Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial

*Anchalee Avihingsanon, Hongzhou Lu, Chee Loon Leong, Chien-Ching Hung, Ellen Koenig, Sasisopin Kiertiburanakul, Man-Po Lee, Khuanchai Supparatpinyo, Fujie Zhang, Sophia Rahman, Michelle L D'Antoni, Hongyuan Wang, Jason T Hindman, Hal Martin, Jared M Baeten, Taisheng Li, on behalf of the ALLIANCE Study Team**

Lancet HIV 2023; 10: e640–52

Published Online July 24, 2023 https://doi.org/10.1016/S2352-3018(23)00151-0

See Comment page e624

*Members listed in the appendix (p 2)

HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand (A Avihingsanon MD); Center of Excellence in Tuberculosis, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (A Avihingsanon); Shanghai Public Health Clinical Centre, Shanghai, China (H Lu MD); Department of Medicine, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia (C L Leong MD); National Taiwan University Hospital, Yunlin, Taiwan (Prof C-C Hung MD); Dominican Institute of Virological Studies, Santo Domingo, Dominican Republic (E Koenig MD); Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (Prof S Kiertiburanakul MD); Queen Elizabeth Hospital, Hong Kong Special Administrative Region, China (M-P Lee MBBS); Chiang Mai University, Chiang Mai, Thailand (K Supparatpinyo MD); Beijing Ditan Hospital, Capital Medical University, Beijing, China (F Zhang MD); Gilead Sciences, Foster City, CA, USA (S Rahman MPH, M L D'Antoni PhD, H Wang PhD, J T Hindman PharmD, H Martin MD, J M Baeten MD); Peking Union Medical College Hospital, Beijing, China (Prof T Li MD)

Summary

Background For most adults with HIV-1 and hepatitis B virus (HBV) coinfection, initial recommended treatment is a tenofovir-containing antiretroviral regimen, but no randomised studies have compared tenofovir disoproxil fumarate with tenofovir alafenamide. We aimed to investigate whether bictegravir, emtricitabine, and tenofovir alafenamide is non-inferior to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for viral suppression in individuals with HIV-1 and HBV coinfection at 48 and 96 weeks.

Methods We did this randomised, double-blind, active-controlled, phase 3, non-inferiority trial at 46 outpatient centres in China, Dominican Republic, Hong Kong, Japan, Malaysia, South Korea, Spain, Taiwan, Thailand, Turkey, and the USA. Eligible participants were treatment-naive adults (aged ≥18 years) with plasma HIV-1 RNA of at least 500 copies per mL and plasma HBV DNA of at least 2000 IU/mL. Participants were randomly assigned (1:1) to receive daily oral bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg, or dolutegravir 50 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg, each with corresponding matching placebo. Randomisation was stratified by hepatitis B e antigen (HBeAg) status (positive *vs* negative), HBV DNA (<8 *vs* ≥8 $\log_{10}$ IU/mL), and CD4 count (<50 *vs* ≥50 cells per μL) at screening. All investigators, participants, and staff providing treatment, assessing outcomes, and collecting data were masked to study treatment for 96 weeks. Coprimary endpoints were the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL (defined by the US Food and Drug Administration snapshot algorithm) and plasma HBV DNA less than 29 IU/mL (using the missing-equals-failure approach) at week 48, with a prespecified non-inferiority margin of –12%. Coprimary endpoints were assessed in the full analysis set, which included all randomly assigned participants 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. Safety endpoints were assessed in all randomly assigned participants who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03547908.

Findings Between May 30, 2018 and March 16, 2021, 381 participants were screened, of whom 243 initiated treatment (121 in the receive bictegravir, emtricitabine, and tenofovir alafenamide group; 122 in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group). At week 48, both endpoints met the criteria for non-inferiority: 113 (95%) of 119 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and 111 (91%) of 122 participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group had HIV-1 RNA less than 50 copies per mL (difference 4·1, 95% CI –2·5 to 10·8; p=0·21), and 75 (63%) of 119 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group versus 53 (43%) of 122 participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group had HBV DNA suppression (difference 16·6, 5·9 to 27·3; nominal p=0·0023). Drug-related adverse events up to week 96 occurred in 35 (29%) of 121 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and 34 (28%) of 122 participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group. One (1%) of 121 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group reported a serious adverse event (cryptococcal meningitis attributed to immune reconstitution inflammatory syndrome) that was deemed to be treatment-related.

Interpretation Coformulated bictegravir, emtricitabine, and tenofovir alafenamide is an effective therapy for adults with HIV-1 and HBV coinfection starting antiviral therapy.

Funding Gilead Sciences.

Correspondence to:
Dr Jason Hindman, Gilead Sciences, Foster City, CA 94404, USA
jason.hindman@gilead.com

See Online for appendix

Introduction

Approximately 2·7 million individuals are chronically infected with both HIV-1 and hepatitis B virus (HBV).[1] Coinfection rates vary globally, with an estimated 8·3% of people with HIV and hepatitis B surface antigen (HBsAg) seropositivity.[1] Antiviral treatments with dual activity against HBV and HIV-1 infections have improved control of HBV viraemia and reduced the risk of liver fibrosis and HBV drug resistance.[2,3] However, relative to HBV monoinfection, HIV-1 and HBV coinfection remains associated with poorer outcomes and higher health-care use.[4] Given the risk of accelerated disease and the need for lifelong antiviral therapy because of typically low rates of functional cure (ie, loss of HBsAg),[5] individuals with HIV-1 and HBV coinfection represent a large population with substantial clinical need.

For most adults with HIV-1 and HBV coinfection, initial recommended treatment is an antiretroviral regimen containing a tenofovir-based prodrug.[6,7] When assessed in people with chronic HBV monoinfection, tenofovir disoproxil fumarate and tenofovir alafenamide were highly effective in phase 3 studies, achieving viral suppression without emergence of resistance.[8–10] With tenofovir disoproxil fumarate, the pharmacologically active tenofovir is widely distributed in different tissues, whereas with tenofovir alafenamide its distribution is restricted to cells with high carboxylesterase and cathepsin A activity; this results in higher intracellular tenofovir concentrations in hepatocytes and lymphocytes, approximately 90% lower circulating tenofovir concentrations, and more favourable renal and bone safety.[8,9,11] In adults with HIV-1 and HBV coinfection, retrospective and open-label studies of switching from tenofovir disoproxil fumarate-based regimens to tenofovir alafenamide-based regimens, usually with emtricitabine or lamivudine, which also have activity against HIV-1 and HBV, show that both are effective at suppressing HBV replication.[12,13] There have been no randomised studies comparing tenofovir alafenamide with tenofovir disoproxil fumarate in people with HIV-1 and HBV coinfection.

