Factors Associated With Lack of Alanine Aminotransferase Normalisation in Patients With Chronic Hepatitis B Virus After 8 Years of Tenofovir-Based Treatment

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Viral Hepatitis B and D: Current Therapies

Conclusions

- After up to 8 years of treatment with tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) followed by TAF, approximately 20% of patients with chronic hepatitis B (CHB) had persistently elevated alanine aminotransferase (pALT) levels, often despite durable viral suppression
- Patients with normal ALT levels had higher rates of hepatitis B e antigen (HBeAg) loss and seroconversion; however, meaningful virologic responses were also observed in patients with pALT
- Changes in lipid parameters were generally modest and similar between groups; however, numerically greater increases in triglyceride and glucose levels were observed in patients with pALT
- Consistent with prior TDF studies, pALT was frequently associated with host factors, including younger age and increased body mass index (BMI), rather than with inadequate antiviral efficacy

Plain Language Summary

- Alanine aminotransferase levels can be tested to evaluate ongoing liver inflammation or damage
- In two Phase 3 trials, most people treated for hepatitis B virus infection had very low or undetectable virus levels after 8 years of treatment, even if their alanine aminotransferase levels remained above normal
- People with normal alanine aminotransferase levels at year 8 were more likely to attain clinical benefits, such as an improvement in fibrosis and loss of hepatitis B e antigen, but these improvements were also seen in many people whose alanine aminotransferase levels did not return to normal levels
- People whose alanine aminotransferase levels did not normalise had numerically greater increases in the levels of triglycerides and glucose than those with normal levels
- Younger people, those with a higher body mass index, and those infected with certain types of hepatitis B virus were more likely to have persistently elevated alanine aminotransferase levels after 8 years of treatment

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Introduction

- CHB is a major global health problem affecting approximately 250 million individuals[1]
- Long-term therapy with nucleos(t)ide analogues, including TAF and TDF, is recommended as a first-line antiviral treatment for CHB and effectively suppresses hepatitis B virus (HBV) replication and improves clinical outcomes[2-4]
- ALT is routinely monitored as a biochemical marker of treatment response; however, a subset of patients do not achieve ALT normalisation despite durable viral suppression[2,5]
  - pALT during antiviral therapy is associated with an increased risk of adverse clinical outcomes, including hepatocellular carcinoma[6]
  - Prior long-term TDF studies demonstrated that pALT is frequently associated with host and metabolic factors, including increased BMI and diabetes mellitus, rather than with inadequate antiviral efficacy[5]
- This analysis extends prior observations by evaluating factors associated with pALT after 8 years of treatment with TAF or TDF followed by TAF in two large Phase 3 studies

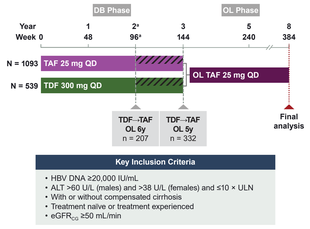
Objective

- To identify host, metabolic, and viral factors associated with pALT in patients with CHB who received TAF or TDF followed by TAF for a total of 8 years of treatment

Methods

- Patients in this analysis were enrolled in two Phase 3 trials with similar designs
  - Study 108: HBeAg-negative patients (global and China cohorts: NCT01940341 and NCT02836236)[7-9]
  - Study 110: HBeAg-positive patients (global and China cohorts: NCT01940471 and NCT02836249)[7,9,10]
- Patients were randomised 2:1 to the following treatment groups:
  - TAF 25 mg once daily (QD) for up to 144 weeks (3 years) followed by open-label (OL) TAF
  - TDF 300 mg QD for up to 3 years followed by OL TAF
- All patients received OL TAF through 384 weeks (8 years)

Study Design



TDF→TAF OL6y, patients received DB TDF for 2 years (96 weeks), then OL TAF for 6 years; and TDF→TAF OL5y, patients received DB TDF for 3 years (144 weeks), then OL TAF for 5 years.
*Amendment 3 was enacted to extend DB to week 144 and OL to week 384 (year 8).
Shaded/slashed areas represent patients who rolled over to OL TAF at week 96 (OL 6y).
ALT, alanine aminotransferase; DB, double-blind; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault method; HBV, hepatitis B virus; OL, open-label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; y, year.

