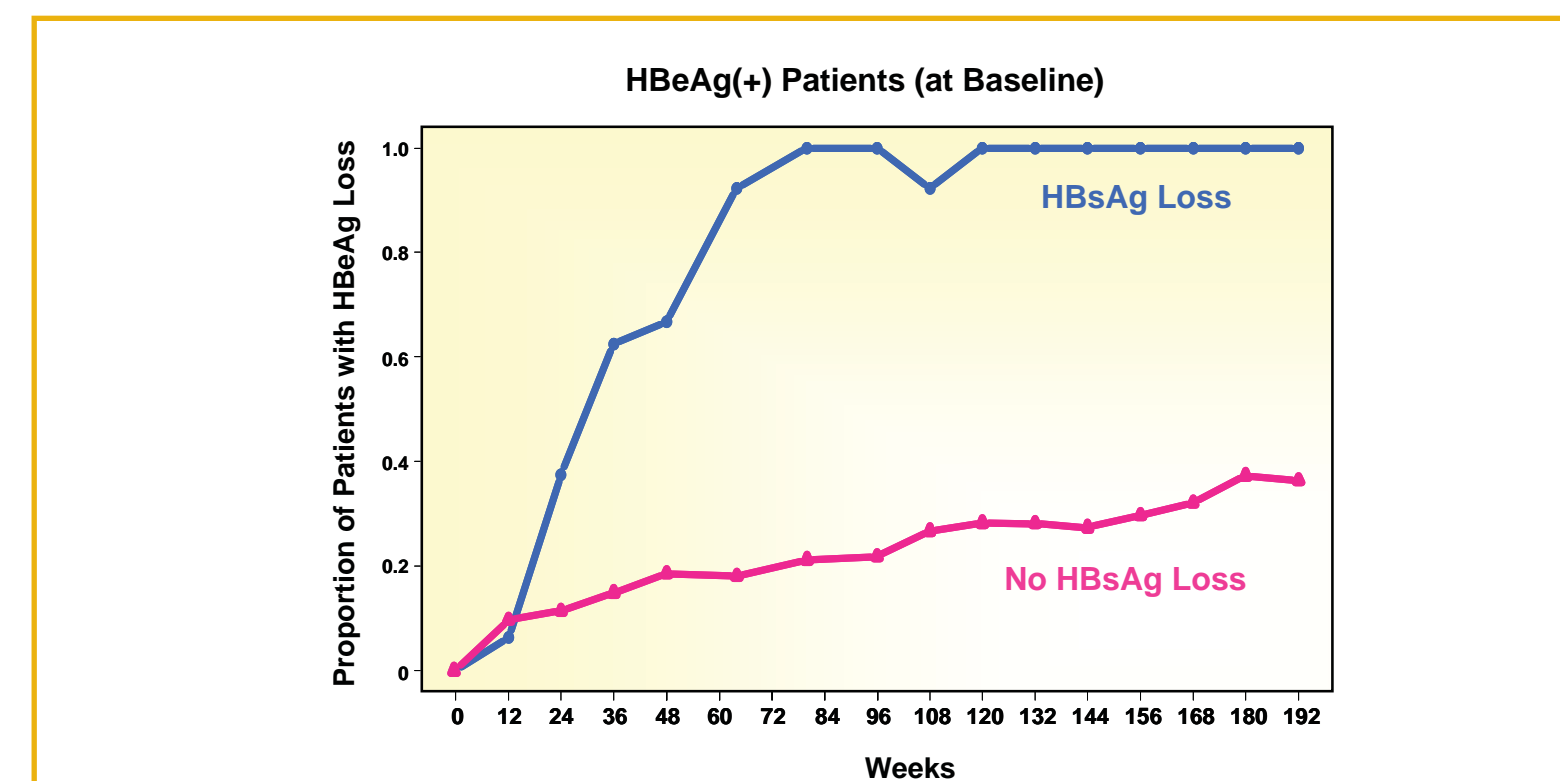
Characteristic*	WITH HBsAg Loss HBeAg(+) (n = 23)*	NO HBsAg Loss HBeAg(+) (n = 243)*	NO HBsAg Loss HBeAg(-) (n = 375)
Median Age, Years	35 (26, 44)	32 (24, 44)	44 (37, 51)
Race (%)			
Caucasian	21 (91%)	117 (48%)	242 (64%)
Asian	0	95 (39%)	94 (22%)
Black	2 (9%)	17 (7%)	11 (3%)
Others	0	14 (6%)	28 (7%)
Male (%)	18 (78%)	166 (68%)	289 (77%)
Median HBsAg, log <sub>10</sub> IU/mL	5.07 (3.28, 5.40)	4.51 (1.01, 5.40)	3.81 (1.10, 5.29)
Median HBV DNA, log <sub>10</sub> copies/mL	9.31 (7.68, 9.64)	8.82 (5.32, 10.92)	6.92 (2.23, 9.84)
Median ALT, U/L	140 (50, 425)	110 (23, 964)	98 (16, 884)
Median Knodell Necroinflammatory Score	7 (4, 11)	7 (1, 11)	6 (2, 10)
Median Knodell Fibrosis Score	3 (1, 4)	2 (1, 4)	2 (1, 4)
Previous Interferon Experience (%)	3 (13%)	42 (17%)	63 (17%)
Viral Genotype (%)			
A	14 (61%)	46 (19%)	41 (11%)
B	1 (4%)	32 (13%)	41 (11%)
C	0	69 (28%)	41 (11%)
D	7 (30%)	79 (33%)	235 (63%)
E	0	5 (2%)	6 (2%)
F	1 (4%)	7 (3%)	1 (<1%)

