

Kinetics of Hepatitis B Surface Antigen Loss Following 8 Years of Tenofovir-Based Treatment in Hepatitis B e Antigen–Negative and Hepatitis B e Antigen–Positive Patients With Chronic Hepatitis B

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Author Disclosures

JH has received grant support from Gilead Sciences, Inc., and Roche, has received consultant fees from Roche and lecture fees from AbbVie Korea; Gilead Sciences, Inc.; Oncolys; Roche; and Yuhan Korea; and is a steering committee member for AstraZeneca. **RM, TY, FA, JFF, TA, YH, SC, HW,** and **HM** are employees of Gilead Sciences, Inc., and may own stock or stock options. **SKF** served as an advisor for AbbVie; Gilead Sciences, Inc.; Novo Nordisk; and Pfizer; reports speaker fees from AbbVie; Gilead Sciences, Inc.; and Lupin; and received research support from Gilead Sciences, Inc. **MB** reports speaker fees, research support, and consulting fees from AbbVie; Gilead Sciences, Inc.; and Janssen. **EJG** served as an advisor for AbbVie; Aligos Therapeutics; Arbutus Biopharma; Gilead Sciences, Inc.; Janssen; Roche; Vir Biotechnology; and Virion Therapeutics. **YSL** reports no conflicts of interest. **KA** served as a speaker, consultant, and/or advisory board member for Aligos Therapeutics; Arbutus Biopharma; Assembly Biosciences; Boehringer Ingelheim; Bristol Myers Squibb; Drug Farm; Gilead Sciences, Inc.; GSK; Janssen; Roche; Sagimet Biosciences; and Sobi and his institution received research support from Gilead Sciences, Inc.

Background

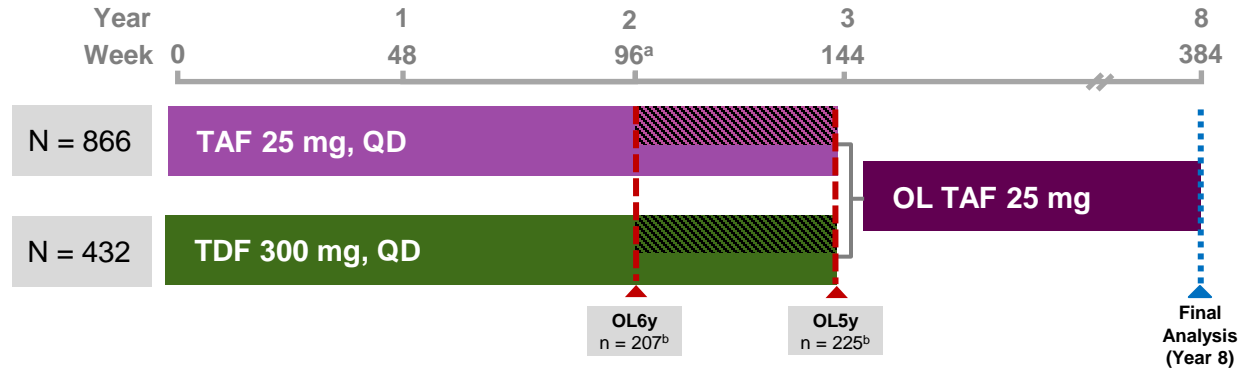
- Hepatitis B virus (HBV) infection affects 254 million individuals globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma if not properly treated^{1,2}
- Sustained hepatitis B surface antigen (HBsAg) loss is associated with improved long-term outcomes and allows for the possibility of stopping nucleos(t)ide analogue (NA) treatment¹
- Although highly effective at suppressing viral replication, first-line NA therapies for chronic HBV (CHB) infection rarely achieve HBsAg loss³
- Long-term treatment with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) can result in HBsAg loss in a small subset of patients; the mechanism for this remains unclear⁴

Objective: To assess HBsAg kinetics and characterize patients with CHB who achieved HBsAg loss after receiving antiviral treatment for up to 8 years in 2 large, recently completed, multicenter, randomized Phase 3 studies of TAF

Study Design

Key Inclusion Criteria

- HBV DNA $\geq 20,000$ IU/mL
- ALT >60 U/L (males) and >38 U/L (females) and $\leq 10 \times$ ULN
- Treatment naïve or treatment experienced
- Study 108: HBeAg negative and HBeAb positive at screening
- Study 110: HBeAg positive at screening



^aAmendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded areas represent patients who rolled over to OL TAF at week 96 (OL6y) or week 144 (OL5y).

^bPatients who received DB TDF and switched to TAF.