For HIV-1 infection, the integrase strand transfer inhibitors bictegravir and dolutegravir are recommended

Research in context

Evidence before this study

We searched PubMed for clinical trials evaluating tenofovir disoproxil fumarate and tenofovir alafenamide-based regimens in adults with HIV-1 and hepatitis B virus (HBV) coinfection. We ran two searches using the following search criteria: 1) clinical trials published between March 15, 2008 and March 15, 2023, in any language, with the search terms "tenofovir alafenamide" AND "tenofovir disoproxil fumarate" AND "hepatitis B"; and 2) clinical trials published between March 15, 2008 and March 15, 2023, in any language, with the search terms "tenofovir alafenamide" OR "TAF" AND "tenofovir disoproxil fumarate" OR "TDF" and "hepatitis B" OR "HBV" AND "human immunodeficiency virus" OR "HIV". Our searches identified two published phase 3, commercially sponsored studies evaluating tenofovir disoproxil fumarate and tenofovir alafenamide as monotherapy for chronic HBV monoinfection. These studies reported high effectiveness of tenofovir disoproxil fumarate and tenofovir alafenamide in achieving HBV suppression without emergence of resistance, and more favourable bone and renal effects with tenofovir alafenamide than tenofovir disoproxil fumarate. Studies in adults with HIV-1 and HBV coinfection were limited to small studies of people who were already virologically suppressed or switching to another regimen. In these studies, switching from a tenofovir disoproxil fumarate-based regimen to a tenofovir alafenamide-based regimen was associated with continued effectiveness in achieving HBV suppression, and improved renal and bone effects. Few previously published studies have evaluated tenofovir disoproxil fumarate and tenofovir alafenamide in people with HBV infection. No previous randomised studies comparing tenofovir disoproxil fumarate and tenofovir alafenamide in people with HIV-1 and HBV coinfection were identified.

Added value of this study

Although tenofovir alafenamide or tenofovir disoproxil fumarate are recommended in global guidelines for the treatment of people with HIV-1 and HBV coinfection, to our knowledge, this is the first randomised study to compare efficacy and safety of the single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide with that of dolutegravir, emtricitabine, and tenofovir disoproxil fumarate, taken as two tablets, in treatment-naive people with HIV-1 and HBV coinfection. We found that bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for HIV-1 RNA and HBV DNA suppression at week 48, with a similar incidence of adverse events observed in both treatment groups. Therefore, this study provides new evidence to support treatment with the single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide in people with HIV-1 and HBV coinfection.

Implications of all the available evidence

These findings, in addition to the improved bone and renal safety of tenofovir alafenamide versus tenofovir disoproxil fumarate and the benefits of a single-tablet versus a multi-tablet regimen, provide important information to guide the optimal treatment of people with HIV-1 and HBV coinfection.

for initial combination antiretroviral therapy,[6,7] and bictegravir coformulated with emtricitabine and tenofovir alafenamide has shown non-inferiority to dolutegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors.[14,15] For HIV-1 and HBV coinfection, data on bictegravir or dolutegravir are limited to small studies of people who are already virologically suppressed and switching regimens.[12,16–18] Considering the established non-inferiority of a tenofovir alafenamide-based regimen to a tenofovir disoproxil fumarate-based regimen in people with HIV-1 monoinfection[14,19,20] or HBV monoinfection,[8,9] the benefits of tenofovir alafenamide versus tenofovir disoproxil fumarate in terms of improved renal and bone safety,[8,9] and the improvements in clinical outcomes with single-tablet versus multi-tablet regimens,[21] we aimed to investigate whether bictegravir, emtricitabine, and tenofovir alafenamide is non-inferior to dolutegravir, emtricitabine, tenofovir disoproxil fumarate for suppression of HIV-1 RNA and HBV DNA in people with HIV-1 and HBV coinfection who are starting antiviral therapy.

Methods

Study design and participants

This randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial (ALLIANCE) was done at 46 outpatient centres in China, Dominican Republic, Hong Kong, Japan, Malaysia, South Korea, Spain, Taiwan, Thailand, Turkey, and the USA. Eligible participants (appendix pp 3–4) were aged 18 years or older with plasma HIV-1 RNA of at least 500 copies per mL and plasma HBV DNA of at least 2000 IU/mL. Participants who had previously received treatment for chronic HBV or HIV-1 infection were excluded. HIV-1 sensitivity to emtricitabine and tenofovir was confirmed via resistance genotyping. All participants provided written informed consent. The study was done in accordance with the Declaration of Helsinki and was approved by central or site-specific review boards or ethics committees (appendix pp 5–8).

Randomisation and masking

Participants were randomly assigned (1:1) via computer-generated allocation sequence with a block size of four, using an interactive web response system (Signant Health, San Francisco, CA, USA) to receive bictegravir 50 mg, emtricitabine 200 mg , and tenofovir alafenamide 25 mg, or dolutegravir 50 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg, each with corresponding matching placebo tablets. Randomisation was stratified by hepatitis B e antigen (HBeAg) status (positive *vs* negative), HBV DNA (<8 *vs* ≥8 $\log_{10}$ IU/mL), and CD4 count (<50 *vs* ≥50 cells per µL) at screening. Investigators, participants, and staff providing treatment, assessing outcomes, and collecting data were masked to study treatment for 96 weeks. Study investigators confirmed eligibility, obtained a participant number, and received an automated treatment assignment based on the randomisation sequence.

Procedures

Study drugs were administered orally daily, regardless of food intake. Participant visits were scheduled for screening, day 1, and every 4 weeks until week 12, then quarterly thereafter until week 96. Laboratory analyses including HIV-1 RNA, CD4 cell count, CD4 cell percentage, serum chemistry, liver function tests, haematology, urinalysis, and pregnancy testing were done at screening, day 1, and all subsequent study visits. HIV-1 genotyping was done at screening, and genotyping and phenotyping were done in participants with virological failure (appendix p 9). HBV serology (HBsAg and reflex antibody to surface antigen [anti-HBsAg]; HBeAg and reflex anti-HBeAg) was done at screening, day 1, and every 12 weeks thereafter. HBV DNA was monitored at all study visits. HBV genotyping and phenotyping was done in participants who remained viraemic at weeks 48 or 96 or at early study drug discontinuation visit, and for those with virological breakthrough (appendix pp 9–10).

Safety was assessed at each visit by physical examinations, laboratory tests, 12-lead electrocardiogram, concomitant drugs, and recording of adverse events (coded using the Medical Dictionary for Regulatory Activities [version 24·1 for week 48; version 25·1 for week 96]). Relatedness of adverse events to study drugs was determined by the investigator in a binary manner (yes or no) and adverse events were graded by the investigator as grade 1 (mild), 2 (moderate), 3 (severe), or 4 (life-threatening) according to toxicity criteria specified in the protocol.

