PREDICTORS OF HEPATITIS B TREATMENT RESPONSE IN PEOPLE WITH HIV-1/HBV COINFECTION

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Hepatitis B Treatment Response With HIV/HBV Coinfection

- Chronic hepatitis B affects ~8% of people with HIV, and HIV/HBV coinfection rates can reach 20% in areas where both viruses are endemic[1-3]

- People with HIV/HBV coinfection should receive treatment to suppress both viruses

  - International guidelines recommend a TDF- or TAF-based ARV regimen in combination with 3TC or FTC as the NRTI backbone for most people with HIV/HBV coinfection[4-7]

- Better understanding of factors that can affect response to treatment is important to help optimize regimen selection

- The **ALLIANCE** study investigated B/F/TAF vs. DTG + F/TDF for HIV/HBV coinfection

- Primary results from the **ALLIANCE** study, presented at AIDS 2022, showed that B/F/TAF was noninferior to DTG + F/TDF for achieving HIV-1 RNA < 50 c/mL and superior for achieving HBV DNA < 29 IU/mL[8]

This subanalysis of the Week 48 results from the ALLIANCE study examines predictors of HBV response to treatment for people with HIV and HBV initiating treatment with B/F/TAF or DTG + F/TDF

3TC, lamivudine; ARV, antiretroviral; B, bictegravir; c/mL, copies per milliliter; DTG, dolutegravir; F/FTC, emtricitabine; HBV, hepatitis B virus; IU/mL, international units per milliliter; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate
1. Leumi S, et al. Clin Infect Dis 2020;71:2799-2806; 2. Kellerman SE, et al. J Infect Dis 2003;188:571-577; 3. Thio CL. Hepatology 2009;49:S138-S145; 4. WHO. https://www.who.int/publications/i/item/9789240031593 (accessed Jan, 2023); 5. EACS. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf (accessed Jan, 2023); 6. DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed Nov. 10, 2022); 7. Saag MS, et al. JAMA 2020;324:1651-1669; 8. Avihingsanon A, et al. AIDS 2022, Oral OALBX0105

ALLIANCE Study Design and Analyses
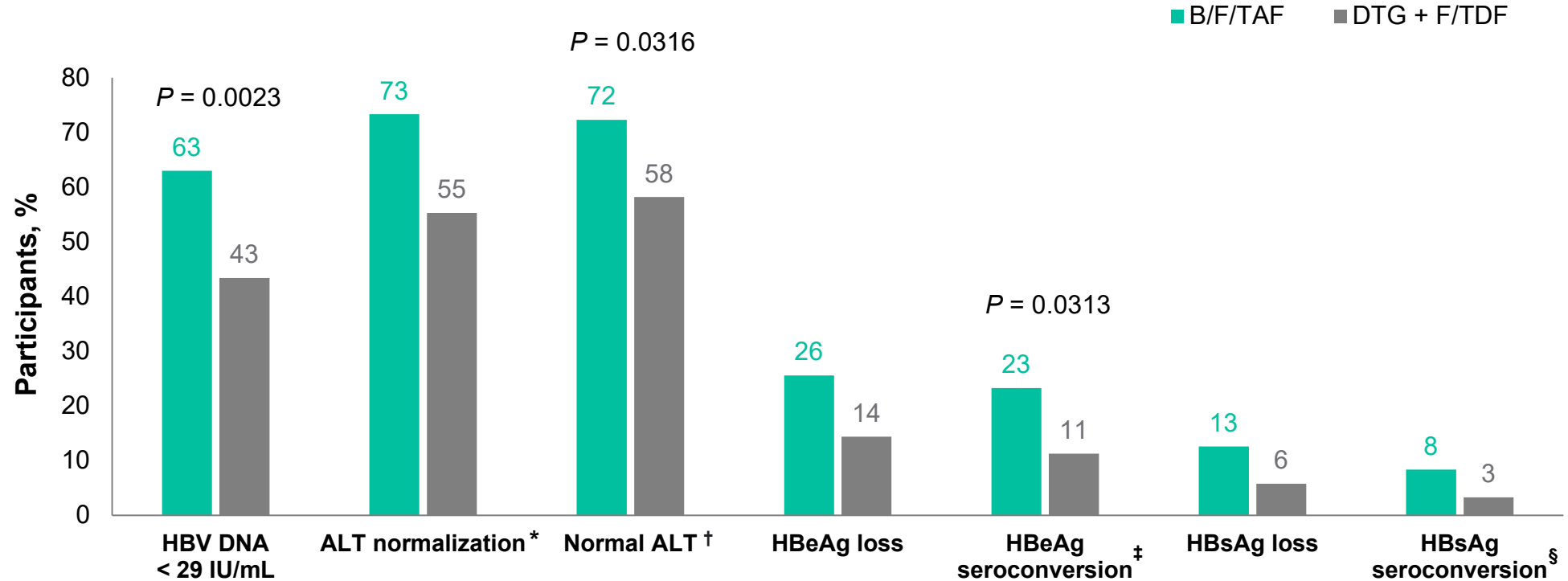
Adults with HIV/HBV coinfection HIV and HBV treatment-naïve

