Factors Associated With HBV Response to B/F/TAF Versus DTG + F/TDF at Week 96 in People With HIV-1 and HBV

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Conclusions

- Consistent with the overall population of people with HIV-1/HBV coinfection,[1] in several subgroups, B/F/TAF was associated with:
  - Significantly higher rates of HBeAg loss/seroconversion compared with DTG + F/TDF at Week 96
  - Numerically higher rates of HBsAg loss and ALT normalization compared with DTG + F/TDF at Week 96
- This analysis suggests that, in people with HIV-1/HBV coinfection, the treatment response of TAF- versus TDF-based therapy for some or all HBV treatment outcomes may be greater for certain subgroups
  - These include people < 30 years of age, or with baseline HBV DNA < 8 log_{10} IU/mL, baseline HIV-1 RNA ≤ 100,000 c/mL, HBV genotype B/C, baseline CD4 count ≥ 200 cells/µL, abnormal baseline ALT levels, abnormal ALT levels at Week 12, or HBV DNA < 29 IU/mL at Week 48.
  - The finding that lower baseline HBV and HIV viral loads, higher baseline CD4 count, and higher ALT levels at baseline and Week 12 may be associated with a larger treatment difference with TAF versus TDF for HBeAg loss/seroconversion may indicate a better response to TAF versus TDF in people early in disease progression, or in those who are in the immune active phase of the disease

Plain Language Summary

- This study (the ALLIANCE study) looked at how two treatments called B/F/TAF and DTG + F/TDF work to treat adults with both HIV-1 and HBV infection
- The main purpose of the study was to compare how effective B/F/TAF and DTG + F/TDF were at reducing levels of the two viruses (HIV-1 and HBV) in the blood
  - After 96 weeks, both treatments reduced the levels of HIV-1 and HBV. These results were published in 2023 in a medical journal called *The Lancet HIV*[1]
- The published study also showed that B/F/TAF reduced the levels of two proteins (called HBeAg and HBsAg) in the blood, more than DTG + F/TDF did after 96 weeks of treatment
  - HBeAg and HBsAg are signs of HBV infection – a goal of treatment is to lower HBeAg and HBsAg levels as much as possible
- In the ALLIANCE study, researchers wanted to understand if some groups of people might be more likely to benefit from B/F/TAF than others
  - They grouped participants by common features (such as age, race, or how much HIV and HBV participants had in their blood at the start of the study)
  - They looked at how HBeAg and HBsAg levels changed with B/F/TAF or DTG + F/TDF treatment, and whether B/F/TAF was able to lower the levels of these proteins more in some groups of people compared with DTG + F/TDF
- The results of this study showed that B/F/TAF might work better than DTG + F/TDF for some groups of people than for others. For example, B/F/TAF may work better for people younger than 30 years, and for people with less HBV in their blood at the start of the treatment