Outcomes

The coprimary efficacy endpoints were proportion of participants with HIV-1 RNA less than 50 copies per mL at week 48 using the US Food and Drug Administration (FDA) snapshot algorithm,[22] and proportion of participants with HBV DNA less than 29 IU/mL at week 48 using the missing-equals-failure approach.

Secondary endpoints included the proportion of participants with HIV-1 RNA less than 50 copies per mL and the proportion of participants with HBV DNA less than 29 IU/mL at week 96. Other HIV secondary efficacy endpoints were change from baseline in CD4 cell count and CD4 cell percentage at weeks 48 and 96. Other HBV secondary efficacy endpoints were the proportion of participants with normalisation of alanine aminotransferase (change in alanine aminotransferase concentration from higher than 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 criteria[23]] at baseline to alanine aminotransferase ≤ULN) at weeks 48 and 96, and the proportion of participants with HBsAg loss at weeks 48 and 96. Adverse

events and laboratory abnormalities up to week 96 were also included as secondary endpoints to evaluate the safety and tolerability of bictegravir, emtricitabine, and tenofovir alafenamide, and dolutegravir, emtricitabine, and tenofovir disoproxil fumarate.

Additional prespecified efficacy endpoints were HBeAg loss, HBeAg seroconversion, HBsAg seroconversion, and change from baseline in $\log_{10}$ HBV DNA, all at weeks 48 and 96. All HBV endpoints involving proportions were defined by use of a missing-equals-failure approach.

Alanine aminotransferase flares were defined as alanine aminotransferase elevations (serum alanine aminotransferase >2×baseline concentration and alanine aminotransferase >10×ULN), with or without associated symptoms, at two or more consecutive post-baseline visits based on on-treatment data.[24]

Statistical analysis

We estimated that around 240 participants with HIV-1 and HBV coinfection (120 participants per treatment group) would be required to achieve 90% power to detect a non-inferiority margin of a 12% difference in HIV-1 RNA response rate between treatments, assuming a response rate of 91%[14,15] and a one-sided α of 0·025. This sample size also provided 81% power to detect a non-inferiority margin of 12% for the proportion of participants with HBV DNA less than 29 IU/mL, assuming a response rate of 88% (the expected response in people with HBV monoinfection).[8,9]

Efficacy endpoints at weeks 48 and 96 were analysed after enrolled participants had completed their week 48 or 96 study visit, or had prematurely discontinued the study drug. All efficacy endpoints, with the exception of HBsAg and HBeAg loss or seroconversion, were assessed in the full analysis set, which included all randomly assigned participants 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 analysis set was used for assessment of HBsAg and HBeAg loss or seroconversion (appendix p 10).

For the HIV-1 efficacy endpoint, non-inferiority was assessed using the conventional 95% CI approach for difference in virological response rates (bictegravir, emtricitabine, and tenofovir alafenamide *vs* dolutegravir, emtricitabine, and tenofovir disoproxil fumarate) with a prespecified non-inferiority margin of –12%, based on FDA regulatory guidance.[22] A planned independent data monitoring committee interim analysis for safety monitoring was performed after all participants completed their week 24 study visit or prematurely discontinued study drugs, and recommended continuation of the trial. An α penalty of 0·00001 was therefore applied, resulting in a significance level for the two-sided non-inferiority test at week 48 of 0·04999, corresponding to a 95·001% CI (referred to in the Results as 95% CI for simplicity). The baseline stratum-weighted difference in the response rate and its two-sided 95·001% CI were constructed with a normal approximation method based on Mantel-Haenszel proportions stratified by baseline HIV-1 RNA (≤100 000 *vs* >100 000 copies per mL) following FDA industry guidance for HIV-1.[22] If non-inferiority of bictegravir, emtricitabine, and tenofovir alafenamide to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate was established, the same CI was to be used to evaluate superiority. If the lower bound of the 95·001% CI was higher than 0, then superiority of bictegravir, emtricitabine, and tenofovir alafenamide to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate was established.

For the HBV coprimary endpoint, non-inferiority and superiority were assessed similarly to the HIV-1 endpoint, with the exception of stratification factors, which included HBeAg status (positive *vs* negative) and baseline HBV DNA (<8 *vs* ≥8 $\log_{10}$ IU/mL).

To control type I error in assessing the coprimary endpoints, hypotheses were tested with the fixed-sequence testing procedure[25] in sequential order with the prespecified one-sided, 0·024995 α level. Non-inferiority of the coprimary HIV-1 endpoint was tested first; if established, the hypothesis of non-inferiority of the coprimary HBV endpoint was to be tested (otherwise, the coprimary HBV endpoint was not tested). No adjustment for multiplicity was made for endpoints other than the coprimary endpoints. Nominal p values (p values without multiplicity adjustment) were provided.

Comparison of the HIV coprimary endpoint between treatment groups was performed using a two-sided Cochran-Mantel-Haenszel test as a secondary assessment, adjusted by baseline HIV-1 RNA stratum. The HBV coprimary endpoint was compared between groups using a Cochran-Mantel-Haenszel test with baseline strata of HBeAg status and HBV DNA level. Other categorical endpoints were compared between treatment groups using a Cochran-Mantel-Haenszel test with baseline strata of HBV DNA concentration (for HBeAg loss or seroconversion) or both HBeAg status and HBV DNA concentration (for alanine aminotransferase normalisation and HBsAg loss or seroconversion). CD4 cell count and CD4 cell percentage were compared between treatment groups using an ANOVA model adjusted by baseline HIV-1 RNA stratum.

Subgroup analyses of the coprimary endpoints at week 48 and corresponding secondary endpoints at week 96 were based on age, sex, region, study drug adherence by pill counts, race, HIV-1 RNA level, CD4 cell count, HBeAg status, HBV DNA level, HBV genotype, and alanine aminotransferase concentration (as per American Association for the Study of Liver Diseases criteria[23]) at baseline (as appropriate).

