

Original Research Report

Bictegravir/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir Plus Emtricitabine/Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 and Hepatitis B Coinfection in Adults of Asian Descent : A Sub-Analysis of the ALLIANCE Trial

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Introduction : Tenofovir disoproxil fumarate (TDF)- or tenofovir alafenamide (TAF)-containing therapy is recommended for most adults with HIV-1/hepatitis B virus (HBV) coinfection, but evidence from the ALLIANCE study suggests advantages of TAF- over TDF-based therapy. We conducted a post-hoc analysis of data pertaining to ALLIANCE study participants of Asian descent.

Methods : The ALLIANCE study enrolled treatment-naïve adults with plasma HIV-1 ribonucleic acid (RNA) ≥ 500 copies/mL and HBV deoxyribonucleic acid (DNA) of $\geq 2,000$ IU/mL, who were randomized to coformulated bictegravir 50 mg, emtricitabine 200 mg and TAF 25 mg, or dolutegravir 50 mg + coformulated emtricitabine 200 and TDF 300 mg for 96 weeks. Coprimary study endpoints were the proportions of participants with plasma HIV-1 RNA < 50 copies/mL and HBV DNA < 29 IU/mL at week 48.

Results : 214 Asian study participants were included in this analysis. At week 48, the treatment groups had similarly high rates of HIV-1 RNA suppression, but bictegravir/emtricitabine/TAF was associated with a significantly higher rate of HBV DNA suppression than dolutegravir + emtricitabine/TDF. At week 96, both regimens had similarly high efficacy for these endpoints. Significantly higher rates of hepatitis B e antigen (HBeAg) loss/seroconversion and hepatitis B surface antigen (HBsAg) loss occurred with bictegravir/emtricitabine/TAF versus dolutegravir + emtricitabine/TDF at weeks 48 and 96, as well as a significantly higher rate of HBsAg seroconversion at week 48.

Conclusion : Bictegravir/emtricitabine/TAF is an effective initial treatment for Asian people with HIV-1/HBV coinfection.

Key words : Asian, coinfection, hepatitis B virus, HIV-1, bictegravir, emtricitabine, tenofovir alafenamide drug combination, dolutegravir, emtricitabine, tenofovir disoproxil fumarate drug combination

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Introduction

Globally, approximately 8% of people with HIV-1 are chronically infected with hepatitis B virus (HBV), but the prevalence of coinfection varies by region.^{1,2)} In the Asia-Pacific and South/South-East Asia regions, where the HBV burden is very high, approximately 10 to 12% of the HIV-1-infected population is coinfecting with HBV.^{1,2)} Compared with HBV monoinfection, HIV-1 and HBV coinfection is associated with accelerated progression of liver disease and increased risk of hepatocellular carcinoma and end-stage liver disease,^{3,4)} which are leading causes of morbidity and mortality in coinfecting individuals.^{5,6)}

The high prevalence of chronic HBV infection among people with HIV-1 in the Asian region, along with the elevated risk of liver-related disease in coinfecting individuals, underscores the urgent need to optimize treatment for HIV-1 and HBV coinfection in Asian people.^{1,2)} Initiation of an antiretroviral regimen containing a nucleos(t)-ide analogue (NA) backbone that includes a tenofovir-based prodrug (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) plus emtricitabine or lamivudine, all of which have activity against HIV-1 and HBV, is recommended for most coinfecting people.⁷⁻¹²⁾ Addition of an integrase strand transfer inhibitor (bictegravir or dolutegravir) is also recommended.^{7,8)}

Results from the first randomized clinical trial to compare a TAF-based regimen with a TDF-based regimen (bictegravir, emtricitabine and TAF versus dolutegravir, emtricitabine and TDF) in people with HIV-1 and HBV coinfection (ALLIANCE) suggest benefits of the TAF-over TDF-based regimen with regard to HBV suppression and other markers of anti-HBV activity, including hepatitis B envelope antigen (HBeAg) loss and seroconversion.¹³⁾ Whereas pharmacologically active tenofovir diphosphate is widely distributed in different tissues after TDF administration, its distribution after TAF administration is restricted to cells with high carboxylesterase and cathepsin A activity, resulting in relatively high intracellular tenofovir concentrations in hepatocytes and lymphocytes.¹⁴⁻¹⁶⁾ This pharmacokinetic difference may have contributed to the superior HBV suppression observed with TAF- versus TDF-based therapy in the ALLIANCE study.¹³⁾

The ALLIANCE study data represent an important step towards defining optimal treatment for HIV-1 and HBV coinfection,¹³⁾ but ethnicity could potentially affect TAF and TDF pharmacokinetics and treatment outcomes.¹⁷⁻¹⁹⁾ It is therefore important to evaluate the clinical activity of TAF- and TDF-based therapies specifically in HIV-1- and HBV-coinfecting Asian populations. Here, we report efficacy and safety data for the Asian subpopulation of the ALLIANCE study.

Methods

1. Study Design and Participants

The ALLIANCE study (NCT03547908) was conducted in Mainland China, the Dominican Republic, Hong Kong, Japan, Malaysia, South Korea, Spain, Taiwan, Thailand, Turkey, and the United States of America (USA). ALLIANCE study participants of Asian descent (enrolled at study centers in Mainland China, Hong Kong, Japan, Malaysia, South Korea, Taiwan, Thailand and the USA) were included in this post-hoc sub-analysis. The ALLIANCE study design has been described previously.¹³⁾

Briefly, eligible participants were aged ≥ 18 years and had plasma HIV-1 ribonucleic acid (RNA) ≥ 500 copies/mL and plasma HBV deoxyribonucleic acid (DNA) $\geq 2,000$ IU/mL. Individuals who had previously received treatment for chronic HBV or HIV-1 infection were excluded. Written informed consent was obtained from all participants. The ALLIANCE study was conducted in accordance with the Declaration of Helsinki and was approved by central or site-specific review boards or ethics committees.

ALLIANCE study participants were randomly assigned (1 : 1) to receive once daily double-blind treatment with coformulated (single-tablet regimen) bictegravir 50 mg, emtricitabine 200 mg and TAF 25 mg, or dolutegravir 50 mg plus coformulated emtricitabine 200 mg and TDF 300 mg, each with corresponding matching placebo tablets. Randomization was stratified by HBeAg status (positive vs negative), HBV DNA (< 8 vs ≥ 8 log₁₀ IU/mL), and CD4 count (< 50 vs ≥ 50 cells/L) at screening. Investigators, participants, and staff providing treatment, assessing outcomes, and collecting data were masked to study treatment for 96 weeks.