- HIV-1 RNA ≥ 500 c/mL
- HBV DNA ≥ 2,000 IU/mL
- Genotypic sensitivity of HIV to FTC, TFV
- $eGFR_{CG}$ ≥ 50 mL/min

1:1

n = 121
B/F/TAF QD
DTG + F/TDF Placebo QD

n = 122
DTG + F/TDF QD
B/F/TAF Placebo QD

Week 0 — **48** — 96

1º Endpoints

Randomization stratified by
- HBeAg (positive vs. negative)
- HBV DNA (< vs. ≥ 8 $\log_{10}$ IU/mL)
- CD4+ cell count (< vs. ≥ 50 cells/µL)

HIV-1 RNA < 50 c/mL (FDA Snapshot algorithm), 12% noninferiority margin

HBV DNA < 29 IU/mL (missing = failure analysis), 12% noninferiority margin

- **Prespecified subgroup analysis of between-treatment differences in the proportion of people with HBV DNA < 29 IU/mL**
- **Multivariate analysis to identify baseline predictors of HBV DNA < 29 IU/mL, HBeAg loss and HBsAg loss**

ALT, alanine aminotransferase; B, bictegravir; c/mL, copies per mL; DTG, dolutegravir; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft–Gault method; F/FTC, emtricitabine; FDA, U.S. Food and Drug Administration; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU/mL, international units per milliliter; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir https://clinicaltrials.gov/ct2/show/NCT03547908 (accessed Jan, 2023)

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Baseline Characteristics

	B/F/TAF n = 121	DTG + F/TDF n = 122
HBV genotype, n (%)*		
A/D	22 (20)	33 (30)
B/C	84 (75)	74 (68)
HBV DNA		
Median, $\log_{10}$ IU/mL (IQR)	8.0 (6.5, 8.4)	8.1 (6.6, 8.5)
≥ 8 $\log_{10}$ IU/mL, n (%)	60 (50)	66 (54)
HBeAg positive, n (%)	92 (76)	97 (80)
ALT > ULN, n (%)†	60 (50)	47 (39)

The overall median age was 32 years, 95% were male at birth and 88% were from Asia
Median HIV-1 RNA was 4.7 $\log_{10}$ c/mL and median CD4 cell count was 243 cells/μL