Introduction

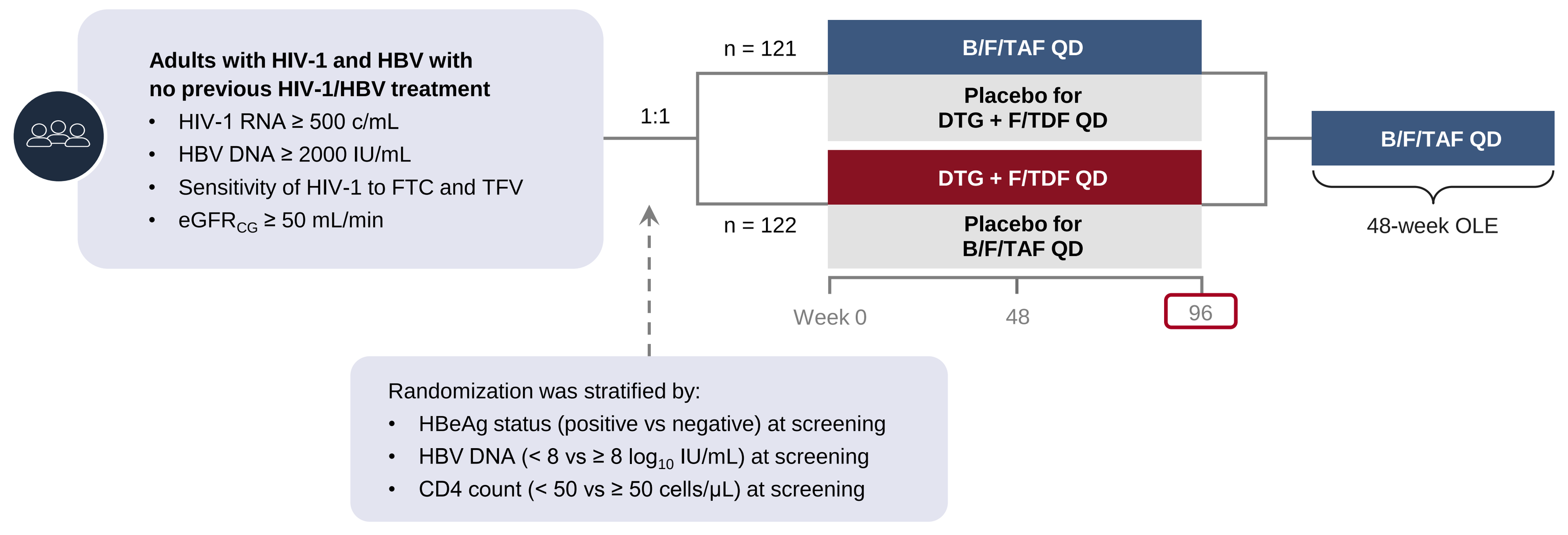
- Approximately 2.7 million people are living with both HIV-1 and HBV infection globally, with coinfection rates of up to 20% in areas where both viruses are endemic[2,3]
- An initial tenofovir alafenamide (TAF)– or tenofovir disoproxil fumarate (TDF)–containing antiretroviral (ARV) regimen is recommended for most adults and adolescents with HIV-1 and HBV[4-7]
- The Phase 3 ALLIANCE study (NCT03547908) was the first randomized study to compare a TAF- versus TDF-based regimen as initial therapy in this important population[1]
- In ALLIANCE, treatment with bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) resulted in significantly higher rates of hepatitis B e antigen (HBeAg) loss/seroconversion, and numerically higher rates of hepatitis B surface antigen (HBsAg) loss/seroconversion and alanine aminotransferase (ALT) normalization, versus dolutegravir (DTG) + emtricitabine/tenofovir disoproxil fumarate (F/TDF) at Week 96[1]
  - Overall, rates of HBeAg and HBsAg loss/seroconversion and ALT normalization at Week 96 were substantially higher in the ALLIANCE population compared with TDF or TAF studies in HBV monoinfection, especially with B/F/TAF[1]
  - The reason(s) behind these differences remain(s) unclear

Objective

- To explore factors associated with the HBV treatment response of B/F/TAF versus DTG + F/TDF in adults coinfected with HIV-1 and HBV in the ALLIANCE study at Week 96 by subgroup analysis

Methods

Study Design


Adults with HIV-1 and HBV with no previous HIV-1/HBV treatment
HIV-1 RNA ≥ 500 c/mL
HBV DNA ≥ 2000 IU/mL
Sensitivity of HIV-1 to FTC and TFV
eGFR$_{CG}$ ≥ 50 mL/min
1:1
n = 121
B/F/TAF QD
Placebo for DTG + F/TDF QD
n = 122
DTG + F/TDF QD
Placebo for B/F/TAF QD
B/F/TAF QD
48-week OLE
Week 0
48
96
Randomization was stratified by:
HBeAg status (positive vs negative) at screening
HBV DNA (< 8 vs ≥ 8 log_{10} IU/mL) at screening
CD4 count (< 50 vs ≥ 50 cells/µL) at screening

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft–Gault equation; F/TDF, emtricitabine/tenofovir disoproxil fumarate; FTC, emtricitabine; HBeAg, hepatitis B e antigen; OLE, open-label extension; QD, once daily; TFV, tenofovir.