2. Endpoints and Assessments

ALLIANCE study endpoints assessed for the Asian subpopulation included the study's coprimary efficacy endpoints : the proportion of participants with HIV-1 RNA < 50 copies/mL at week 48 (using the US Food and Drug Administration snapshot algorithm²⁰⁾), and the proportion of participants with HBV DNA < 29 IU/mL at week 48. The following ALLIANCE study secondary endpoints were also assessed in the Asian subpopulation : the proportion of participants with HIV-1 RNA < 50 copies/mL and the proportion of participants with HBV DNA < 29 IU/mL at week 96, changes from baseline in CD4 cell count and CD4 cell percentage at weeks 48 and 96, proportions of participants with normalization of alanine aminotransferase (ALT) at weeks 48 and 96, and proportions of participants with hepatitis B surface antigen (HBsAg) loss at weeks 48 and 96. Additional prespecified ALLIANCE study efficacy endpoints assessed in this Asian subpopulation analysis were HBeAg loss, HBeAg seroconversion and HBsAg seroconversion,

all at weeks 48 and 96. A missing-equals-failure approach was used for all HBV endpoints involving proportions. ALT normalization was defined as change in ALT concentration from higher than the upper limit of normal (ULN ; 25 U/L for females and 35 U/L for males, as per 2018 American Association for the Study of Liver Diseases criteria²¹) at baseline to $ALT \leq ULN$.

Safety was assessed throughout the ALLIANCE study. Adverse events and laboratory abnormalities up to week 96 are reported here for study participants of Asian descent. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 24.1 for week 48 ; version 25.1 for week 96). ALT flares were defined as ALT elevations (serum ALT $>2 \times$ baseline concentration and ALT $>10 \times$ ULN), with or without associated symptoms, at two or more consecutive post-baseline visits.

Study visits were scheduled for screening, day 1, and every 4 weeks until week 12, and quarterly thereafter until week 96. Laboratory analyses, including HIV-1 RNA, CD4 cell count, serum chemistry and liver function tests, were performed at all study visits. HBV DNA was also monitored at all study visits. HBV serology (HBsAg and anti-HBs antibody [HBsAb], and HBeAg and anti-HBe antibody [HBeAb]) was performed at screening, day 1, and every 12 weeks thereafter.

3. Statistical Analysis

Asian subpopulation analyses were performed post hoc using statistical testing methods similar to those used for the overall population analysis. Except for HBsAg and HBeAg loss or seroconversion, efficacy endpoints were assessed in the full Asian analysis set, which included all randomly assigned participants of Asian descent who received at least one dose of study drug and had at least one post-baseline HIV-1 RNA or HBV DNA result while on study drug. The serologically evaluable full Asian analysis set (all participants in the full Asian analysis set who were HBeAg- or HBsAg-positive and HBeAb- or HBsAb-negative or missing at baseline) was used for assessment of HBsAg and HBeAg loss or seroconversion. Adverse events, clinical and laboratory abnormalities, and weight were summarized using descriptive statistics based on the Asian subpopulation safety analysis set, which included all randomly assigned participants of Asian descent who received at least one dose of study drug.

Cochran-Mantel-Haenszel tests were used to compare the ALLIANCE coprimary endpoints and other categorical endpoints between treatment groups for the Asian subpopulation. Tests were adjusted by baseline HIV-1 RNA (for the HIV-1 RNA endpoint), by HBeAg status and HBV DNA level (for the HBV DNA endpoint, ALT normalization, and HBsAg loss or seroconversion), or by HBV DNA level (for HBeAg loss or seroconversion). CD4 cell count and CD4 cell percentage were compared

between Asian subpopulation treatment groups using an ANOVA model adjusted by baseline HIV-1 RNA stratum. A two-sided Wilcoxon rank sum test was used to compare between-group changes from baseline in laboratory parameters. Two-sided statistical tests were performed at the 5% significance level.

Results

In the ALLIANCE study, 214 (88%) of the 243 participants who initiated treatment were of Asian descent (108 in the bicitgravir/emtricitabine/TAF treatment group and 106 in the dolutegravir + emtricitabine/TDF treatment group). ALLIANCE study participants of Asian descent were mainly from Thailand ($n=94$), Mainland China (56) and Malaysia (37). There were also 12 participants from Taiwan, 7 from Japan, 5 from Hong Kong, 2 from South Korea, and 1 participant of Asian descent from the USA. Of these 214 participants, 203 (95%) remained on treatment at week 48, and 198 (93%) remained on treatment at week 96.

Baseline characteristics of participants of Asian descent were well balanced between the two treatment groups (Table 1). The population was primarily male (95%), and 30% had HIV-1 RNA $>100,000$ copies/mL, 12% had CD4 counts <50 cells/ μ L, 50% had HBV DNA $\geq 8 \log_{10}$ IU/mL, and 79% were HBeAg-positive at baseline.

1. HIV-1 Endpoints

As shown in Fig. 1, 94% of participants of Asian descent in the bicitgravir/emtricitabine/TAF group and 93% of those in the dolutegravir + emtricitabine/TDF group had HIV-1 RNA <50 copies/mL at week 48 (difference 1.9, 95% CI -5.2 to 8.9 ; $p=0.58$). At week 96, 88% of participants in both treatment groups had HIV-1 RNA <50 copies/mL. Mean CD4 cell counts and CD4 cell percentages increased similarly from baseline in both treatment groups at both week 48 and week 96. At week 96, CD4 cell count had increased by a mean of 267 cells/ μ L in the bicitgravir/emtricitabine/TAF group and by 238 cells/ μ L in the dolutegravir + emtricitabine/TDF group (difference 28 cells/ μ L, 95% CI -20 , 76 ; $p=0.25$), and CD4 percentage had increased by 10.5% in both treatment groups.

2. HBV Endpoints

Results for week 48 and week 96 anti-HBV efficacy endpoints are shown in Fig. 1.

At week 48, 61% of participants in the bicitgravir/emtricitabine/TAF group had HBV DNA <29 IU/mL compared with 43% of participants in the dolutegravir + emtricitabine/TDF group (difference 16.1, 95% CI 4.8 to 27.5 ; $p=0.0054$). The proportion of participants achieving HBV DNA <29 IU/mL was higher in the bicitgravir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group from week 24, with the difference reaching statistical significance at weeks 48

Table 1 Baseline demographic and clinical characteristics of the Asian subpopulation (safety analysis set).