ALT, alanine aminotransferase; **DB**, double blind; **HBeAb**, hepatitis B e antibody; **HBeAg**, hepatitis B e antigen; **HBV**, hepatitis B virus; **OL**, open label; **QD**, once daily; **TAF**, tenofovir alafenamide; **TDF**, tenofovir disoproxil fumarate; **ULN**, upper limit of normal.

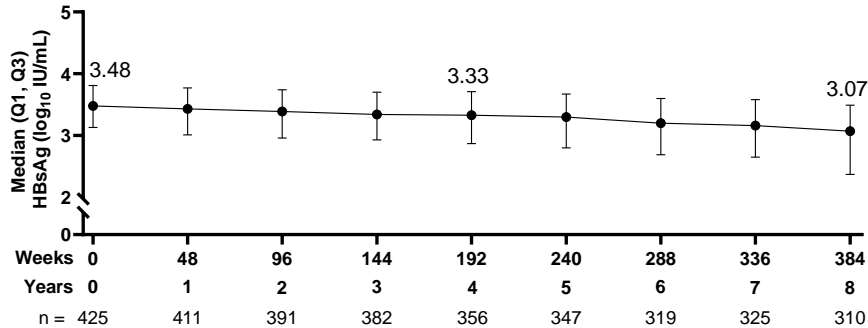
Baseline Demographic and Disease Characteristics

	TAF, N = 866								TDF → TAF, N = 432							
	HBeAg Negative n = 285				HBeAg Positive n = 581				HBeAg Negative n = 140				HBeAg Positive n = 292			
Age, years, mean (SD)	45 (11.6)				38 (11.0)				48 (10.4)				38 (11.7)			
Male, n (%)	173 (61)				371 (64)				86 (61)				189 (65)			
Asian, n (%)	205 (72)				482 (83)				101 (72)				232 (80)			
White, n (%)	71 (25)				96 (17)				35 (25)				52 (18)			
Black or African American, n (%)	5 (2)				2 (<1)				3 (2)				3 (1)			
BMI, kg/m ² , mean (SD)	24.6 (4.04)				23.8 (4.14)				24.9 (3.81)				24.1 (4.00)			
HBV DNA, log ₁₀ IU/mL, mean (SD)	5.7 (1.34)				7.6 (1.34)				5.8 (1.32)				7.6 (1.41)			
ALT, U/L, median (Q1, Q3)	67 (44, 102)				85 (61, 139)				67 (47, 102)				86 (57, 137)			
HBsAg, log ₁₀ IU/mL, mean (SD)	3.4 (0.66)				4.0 (0.79)				3.4 (0.73)				4.1 (0.68)			
HBV GT (A, B, C, D), n (%)	15 (5)	60 (21)	115 (40)	90 (32)	39 (7)	100 (17)	303 (52)	134 (23)	6 (4)	40 (29)	47 (34)	42 (30)	25 (9)	48 (16)	153 (52)	63 (22)
FibroTest score ≥0.75, n/N (%) (Metavir F4/cirrhosis)	31/280 (11)				45/566 (8)				20/139 (14)				22/282 (8)			
Previous nucleos(t)ide use, n (%)	60 (21)				151 (26)				31 (22)				77 (26)			

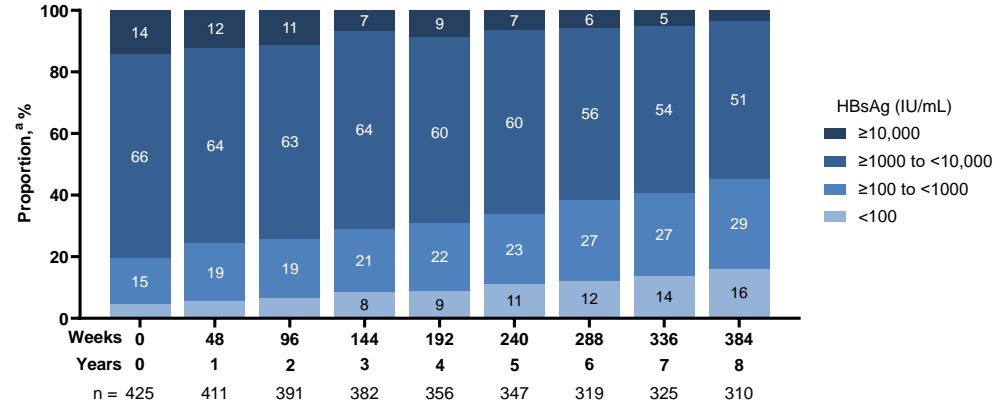
ALT, alanine aminotransferase; BMI, body mass index; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