Subgroup Analysis

- This univariate subgroup analysis compared the proportions of participants with HBeAg loss/seroconversion, HBsAg loss, and ALT normalization with B/F/TAF versus DTG + F/TDF at Week 96, according to baseline demographics, HBV genotype, and baseline and on-treatment markers of HIV-1/HBV disease severity
- ALT normalization was evaluated using the 2018 American Association for the Study of Liver Diseases (AASLD) criteria, ie, change in ALT concentration from > upper limit of normal (ULN; female participants: 25 U/mL; male participants: 35 U/mL) at baseline to ≤ ULN at Week 96[8]
- Study drug adherence by pill count was based on available adherence data up to the Week 96 visit for the active study drug
- Treatment differences and 95% CIs were calculated based on Mantel–Haenszel (MH) proportions adjusted by baseline HBV DNA category (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL) and baseline HBeAg status (positive vs negative), if not the subgroup factor or endpoint factor
- An analysis of quantitative HBsAg levels is ongoing

Key Baseline Demographics and Disease Characteristics[1]

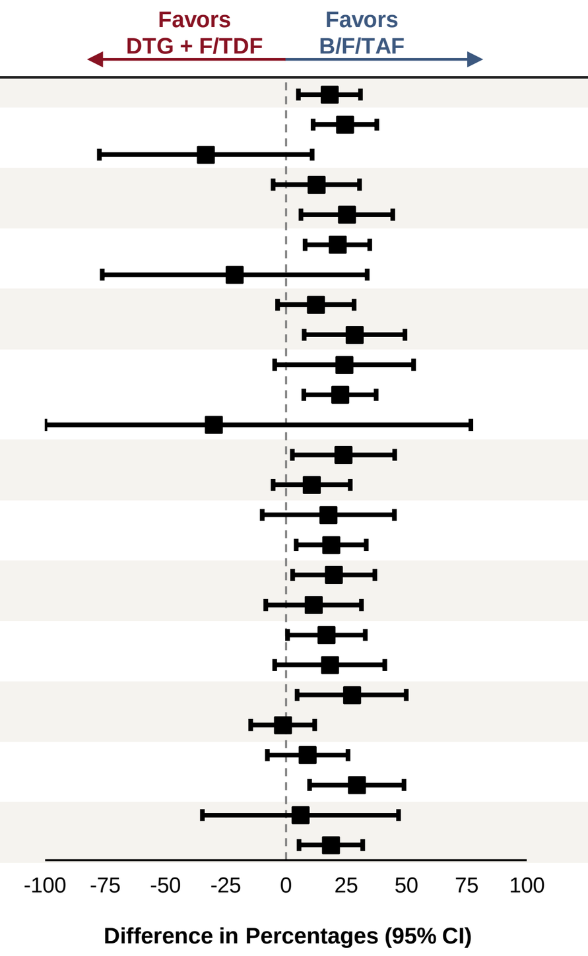
B/F/TAF n = 121		DTG + F/TDF n = 122
31 (27-39)	Age, years	32 (25-38)
112 (93)	Male sex at birth	120 (98)
108 (89)	Asian race	106 (87)
83 (69)	HIV disease status: asymptomatic	81 (66)
4.66 (4.22, 5.12)	HIV-1 RNA, log_{10} c/mL	4.69 (4.26, 5.04)
245 (127, 383)	CD4 cell count, cells/µL	236 (121, 380)
7 / 21 / 63 / 15 / 6 (6 / 19 / 56 / 13 / 5)	HBV genotype: A / B / C / D / other[a]	19 / 24 / 50 / 14 / 2 (17 / 22 / 46 / 13 / 2)
7.96 (6.52, 8.38)	HBV DNA, log_{10} IU/mL	8.08 (6.59, 8.50)
92 (76)	HBeAg positive	97 (80)
34 (23, 60)	ALT, U/L	27 (19, 51)
60 (50)	ALT > ULN (AASLD)	47 (39)

Data shown as n (%), except median (range) for age and median (Q1, Q3) for HIV-1 RNA, CD4 cell count, HBV DNA, and ALT.
[a]'Other' consists of HBV genotype F and mixed. Percentage based on participants with available HBV genotype (missing genotype: n = 9 for B/F/TAF, n = 13 for DTG + F/TDF).
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBeAg, hepatitis B e antigen; Q, quartile; ULN, upper limit of normal.