*B/F/TAF: n = 112, DTG + F/TDF: n = 109; †American Association for the Study of Liver Diseases (AASLD) criteria: 25 U/L (females), 35 U/L (males)
ALT, alanine aminotransferase; B, bictegravir; c/mL, copies per milliliter; DTG, dolutegravir; F, emtricitabine; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; IQR, interquartile range; IU/mL, international units per milliliter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal
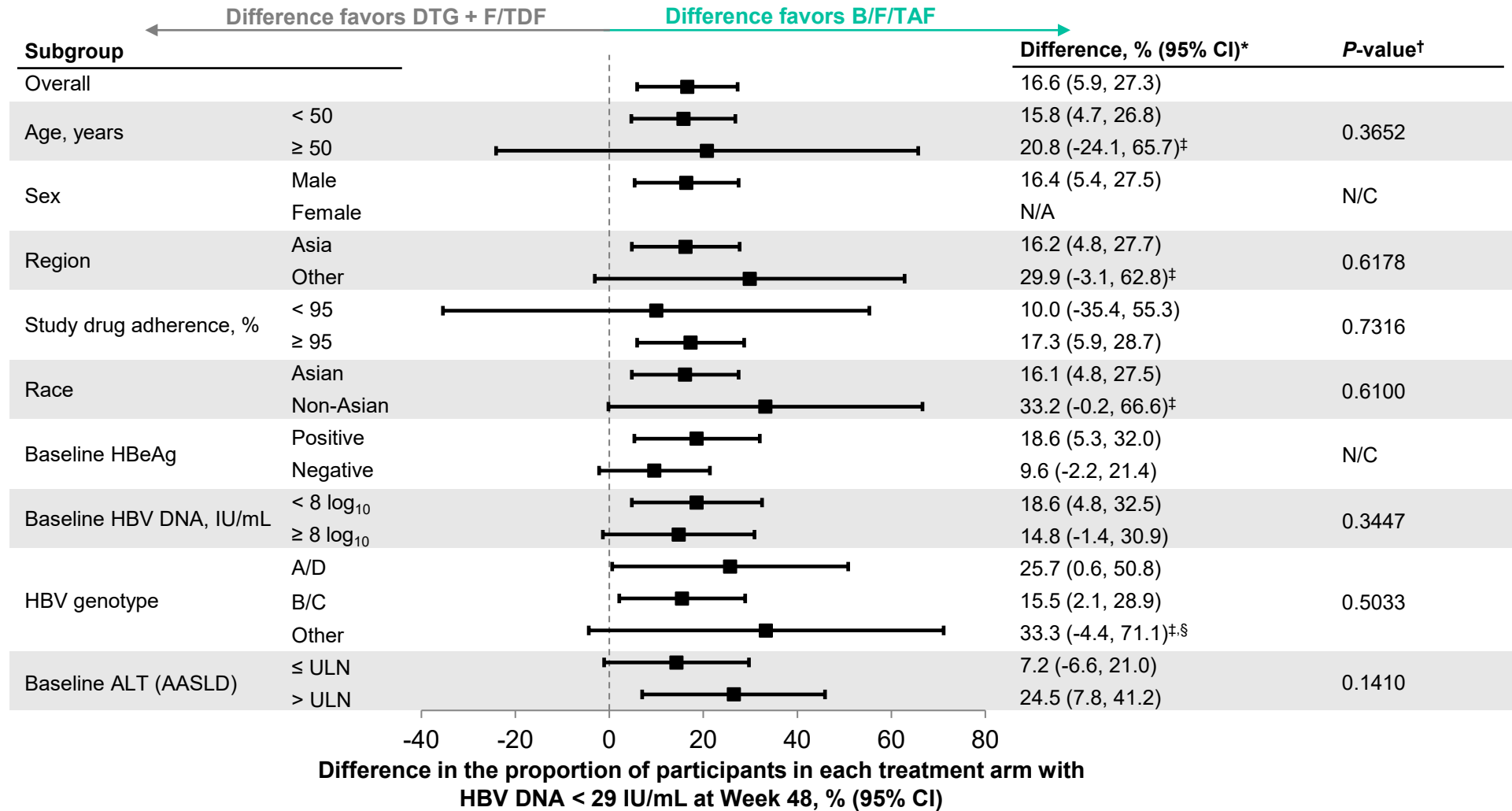
HBV Outcomes at Week 48 (M = F)

Chart: Participants, % (y-axis) by outcome category.