- Data from Studies 108 and 110 were pooled and evaluated using missing-equals-excluded analysis, with patients categorised by ALT status at year 8
- ALT levels were assessed using both the American Association for the Study of Liver Diseases (AASLD) reference ranges (upper limit of normal [ULN]: 25 U/L for females and 35 U/L for males) and central laboratory criteria (ULN of 34 U/L for females and 43 U/L for males [≥69 years of age: 32 and 35 U/L, respectively])[3]
- pALT was defined as an ALT level greater than the ULN at the year 8 measurement
- Baseline characteristics and on-treatment virologic and metabolic parameters were compared between patients with pALT and those with normal ALT levels
- Univariate and multivariate logistic regression analyses were performed to identify factors associated with pALT

Results

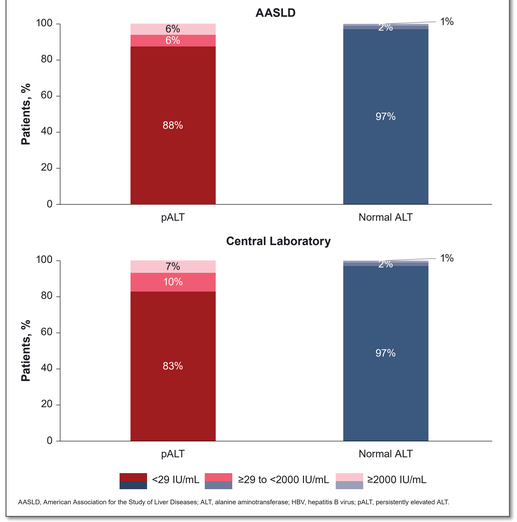
Baseline Characteristics of Patients with pALT and Normal ALT at Year 8 by AASLD Criteria

	pALT (n = 252)	Normal ALT (n = 907)	*P*-Value
Age, years, mean (SD)	38 (10.9)	42 (11.3)	<.0001
Age <50 years	208 (82.5)	660 (72.8)	.0016
Male	184 (73.0)	589 (64.9)	.0162
Not Hispanic/Latino ethnicity	249 (98.8)	904 (99.7)	.0269
BMI, kg/m², mean (SD)	25.5 (4.02)	23.9 (3.70)	<.0001
BMI category			<.0001
<18.5 (underweight)	8 (3.2)	41 (4.5)	
≥18.5 to <25.0 (normal)	105 (41.7)	545 (60.1)	
≥25.0 to <30.0 (overweight)	115 (45.6)	271 (29.9)	
≥30.0 (obesity)	24 (9.5)	50 (5.5)	
ALT level by AASLD			.0108
≤ULN	5 (2.0)	58 (6.4)	
ULN to 5 × ULN	208 (82.5)	672 (74.1)	
>5 × to 10 × ULN	30 (11.9)	125 (13.8)	
>10 × ULN	9 (3.6)	52 (5.7)	
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.90 (0.819)	3.72 (0.810)	.0004
HBeAb positive	88 (79.3)	360 (86.7)	.0495
HBV genotype A / B / C / D[a]	22 (8.7) / 60 (23.8) / 116 (46.0) / 53 (21.0)	32 (3.5) / 198 (21.8) / 510 (56.2) / 155 (17.1)	.0021
Previous interferon experience	46 (18.3)	106 (11.7)	.0063
FibroTest score, mean (SD)	0.34 (0.211)	0.40 (0.234)	.0011
Fibrosis stage by FibroTest score			.0131
0.00–0.48	185 (75.5)	588 (66.1)	
0.49–0.74	45 (18.4)	205 (23.1)	
0.75–1.00	15 (6.1)	96 (10.8)	
eGFR by CG method, mL/min, mean (SD)	118.5 (29.56)	108.2 (25.68)	<.0001
Hypertension	34 (13.5)	112 (12.3)	.6285
Diabetes mellitus	23 (9.1)	63 (6.9)	.2428
Cardiovascular disease	7 (2.8)	32 (3.5)	.5592
Hyperlipidaemia	26 (10.3)	70 (7.7)	.1855