HBsAg Kinetics Over 8 Years: HBeAg-Negative Population

Median HBsAg Levels



Categorical Shifts in HBsAg Levels



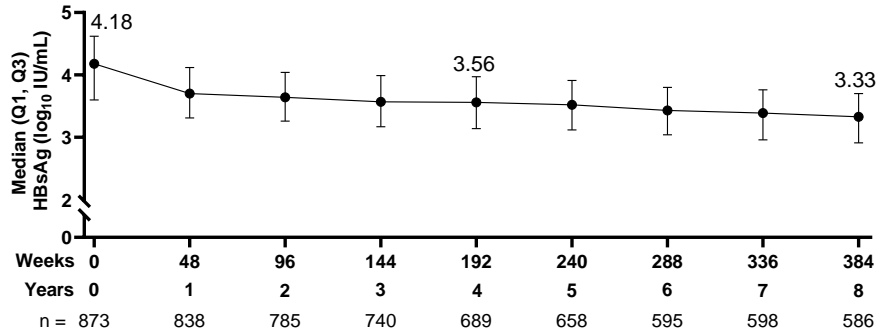
^aProportions of the stacked bar graph (ie, shaded regions) without a data label represent ≤5% of patients.

HBeAg, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen.

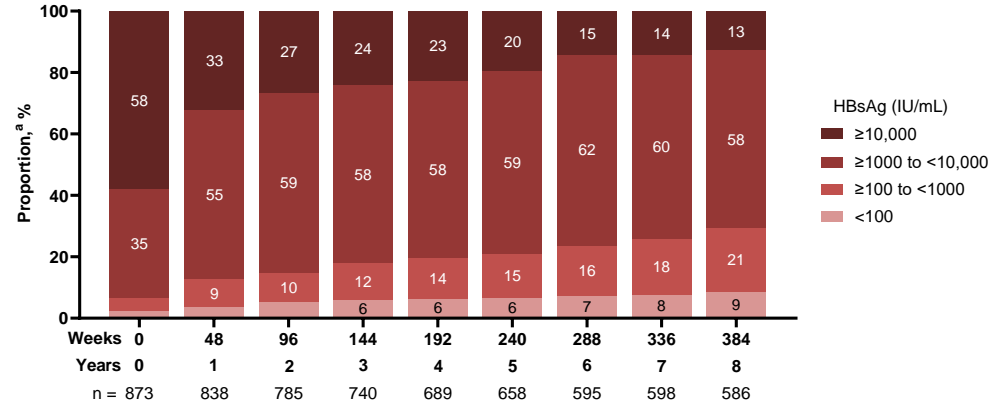
- The proportions of patients with HBsAg level of ≥1000 IU/mL decreased from 80% at baseline to 69% at week 192 [year 4] and 55% at week 384 [year 8]
- The proportions of patients with HBsAg level of <1000 IU/mL increased from 20% at baseline to 31% at week 192 [year 4] and 45% at week 384 [year 8]
 - The proportions of patients with HBsAg level of <100 IU/mL increased from 5% at baseline to 9% at week 192 [year 4] and 16% at week 384 [year 8]

HBsAg Kinetics Over 8 Years: HBeAg-Positive Population

Median HBsAg Levels



Categorical Shifts in HBsAg Levels

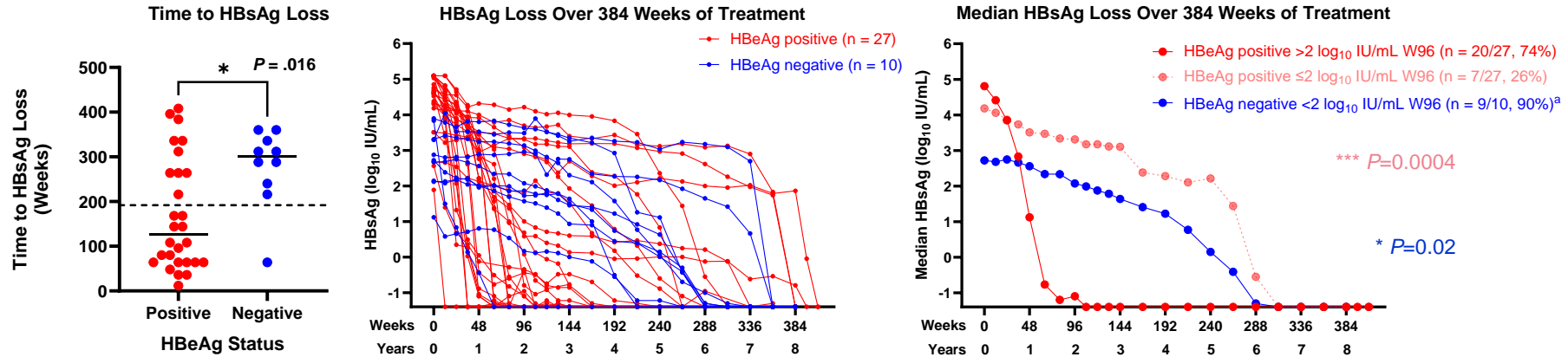


^aProportions of the stacked bar graph (ie, shaded regions) without a data label represent ≤5% of patients.