Legend: ■ B/F/TAF ■ DTG + F/TDF

Outcome	B/F/TAF (%)	DTG + F/TDF (%)	P value
HBV DNA < 29 IU/mL	63	43	P = 0.0023
ALT normalization *	73	55	
Normal ALT †	72	58	P = 0.0316
HBeAg loss	26	14	
HBeAg seroconversion ‡	23	11	P = 0.0313
HBsAg loss	13	6	
HBsAg seroconversion §	8	3	

n/N =

	HBV DNA < 29 IU/mL	ALT normalization *	Normal ALT †	HBeAg loss	HBeAg seroconversion ‡	HBsAg loss	HBsAg seroconversion §
B/F/TAF	75/119	44/60	86/119	23/90	21/90	15/119	10/119
DTG + F/TDF	53/122	26/47	71/122	14/97	11/97	7/121	4/121

*Proportion of participants with ALT > ULN at baseline with a normal ALT [≤ 25 U/L (females), ≤ 35 U/L (males)] at Week 48; †Proportion of participants with normal ALT (by AASLD criteria) at Week 48;
‡Defined as loss of serum HBeAg and development of anti-HBeAg antibodies; §Defined as loss of serum HBsAg and development of anti-HBsAg antibodies
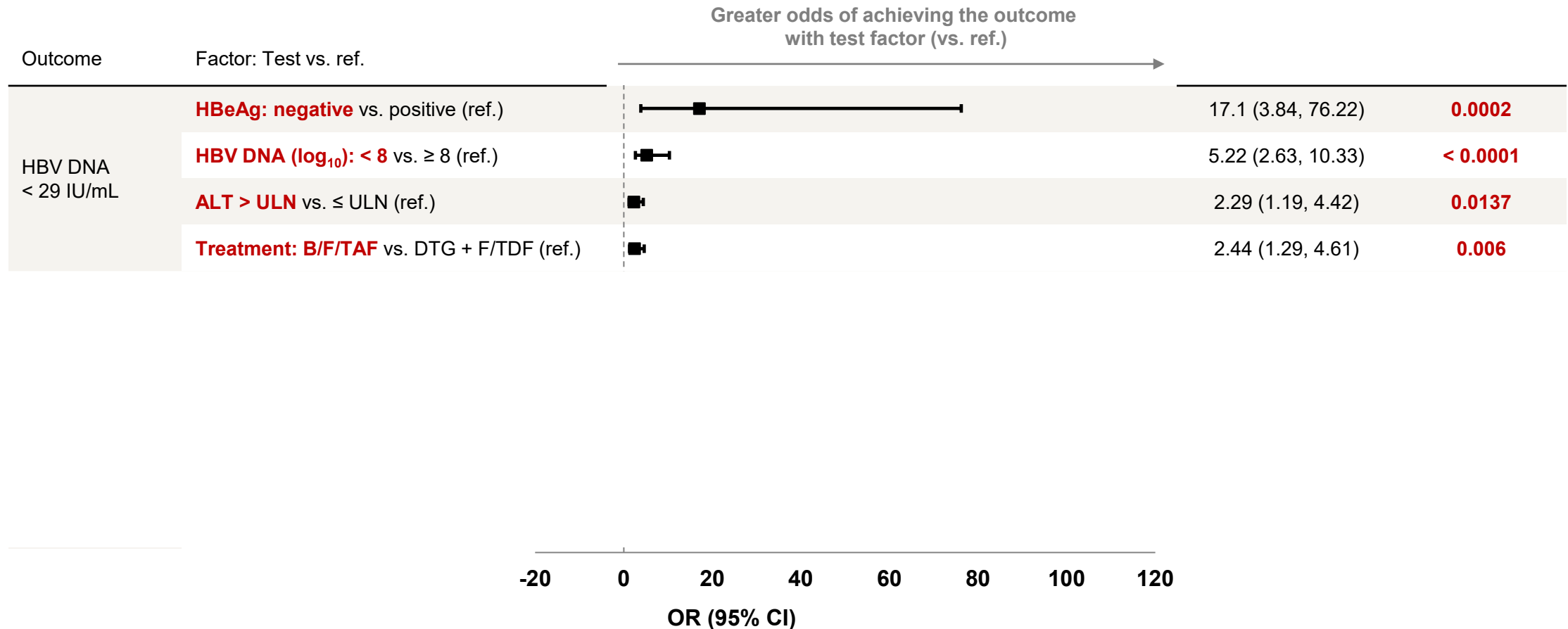ALT, alanine aminotransferase; AASLD, American Association for the Study of Liver Diseases; B, bictegravir; DTG, dolutegravir; F, emtricitabine; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen;
HBV, hepatitis B virus; IU/mL, international units per milliliter; M = F, missing = failure; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal

Treatment Difference in Proportion of Participants with HBV DNA < 29 IU/mL at Week 48, by Subgroup (M = F)

Subgroup		Difference, % (95% CI)*	P-value[†]
Overall		16.6 (5.9, 27.3)	
Age, years	< 50	15.8 (4.7, 26.8)	0.3652
	≥ 50	20.8 (-24.1, 65.7)[‡]	
Sex	Male	16.4 (5.4, 27.5)	N/C
	Female	N/A	
Region	Asia	16.2 (4.8, 27.7)	0.6178
	Other	29.9 (-3.1, 62.8)[‡]	
Study drug adherence, %	< 95	10.0 (-35.4, 55.3)	0.7316
	≥ 95	17.3 (5.9, 28.7)	
Race	Asian	16.1 (4.8, 27.5)	0.6100
	Non-Asian	33.2 (-0.2, 66.6)[‡]	
Baseline HBeAg	Positive	18.6 (5.3, 32.0)	N/C
	Negative	9.6 (-2.2, 21.4)	
Baseline HBV DNA, IU/mL	< 8 log$_{10}$	18.6 (4.8, 32.5)	0.3447
	≥ 8 log$_{10}$	14.8 (-1.4, 30.9)	
HBV genotype	A/D	25.7 (0.6, 50.8)	0.5033
	B/C	15.5 (2.1, 28.9)	
	Other	33.3 (-4.4, 71.1)[‡,§]	
Baseline ALT (AASLD)	≤ ULN	7.2 (-6.6, 21.0)	0.1410
	> ULN	24.5 (7.8, 41.2)	

Difference favors DTG + F/TDF ← | → Difference favors B/F/TAF

Difference in the proportion of participants in each treatment arm with HBV DNA < 29 IU/mL at Week 48, % (95% CI)

