Presentation # OS-067

Long-term Efficacy of Tenofovir Alafenamide in HBeAg-positive and HBeAg-negative Chronic Hepatitis B Patients Treated for up to 8 Years in 2 Phase 3 Studies

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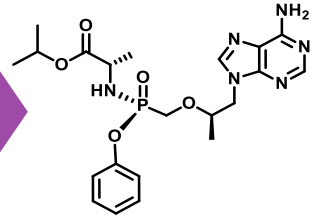
Background

- Hepatitis B virus (HBV) infection affects 296 million individuals globally and is associated with cirrhosis, hepatic decompensation, and hepatocellular carcinoma if not properly treated[1,2]

- In Phase 3 trials, tenofovir alafenamide (TAF) showed noninferior antiviral efficacy, higher ALT normalization, and improved renal and bone safety vs tenofovir disoproxil fumarate (TDF) at weeks 48 and 96 in viremic and virally suppressed hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients[3-5]

TAF
Nucleotide reverse transcriptase inhibitor



- **Objective:** To evaluate final efficacy outcomes at year 8 (week 384) among patients with HBeAg-positive or HBeAg-negative chronic HBV treated with TAF (double blind [DB] and open label [OL]) or TDF (DB) followed by TAF (OL)

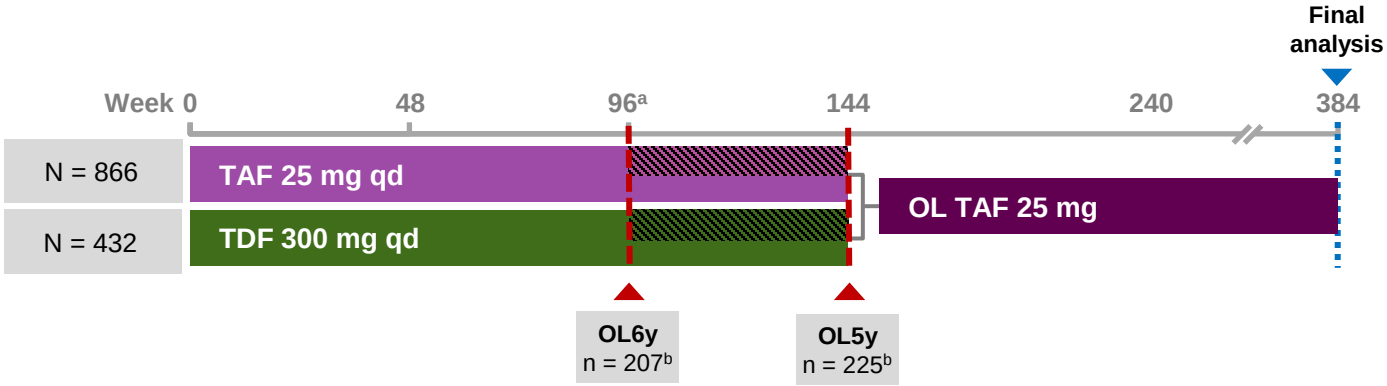
ALT, alanine aminotransferase; DB, double blind; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

1. World Health Organization. Hepatitis B fact sheet. 2022; 2. Seto WK, et al. *Lancet*. 2018;392:2313-24; 3. Agarwal K, et al. *J Hepatol*. 2018;68:672-81; 4. Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1(3):196-206; 5. Chan HL, et al. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-95.

Study Design

Key inclusion criteria

- HBV DNA ≥20,000 IU/mL
- ALT >60 (males) and >38 U/L (females)
- With/without compensated cirrhosis
- Treatment naïve or treatment experienced
- $eGFR_{CG}$ ≥50 mL/min



— Two Phase 3, randomized, DB, multicenter trials
  - Study 108 (NCT01940341; N = 425 originally randomized and treated): HBeAg-negative patients[1,2]
  - Study 110 (NCT01940471; N = 873 originally randomized and treated): HBeAg-positive patients[2,3]

— Study phases
  - DB phase: randomized 2:1 (TAF 25 mg:TDF 300 mg once daily) and stratified by HBV DNA level and treatment status (naïve/experienced)
  - OL phase: TAF 25 mg in patients who received TAF or TDF for 2 (TDF→TAF OL6y) or 3 years (TDF→TAF OL5y)

[a]Amendment 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). [b]Patients who received DB TDF and switched to TAF. ALT, alanine aminotransferase; DB, double blind; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; qd, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

1. Buti M, et al. *Lancet Gastroenterol Hepatol*. 2016;1(3):196-206; 2. Agarwal K, et al. *J Hepatol*. 2018;68(4):672-81; 3. Chan HL, et al. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-95.