As specified in the statistical analysis plan, rates of HIV-1 RNA and HBV DNA suppression and change in

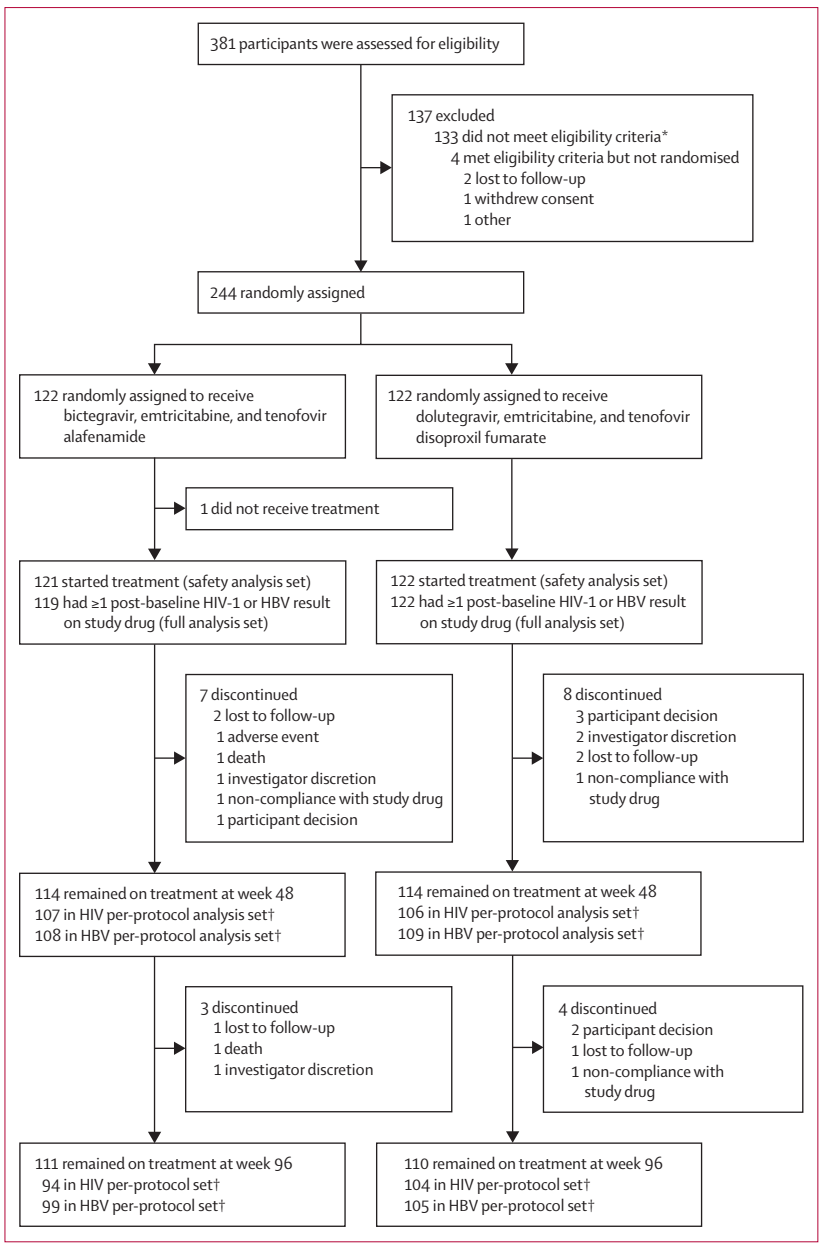

Figure 1: **Trial profile**
HBV=hepatitis B virus. *Among the 133 individuals screened but not randomised due to not meeting eligibility criteria, 103 (77%) did not have HBV DNA of at least 2000 IU/mL at screening (see appendix p 15). †Participants who did not have an HIV-1 RNA or HBV DNA value in the specified analysis window because of study drug discontinuation for reasons other than lack of efficacy, who had adherence below the 2·5th percentile, or who violated key entry criteria, were excluded from the per-protocol analysis sets.

CD4 cell count from baseline were also assessed at weeks 48 and 96 using the per-protocol analysis set for the HIV or HBV efficacy analysis, which excluded participants who did not have an HIV-1 RNA or HBV DNA value in the specified analysis window because of study drug discontinuation for reasons other than poor efficacy, who had low adherence (defined as adherence below the 2·5th percentile), or who violated key entry criteria.

Adverse events, clinical and laboratory abnormalities, and weight were summarised using descriptive statistics based on the safety analysis set, which included all randomly assigned participants who received at least one dose of study drug. All safety data collected up to 30 days after permanent discontinuation of study drug and all available data up to the week 48 and 96 data cutoffs for participants remaining on study drug were summarised. Aspartate aminotransferase to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) scores were retrospectively calculated over 48 weeks and were compared between treatment groups using the two-sided Wilcoxon rank-sum test. This study is registered with ClinicalTrials.gov (NCT03547908).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between May 30, 2018 and March 16, 2021, 381 participants were screened (figure 1; appendix p 15). 243 participants initiated treatment (121 in the bictegravir, emtricitabine, and tenofovir alafenamide group; 122 in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group; figure 1).

213 (88%) of 243 participants were from Asia, mainly Thailand (39%), China (23%), and Malaysia (15%). Demographic and baseline characteristics were well balanced between groups (table 1). Overall, 30% of participants had HIV-1 RNA higher than 100 000 copies per mL, 11% had CD4 counts less than 50 CD4 cells per µL, 52% had HBV DNA of at least 8 $\log_{10}$ IU/mL, and 78% were HBeAg positive at baseline.

The final week 48 visit was completed on Feb 25, 2022, and the final week 96 visit on Dec 28, 2022. Adherence to study drugs was high, with a mean adherence rate of 98·5% (SD 2·77) for bictegravir, emtricitabine, and tenofovir alafenamide and 98·3% (3·02) for dolutegravir, emtricitabine, and tenofovir disoproxil fumarate up to week 96 (appendix p 16).

At week 48, 95% of participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and 91% of participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group had HIV-1 RNA of less than 50 copies per mL (difference 4·1, 95% CI −2·5 to 10·8; p=0·21), demonstrating non-inferiority (table 2, figure 2A). 63% of participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had HBV DNA less than 29 IU/mL compared with 43% in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (difference 16·6, 95% CI 5·9 to 27·3; nominal p=0·0023), demonstrating superiority of the bictegravir, emtricitabine, and tenofovir alafenamide regimen.