*The difference in proportion of participants with HBV DNA < 29 IU/mL between treatment groups (B/F/TAF vs. DTG + F/TDF) calculated based on the MH proportions adjusted by baseline HBeAg status (positive vs. negative) and baseline HBV DNA (< 8 log$_{10}$ IU/mL vs. ≥ 8 log$_{10}$ IU/mL), if not the subgroup factor; †P-value for the homogeneity test was from the Wald test of the interaction between treatment and subgroup based on a logistic regression model; ‡Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum-adjusted MH method; §'Other' HBV genotype excluded from the logistic regression model for P-value calculation due to small sample size. ALT, alanine aminotransferase; B, bictegravir; CI, confidence interval; DTG, dolutegravir; F, emtricitabine; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; IU/mL, international units per milliliter; M = F, missing = failure; MH, Mantel–Haenszel; N/A, not applicable; N/C, not calculable (due to lack of variance in subgroup[s]); TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal
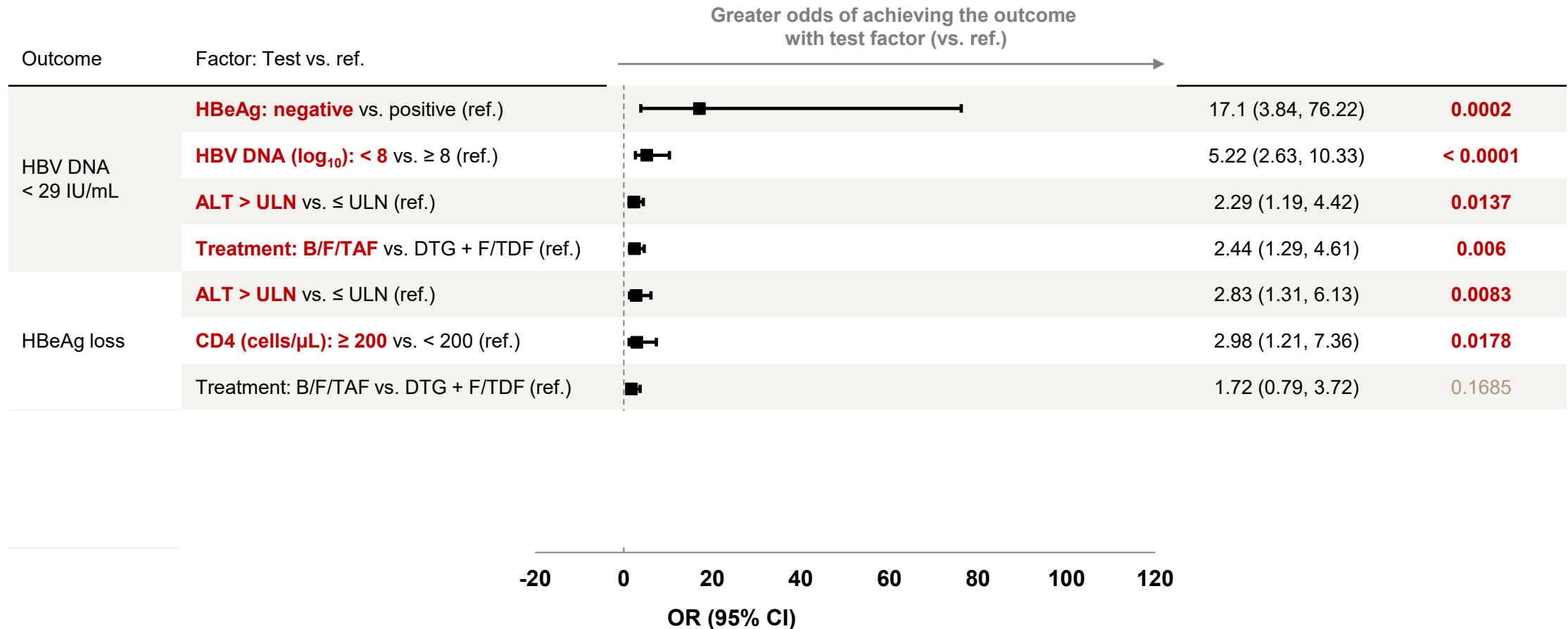
Baseline Predictors of HBV Treatment Response: Multivariate Logistic Regression Analysis (Full Analysis Set)

Outcome	Factor: Test vs. ref.		OR (95% CI)	p-value
		Greater odds of achieving the outcome with test factor (vs. ref.) →		
HBV DNA < 29 IU/mL	**HBeAg: negative** vs. positive (ref.)		17.1 (3.84, 76.22)	**0.0002**
	HBV DNA (log$_{10}$): < 8 vs. ≥ 8 (ref.)		5.22 (2.63, 10.33)	**< 0.0001**
	ALT > ULN vs. ≤ ULN (ref.)		2.29 (1.19, 4.42)	**0.0137**
	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)		2.44 (1.29, 4.61)	**0.006**