Efficacy Outcomes

Viral efficacy

- HBV DNA <29 IU/mL at year 8 (week 384; missing = excluded analysis)
  - COBAS TaqMan HBV Test, v2.0 (Roche Diagnostics, Indianapolis, IN; lower limit of quantitation 20 IU/mL)

Biochemical efficacy

- ALT normalization by central laboratory and 2018 AASLD criteria (missing = excluded analysis)[a]

Serology

- HBeAg loss/seroconversion (missing = excluded analysis)
- Hepatitis B surface antigen (HBsAg) loss/seroconversion
- Change in quantitative HBsAg (qHBsAg) from baseline

Resistance

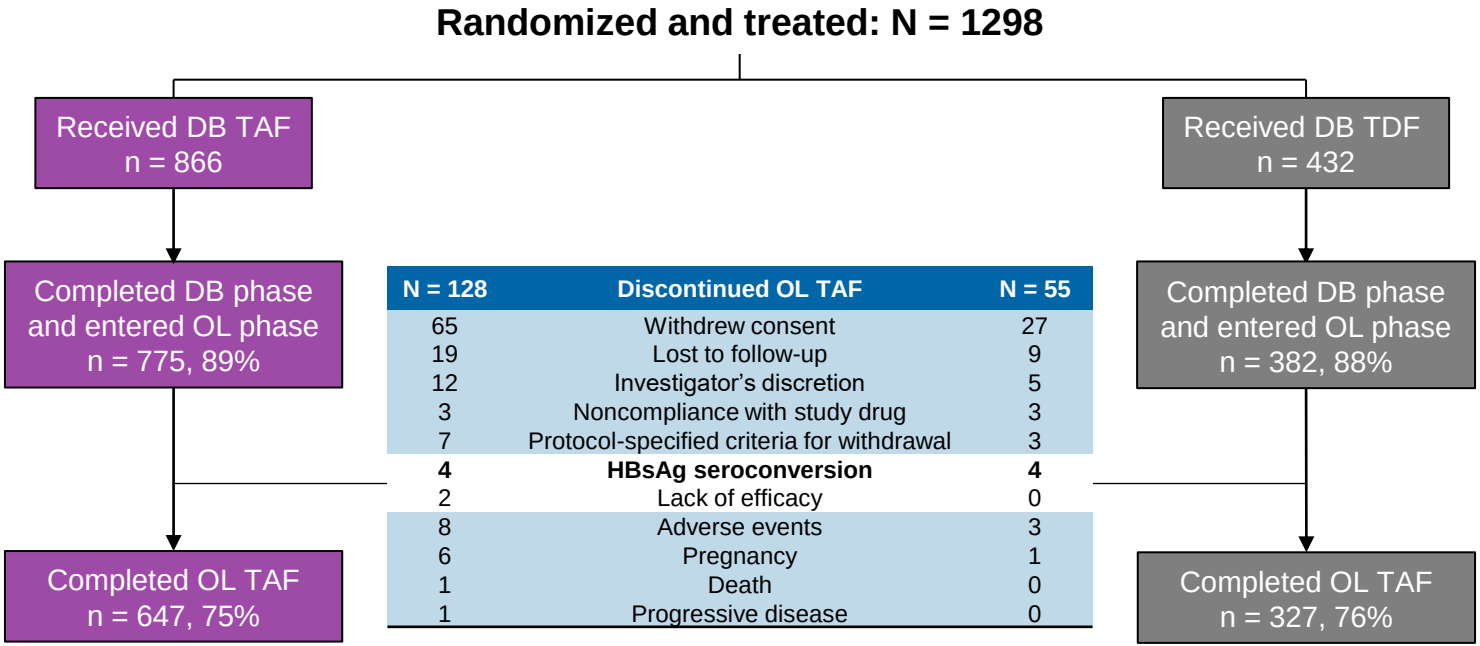
- Deep sequencing of polymerase/reverse transcriptase for viral blip, breakthrough, persistent viremia, or discontinuation with viremia (HBV DNA ≥69 IU/mL)

— A companion pooled safety analysis will be presented in poster SAT-153 by Lim YS et al

[a]ALT normalization ≤ULN: central laboratory— men ≤43 U/L and women ≤34 U/L (≥69 y: men ≤35 U/L and women ≤32 U/L); 2018 AASLD[1]— men ≤35 U/L and women ≤25 U/L.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; qHBsAg, quantitative HBsAg; ULN, upper limit of normal; y, year.