Results

Treatment Difference in Proportion of Participants With HBeAg Loss at Week 96, by Subgroup

HBeAg Loss



Subgroup		n/N (%) B/F/TAF	n/N (%) DTG + F/TDF	Difference in % (95% CI)
Overall		34/90 (38)	19/97 (20)	18.1 (5.2, 31.0)
Race	Asian	32/82 (39)	12/84 (14)	24.5 (11.3, 37.7)
	Non-Asian	2/8 (25)	7/13 (54)	-33.3 (-77.5, 10.9)
Age, years	≥ 30	18/49 (37)	13/54 (24)	12.7 (-5.3, 30.6)
	< 30	16/41 (39)	6/43 (14)	25.3 (6.3, 44.3)
Study drug adherence	≥ 95%	32/81 (40)	16/89 (18)	21.4 (8.0, 34.8)
	< 95%	2/9 (22)	3/7 (43)	-21.3 (-76.3, 33.8)
Baseline HBV DNA,[a] IU/mL	≥ 8 log_{10}	19/56 (34)	14/65 (22)	12.4 (-3.5, 28.3)
	< 8 log_{10}	15/34 (44)	5/32 (16)	28.5 (7.6, 49.4)
HBV genotype	A/D	9/18 (50)	8/30 (27)	24.2 (-4.6, 53.0)
	B/C	23/63 (37)	8/59 (14)	22.5 (7.5, 37.4)
	Other	1/5 (20)	1/2 (50)	-30.0 (-100.0, 76.8)
Baseline ALT (AASLD)	> ULN	21/43 (49)	9/36 (25)	23.8 (2.6, 45.1)
	≤ ULN	13/47 (28)	10/61 (16)	10.7 (-5.3, 26.7)
Baseline HIV-1 RNA, c/mL	> 100,000	11/24 (46)	8/28 (29)	17.6 (-9.8, 45.0)
	≤ 100,000	23/66 (35)	11/69 (16)	18.8 (4.2, 33.4)
Baseline CD4, cells/µL	≥ 200	26/59 (44)	13/55 (24)	19.8 (2.8, 36.9)
	< 200	8/31 (26)	6/42 (14)	11.5 (-8.4, 31.3)
Baseline HIV-1 disease status	Asymptomatic	24/62 (39)	13/62 (21)	16.8 (0.7, 33.0)
	Symptomatic/AIDS	10/28 (36)	6/35 (17)	18.2 (-4.6, 41.0)
HBV DNA at Week 48, IU/mL	< 29	29/46 (63)	11/30 (37)	27.4 (4.7, 50.0)
	≥ 29	5/44 (11)	8/67 (12)	-1.3 (-14.6, 12.0)
Normal ALT at Week 12 (AASLD)	Yes	13/49 (27)	8/47 (17)	9.0 (-7.7, 25.7)
	No	21/41 (51)	11/50 (22)	29.4 (9.8, 49.0)
TE Grade ≥ 3 ALT by Week 12	Yes	9/15 (60)	7/13 (54)	6.0 (-34.7, 46.7)
	No	25/75 (33)	12/84 (14)	18.7 (5.5, 31.9)