OR (95% CI)
-20   0   20   40   60   80   100   120

Stepwise logistic regression was conducted. The significance level for entry into the model = 0.025, the significance level for staying in the model = 0.05. Candidate independent variables included: demographics (group of age, sex, race and ethnicity), baseline HBV DNA, HBV genotype baseline ALT, baseline BMI, baseline HIV1-RNA, baseline CD4 cell count and HIV-1 disease status. The final multivariate model included treatment and variables selected by the stepwise method as independent variables

ALT, alanine aminotransferase; B, bictegravir; BMI, body mass index; CI, confidence interval; DTG, dolutegravir; F, emtricitabine; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; IU/mL, international units per milliliter; OR, odds ratio; ref., reference; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal
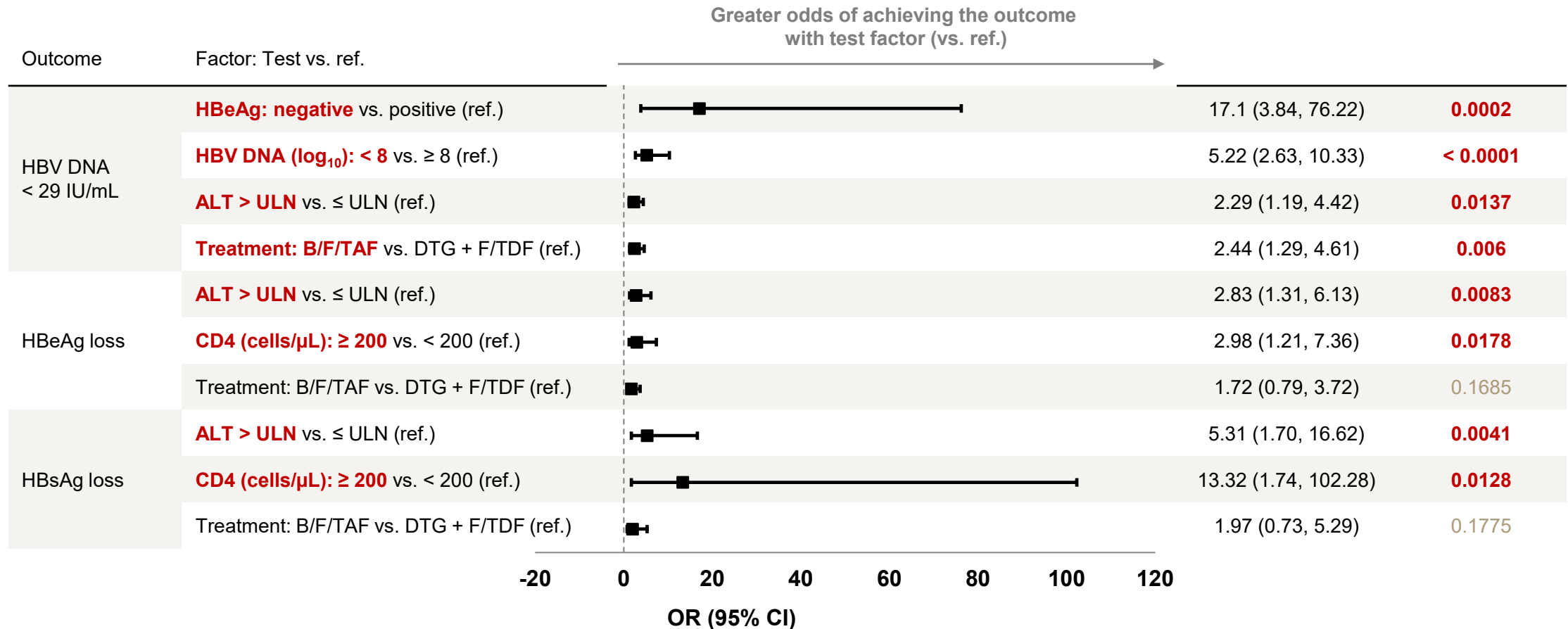
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	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)		2.44 (1.29, 4.61)	**0.006**
HBeAg loss	**ALT > ULN** vs. ≤ ULN (ref.)		2.83 (1.31, 6.13)	**0.0083**
	CD4 (cells/µL): ≥ 200 vs. < 200 (ref.)		2.98 (1.21, 7.36)	**0.0178**
	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)		1.72 (0.79, 3.72)	0.1685