1. Terrault NA, et al. *Hepatology*. 2018;67(4):1560-99.

Patient Disposition



N = 128	Discontinued OL TAF	N = 55
65	Withdrew consent	27
19	Lost to follow-up	9
12	Investigator's discretion	5
3	Noncompliance with study drug	3
7	Protocol-specified criteria for withdrawal	3
4	**HBsAg seroconversion**	**4**
2	Lack of efficacy	0
8	Adverse events	3
6	Pregnancy	1
1	Death	0
1	Progressive disease	0

— 974 of 1298 (75%) patients completed both studies

DB, double blind; HBsAg, hepatitis B surface antigen; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

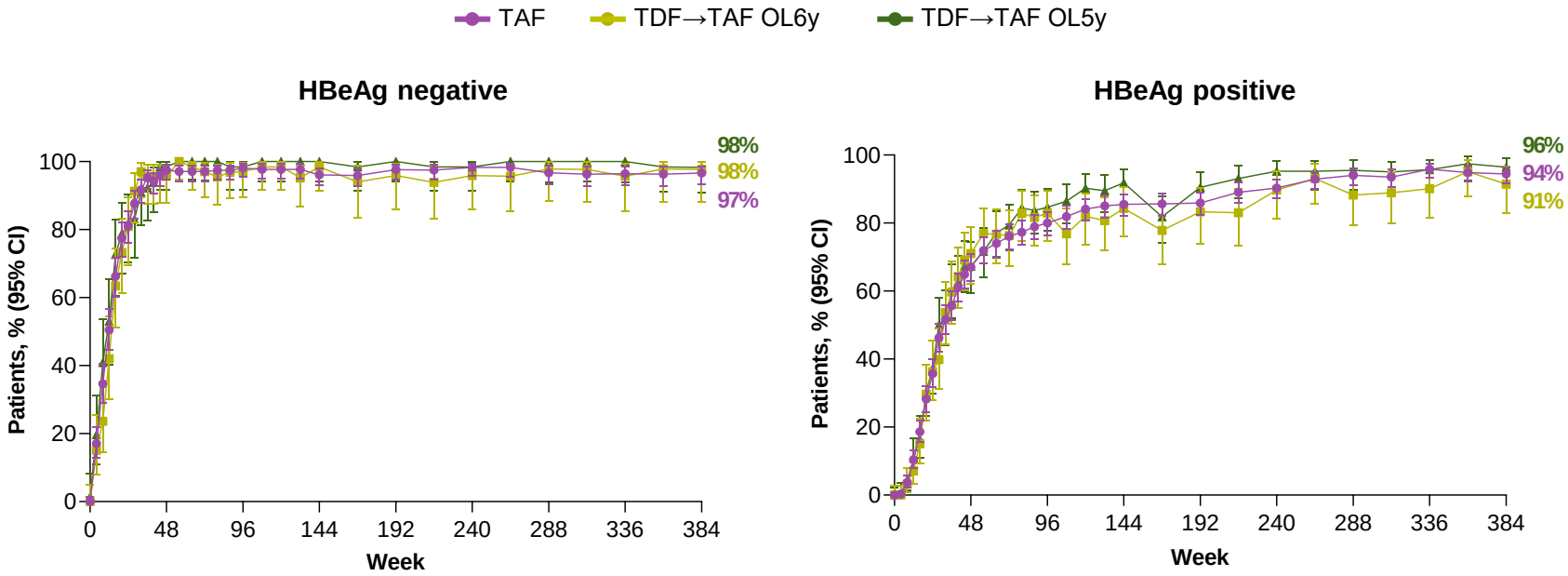
Baseline Demographic and Disease Characteristics

	TAF								TDF→TAF							
	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 genotype (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; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; HBV, hepatitis B virus; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Viral Suppression (HBV DNA <29 IU/mL) Over 8 Years

Studies 108 and 110 (missing = excluded analysis)