	Bictegravir/emtricitabine/TAF (<i>n</i> =108)	Dolutegravir + emtricitabine/TDF (<i>n</i> =106)
Age, years	31 (26–38)	32 (25–36)
Sex at birth		
Male	100 (92.6%)	104 (98.1%)
Female	8 (7.4%)	2 (1.9%)
BMI, kg/m ²	22.2 (19.8–24.5)	21.6 (19.3–23.5)
Weight, kg	63.0 (56.2–72.9)	63.5 (56.1–70.0)
eGFR, mL/min ^a	105.9 (93.6–126.3)	104.1 (93.0–124.2)
HIV-1 RNA		
log ₁₀ copies/mL	4.7 (4.2–5.1)	4.7 (4.2–5.1)
>100,000 copies/mL	32 (29.6%)	32 (30.2%)
CD4		
Cell count/μL	242 (119–380)	228 (100–365)
<200 cells/μL	43 (39.8%)	48 (45.3%)
Percentage	14.7 (9.4–22.1)	13.3 (8.6–19.0)
ALT concentration		
U/L	34 (23–59)	27 (19–54)
>ULN ^b	53 (49.0%)	39 (36.8%)
HBV DNA		
log ₁₀ IU/mL	8.0 (6.4–8.4)	8.0 (6.5–8.5)
≥ 8 log ₁₀ IU/mL	52 (48.1%)	54 (50.9%)
HBeAg positive	84 (77.8%)	84 (79.2%)
HBV genotype ^c		
A	3 (3.0%)	12 (12.6%)
B	21 (20.8%)	24 (25.3%)
C	63 (62.4%)	50 (52.6%)
D	11 (10.9%)	8 (8.4%)
F	0	0
Mixed	3 (3.0%)	1 (1.1%)
Missing	7	11

Data are median (IQR) or *n* (%). Abbreviations: AASLD, American Association for the Study of Liver Diseases ; ALT, alanine aminotransferase ; BMI, body mass index ; DNA, deoxyribonucleic acid ; eGFR, estimated glomerular filtration rate ; HBeAg, hepatitis B envelope antigen ; HBsAg, HBV surface antigen ; HBV, hepatitis B virus ; IQR, interquartile range ; RNA, ribonucleic acid ; TAF, tenofovir alafenamide ; TDF tenofovir disoproxil fumarate ; ULN, upper limit of normal. ^a Estimated with the Cockcroft-Gault formula. ^b Based on the 2018 AASLD criteria (ULN 25 U/L for females and 35 U/L for males).

^c Percentage based on individuals with non-missing HBV genotype.

and 72 ($p<0.01$; Fig. 2). At week 96, 75% of participants in the bictegravir/emtricitabine/TAF group had HBV DNA <29 IU/mL compared with 69% of those in the dolutegravir + emtricitabine/TDF group ($p=0.35$).

The proportion of participants with ALT normalization was consistently higher in the bictegravir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group throughout the study, with significant between-group differences as early as weeks 12 and 24, and again

from week 48 to week 72 ($p<0.05$). ALT normalization occurred in 74% of bictegravir/emtricitabine/TAF recipients at both the 48- and 96-week timepoints, and in 49 and 54% of participants in the dolutegravir + emtricitabine/TDF group at weeks 48 and 96, respectively.

HBeAg loss and HBeAg seroconversion occurred in significantly higher proportions of serologically evaluable participants in the bictegravir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group at all

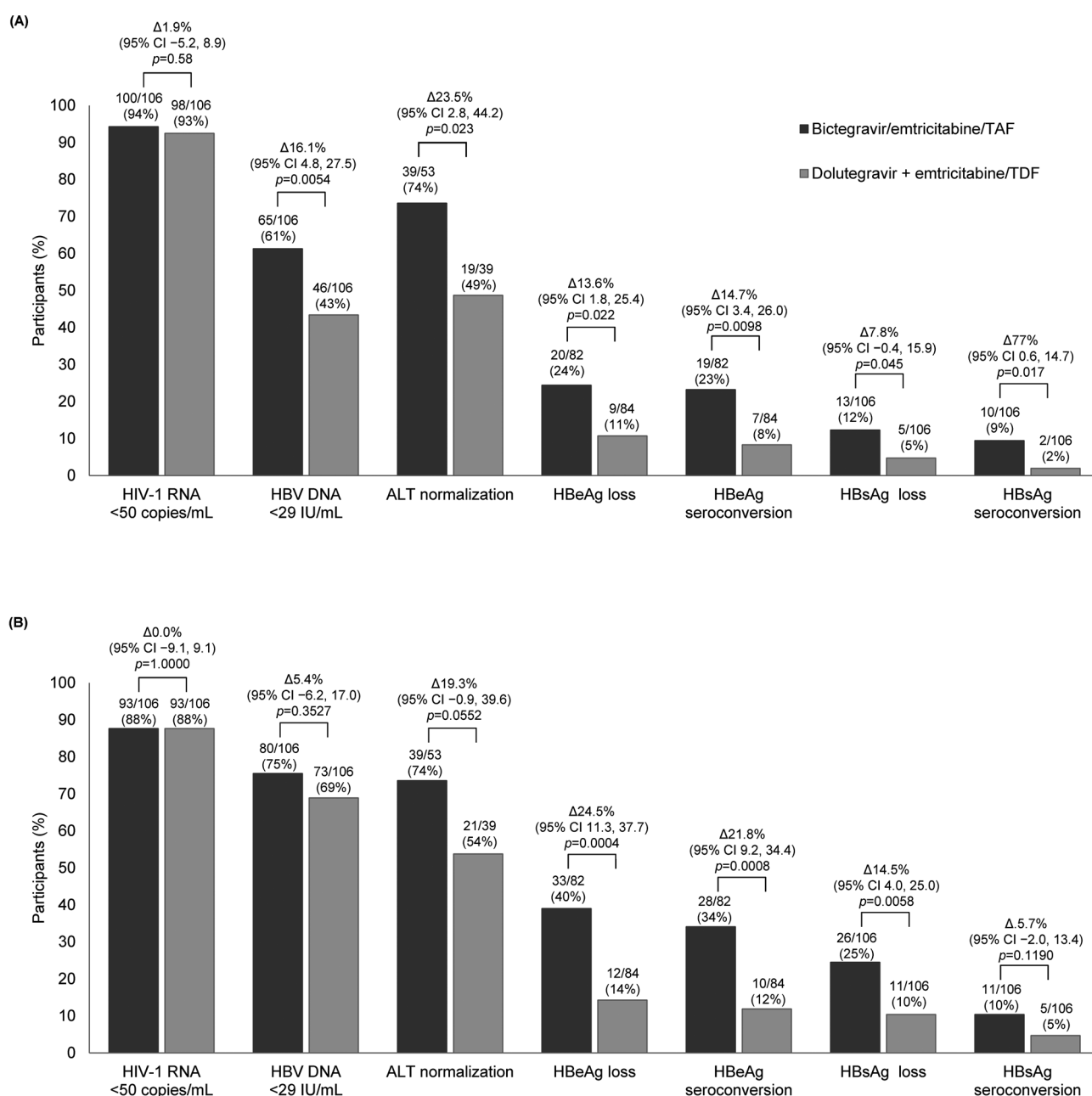


Fig. 1 Virological and immunological outcomes in the Asian subpopulation (full analysis set^a) at (A) week 48 and (B) week 96.