Greater odds of achieving the outcome with test factor (vs. ref.)

OR (95% CI)

Stepwise logistic regression was conducted. The significance level for entry into the model = 0.025, the significance level for staying in the model = 0.05. Candidate independent variables included: demographics (group of age, sex, race and ethnicity), baseline HBV DNA, HBV genotype baseline ALT, baseline BMI, baseline HIV1-RNA, baseline CD4 cell count and HIV-1 disease status. The final multivariate model included treatment and variables selected by the stepwise method as independent variables

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Outcome	Factor: Test vs. ref.	OR (95% CI)	p-value
HBV DNA < 29 IU/mL	**HBeAg: negative** vs. positive (ref.)	17.1 (3.84, 76.22)	**0.0002**
	HBV DNA ($\log_{10}$): < 8 vs. ≥ 8 (ref.)	5.22 (2.63, 10.33)	**< 0.0001**
	ALT > ULN vs. ≤ ULN (ref.)	2.29 (1.19, 4.42)	**0.0137**
	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)	2.44 (1.29, 4.61)	**0.006**
HBeAg loss	**ALT > ULN** vs. ≤ ULN (ref.)	2.83 (1.31, 6.13)	**0.0083**
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	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)	1.72 (0.79, 3.72)	0.1685
HBsAg loss	**ALT > ULN** vs. ≤ ULN (ref.)	5.31 (1.70, 16.62)	**0.0041**
	CD4 (cells/µL): ≥ 200 vs. < 200 (ref.)	13.32 (1.74, 102.28)	**0.0128**
	Treatment: B/F/TAF vs. DTG + F/TDF (ref.)	1.97 (0.73, 5.29)	0.1775

Greater odds of achieving the outcome with test factor (vs. ref.)

Stepwise logistic regression was conducted. The significance level for entry into the model = 0.025, the significance level for staying in the model = 0.05. Candidate independent variables included: demographics (group of age, sex, race and ethnicity), baseline HBV DNA, HBV genotype baseline ALT, baseline BMI, baseline HIV1-RNA, baseline CD4 cell count and HIV-1 disease status. The final multivariate model included treatment and variables selected by the stepwise method as independent variables

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Conclusions

In adults with HIV/HBV coinfection initiating antiviral therapy for the first time, after 48 weeks:

♦ Significantly more participants on B/F/TAF versus DTG + F/TDF had HBV DNA < 29 IU/mL, normal ALT and HBeAg seroconversion

♦ B/F/TAF treatment led to a larger proportion of participants with HBV DNA < 29 IU/mL compared with DTG + F/TDF across all subgroups

♦ Several baseline factors were determined to be predictors of HBV DNA suppression, including B/F/TAF treatment, HBeAg-negative status, HBV DNA < 8 $\log_{10}$ and ALT > ULN at baseline
  – ALT > ULN and CD4 ≥ 200 cells/μL at baseline were predictors of HBeAg and HBsAg loss

The ALLIANCE study will continue in a blinded fashion through Week 96 to determine longer-term safety and efficacy

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C-C Hung	H Nakajima	H Wei
SI Kim	S Oka	C-J Yang
M-P Lee	T Shirasaka	F Zhang
L Li	H-C Tsai	B Zhu

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TS Chow	S Kiertiburanakul	AKA Rahman
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