[a]Other genotypes were seen in 1 (0.4%) and 12 (1.3%) patients with pALT and normal ALT, respectively. Data are presented as n (%) unless otherwise indicated. No significant differences were seen between patients with normal ALT and pALT by race, vitamin D level, mean ALT level, ALT by central laboratory ULN, years positive for HBV, HBV DNA level, HBeAg positivity, IL28B genotype, cirrhosis history, previous NA experience, proteinuria by urinalysis (dipstick), hip BMD status, or spine BMD status.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; BMD, bone mineral density; BMI, body mass index; CG, Cockcroft-Gault; eGFR, estimated glomerular filtration rate; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IL, interleukin; NA, nucleos(t)ide analogue; pALT, persistently elevated ALT; ULN, upper limit of normal.

- After 8 years of treatment, most patients achieved normal ALT levels (907/1159 [78%]); however, a minority had persistently elevated levels based on AASLD criteria, with fewer patients meeting pALT criteria when assessed using the central laboratory cutoff (148/1159 [13%])
- Younger age, higher BMI, and HBV genotype were independent predictors of pALT, whether based on AASLD criteria or by central laboratory criteria (data not shown); however, lifestyle factors such as alcohol use were not evaluated
- No significant differences in baseline comorbidities were seen between patients with pALT and those with normal ALT levels

HBV DNA Levels in Patients with pALT vs Normal ALT at Year 8



AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBV, hepatitis B virus; pALT, persistently elevated ALT.

- At year 8, the vast majority of patients (83%–97%) achieved HBV DNA suppression (HBV DNA <29 IU/mL) regardless of biochemical response
- When HBV DNA levels were greater than the lower limit of quantitation, a substantial proportion of patients had low-level viraemia (HBV DNA <2000 IU/mL); levels ≥2000 IU/mL were uncommon overall (1%–7% of patients)

Serology at Year 8 in Patients with pALT and Normal ALT

	AASLD		Central Laboratory	
	pALT	Normal ALT	pALT	Normal ALT
HBeAg loss, n/N (%)	56/158 (35)	263/526 (50)	31/98 (32)	288/586 (49)
Seroconversion, n/N (%)	36/158 (23)	174/526 (33)	22/98 (22)	188/586 (32)
Change from baseline in HBsAg, $\log_{10}$ IU/mL, mean (SD)	−0.79 (0.898)	−0.88 (1.222)	−0.88 (1.001)	−0.86 (1.181)

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; pALT, persistently elevated ALT.

- Patients who achieved normal ALT levels had the highest rates of HBeAg loss and seroconversion; however, meaningful serologic responses were also seen in those with pALT, demonstrating consistent virologic activity across ALT outcomes

Multivariate Predictors of pALT

	AASLD		Central Laboratory	
	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Baseline BMI	1.142 (1.099, 1.186)	<.0001	1.149 (1.098, 1.202)	<.0001
Age	0.959 (0.946, 0.973)	<.0001	0.957 (0.940, 0.975)	<.0001
HBV genotype A	2.281 (1.278, 4.072)	.0053	–	–
Sex (male vs female)	–	–	1.746 (1.124, 2.713)	.0131

Dashes indicate that the characteristic was not a significant predictor in the multivariate model.
AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; HBV, hepatitis B virus; OR, odds ratio; pALT, persistently elevated alanine aminotransferase.