	Bictegravir, emtricitabine, and tenofovir alafenamide (n=121)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n=122)
Age, years	31 (27–39)	32 (25–38)
Sex at birth		
Male	112 (93%)	120 (98%)
Female	9 (7%)	2 (2%)
Race		
Asian	108 (89%)	106 (87%)
White	10 (8%)	9 (7%)
Black	2 (2%)	6 (5%)
Other	1 (1%)	1 (1%)
Ethnicity		
Hispanic or Latino	7 (6%)	10 (8%)
Country or region		
China	27 (22%)	29 (24%)
Dominican Republic	4 (3%)	6 (5%)
Hong Kong	2 (2%)	3 (2%)
Japan	2 (2%)	5 (4%)
Malaysia	15 (12%)	22 (18%)
South Korea	2 (2%)	0
Spain	4 (3%)	3 (2%)
Taiwan	5 (4%)	7 (6%)
Thailand	55 (45%)	39 (32%)
Turkey	4 (3%)	5 (4%)
USA	1 (1%)	3 (2%)
BMI, kg/m^2	22·2 (19·9–24·7)	21·7 (19·3–23·7)
Weight, kg	63·7 (57·0–73·9)	63·8 (56·6–71·0)
eGFR, mL/min*	106·8 (94·8–130·8)	104·7 (93·0–124·2)
Alanine aminotransferase concentration, U/L	34 (23–60)	27 (19–51)
Alanine aminotransferase concentration >ULN†	60 (50%)	47 (39%)
HIV-1 RNA		
Log_{10} copies per mL	4·66 (4·22–5·12)	4·69 (4·26–5·04)
>100 000 copies per mL	38 (31%)	34 (28%)
CD4		
Cell count per µL	245 (127–383)	236 (121–380)
<50 cells per µL	12 (10%)	14 (11%)
<200 cells per µL	46 (38%)	52 (43%)
Percentage	15·4% (10·0–22·0)	13·8% (9·6–19·9)
HIV-1 infection risk factors‡		
Heterosexual sex	29 (24%)	22 (18%)
Homosexual sex	88 (73%)	99 (81%)
Injecting drug use	0	4 (3%)
Other	2 (2%)	1 (1%)
Unknown	4 (3%)	4 (3%)
(Table 1 continues in next column)		
(Continued from previous column)		
HIV-1 disease status		
Asymptomatic	83 (69%)	81 (66%)
Symptomatic HIV infection	24 (20%)	24 (20%)
AIDS	14 (12%)	17 (14%)
HBV DNA, log_{10} IU/mL	7·96 (6·52–8·38)	8·08 (6·59–8·50)
HBV DNA ≥8 log_{10} IU/mL	60 (50%)	66 (54%)
Positive HBsAg	121 (100%)	121 (99%)
Positive HBeAg	92 (76%)	97 (80%)
HBV genotype§		
A	7 (6%)	19 (17%)
B	21 (19%)	24 (22%)
C	63 (56%)	50 (46%)
D	15 (13%)	14 (13%)
F	3 (3%)	1 (1%)
Mixed	3 (3%)	1 (1%)
Missing	9	13
HBV infection risk factors‡		
Blood product transfusion	1 (1%)	1 (1%)
Injection drug use (current or past)	1 (1%)	1 (1%)
Contact with infected individual (other than vertical transmission)	23 (19%)	25 (20%)
Known vertical transmission	29 (24%)	16 (13%)
Unknown	63 (52%)	78 (64%)
Other	4 (3%)	1 (1%)

Data are median (IQR) or n (%). eGFR=estimated glomerular filtration rate. HBV=hepatitis B virus. ULN=upper limit of normal. AASLD=American Association for the Study of Liver Diseases. HBsAg=HBV surface antigen. HBeAg=HBV e antigen. *Estimated with the Cockcroft-Gault formula. †Based on the 2018 AASLD criteria; ULN is 25 U/L for females and 35 U/L for males. ‡Participant reported. §Percentage based on individuals with non-missing HBV genotype.

Table 1: **Baseline demographic and clinical characteristics (safety analysis set)**

In prespecified subgroup analyses of coprimary endpoints, no significant differences in treatment effects were identified between subgroups (appendix pp 38–40). Among 187 participants who were HBeAg positive at baseline, 46 (51%) of 90 in the bictegravir, emtricitabine, and tenofovir alafenamide group achieved HBV DNA suppression at week 48 compared with 30 (31%) of 97 in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (difference 18·6, 95% CI 5·3 to 32·0). Among participants who were HBeAg negative at baseline, all 29 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and 23 (92%) of 25 in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group achieved HBV DNA suppression at week 48 (difference 9·6, –2·2 to 21·4).

At week 96, 87% of participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had HIV RNA less than 50 copies per mL compared with 88% in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (difference –0·3, 95% CI

	Bictegravir, emtricitabine, and tenofovir alafenamide (n=119)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n=122)	Difference (95% CI)	p value*
Week 48				
HIV-1 RNA virological response, copies per mL				
<50	113 (95%)	111 (91%)	4·1% (–2·5 to 10·8)	0·21
≥50	5 (4%)	7 (6%)	..	..
No data	1 (1%)	4 (3%)	..	..
HBV DNA virological response, IU/mL				
<29	75 (63%)	53 (43%)	16·6% (5·9 to 27·3)	0·0023
≥29	44 (37%)	69 (57%)	..	..
CD4 cell count				
Change from baseline, cells per µL	200 (139·3)	175 (124·7)	24 (–10 to 58)	0·17
Change from baseline, %	8·4% (4·14)	7·8% (4·35)	0·6% (–0·5 to 1·7)	0·28
Alanine aminotransferase normalisation†	44/60 (73%)	26/47 (55%)	17·1% (–1·5 to 35·7)	0·066
HBsAg loss‡§	15 (13%)	7/121 (6%)	7·1% (–0·8 to 15·0)	0·059
HBeAg loss‡§	23/90 (26%)	14/97 (14%)	11·3% (–0·4 to 22·9)	0·055
HBeAg seroconversion‡¶	21/90 (23%)	11/97 (11%)	11·9% (0·9 to 23·0)	0·031
HBsAg seroconversion‡¶	10 (8%)	4/121 (3%)	5·2% (–1·4 to 11·8)	0·088
Week 96				
HIV-1 RNA virological response, copies per mL				
<50	104 (87%)	107 (88%)	–0·3% (–8·9 to 8·3)	0·94
≥50	3 (3%)	8 (7%)	..	..
No data	12 (10%)	7 (6%)	..	..
HBV DNA virological response, IU/mL				
<29	89 (75%)	86 (70%)	2·6% (–8·3 to 13·4)	0·64
≥29	30 (25%)	36 (30%)	..	..
CD4 cell count				
Change from baseline, cells per µL	261 (161·6)	229 (174·0)	30 (–14 to 74)	0·19
Change from baseline, %	10·7% (5·05)	10·4% (5·10)	0·1% (–1·2 to 1·5)	0·85
Alanine aminotransferase normalisation†	43/60 (72%)	27/47 (57%)	14·1% (–4·3 to 32·6)	0·13
HBsAg loss‡§	27 (23%)	17/121 (14%)	9·3% (–0·7 to 19·2)	0·066
HBeAg loss‡§	34/90 (38%)	19/97 (20%)	18·1% (5·2 to 31·0)	0·0064
HBeAg seroconversion‡¶	29/90 (32%)	15/97 (15%)	16·4% (4·2 to 28·6)	0·0084
HBsAg seroconversion‡¶	11 (9%)	8/121 (7%)	2·7% (–4·6 to 10·0)	0·44

Data are n (%), mean (SD), or n/N (%). HBV=hepatitis B virus. HBsAg=hepatitis B surface antigen. HBeAg=hepatitis B e antigen. ULN=upper limit of normal. AASLD=American Association for the Study of Liver Diseases. HBeAb=hepatitis B e antibody. HBsAb=hepatitis B surface antibody. *All p values are nominal. †Reduction in alanine aminotransferase concentrations to ≤ULN for participants who had alanine aminotransferase concentrations > ULN at baseline, based on the 2018 AASLD criteria (25 U/L for females and 35 U/L for males). ‡Assessed in the serologically evaluable full analysis set, defined as all participants in the full analysis set who were HBeAg or HBsAg positive and HBeAb or HBsAb negative or missing at baseline. §Changes from HBeAg or HBsAg positive at baseline to negative at a post-baseline visit with baseline HBeAb or HBsAb negative or missing. ¶HBeAg or HBsAg loss and changes from HBeAb or HBsAb negative or missing at baseline to positive at a post-baseline visit.