^a ALT normalization assessed in participants from the full analysis set who had ALT concentrations >ULN at baseline, based on the 2018 AASLD criteria (25 U/L for females and 35 U/L for males) ; HBeAg and HBsAg loss (change from HBeAg or HBsAg positivity at baseline to negativity at a post-baseline visit with baseline HBeAb or HBsAb negativity or missing), and HBeAg and HBsAg seroconversion (HBeAg or HBsAg loss and change from HBeAb or HBsAb negativity or missing at baseline to positivity at a post-baseline visit) assessed in the serologically evaluable full analysis set (all participants in the full analysis set who were HBeAg- or HBsAg-positive and HBeAb- or HBsAb-negative or missing at baseline). Abbreviations : AASLD, American Association for the Study of Liver Diseases ; ALT, alanine aminotransferase ; CI, confidence interval ; DNA, deoxyribonucleic acid ; HBeAb, hepatitis B envelope antibody ; HBeAg, hepatitis B envelope antigen ; HBsAb, hepatitis B surface antibody ; HBsAg, hepatitis B surface antigen ; HBV, hepatitis B virus ; RNA, ribonucleic acid ; TAF, tenofovir alafenamide ; TDF, tenofovir disoproxil fumarate ; ULN, upper limit of normal.

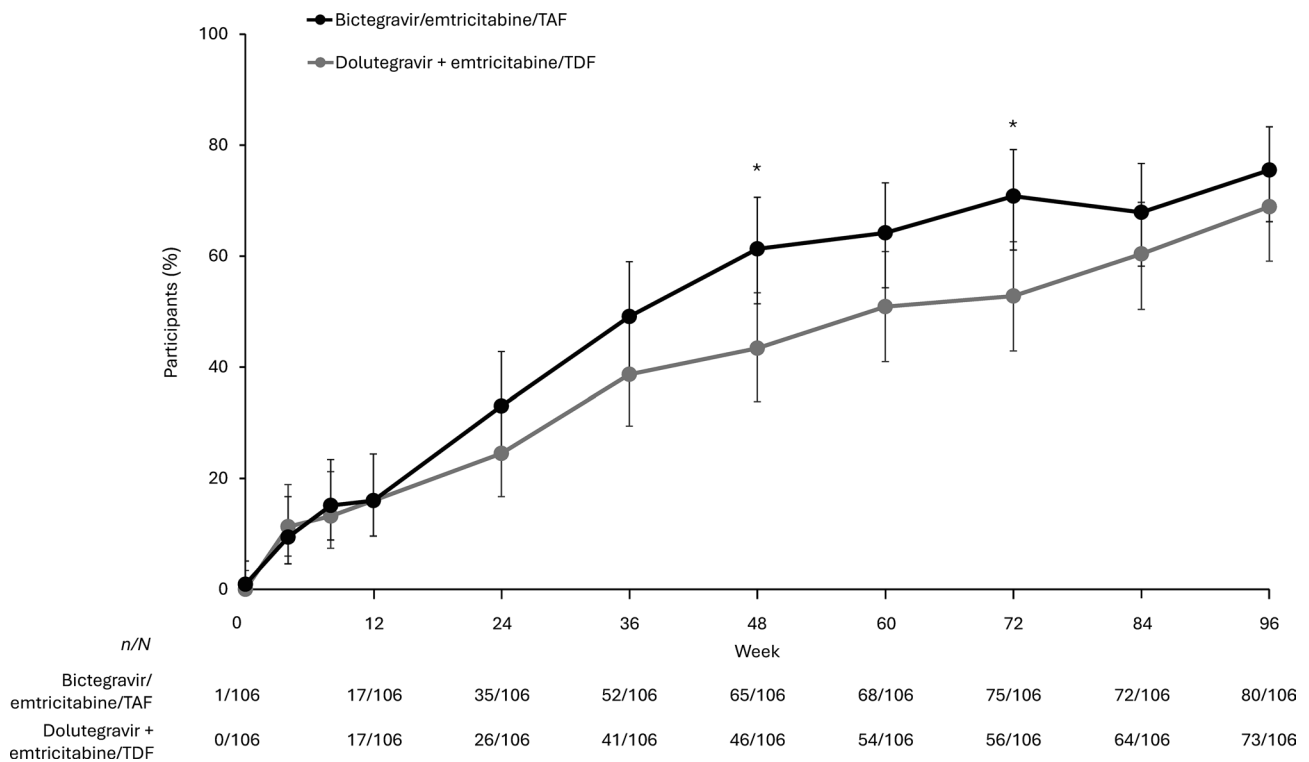


Fig. 2 Proportions of Asian participants with HBV DNA <29 IU/mL up to week 96 (full analysis set).

Error bars are 95% confidence intervals.

Abbreviations : DNA, deoxyribonucleic acid ; HBV, hepatitis B virus ; TAF, tenofovir alafenamide ; TDF tenofovir disoproxil fumarate. * $p < 0.01$ versus dolutegravir + emtricitabine/TDF.

timepoints from week 36 (Fig. 3). At weeks 48 and 96, the proportions of participants with HBeAg loss and HBeAg seroconversion in the bictegravir/emtricitabine/TAF group were more than double those in the dolutegravir + emtricitabine/TDF group. At week 48, 24% of participants in the bictegravir/emtricitabine/TAF group had HBeAg loss compared with 11% of those in the dolutegravir + emtricitabine/TDF group ($p=0.022$), and 23% versus 8% of participants, respectively, had HBeAg seroconversion ($p=0.0098$). At week 96, 40% of bictegravir/emtricitabine/TAF recipients had HBeAg loss compared with 14% of dolutegravir + emtricitabine/TDF recipients ($p=0.0004$), and 34% versus 12% of participants, respectively, had HBeAg seroconversion ($p=0.0008$).

There was a greater proportion of participants with HBsAg loss in the bictegravir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group at all timepoints, with the between-group differences reaching statistical significance at weeks 36, 48, 60 and 96 (Fig. 3). Between week 48 and week 96, the proportion of participants with HBsAg loss in the bictegravir/emtricitabine/TAF group increased from 12 to 25%. The proportion of participants with HBsAg loss in the dolutegravir + emtricitabine/TDF group also doubled from week 48 (5%) to

week 96 (10%). Compared with the dolutegravir + emtricitabine/TDF group, the rate of HBsAg seroconversion in the bictegravir/emtricitabine/TAF group was significantly higher at the three timepoints from week 36 to week 60, and numerically greater at all other timepoints (Fig. 3). Ten (9%) individuals in the bictegravir/emtricitabine/TAF group had HBsAg seroconversion at week 48 compared with 2 (2%) individuals in the dolutegravir + emtricitabine/TDF group ($p=0.017$). At week 96, the rate of HBsAg seroconversion was numerically greater in the bictegravir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group (difference 5.7, 95% CI -2.0 to 13.4 ; $p=0.12$).