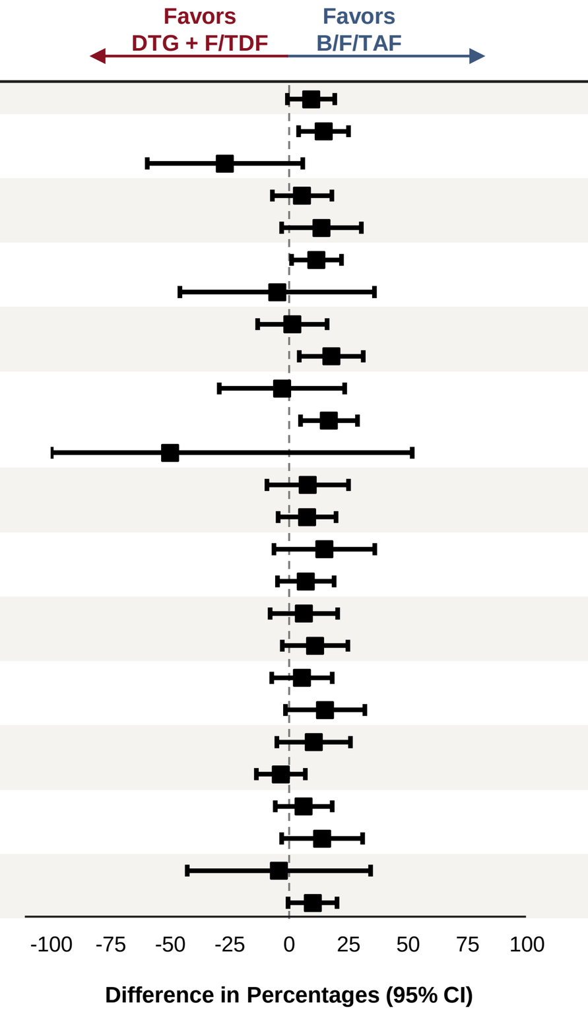
Data are from the serologically evaluable full analysis set for individuals who were HBeAg positive and HBeAb negative/missing at baseline. Difference in percentages and 95% CIs were calculated based on the MH proportions adjusted by baseline HBV DNA category (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL), if not the subgroup factor.
[a]Proportion difference and 95% CI from normal approximation without stratification, as not calculable by stratum-adjusted MH method.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBeAg, hepatitis B e antigen; MH, Mantel–Haenszel; ULN, upper limit of normal; TE, treatment-emergent.

Consistent with the overall population, B/F/TAF resulted in higher rates of HBeAg loss compared with DTG + F/TDF in many subgroups. This difference was significant in several important subgroups:
- Asian race
- Younger age (< 30 years)
- Higher study drug adherence (≥ 95%)
- Lower HBV viral load (baseline HBV DNA < 8 log_{10} IU/mL)
- HBV genotype B/C
- Abnormal baseline ALT levels (> ULN)
- Lower HIV-1 viral load (baseline HIV-1 RNA ≤ 100,000 c/mL)
- Higher CD4 levels (baseline CD4 count ≥ 200 cells/µL)
- Asymptomatic HIV-1 at baseline
- Lower HBV levels at Week 48 (HBV DNA < 29 IU/mL)
- Abnormal ALT levels at Week 12
- No treatment-emergent Grade ≥ 3 ALT elevations by Week 12

Treatment differences were comparable for HBeAg seroconversion

Treatment Difference in Proportion of Participants With HBsAg Loss at Week 96, by Subgroup