\* HBsAg level only available for 263 of 266 HBeAg(+) patients Median (IQR)

Table 2. Genotype Distribution of Patients with HBsAg Loss

Treatment Group	Total	Genotype					
		A	B	C	D	F	
TDF-TDF	16	9	1	0	5	1	
ADV-TDF	7	5	0	0	2	0	
Total	23	14	1	0	7	1	

Figure 2. Loss of HBeAg\* (TDF-TDF Groups)



\* Of the 16 TDF-TDF patients with HBsAg loss, 15 had HBeAg seroconversion prior to or at the same visit as HBsAg loss (n=3), or HBsAg loss with HBsAg seroconversion (n=12). One patient had HBeAg loss prior to HBsAg loss and seroconversion, but no HBeAg seroconversion

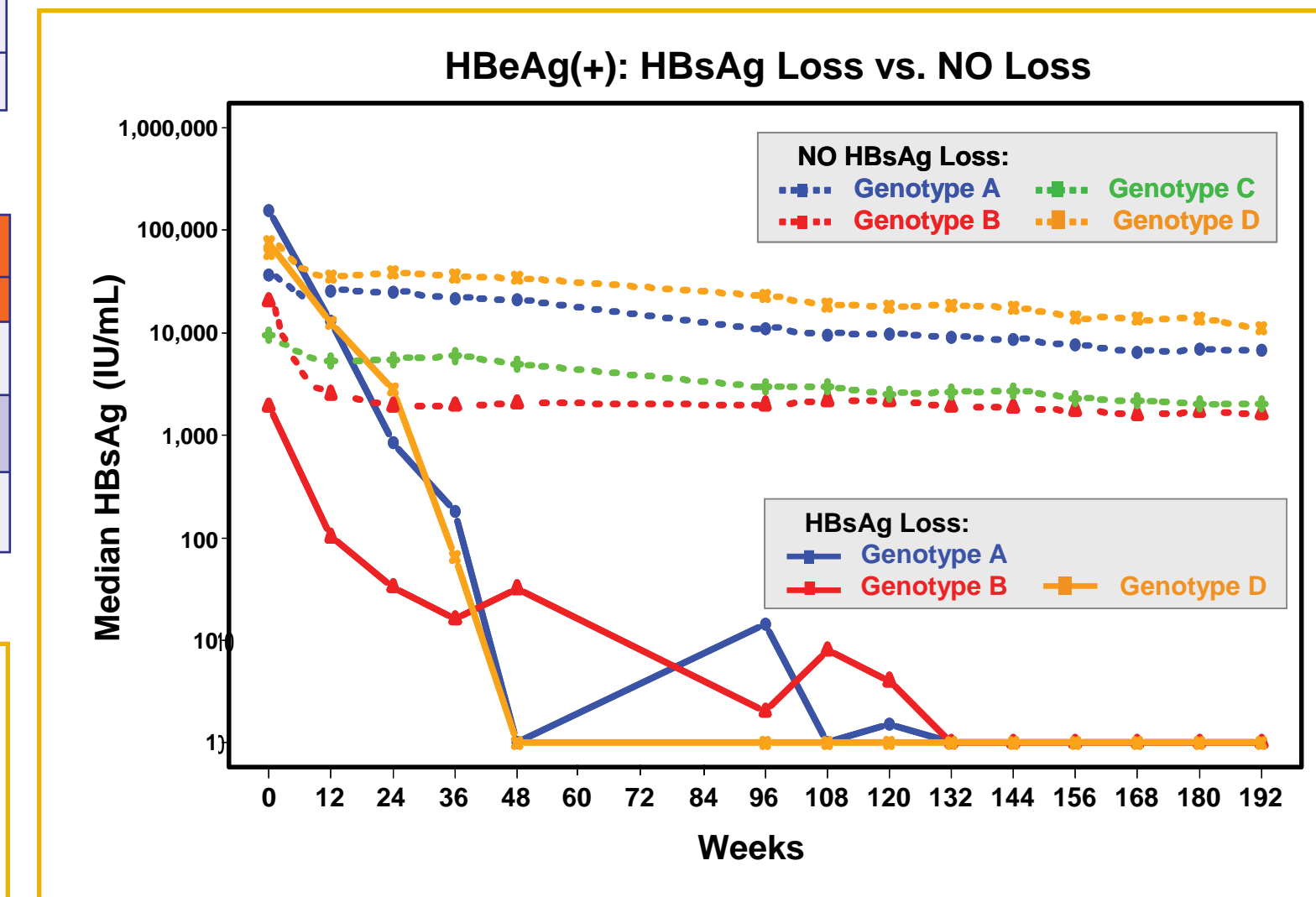
## Results

Table 3. Comparison of HBsAg\* Levels across HBeAg Status and Genotype (TDF-TDF Groups)

Genotype	HBeAg(+) WITH HBsAg Loss			HBeAg(+) NO HBsAg Loss			HBeAg(-) NO HBsAg Loss		