HBeAg, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen.

- The proportions of patients with HBsAg level of ≥1000 IU/mL decreased from 93% at baseline to 81% at week 192 [year 4] and 71% at week 384 [year 8]
- The proportions of patients with HBsAg level of <1000 IU/mL increased from 7% at baseline to 20% at week 192 [year 4] and 30% at week 384 [year 8]
 - The proportions of patients with HBsAg level of <100 IU/mL increased from 2% at baseline to 6% at week 192 [year 4] and 9% at week 384 [year 8]

Time to HBsAg Loss Among Patients Who Achieved Loss: Individual Patient Data and Overall Proportions



^aOne patient had fast HBsAg loss kinetics and was not included in the analysis of median HBsAg loss over 384 weeks of treatment.
HBeAg, hepatitis B e antigen; **HBsAg**, hepatitis B surface antigen; **W**, week.

- At week 384 [year 8], rates of HBsAg loss were similar between HBeAg-negative (10/427, 2%) and HBeAg-positive patients (27/873, 3%). However, HBsAg loss was observed earlier in HBeAg-positive patients (median 126 weeks) compared to HBeAg-negative patients (median 300 weeks; $P = .02$)
- The kinetics of HBsAg decline were faster for HBeAg-positive patients: by week 96, 20 of 27 (74%) achieved a $>2 \log_{10}$ IU/mL decline in HBsAg from baseline compared to only 1 of 10 (10%) HBeAg-negative patients

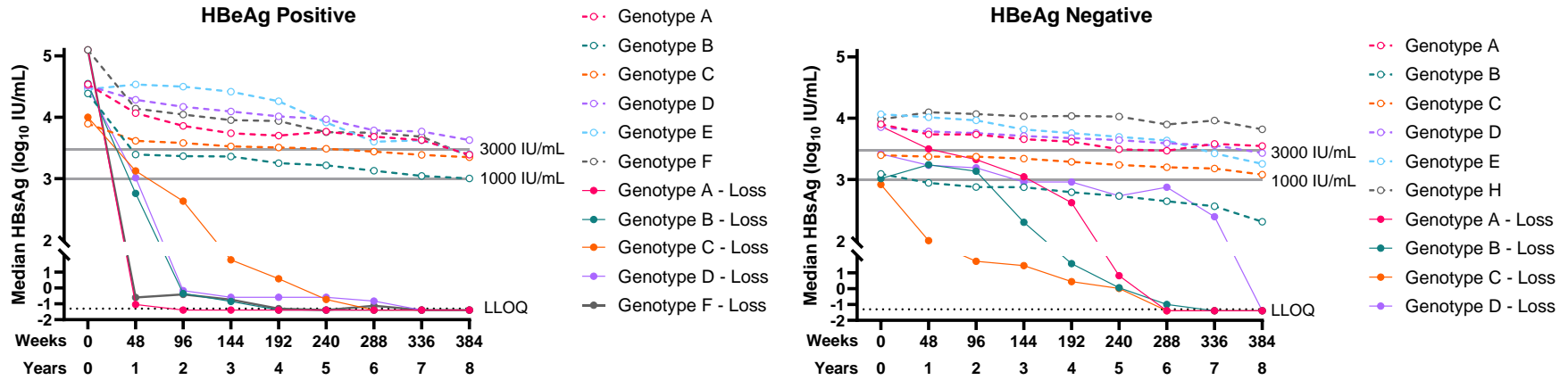
Relationship Between HBsAg Loss and Viral Genotype

HBV GT	HBeAg Positive	HBeAg Negative
	Patients With HBsAg Loss, n/N (%)	Patients With HBsAg Loss, n/N (%)
A	7/64 (11)	2/21 (10)
B	5/148 (3)	1/100 (1)
C	6/456 (1)	5/163 (3)
D	8/197 (4)	2/133 (2)
E	0/3 (0)	0/7 (0)
F	2/5 (40)	NA (NA)
H	NA (NA)	0/2 (0)
Unknown	NA (NA)	0/1 (0)
Total	28/873 (3)	10/427 (2)

GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable.