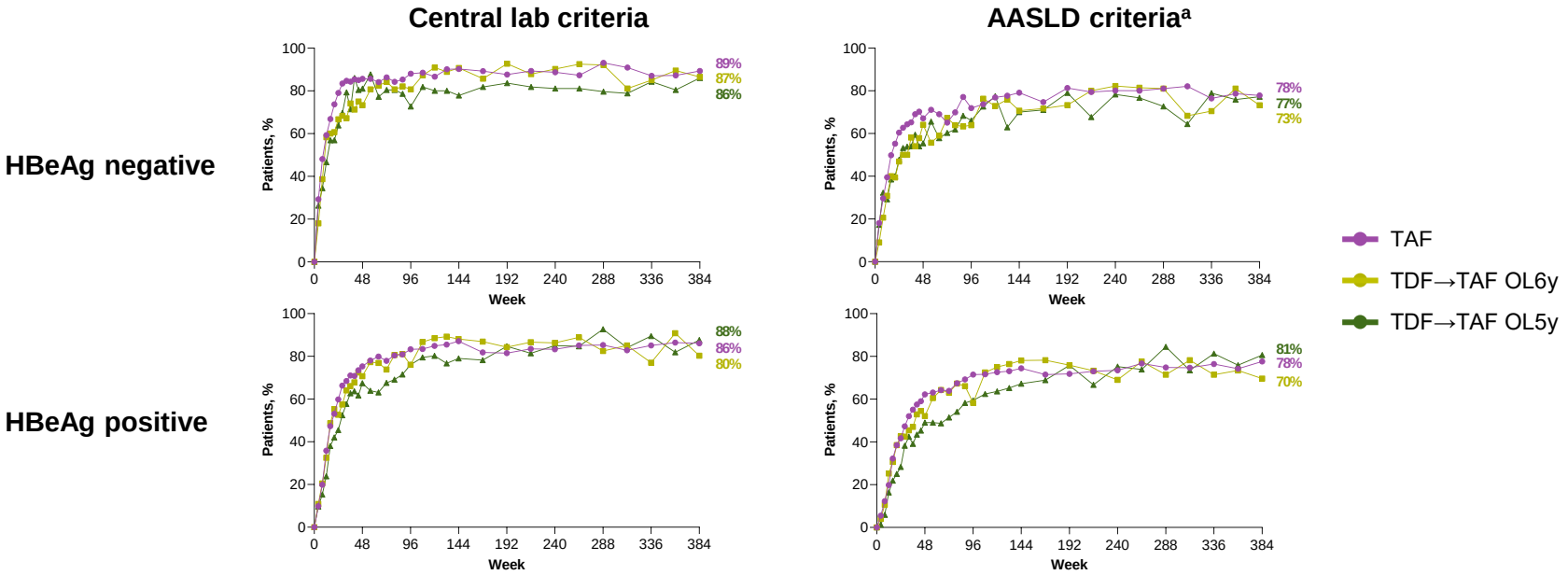


— In both studies, high rates of viral suppression were achieved and maintained over 8 years across all treatment groups

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

ALT Normalization Over 8 Years

Studies 108 and 110 (missing = excluded analysis)



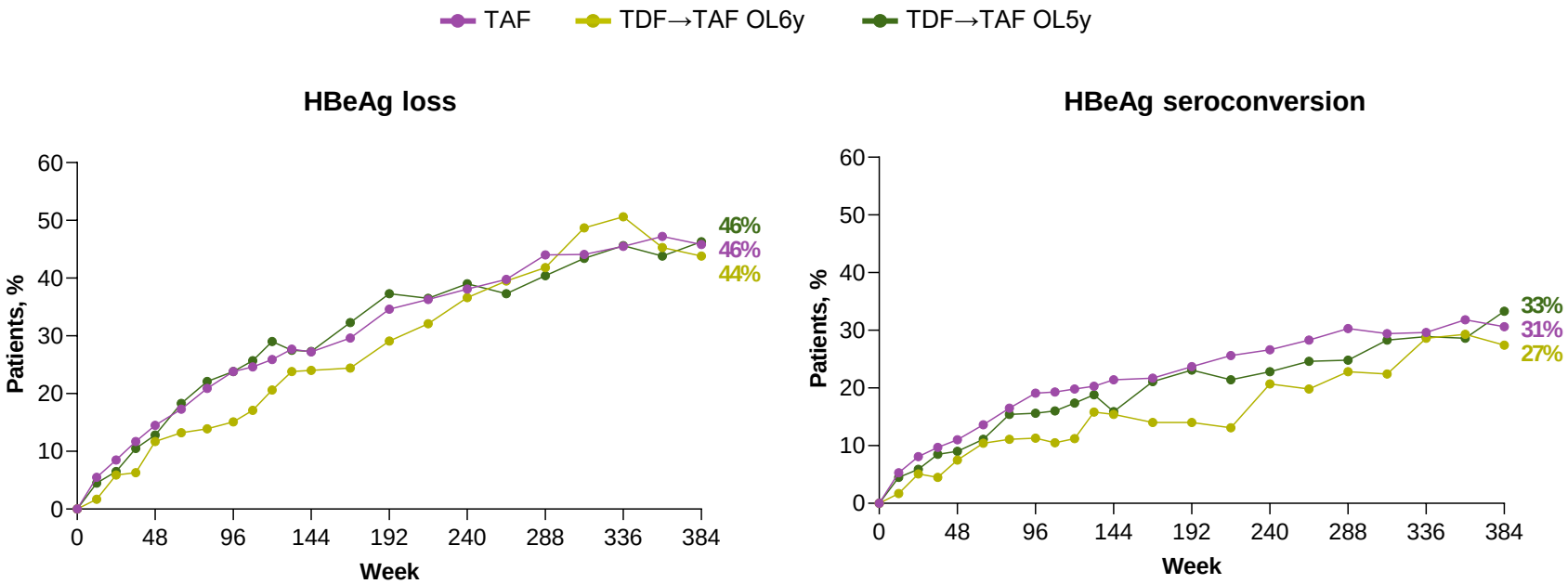
- Patients treated with TAF for 8 years achieved high rates of ALT normalization
- Among TDF-treated patients, ALT normalization rates increased after switching to TAF
- Rates were comparable in HBeAg-positive and HBeAg-negative patients by both methods