HBsAg Loss



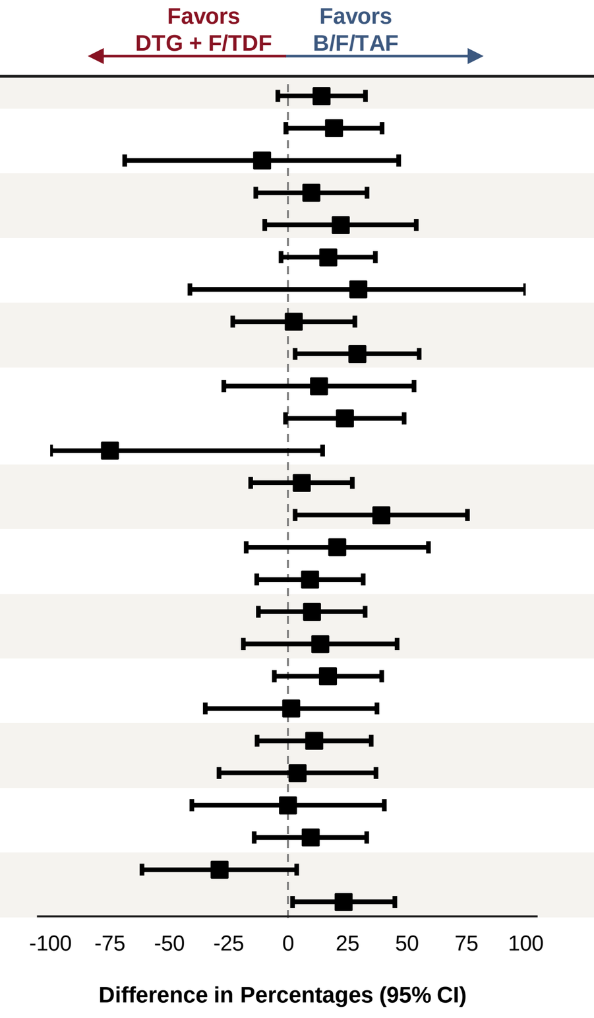
Subgroup		n/N (%) B/F/TAF	n/N (%) DTG + F/TDF	Difference in % (95% CI)
Overall		27/119 (23)	17/121 (14)	9.3 (-0.7, 19.2)
Race	Asian	26/106 (25)	11/106 (10)	14.5 (4.0, 25.0)
	Non-Asian	1/13 (8)	6/15 (40)	-27.0 (-59.7, 5.7)
Age, years	≥ 30	12/69 (17)	9/72 (13)	5.4 (-7.1, 18.0)
	< 30	15/50 (30)	8/49 (16)	13.6 (-3.2, 30.4)
Study drug adherence	≥ 95%	25/107 (23)	14/108 (13)	11.5 (1.0, 22.0)
	< 95%	2/12 (17)	3/12 (25)	-5.0 (-45.9, 35.8)
Baseline HBV DNA,[a] IU/mL	≥ 8 log_{10}	12/59 (20)	13/66 (20)	1.4 (-13.2, 16.0)
	< 8 log_{10}	15/60 (25)	4/55 (7)	17.7 (4.2, 31.2)
HBV genotype	A/D	5/22 (23)	9/32 (28)	-3.0 (-29.4, 23.3)
	B/C	20/82 (24)	6/74 (8)	16.7 (4.8, 28.7)
	Other	0/6 (0)	1/2 (50)	-50.0 (-100.0, 51.7)
Baseline ALT (AASLD)	> ULN	17/60 (28)	10/46 (22)	7.8 (-9.4, 25.0)
	≤ ULN	10/59 (17)	7/75 (9)	7.5 (-4.7, 19.7)
Baseline HIV-1 RNA, c/mL	> 100,000	10/38 (26)	5/34 (15)	14.8 (-6.4, 36.0)
	≤ 100,000	17/81 (21)	12/87 (14)	7.0 (-4.9, 18.9)
Baseline CD4, cells/µL	≥ 200	21/75 (28)	15/70 (21)	6.2 (-8.0, 20.4)
	< 200	6/44 (14)	2/51 (4)	10.9 (-2.9, 24.7)
Baseline HIV-1 disease status	Asymptomatic	20/83 (24)	15/81 (19)	5.4 (-7.3, 18.1)
	Symptomatic/AIDS	7/36 (19)	2/40 (5)	15.1 (-1.6, 31.8)
HBV DNA at Week 48, IU/mL	< 29	25/75 (33)	12/52 (23)	10.3 (-5.2, 25.8)
	≥ 29	2/44 (5)	5/69 (7)	-3.5 (-13.8, 6.8)
Normal ALT at Week 12 (AASLD)	Yes	12/69 (17)	7/62 (11)	6.1 (-5.8, 18.1)
	No	15/50 (30)	10/59 (17)	13.9 (-3.1, 30.9)
TE Grade ≥ 3 ALT by Week 12	Yes	6/18 (33)	5/13 (38)	-4.3 (-42.8, 34.3)
	No	21/101 (21)	12/108 (11)	9.9 (-0.4, 20.1)

Data are from the serologically evaluable full analysis set for individuals who were HBsAg positive and HBsAb negative/missing at baseline. Difference in percentages and 95% CIs were calculated based on the MH proportions adjusted by baseline HBeAg status (positive vs negative) and baseline HBV DNA category (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL), if not the subgroup factor.
[a]Proportion difference and 95% CI from normal approximation without stratification, as not calculable by stratum-adjusted MH method.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBsAg, hepatitis B surface antigen; MH, Mantel–Haenszel; ULN, upper limit of normal; TE, treatment-emergent.