Table 2: **Virological and immunological outcomes (full analysis set)**

–8·9 to 8·3; table 2, figure 2B). 75% of participants in the bictegravir, emtricitabine, and tenofovir alafenamide group had HBV DNA less than 29 IU/mL compared with 70% in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (difference 2·6, –8·3 to 13·4; table 2, figure 2B). The proportion of individuals achieving HBV DNA less than 29 IU/mL was higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group between weeks 24 and 96, with the difference reaching statistical significance at weeks 48 and 72 (figure 2C). Subgroup analyses of both coprimary outcomes at week 96 showed similar virological response rates in all subgroups between treatment groups (95% CIs cross 0; appendix pp 40–43).

Mean CD4 cell counts and CD4 cell percentages increased similarly from baseline in both treatment groups at both week 48 and week 96 (table 2). The proportion of participants with alanine aminotransferase normalisation was higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group at all timepoints (appendix p 44), and greater reductions in median alanine aminotransferase and aspartate aminotransferase concentrations were observed at all timepoints in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (appendix p 46). The proportion of participants with HBsAg loss was numerically higher at both week 48 and week 96 in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (table 2); this difference was significant at weeks 24 and 36 (appendix p 45). Differences between treatment groups in rates of alanine aminotransferase normalisation and HBsAg loss were numerically greater (in favour of bictegravir, emtricitabine, and tenofovir alafenamide) in participants with negative HBeAg status at baseline than in those with positive status (appendix p 17).

Results were consistent in the per-protocol and full analysis set for all prespecified efficacy endpoints (appendix p 18).

Differences in HBV outcomes began to emerge at week 12 (appendix pp 44–45). The mean change in $\log_{10}$ HBV DNA concentration up to week 96 showed a gradual and similar decline over time, with larger reductions observed in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group between week 8 and week 72, which reached statistical significance at week 12 (appendix p 45). Similar kinetics were observed in HBeAg-positive and HBeAg-negative individuals (appendix p 47).

The proportion of participants with HBeAg loss and seroconversion was significantly higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group at all timepoints after 36 weeks, with the exception of HBeAg loss at week 48 (difference 11·3, 95% CI –0·4 to 22·9; table 2; appendix p 44). At 96 weeks, 34 (38%) of 90 individuals

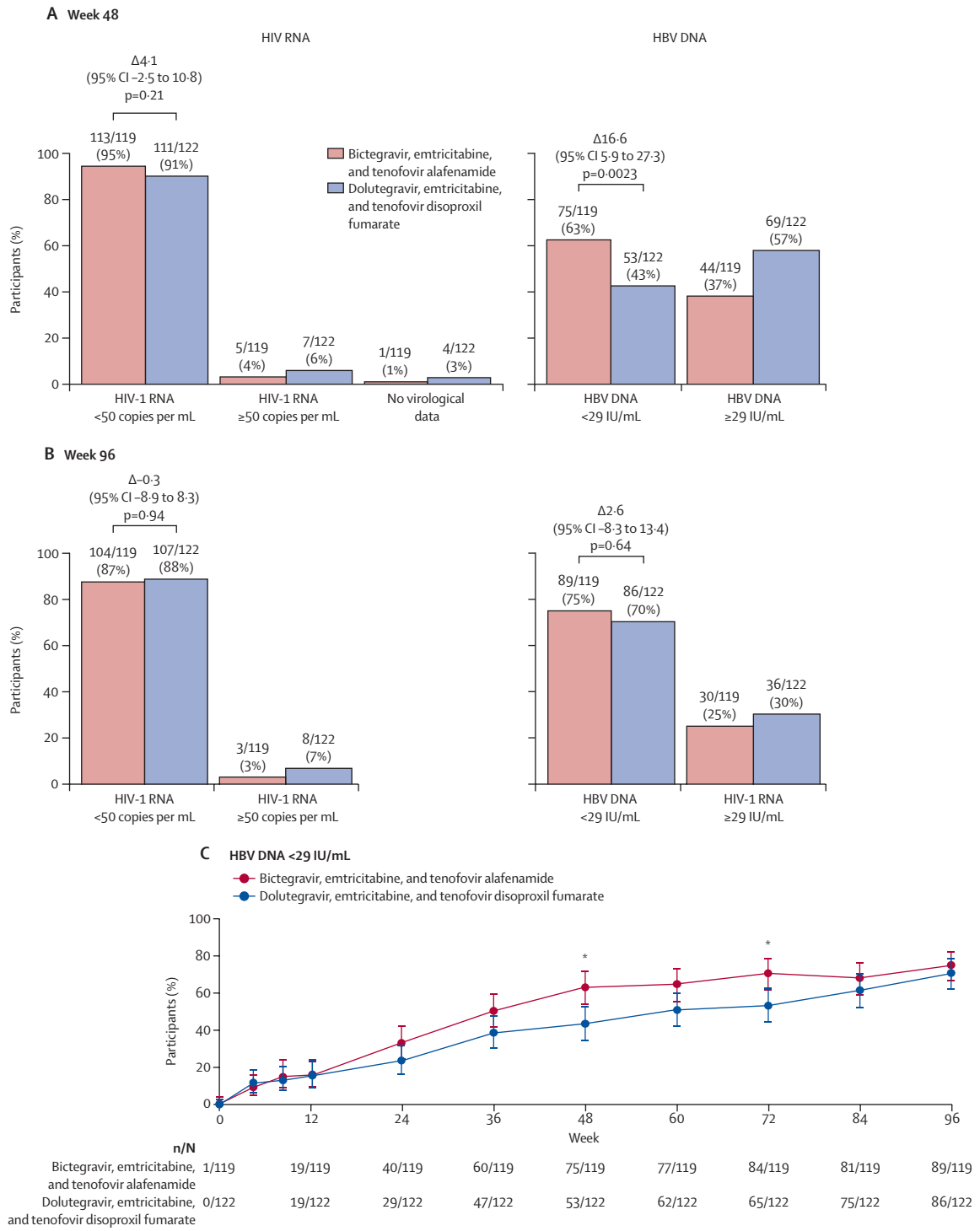

Figure 2: **Virological outcomes (full analysis set)**
HIV RNA suppression and HBV DNA suppression at week 48 (A) and week 96 (B). (C) Proportion of participants with HBV DNA <29 IU/mL up to week 96. Error bars show 95% CIs. All p values are nominal. HBV=hepatitis B virus. HBeAg=hepatitis B e antigen. *p<0·01 calculated using the Cochran-Mantel-Haenszel test, stratified by baseline HBeAg stratum and HBV DNA stratum.