3. Safety

Most adverse events in study participants were of grade 1 or 2 severity (Table 2). The incidence of adverse events was similar between the treatment groups. There was one serious drug-related adverse event (cryptococcal meningitis attributed to immune reconstitution inflammatory syndrome) in the study. This occurred in a participant receiving bictegravir/emtricitabine/TAF.

Weight increase and abnormal weight gain were reported in 7 and 3 participants, respectively, in the bictegravir/emtricitabine/TAF group and in 9 and 3 participants,

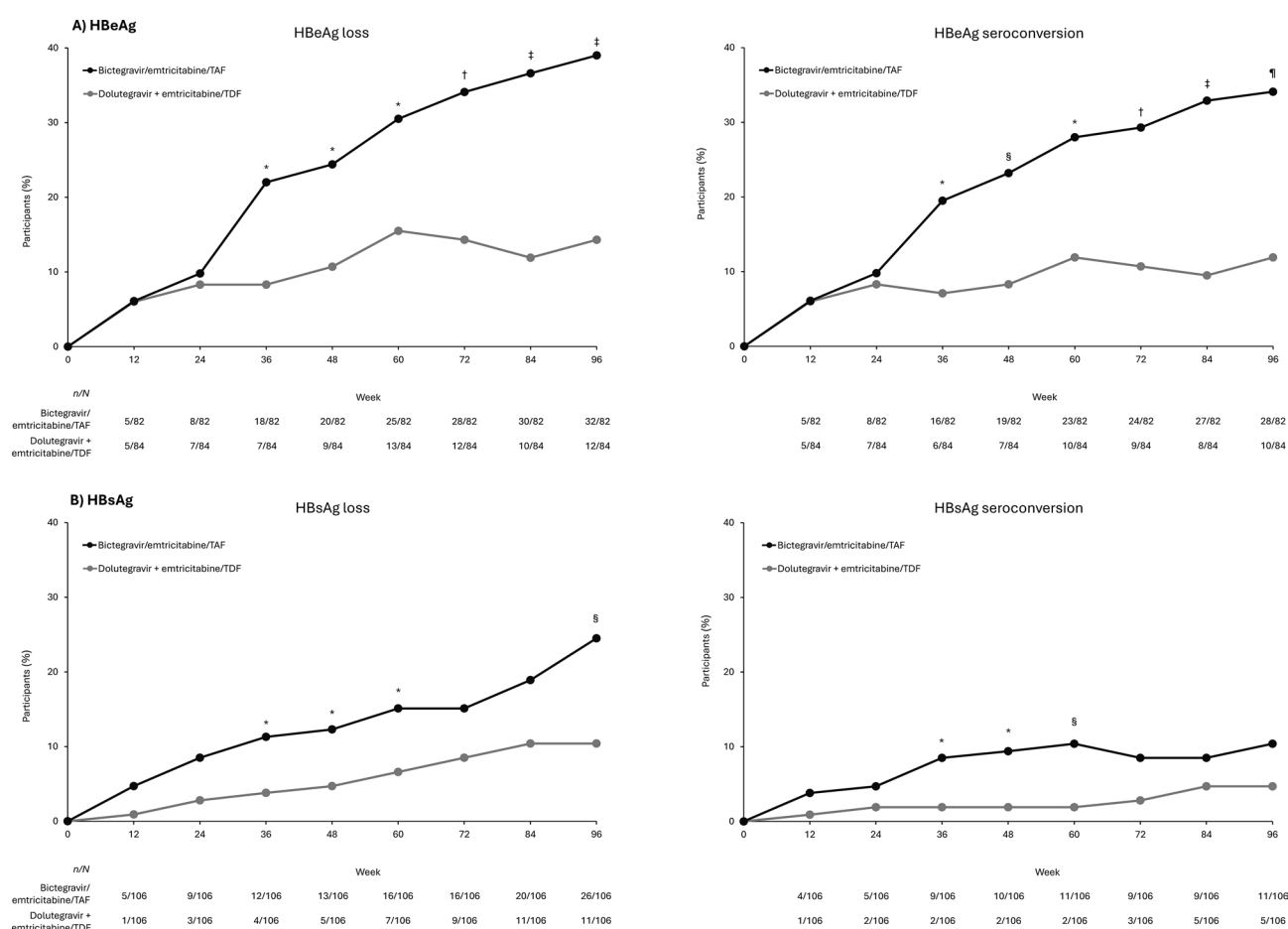


Fig. 3 Proportions of Asian participants with (A) HBeAg and (B) HBsAg loss and seroconversion up to week 96 (serologically evaluable full analysis set).

Abbreviations : HBeAg, hepatitis B envelope antigen ; HBsAg, hepatitis B surface antigen ; TAF, tenofovir alafenamide ; TDF tenofovir disoproxil fumarate. * $p < 0.05$ versus dolutegrovir + emtricitabine/TDF. † $p < 0.005$ versus dolutegrovir + emtricitabine/TDF. ‡ $p < 0.0005$ versus dolutegrovir + emtricitabine/TDF. § $p < 0.01$ versus dolutegrovir + emtricitabine/TDF. ¶ $p < 0.001$ versus dolutegrovir + emtricitabine/TDF.

respectively, in the dolutegrovir + emtricitabine/TDF group. Together, these were the most common drug-related adverse events (Table 2). By week 48, a median increase in body weight from baseline of 4.0 kg (interquartile range [IQR] 0.8 to 7.1) had occurred in the bictegrovir/emtricitabine/TAF group versus 2.2 kg (IQR -1.4 to 4.4) in the dolutegrovir + emtricitabine/TDF group ; at week 96, the median increase from baseline was 4.0 kg (IQR 0.7 to 7.7) in the bictegrovir/emtricitabine/TAF group and 2.3 kg (IQR -0.3 to 5.7) in the dolutegrovir + emtricitabine/TDF group. At weeks 48 and 96, there were median increases in body mass index (BMI) of 1.3 kg/m² (IQR 0.3 to 2.5) and 1.4 kg/m² (IQR 0.3 to 2.5), respectively, in the bictegrovir/emtricitabine/TAF group and 0.7 kg/m² (IQR -0.5 to 1.5) and 0.8 kg/m² (IQR -0.1 to 2.1), respectively,

in the dolutegrovir + emtricitabine/TDF group. Changes in fasting glucose were comparable between the treatment groups, and at week 96, total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio was reduced by a median of 0.2 in both treatment groups (Table 3). A median 2 mg/dL (IQR -18 to 26) increase in low-density lipoprotein cholesterol (LDL-C) occurred at week 96 in the bictegrovir/emtricitabine/TAF group versus a 15 mg/dL (IQR -35 to 5) decrease in the dolutegrovir + emtricitabine/TDF group ($p < 0.001$).