- A greater proportion of patients with GTs F (2/5; 40%) and A (9/85; 11%) had HBsAg loss compared to patients with GTs D (10/330; 3%), B (6/248; 2%), and C (11/619; 2%)

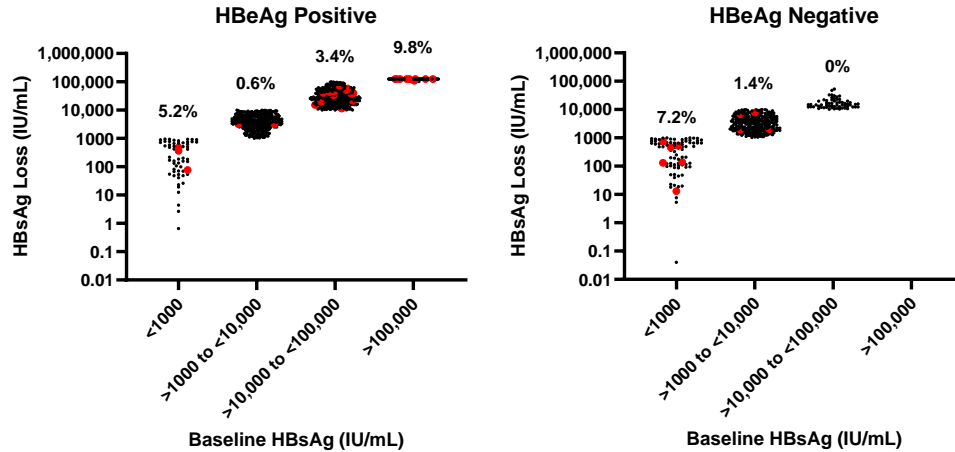
Kinetics of HBsAg Loss in Relation to HBeAg Status and Viral Genotype



HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation.

- Regardless of the HBV genotype, kinetics of HBsAg decline were faster for HBeAg-positive patients compared to HBeAg-negative patients, with genotypes A and F having the fastest kinetics

Baseline HBsAg Levels and Rates of HBsAg Loss in HBeAg-Positive and HBeAg-Negative Patients



- Influence of BL HBsAg levels on HBsAg loss
 - HBeAg-positive patients with BL HBsAg levels >100,000 IU/mL showed the highest rates of HBsAg loss, followed by those with BL levels <1000 IU/mL
 - HBeAg-negative patients had the highest rate of HBsAg loss when BL HBsAg levels were <1000 IU/mL

Percentages reflect the percentage of patients among those within each x-axis category of baseline HBsAg. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

Multivariate Analysis of Baseline and On-Treatment Predictors for HBsAg Loss

Predictor	HR (95% CI)	P-Value
Baseline		
White	2.98 (1.46, 6.07)	.0026
Baseline fibrosis score >0.48 ^a	2.60 (1.29, 5.25)	.0078
GT A	2.35 (1.02, 5.41)	.0445
On-treatment		
≥1 log ₁₀ IU/mL decline in HBsAg at Week 24	9.40 (4.29, 20.62)	<.0001
≥75% decline in HBsAg (log ₁₀ IU/mL) at week 24	12.41 (3.10, 49.66)	.0004
Abnormal ALT level at week 24	2.28 (1.13, 4.62)	.0221

Multivariate Cox regression analysis.
^aIndicative of moderate to severe (0.49 to 0.74) fibrosis and cirrhosis (>0.74 to 1.00) by FibroTest.
ALT, alanine aminotransferase; **CI**, confidence interval; **GT**, genotype; **HBsAg**, hepatitis B surface antigen; **HR**, hazard ratio.

Conclusions

- Several baseline and on-treatment factors, such as a decline in HBsAg levels of $\geq 75\%$ at week 24, a $\geq 1 \log_{10}$ IU/mL decline in HBsAg levels at week 24, White race, and lack of early ALT normalization at week 24 were significantly associated with HBsAg loss
- Although the proportions of HBsAg loss were similar for patients with negative and positive HBeAg status, HBeAg-positive patients required less time to achieve HBsAg loss
- High baseline HBsAg levels ($> 100,000$ IU/mL) were associated with higher rates of HBsAg loss in HBeAg-positive patients, while HBsAg levels < 1000 IU/mL were associated with higher rates of HBsAg loss in HBeAg-negative patients
- Patients with GT A, while representing a minority of patients in this study, experienced higher rates of HBsAg loss

Acknowledgments

- We extend our thanks to the patients, their families, and all participating investigators
- These studies were funded by Gilead Sciences, Inc.
- All authors contributed to and approved the presentation
- Medical writing and editorial support were provided by Andrey Verendeev, PhD, of Red Nucleus, and were funded by Gilead Sciences, Inc.
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