in the bictegravir, emtricitabine, and tenofovir alafenamide group had HBeAg loss compared with 19 (20%) of 97 individuals in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group; 29 (32%) individuals had HBeAg seroconversion compared with 15 (15%) individuals. Rates of HBsAg seroconversion were similar between groups at week 96: 11 (9%) of 119 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and eight (7%) of 121 participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (appendix p 45).

Safety data are presented up to the week 96 data cutoff (table 3; appendix pp 19–33). Most reported adverse events were grade 1 or 2 in severity. The proportions of participants in each treatment group who reported any grade 3 or 4 adverse events or adverse events considered related to study drug were similar. Adverse events and laboratory abnormalities up to week 48 are shown in the appendix (pp 34–35). The incidence of adverse events remained similar between treatment groups across all prespecified subgroups (appendix p 36).

One serious adverse event (cryptococcal meningitis) was reported as study drug related (attributed to immune reconstitution inflammatory syndrome) in the bictegravir, emtricitabine, and tenofovir alafenamide group. 29 (24%) of 121 participants in the bictegravir, emtricitabine, and tenofovir alafenamide group and 29 (24%) of 122 participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group reported hepatic adverse events (appendix p 37).

The most frequent laboratory abnormalities were elevated transaminase concentrations, none of which resulted in treatment discontinuation. 11 participants (seven in the bictegravir, emtricitabine, and tenofovir alafenamide group and four in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group) had confirmed alanine aminotransferase flares. Six participants in the bictegravir, emtricitabine, and tenofovir alafenamide group who had alanine aminotransferase flares were HBeAg positive at baseline: all six had HBeAg loss and five had HBeAg seroconversion during study treatment; four had HBsAg loss and three had HBsAg seroconversion. All four participants in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group with alanine aminotransferase flares were HBeAg positive at baseline: two had HBeAg loss and seroconversion; one had HBsAg loss, and none had HBsAg seroconversion. Most flares occurred in the first 12 weeks of treatment, and all cases eventually resolved on treatment. No cases of proximal renal tubulopathy or discontinuations due to renal adverse events were observed in either treatment group.

At week 48, the median increase in bodyweight from baseline was 4·0 kg (IQR 0·8 to 7·5) in the bictegravir, emtricitabine, and tenofovir alafenamide group versus 2·4 kg (–1·5 to 4·6) in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group; at week 96, the median increase in bodyweight from baseline was 4·3 kg (0·9 to 8·0) in the bictegravir, emtricitabine, and tenofovir alafenamide group versus 2·3 kg (–0·5 to 5·7) in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group. At week 48, the median increase in BMI from baseline was 1·3 kg/m² (IQR 0·3 to 2·7) in the bictegravir, emtricitabine, and tenofovir alafenamide group versus 0·8 kg/m² (–0·5 to 1·5) in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group; at week 96, the median increase in BMI from baseline was 1·4 kg/m² (0·3 to 2·6) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 0·8 kg/m² (–0·2 to 2·0) in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group. Study

	Bictegravir, emtricitabine, and tenofovir alafenamide (n=121)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n=122)	Difference (95% CI)
Any adverse event	116 (96%)	117 (96%)	−0·0 (−6·3 to 6·2)
Any grade 3 or 4 adverse event	22 (18%)	21 (17%)	1·0 (−9·3 to 11·2)
Serious adverse event	17 (14%)	16 (13%)	0·9 (−8·4 to 10·3)
Adverse event leading to discontinuation of treatment	1 (1%)*	0	0·8 (−3·1 to 5·2)
Adverse events in ≥10% in either treatment group			
COVID-19	46 (38%)	44 (36%)	..
Upper respiratory tract infection	24 (20%)	18 (15%)	..
Pyrexia	15 (12%)	16 (13%)	..
Nasopharyngitis	15 (12%)	8 (7%)	..
Increased alanine aminotransferase concentration	10 (8%)	15 (12%)	..
Diarrhoea	13 (11%)	11 (9%)	..
Any study drug-related adverse event	35 (29%)	34 (28%)	1·1 (−10·8 to 12·9)
Study drug-related serious adverse event	1 (1%)†	0	0·8 (−3·1 to 5·2)
Study drug-related adverse events in ≥2% in either treatment group‡			
Weight increased§	10 (8%)	12 (10%)	..
Increased alanine aminotransferase concentration	2 (2%)	8 (7%)	..
Nausea	1 (1%)	5 (4%)	..
Headache	4 (3%)	2 (2%)	..
Increased aspartate aminotransferase concentration	3 (2%)	3 (2%)	..
Dizziness	2 (2%)	3 (2%)	..
Protein present in urine	3 (2%)	1 (1%)	..
Dyslipidaemia	3 (2%)	1 (1%)	..
Leukopenia	3 (2%)	0	..
Death¶	2 (2%)	1 (1%)	0·8 (−3·7 to 5·7)
Laboratory abnormalities			
Any grade 3 or 4	45 (38%)	39 (32%)	5·2 (−7·2 to 17·5)
Grade 3 or 4 occurring in ≥10% in either group			
Alanine aminotransferase increase of >5 × ULN	26 (22%)	16 (13%)	..
Aspartate aminotransferase increase of >5 × ULN	16 (13%)	14 (12%)	..

(Table 3 continues on next page)

drug-related adverse events of weight increase and abnormal weight gain were reported in seven and three participants, respectively, in the bictegravir, emtricitabine, and tenofovir alafenamide group and in nine and three participants, respectively, in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group (table 3).

HIV-1 treatment-emergent drug resistance was detected in one participant in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group with documented non-adherence; no HBV amino acid substitutions associated with resistance to tenofovir alafenamide or tenofovir disoproxil fumarate were detected up to week 48 (appendix p 11).

Median APRI and FIB-4 scores (appendix pp 11, 48), retrospectively calculated over 48 weeks, were similar at baseline, and both scores declined modestly during the study in both groups.