- Higher baseline BMI and younger age were significant predictors of pALT according to both AASLD and central laboratory criteria
- Genotype A (AASLD criteria) and male sex (central laboratory criteria) were additional predictors of pALT

FibroTest Categorical Shifts from Baseline at Year 8 by AASLD Criteria

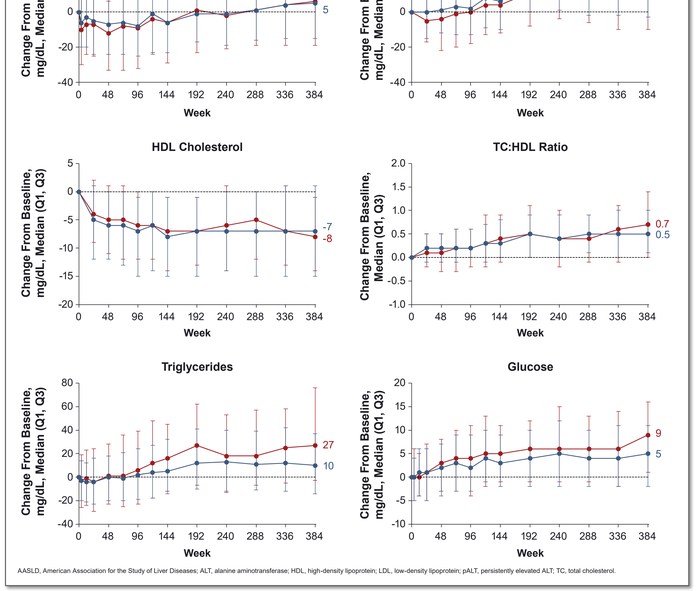
	pALT				Normal ALT			
Year 8	Baseline				Baseline			
FibroTest Category	None–Mild (n = 185)	Mod–Severe (n = 45)	Cirrhosis (n = 15)	Missing (n = 7)	None–Mild (n = 588)	Mod–Severe (n = 205)	Cirrhosis (n = 96)	Missing (n = 18)
None–Mild	165 (90)	22 (49)	4 (29)	6	541 (94)	115 (57)	19 (21)	14
Mod–Severe	17 (9)	19 (42)	5 (36)	0	34 (6)	77 (38)	52 (57)	2
Cirrhosis	2 (1)	4 (9)	5 (36)	1	0	10 (5)	20 (22)	2
Missing	1	0	1	0	13	3	5	0

Increase in Fibrosis Category From Baseline to Year 8 | No Change in Fibrosis Category | Decrease in Fibrosis Category

None–mild = F0–F1, <0.49; mod–severe = F2–F3, 0.49–0.74; cirrhosis = F4, >0.74. Values indicate n (%) based on nonmissing data.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; mod, moderate; pALT, persistently elevated ALT.

- Over 8 years, fibrosis categories based on FibroTest score were stable or improved in most patients, with more frequent improvements observed among patients with normal ALT; stable or improved fibrosis status was also observed in most patients with pALT
- Worsening in fibrosis category was observed in a minority of patients overall, with small differences observed among patients with pALT vs normal ALT levels
- Similar patterns were observed when ALT status was determined using central laboratory criteria (data not shown)

Lipid Changes Over 8 Years in Patients with pALT vs Normal ALT by AASLD Criteria



AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; pALT, persistently elevated ALT; TC, total cholesterol.

- Over 8 years of treatment, changes in total cholesterol (TC), low-density lipoprotein, and high-density lipoprotein (HDL) were modest and generally similar between patients with normal ALT levels and those with pALT
- Minimal median changes in the TC:HDL ratio (0.7 vs 0.5) were observed, while increases in triglycerides (+27 vs +10 mg/dL) and glucose (+9 vs +5 mg/dL) were greater in patients with pALT over 8 years of treatment
- Similar patterns were observed when ALT status was determined using central laboratory criteria (data not shown)