[a]AASLD 2018 criteria.

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; OL, open label; TAF, tenofovir disoproxil fumarate; TDF, tenofovir disoproxil fumarate; y, year.

HBeAg Loss and Seroconversion Over 8 Years

Study 110 (missing = excluded analysis)



— Among HBeAg-positive patients, rates of HBeAg loss and seroconversion progressively increased over 8 years of treatment and were comparable in the TAF and TDF→TAF groups

HBeAg, hepatitis B e antigen; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

HBsAg Loss and Seroconversion at Year 8

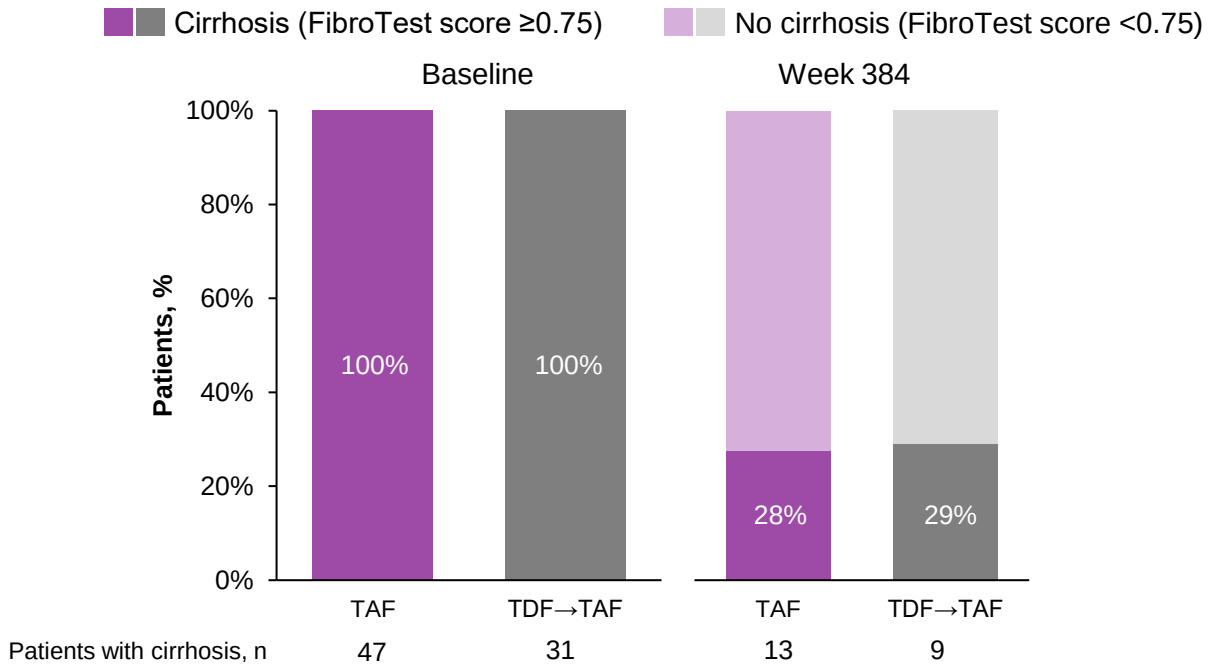
HBsAg	TAF		TDF→TAF OL6y		TDF→TAF OL5y	
	HBeAg negative	HBeAg positive	HBeAg negative	HBeAg positive	HBeAg negative	HBeAg positive
Loss, n/n (%)	8/199 (4)	9/384 (2)	0/41	4/76 (5)	1/58 (2)	3/109 (3)
Seroconversion, n/n (%)	6/199 (3)	6/384 (2)	0/41	4/76 (5)	0/58	3/109 (3)
Change $\log_{10}$ IU/mL mean (SD)	n = 208 –0.62 (0.924)	n = 393 –0.89 (1.211)	n = 44 –0.50 (0.526)	n = 81 –1.09 (1.424)	n = 58 –0.61 (0.758)	n = 112 –1.09 (1.268)