The most frequent laboratory abnormalities among the participants were elevated transaminase concentrations (Table 3), none of which resulted in treatment discontinuation. ALT flares, most of which occurred in the first 12 weeks of treatment and all of which resolved during treat-

Table 2 Adverse events in the Asian subpopulation up to week 96 (safety analysis set).

	Bictegravir/emtricitabine/TAF (n=108)	Dolutegravir + emtricitabine/TDF (n=106)
Any AE	103 (95.4%)	103 (97.2%)
Any grade 3 or 4 AE	21 (19.4%)	17 (16.0%)
Serious AE	17 (15.7%)	15 (14.2%)
AE leading to treatment discontinuation	1 (0.9%)	0
Any study drug-related AE	29 (26.9%)	30 (28.3%)
Any study drug-related grade 3 or 4 AE	6 (5.6%)	1 (0.9%)
Study drug-related serious AE	1 (0.9%)	0
Study drug-related adverse events in >2% in either treatment group		
Weight increased ^a	10 (9.3%)	12 (11.3%)
Increased ALT concentration	1 (0.9%)	8 (7.5%)
Nausea	0	4 (3.8%)
Increased AST concentration	2 (1.9%)	3 (2.8%)
Dyslipidemia	3 (2.8%)	1 (0.9%)
Headache	3 (2.8%)	1 (0.9%)
Proteinuria	3 (2.8%)	1 (0.9%)

Data are n (%). ^a Adverse events of weight increased or abnormal weight gain. Abbreviations : AE, adverse event ; ALT, alanine aminotransferase ; AST, aspartate aminotransferase ; TAF, tenofovir alafenamide ; TDF tenofovir disoproxil fumarate.

ment, occurred in 8 participants (5 in the bictegravir/emtricitabine/TAF group and 3 in the dolutegravir + emtricitabine/TDF group). Two of the participants with ALT flares in the bictegravir/emtricitabine/TAF group had acquired hepatitis C virus (HCV) during the study, one of whom tested anti-HCV-positive at week 192, although the ALT flare occurred at week 4, and the other of whom had detectable HCV RNA when the ALT flare occurred at 48 weeks.

Changes in estimated glomerular filtration rate were similar in the two treatment groups (Table 3). No cases of proximal renal tubulopathy or discontinuations due to renal adverse events were observed in either treatment group.

Among the participants who were assessed for HIV-1 resistance (i.e. those with virologic rebound), none had HIV-1 treatment-emergent drug resistance. No HBV amino acid substitutions associated with resistance to TAF or TDF were detected in participants who remained viremic (HBV DNA ≥ 69 IU/mL) through week 96.

Discussion

In the Asian subpopulation of treatment-naïve adults with HIV-1 and HBV coinfection participating in the ALLIANCE study, the proportion of participants with HBV DNA <29 IU/mL at week 48 was significantly higher in the bictegravir/emtricitabine/TAF treatment group than the dolutegravir + emtricitabine/TDF group. These results are consistent with those reported in the

overall ALLIANCE study population, whereby study participants who received bictegravir/emtricitabine/TAF had a more rapid rate of HBV suppression than those who received the TDF-based regimen, with bictegravir/emtricitabine/TAF demonstrating superiority at 48 weeks.¹³⁾ HIV-1 RNA suppression at week 48 was similar between the two treatment groups in study participants of Asian descent and the overall population, in which bictegravir/emtricitabine/TAF met the protocol-defined definition for non-inferiority to dolutegravir + emtricitabine/TDF.¹³⁾

A high proportion (88%) of participants in the ALLIANCE study were of Asian descent.¹³⁾ Not surprisingly, therefore, baseline characteristics were similar between study participants of Asian descent and the overall study population,¹³⁾ including a high proportion of participants who were HBeAg-positive at baseline (79% of Asian participants and 78% of the overall population) and a low proportion of participants with baseline ALT concentration >ULN (43% of Asian participants and 44% overall).

In addition to similarities with regard to the co-primary endpoints (HBV DNA levels <29 IU/mL and HIV-1 RNA <50 copies/mL at week 48), there were similarities in HIV-1 and HBV treatment responses observed for the Asian subpopulation and the overall population at 96 weeks.¹³⁾ High proportions of participants, both overall¹³⁾ and of Asian descent, achieved HBV DNA suppression to <29 IU/mL at week 96 in both treatment groups (approximately 75% with bictegravir/emtricitabine/TAF and 70% with dolutegravir + emtricitabine/TDF). This was also the

Table 3 Laboratory and metabolic health parameters in the Asian subpopulation (safety analysis set).

	Bictegravir/emtricitabine/TAF (<i>n</i> =108)	Dolutegravir + emtricitabine/TDF (<i>n</i> =106)
Laboratory abnormalities up to week 96 ^a		
Any grade 3 or 4	40/107 (37.4%)	33/105 (31.4%)
Grade 3 or 4 occurring in >5% in either group		
ALT increase	21/107 (19.6%)	13/105 (12.4%)
AST increase	11/107 (10.3%)	10/105 (9.5%)
Amylase increased	7/107 (6.5%)	8/105 (7.6%)
Fasting LDL-C increase	9/106 (8.5%)	2/105 (1.9%)
Changes in laboratory parameters from baseline at week 96		
ALT, U/L	− 11 (− 39 to 5)	0 (− 23 to 14)
eGFR, mL/min ^b	− 9.6 (− 21.6 to − 0.6)	− 11.4 (− 17.4 to − 4.8)
Fasting TC, mg/dL	17 (− 9 to 35)	− 17 (− 36 to 4) ^c
Fasting LDL-C, mg/dL	2 (− 18 to 26)	− 15 (− 35 to 5) ^c
Fasting HDL-C, mg/dL	4 (− 3, 12)	− 3 (− 9, 4) ^c
Fasting TC/HDL ratio	− 0.2 (− 0.6 to 0.5)	− 0.2 (− 0.7 to 0.3)
Fasting TG, mg/dL	− 2 (− 36 to 35)	− 12 (− 40 to 24)
Fasting glucose, mg/dL	3 (− 2 to 11)	2 (− 4 to 8)
Other laboratory results at week 96		
eGFR <60 mL/min ^b	0/95	2/95 (2.1%)
Fasting TC >200 mg/dL	35/96 (36.5%)	5/96 (5.2%) ^c
Fasting HDL ≥ 40 mg/dL	73/96 (76.0%)	57/96 (59.4%) ^d
Fasting TG >150 mg/dL	28/96 (29.2%)	16/96 (16.7%)
Body weight		
Change from baseline at week 96, kg	4.0 (0.7 to 7.7)	2.3 (− 0.3 to 5.7)
Increase of >10%	36/97 (37.1%)	26/98 (26.5%)