	Baseline	Week 12	Change	Baseline	Week 12	Change	Baseline	Week 12	Change
A	156,753 (5.20)	12,835 (4.11)	143,918 (1.09)	36,695 (4.56)	25,770 (4.41)	10,925 (0.15)	11,758 (4.07)	9,342 (3.97)	2,416 (0.10)
B	1,915 (3.28)	102 (2.01)	1,816 (1.27)	20,420 (4.31)	2,520 (3.40)	17,900 (0.91)	1,585 (3.20)	1,185 (3.07)	400 (0.13)
C	NA	NA	NA	9,070 (3.96)	5,272 (3.72)	3,798 (0.24)	2,080 (3.32)	2,225 (3.35)	-145 (-0.03)
D	75,610 (4.88)	12,595 (4.10)	63,015 (0.78)	60,105 (4.78)	35,440 (4.55)	24,665 (0.23)	7,220 (3.86)	7,298 (3.86)	-78 (0.00)
E	NA	NA	NA	38,528 (4.59)	23,742 (4.38)	14,786 (0.21)	13,400 (4.13)	12,430 (4.09)	970 (0.03)
F	249,751 (5.40)	17,695 (4.25)	232,056 (1.15)	144,775 (5.16)	181,039 (5.26)	-36,264 (-0.10)	24,390 (4.39)	15,190 (4.18)	9,200 (0.21)