— Low rates of HBsAg loss (≤5%) and small mean declines in qHBsAg were seen at year 8

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OL, open label; qHBsAg, quantitative HBsAg; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

Regression of Cirrhosis at Year 8 by FibroTest

Studies 108 and 110 (pooled analysis; missing = excluded)



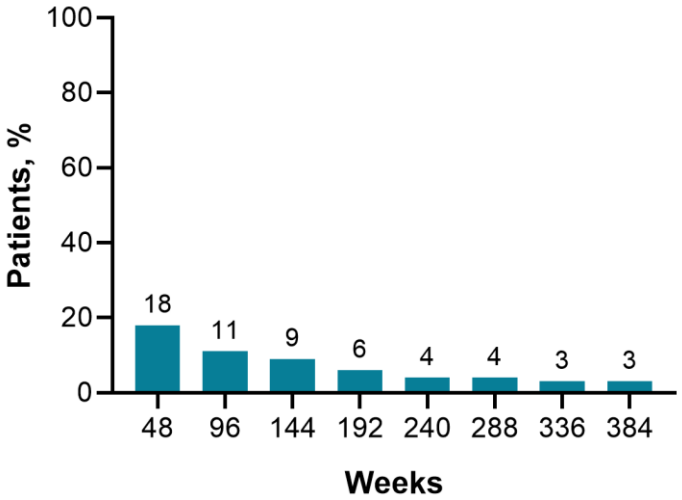
— Of 78 patients with paired baseline and year 8 data, 2/3 showed lack of cirrhosis by FibroTest

TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

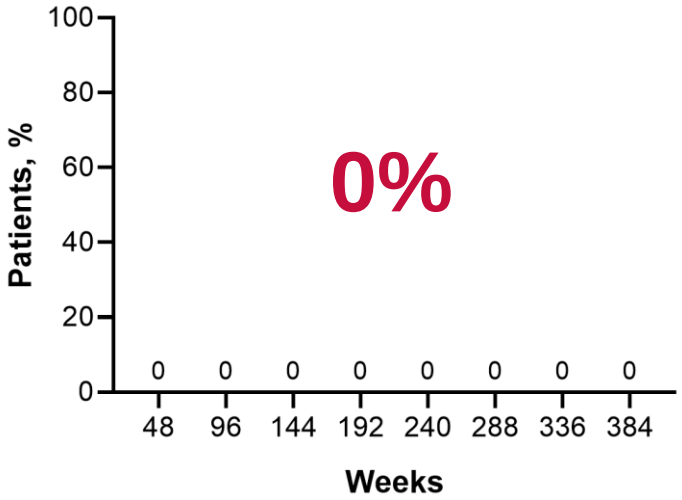
Resistance Analysis

— 29/895 (3%) patients entering year 8 of the study qualified for sequencing

Qualified for sequencing analysis, %[a]



Resistance to TAF, %



— No amino acid substitutions in HBV pol/RT with reduced susceptibility to TAF were found throughout 8 years of treatment

[a]Patients with HBV DNA ≥69 IU/mL were sequenced.
HBV, hepatitis B virus; pol/RT, polymerase/reverse transcriptase; TAF, tenofovir alafenamide.

Conclusions

— Patients with chronic HBV treated with TAF only and those switched from TDF to TAF over 8 years demonstrated:
  - High rates of persistent viral suppression (91%–98%)
  - High rates of ALT normalization were achieved early and maintained with TAF, while ALT normalization increased in TDF-treated patients switched to TAF in the OL period
  - With long-term TAF treatment in HBeAg-positive patients, the rates of HBeAg loss and seroconversion increased progressively (approximately 45% and 30%, respectively)
  - In patients with cirrhosis based on FibroTest at baseline, the majority showed improvement in fibrosis with long-term treatment
  - No resistance to TAF was observed

— Treatment with TAF was highly effective in patients with chronic HBV. These results provide continued support for TAF as the preferred treatment for chronic HBV infection