Data are *n*/*N* (%) or median (IQR). ^aPercentages are for the number of participants in the safety analysis set with ≥1 post-baseline value for the test under evaluation. ^bEstimated with the Cockcroft-Gault formula. ^c*p*<0.0001 versus bictegravir/emtricitabine/TAF. ^d*p*<0.05 versus bictegravir/emtricitabine/TAF. Abbreviations : ALT, alanine aminotransferase ; AST, aspartate aminotransferase ; eGFR, estimated glomerular filtration rate ; HDL-C, high-density lipoprotein cholesterol ; IQR, interquartile range ; LDL-C, low-density lipoprotein cholesterol ; TAF, tenofovir alafenamide ; TC, total cholesterol ; TDF, tenofovir disoproxil fumarate ; TG, triglycerides.

case for HIV-1 RNA suppression to <50 copies/mL, which occurred at week 96 in approximately 88% of both the overall population¹³⁾ and Asian sub-population. The observed HBV suppression rates did, however, differ markedly from the expected response rate of 88% for both treatment groups. It was originally assumed that approximately 80% of enrolled participants would be HBeAg-negative (with a suppression rate of 94% versus 64% for HBeAg-positive participants).¹³⁾ The relatively high proportion of study participants who were HBeAg-positive at baseline may have helped to account for this difference.¹³⁾

In HBV mono-infection, persistent ALT elevation is an independent factor for the development of hepatic events including hepatocellular carcinoma, suggesting that early and sustained ALT normalization could be clinically beneficial.²²⁾ In the overall ALLIANCE study popula-

tion¹³⁾ and the subpopulation of Asian descent, proportions of individuals with ALT concentrations >ULN at baseline who achieved ALT normalization were significantly higher in the TAF-based treatment group than the TDF group at some post-baseline timepoints, not including weeks 48 and 96 for the overall population but including week 48 for the Asian subpopulation. Studies in HBV mono-infection have reported significantly higher ALT normalization rates among TAF versus TDF recipients after 48 and 96 weeks of treatment.^{14, 15, 23)} The absence of significant differences between treatment groups at weeks 48 and 96 in the overall ALLIANCE study population and at week 96 in ALLIANCE study participants of Asian descent is probably a consequence of the relatively small proportions of participants with ALT concentration >ULN at baseline, which was an inclusion criterion for the

monoinfection studies.^{14, 15, 23)}

Several similarities were observed for the Asian sub-population and the overall population with respect to the HBeAg and HBsAg loss/seroconversion endpoints, but there were also some potentially important differences in favor of TAF-based treatment for coinfecting individuals of Asian descent. Except for HBeAg loss at week 48 in the overall study population,¹³⁾ the proportions of participants with HBeAg loss and seroconversion in the overall population and the Asian sub-population were significantly higher in the bicittegrivir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group from week 36 onwards. In both the overall and Asian subpopulation analyses, the proportions of participants with HBsAg loss at week 48 and week 96 were higher in the bicittegrivir/emtricitabine/TAF group than the dolutegravir + emtricitabine/TDF group, but the between-group differences reached statistical significance only in the Asian sub-population. Higher proportions of bicittegrivir/emtricitabine/TAF versus dolutegravir + emtricitabine/TDF recipients in the overall population and the Asian sub-population had HBsAg seroconversion at week 48, but again the between-group difference reached statistical significance only in the Asian sub-population; by week 96, there was a numerical between-group difference in favor of bicittegrivir/emtricitabine/TAF in the Asian sub-population, and rates of HBsAg seroconversion were similar between treatment groups in the overall population.

An important finding of both the overall study analysis and the Asian sub-population analysis was the high rates of HBsAg loss (23 and 25% with bicittegrivir/emtricitabine/TAF in the overall and Asian sub-population, respectively, at week 96, and 14% and 10%, respectively, with dolutegravir + emtricitabine/TDF). In contrast, HBsAg loss has rarely been observed with in HBV monoinfection studies, occurring in $\leq 1\%$ of TAF recipients at 96 weeks and $\leq 2.5\%$ at 5 years.^{23, 24)} A younger age at baseline has been associated with HBsAg loss among HIV and HBV coinfecting individuals.²⁵⁾ A recent publication on HIV and HBV coinfecting, treatment-naïve participants in Thailand and Malaysia also observed high rates of HBsAg loss (22%) after the initiation of HBV-active antiretroviral therapy²⁵⁾ – both this and the ALLIANCE study included patients who were younger (median age 31 or 32 years) than those in HBV monoinfection trials.^{13, 23–25)} In a Taiwanese cohort of HBsAg-positive people with HIV who received TDF- or TAF-containing therapy (median age 37 years), 11% achieved HBsAg loss.²⁶⁾ Since Asian ethnicities with chronic HBV monoinfection tend to have lower rates of nucleos(t)ide analogue-induced HBsAg loss than non-Asian ethnicities,^{24, 27–29)} these findings highlight potential differences in treatment response among people with HIV-1 and HBV coinfection

compared with people with HBV monoinfection, as well as the importance of conducting further investigations in Asian populations with HIV-1 and HBV coinfection to inform the expected response to treatment.

As previously noted in the primary ALLIANCE study report,¹³⁾ the high rates of HBsAg loss observed in the study might be partly explained by the immune reconstitution hypothesis, whereby the immune system begins to reconstitute after initiation of antiretroviral therapy for HIV-1, and the likelihood of clearing HBsAg increases.³⁰⁾ Given the similar HIV-1 suppression rates and similar CD4 cell counts and percentages at 48 and 96 weeks in the two treatment groups in both the overall ALLIANCE study population¹³⁾ and the Asian sub-population, this does not, however, explain differences between the treatment groups with regard to HBsAg loss. A possible explanation is that TAF delivers higher levels of tenofovir diphosphate to hepatocytes than TDF.¹⁶⁾ When combined with an immune boost caused by HIV-1 suppression, higher intracellular concentrations of the pharmacologically active tenofovir after TAF versus TDF administration might have helped drive the higher rates of HBsAg loss and HBeAg seroconversion observed with bicittegrivir/emtricitabine/TAF versus dolutegravir + emtricitabine/TDF in the ALLIANCE study.¹³⁾ This may be particularly beneficial for Asian people coinfecting with HIV-1 and HBV, in whom a significant difference in the rate of HBsAg loss in favor of TAF-based treatment was seen as early as week 36, with the difference beginning to emerge at week 12. Such early attainment of HBsAg loss, representing functional cure, might help reduce the risk of progression to liver disease or hepatocellular carcinoma and improve outcomes in coinfecting individuals.³¹⁾ It is worth noting that in the overall population and Asian sub-population of the ALLIANCE study, the median BMI at baseline was $< 23 \text{ kg/m}^2$ for both treatment groups; in an observational, prospective study, a baseline BMI of $< 25 \text{ kg/m}^2$ was a predictive factor for a significant decline in HBsAg among patients with chronic hepatitis B who received TAF.³²⁾ However, this has yet to be demonstrated in randomized trials and further studies are warranted.