\*Results are median IU/mL, or log<sub>10</sub> median IU/mL

Figure 3. HBsAg Decline across Genotypes (TDF-TDF Groups)



### Summary of HBsAg Kinetics

- HBeAg(+) patients had higher baseline HBsAg compared to HBeAg(-) patients of the corresponding genotypes
- Rapid and continuous decline of HBsAg was observed in patients who had HBsAg loss. Decline at Week 12 was  $> 0.5 \log_{10}$  IU/mL
- Regardless of HBeAg status, the patients with NO HBsAg loss had much slower decline of HBsAg ( $< 0.5 \log_{10}$  IU/mL at Week 12)
  - As an exception, genotype B HBeAg(+) patients with NO loss of HBsAg had decline of  $0.9 \log_{10}$  IU/mL at Week 12

Table 4. Significant Markers Associated with HBsAg Loss in TDF-TDF Group Univariate Models: HBeAg(+) and HBeAg(-); Genotype A to D

Characteristic	Odds Ratio	95% CI for OR	P-value
HBeAg Loss in first 24 Weeks	14.314	(4.570, 44.834)	<0.0001
Baseline HBsAg log <sub>10</sub> IU/mL	12.123	(3.950, 37.208)	<0.0001
Log <sub>10</sub> Slope of HBsAg: Baseline to Week 12	8.710	(3.102, 24.457)	<0.0001
ALT Flare in first 12 weeks	7.952	(2.759, 22.920)	0.0001
Baseline HBV DNA log <sub>10</sub> IU/mL	3.380	(1.780, 6.421)	0.0002
Baseline Knodell Necroinflammatory Score	1.376	(1.009, 1.877)	0.0437
Years from Diagnosis of HBV: $\leq 4$ vs. $5+$	10.000	(2.212, 45.455)	0.0028
HBV Genotype: A vs. B-D	8.050	(2.764, 23.447)	0.0001
Race: Caucasian vs. Non-Caucasian	4.487	(0.998, 20.161)	0.0502

### Multivariate Models: HBeAg(+); Genotype A and D\*

Characteristic	Odds Ratio	95% CI for OR	P-value
HBeAg Loss in first 24 Weeks	13.460	(2.159, 83.927)	0.0054
Log <sub>10</sub> Slope of HBsAg: Baseline to Week 12	12.440	(1.888, 81.961)	0.0088
Years from Diagnosis of HBV: $\leq 4$ vs. $5+$	6.944	(1.119, 43.478)	0.0375

\* Multivariate analysis of Genotypes A to D gave similar results

Table 5. HBsAg Loss by Years from Diagnosis of HBV and Genotype: HBeAg(+) Patients (TDF-TDF)

Genotype	HBsAg Loss (n)				
	0-4 yrs	5-10 yrs	11-15 yrs	16+ yrs	Unknown
A	7	0	1	0	1
B	1	0	0	0	0
C	0	0	0	0	0
D	4	0	1	0	0
F	1	0	0	0	0
All	13	0	2	0	1

## Conclusions

- Several baseline characteristics and early response factors (years from diagnosis of HBV infection, HBeAg loss, HBsAg decline) have been identified to be significantly associated with HBsAg loss
- The strongest associated factors for HBeAg(+) patients are:
  - Steep slope of HBsAg decline during the first 12 weeks
  - HBeAg loss during the first 24 weeks
  - Shorter known duration of infection

## References

- Heathcote et al, AASLD (2010) poster 477
- Gane et al, EASL (2010) poster 1006