As observed in the overall population, B/F/TAF resulted in higher rates of HBsAg loss compared with DTG + F/TDF in many subgroups. This difference was significant in the following subgroups:
- Asian race
- Higher study drug adherence (≥ 95%)
- Lower HBV viral load (baseline HBV DNA < 8 log_{10} IU/mL)
- HBV genotype B/C

Treatment Difference in Proportion of Participants With ALT Normalization (AASLD) at Week 96, by Subgroup

ALT Normalization



Subgroup		n/N B/F/TAF	n/N DTG + F/TDF	Difference in % (95% CI)
Overall		43/60 (72)	27/47 (57)	14.1 (-4.3, 32.6)
Race	Asian	39/53 (74)	21/39 (54)	19.3 (-0.9, 39.6)
	Non-Asian	4/7 (57)	6/8 (75)	-11.0 (-68.7, 46.6)
Age, years	≥ 30	24/36 (67)	18/31 (58)	9.8 (-13.6, 33.3)
	< 30	19/24 (79)	9/16 (56)	22.1 (-9.8, 54.0)
Study drug adherence	≥ 95%	41/54 (76)	24/41 (59)	16.9 (-2.9, 36.7)
	< 95%	2/6 (33)	3/6 (50)	29.5 (-41.3, 100.0)
Baseline HBV DNA,[a] IU/mL	≥ 8 log_{10}	19/33 (58)	15/27 (56)	2.4 (-23.3, 28.2)
	< 8 log_{10}	24/27 (89)	12/20 (60)	29.1 (3.0, 55.2)
HBV genotype	A/D	9/12 (75)	9/14 (64)	13.0 (-27.0, 53.0)
	B/C	28/38 (74)	12/25 (48)	23.9 (-1.1, 48.9)
	Other	2/5 (40)	2/2 (100)	-75.0 (-100.0, 14.6)
Baseline HBeAg	Positive	29/43 (67)	22/36 (61)	5.7 (-15.7, 27.1)
	Negative	14/17 (82)	5/11 (45)	39.2 (3.0, 75.5)
Baseline HIV-1 RNA, c/mL	> 100,000	17/22 (77)	6/12 (50)	20.7 (-17.6, 59.1)
	≤ 100,000	26/38 (68)	21/35 (60)	9.2 (-13.2, 31.6)
Baseline CD4, cells/µL	≥ 200	30/42 (71)	19/31 (61)	10.0 (-12.5, 32.4)
	< 200	13/18 (72)	8/16 (50)	13.5 (-18.8, 45.9)
Baseline HIV-1 disease status	Asymptomatic	32/44 (73)	17/30 (57)	16.8 (-5.7, 39.4)
	Symptomatic/AIDS	11/16 (69)	10/17 (59)	1.3 (-34.8, 37.4)
HBV DNA at Week 48, IU/mL	< 29	35/44 (80)	15/22 (68)	11.0 (-13.0, 35.0)
	≥ 29	8/16 (50)	12/25 (48)	4.0 (-29.0, 37.0)
Normal ALT at Week 12 (AASLD)	Yes	21/25 (84)	6/9 (67)	-0.0 (-40.5, 40.5)
	No	22/35 (63)	21/38 (55)	9.5 (-14.2, 33.1)
TE Grade ≥ 3 ALT by Week 12	Yes	13/17 (76)	10/10 (100)	-28.9 (-61.5, 3.7)
	No	30/43 (70)	17/37 (46)	23.4 (1.9, 45.0)

Data are from the full analysis set for individuals with baseline ALT > ULN. Difference in percentages and 95% CIs were calculated based on the MH proportions adjusted by baseline HBeAg status (positive vs negative) and baseline HBV DNA category (< 8 log_{10} IU/mL vs ≥ 8 log_{10} IU/mL), if not the subgroup factor.
[a]Proportion difference and 95% CI from normal approximation without stratification, as not calculable by stratum-adjusted MH method.
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Consistent with the overall population, B/F/TAF resulted in higher rates of ALT normalization than DTG + F/TDF in most subgroups. This difference was significant in the following subgroups:
- Lower HBV viral load (baseline HBV DNA < 8 log_{10} IU/mL)
- HBeAg negative at baseline
- No treatment-emergent Grade ≥ 3 ALT elevations by Week 12

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