Safety outcomes were similar between the two treatment groups and consistent with those in the overall population,¹³⁾ with no unexpected findings in the Asian subpopulation. Asian study participants receiving TAF-based treatment tended to have an increase in body weight (median 4.0 kg vs 2.3 kg with TDF-based treatment). Given previous clinical trial evidence indicating that dolutegravir, bicittegrivir and TAF all have a neutral effect on body weight, and that TDF suppresses weight gain,³³⁾ more weight gain is to be expected with bicittegrivir/emtricitabine/TAF than with dolutegravir + emtricitabine/TDF. A return-to-health weight gain often occurs shortly after initiation of antiretroviral therapy and levels off

within the first year of treatment.³³⁾ Although there was a small 2 mg/dL increase in LDL-C in the bicitegravir/emtricitabine/TAF group versus a 15 mg/dL decrease in the dolutegravir + emtricitabine/TDF group, median change in TC/HDL-C ratio was minimal (-0.2) in both treatment groups. As previously mentioned in the primary ALLIANCE study report,¹³⁾ significant differences in long-term safety outcomes, attributed to lower circulating concentrations of pharmacologically active tenofovir diphosphate after TAF administration, have been observed between TAF and TDF in larger studies of HBV monoinfection.^{14–16)}

Limitations of the ALLIANCE study also apply to this subpopulation analysis, including a predominantly male population and the low proportion of participants who were HBeAg-negative at baseline.¹³⁾ Additionally, although the Asian sub-population accounted for 88% of the overall ALLIANCE study population, its size ($n=214$) fell short of the estimated total sample size ($n=240$; 120 participants per treatment group) required to formally assess non-inferiority and superiority of TAF-versus TDF-based treatment for the study's coprimary endpoints.¹³⁾ However, although the small sample size and the post-hoc nature of this Asian subpopulation analysis limits the conclusions that can be made, the benefits of TAF- versus TDF-based therapy was consistent across HBV efficacy outcomes, and generally similar to those in the overall population, with some evidence that TAF-based therapy may be particularly advantageous in HIV-1 and HBV coinfecting Asian populations with respect to HBsAg loss. Longer observational studies are required to assess the effects of treatment on liver disease outcomes.

In summary, this post-hoc Asian subpopulation analysis of the ALLIANCE study demonstrated that at week 48, bicitegravir/emtricitabine/TAF had similar efficacy to dolutegravir + emtricitabine/TDF for HIV-1 RNA suppression to <50 copies/mL, but was associated with significantly higher rates of HBV DNA suppression to <29 IU/mL. At 96 weeks, these endpoints demonstrated similar efficacy for both regimens. Compared with dolutegravir + emtricitabine/TDF, significantly higher rates of HBeAg loss and seroconversion were observed with bicitegravir/emtricitabine/TAF at week 96, along with numerically higher rates of HBsAg seroconversion. Although the bicitegravir/emtricitabine/TAF group attained higher rates of HBsAg loss than the dolutegravir + emtricitabine/TDF group in both the overall population and Asian subpopulation, the differences at weeks 48 and 96 were statistically significant only in the Asian subpopulation. Bicitegravir/emtricitabine/TAF is therefore an effective and well-tolerated initial treatment for Asian people with HIV-1 and HBV coinfection.

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アジア系成人を対象とした HIV-1 および B 型肝炎の重複感染の 初期治療におけるビクテグラビル/エムトリシタビン/ テノホビル アラフェナミドとドルテグラビル+エムトリシタビン/ テノホビル ジソプロキシシルフマル酸塩の比較： ALLIANCE 試験のサブ解析

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序論：成人で HIV-1 と B 型肝炎ウイルス (HBV) の重複感染がみられる場合、ほとんどの症例に対し、テノホビル ジソプロキシシルフマル酸塩 (TDF) またはテノホビル アラフェナミド (TAF) を含む治療法が推奨されている。しかし ALLIANCE 試験においては、TAF ベースの治療法は TDF ベースの治療法よりも優れていることを示唆するエビデンスが得られている。今回われわれは、ALLIANCE 試験のアジア系のサブグループの Post-hoc 解析を行ったので報告する。

方法：本試験では、血漿中の HIV-1 RNA 量が 500 コピー/mL 以上かつ HBV DNA 量が 2,000 IU/mL 以上の治療歴のない成人が組み入れられ、96 週にわたり、ビクテグラビル 50 mg/エムトリシタビン 200 mg/TAF 25 mg (B/F/TAF) の配合剤群か、ドルテグラビル 50 mg+エムトリシタビン 200 mg/TDF 300 mg の配合剤群 (DTG+F/TDF) のいずれかに無作為に割り付けられた。主要評価項目は、48 週時点における HIV-1 RNA 量 50 コピー/mL 未満および HBV DNA 量 29 IU/mL 未満とした。

結果：本解析ではアジア系の試験参加者 214 名を対象とした。48 週時点では、両群の HIV-1 RNA 抑制率は同程度に高かったが、B/F/TAF 群は DTG+F/TDF 群よりも HBV DNA 抑制率が有意に高かった。96 週時点では、これらの評価項目における有効性は、いずれのレジメンも同程度に高かった。B/F/TAF 群は、DTG+F/TDF 群と比較して、48 週時点および 96 週時点の HBe 抗原の消失/セロコンバージョン率および HBs 抗原の消失率が有意に高く、48 週時点の HBs 抗原のセロコンバージョン率も有意に高かった。

結論：B/F/TAF は、HIV-1 と HBV に重複感染したアジア人に対する有効な初期治療法である。

キーワード：アジア人、重複感染、B 型肝炎ウイルス、HIV-1、ビクテグラビル、エムトリシタビン、テノホビル アラフェナミド配合剤、ドルテグラビル、エムトリシタビン、テノホビル ジソプロキシシルフマル酸塩配合剤