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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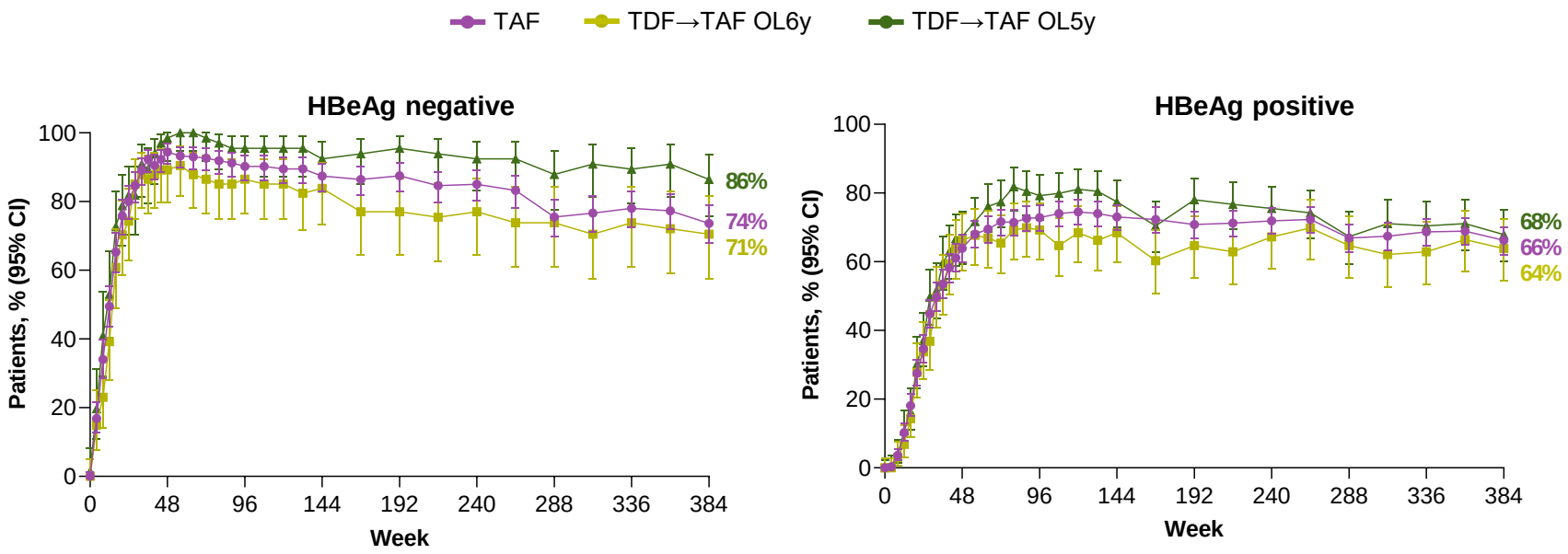
Backup slides

Viral Suppression (HBV DNA <29 IU/mL) Over 8 Years

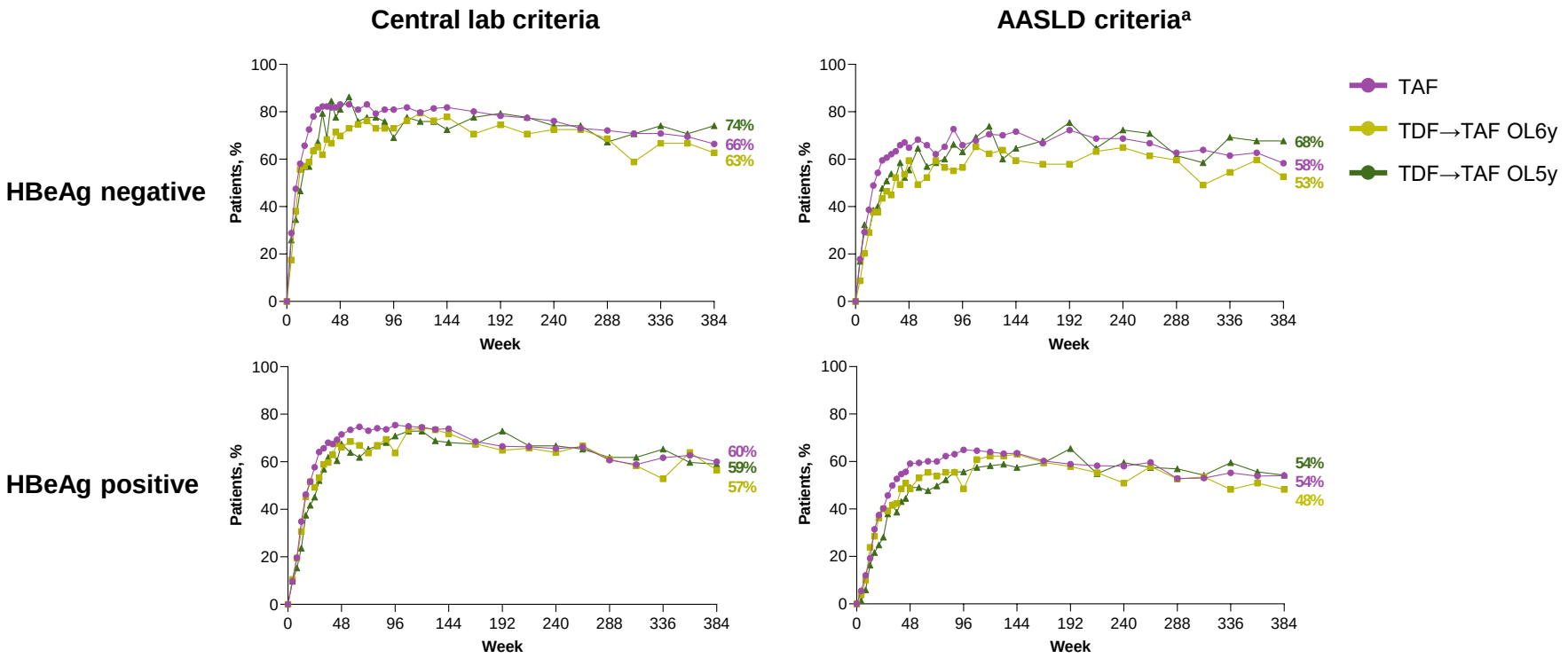
Studies 108 and 110 (missing = failure analysis)



HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

ALT Normalization Over 8 Years

Studies 108 and 110 (missing = failure analysis)



[a]AASLD 2018 criteria.

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HBeAg Loss and Seroconversion Over 8 Years

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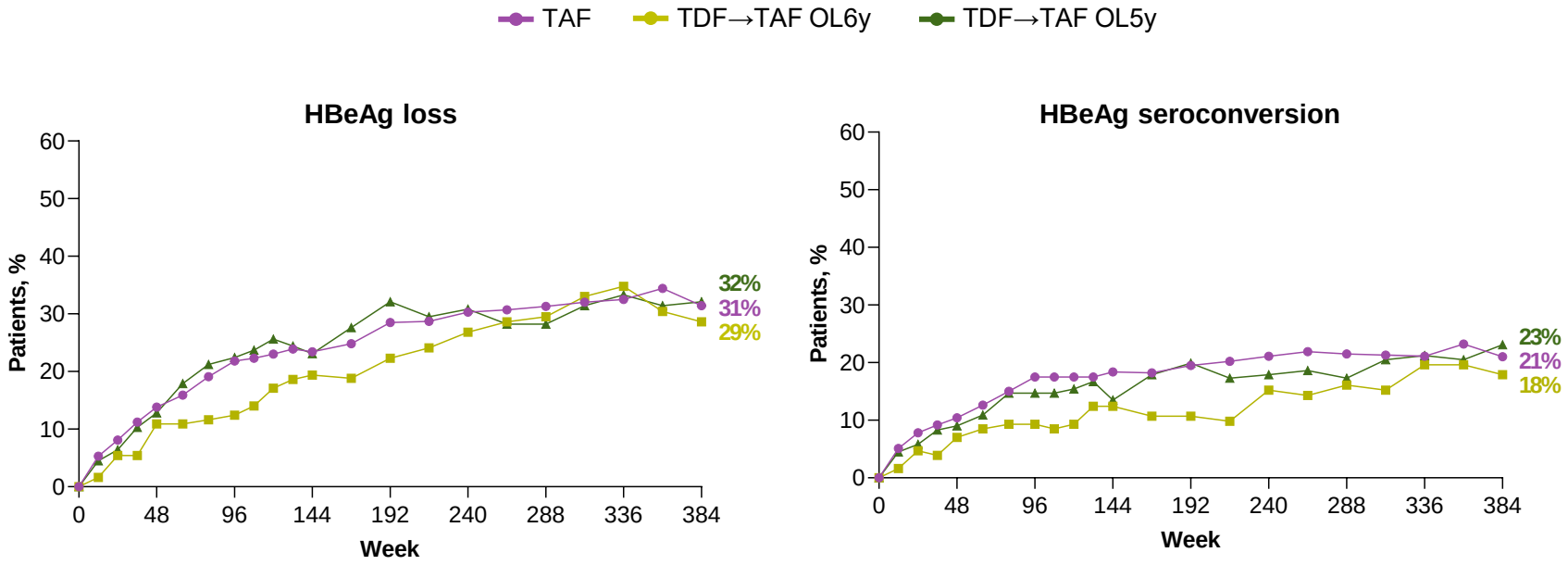

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