	Bictegravir, emtricitabine, and tenofovir alafenamide (n=121)	Dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n=122)	Difference (95% CI)
(Continued from previous page)			
Other laboratory results at week 96			
Change in eGFR from baseline, mL per min‖	−9·9 (−21·6 to −0·6)	−12·0 (−17·4 to −5·3)	..
Change in fasting cholesterol from baseline, mg/dL	16 (−9 to 35)	−15 (−34 to 6)	..
Change in fasting LDL from baseline, mg/dL	3 (−13 to 26)	−14 (−33 to 5)	..

Data are n (%) or median (IQR). 95% CIs were calculated by Wilson (Score) method. Multiple adverse events were counted once per participant for the highest severity grade for each preferred term. A full list of adverse events, study drug-related adverse events, and grade 3 or 4 adverse events occurring below the cutoffs stipulated in this table are reported in the appendix (p 19). eGFR=estimated glomerular filtration rate. *Hepatocellular carcinoma on day 1115 (subsequently died in hospice). †Cryptococcal meningitis attributed to immune reconstitution inflammatory syndrome on day 32 (resolved on day 40). ‡At week 48, an increase in aspartate aminotransferase concentration was observed in two participants in each treatment group; protein was present in urine of one participant in the bictegravir, emtricitabine, and tenofovir alafenamide group; dyslipidaemia occurred in one participant in each treatment group; and leukopenia occurred in one participant in the bictegravir, emtricitabine, and tenofovir alafenamide group, corresponding to <2% of either treatment group. §Adverse events of weight increased or abnormal weight gain. ¶Two participants in the bictegravir, emtricitabine, and tenofovir alafenamide group died (one due to ischaemic heart disease and one due to unknown causes) and one participant in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group died due to unknown causes; a fourth participant, in the bictegravir, emtricitabine, and tenofovir alafenamide group, discontinued study treatment after week 48, on day 1115, after developing hepatocellular carcinoma; this participant subsequently died in hospice. ||Estimated with the Cockcroft-Gault formula.

Table 3: **Adverse events and laboratory abnormalities up to the week 96 data cutoff (safety analysis set)**

Discussion

In adults with HIV-1 and HBV coinfection, the proportion of participants who achieved suppression of HBV DNA to less than 29 IU/mL was significantly higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group after 48 weeks of treatment (coprimary endpoint), meeting the protocol-defined definition for superiority. At 48 weeks, HIV-1 RNA suppression was similar between groups, with bictegravir, emtricitabine, and tenofovir alafenamide demonstrating non-inferiority versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (co-primary endpoint). At 96 weeks, a large proportion of participants in both treatment groups had achieved HBV DNA suppression and HIV-1 RNA suppression.

In the present trial, a non-inferiority design was used to assess coprimary endpoints, and similar findings were expected for both endpoints, because previous studies of HIV-1 and HBV monoinfection showed that tenofovir disoproxil fumarate-based therapies and tenofovir alafenamide-based therapies are highly effective for both viruses.[8,9,24] The finding that participants who received the tenofovir alafenamide-based regimen had a more rapid rate of HBV suppression than those who received the tenofovir disoproxil fumarate-based regimen, with superiority at the primary endpoint of 48 weeks and some signs of improvement in other markers of anti-HBV activity over 96 weeks, was unexpected and emphasises the importance of trials treating populations with coinfection. HIV-1 coinfection produces an accelerated HBV natural history;[4] thus, optimal treatment of HBV might differ in the context of coinfection compared with HBV monoinfection. The observed HBV suppression rates differed markedly from the expected response rate of 88% (for both treatment groups). This difference might have been due to the initial assumption that approximately 20% of enrolled participants would be HBeAg positive at baseline (with a suppression rate of 64%) and 80% would be HBeAg negative (with a suppression rate of 94%), when in fact 78% of participants in the trial were HBeAg positive at baseline and 22% were HBeAg negative at baseline. Furthermore, the expected results were based on studies in HBV monoinfection and did not take into consideration any possible effect of HIV coinfection on response rates. Because, to our knowledge, this is the first randomised clinical trial to compare a tenofovir alafenamide-based regimen with a tenofovir disoproxil fumarate-based regimen in HIV-1 and HBV coinfection, these results are important in informing future expected response rates.

Other differences in HBV response were also observed between the tenofovir alafenamide and tenofovir disoproxil fumarate groups throughout the treatment course. HBeAg seroconversion rates at week 96 were significantly higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group, with significant differences observed at each timepoint from week 36 onwards. Rates of HBsAg loss at week 96 were numerically higher in the bictegravir, emtricitabine, and tenofovir alafenamide group than the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group; however, this difference was not statistically significant. The proportion of individuals with alanine aminotransferase concentrations higher than the ULN at baseline who achieved alanine aminotransferase normalisation was significantly higher at some

post-baseline timepoints. Studies in HBV monoinfection have also reported significantly higher alanine aminotransferase normalisation rates among participants receiving tenofovir alafenamide versus tenofovir disoproxil fumarate at 48 and 96 weeks.[8,9,24] Although differences in alanine aminotransferase normalisation did not reach statistical significance in our study, different from previous HBV monoinfection studies, this finding probably reflects the smaller population in our study who had alanine aminotransferase concentrations higher than the ULN at baseline (whereas this was an entry requirement for both monoinfection studies).[8,9,24]

Safety outcomes were similar between the two groups, with most adverse events being mild or moderate in severity. In larger studies in HBV monoinfection, significant differences in safety outcomes have been identified between groups treated with tenofovir alafenamide versus tenofovir disoproxil fumarate, attributed to lower circulating concentrations of active tenofovir;[8,9,11] however, given that fewer people globally have HIV-1 and HBV coinfection than HBV monoinfection, it would have been extremely challenging to do a trial large enough to detect these differences in this population.

Compared with previous studies, the rates of HIV-1 suppression in this study were consistent with those observed with bictegravir-containing and dolutegravir-containing antiretroviral regimens in people with HIV-1.[14,15] In our study, HBV suppression rates were generally similar to those in a phase 3 study of HBeAg-positive individuals with HBV monoinfection (with the exception of week 48, whereby HBV suppression rate was lower in the tenofovir disoproxil fumarate-containing group),[9,24] and lower than those observed in a previous phase 3 study of HBeAg-negative individuals with HBV monoinfection,[8,24] reflecting the high proportion of HBeAg-positive participants in our study (appendix p 17). Overall, our results are consistent with observational studies of HIV-1 and HBV coinfection (which also included both HBeAg-negative and HBeAg-positive participants).[26] Differences in the treatment effect on HBV DNA suppression between HBeAg-positive versus HBeAg-negative participants probably reflect the small number of HBeAg-negative individuals included, and the higher rates of HBV suppression observed in the control group among HBeAg-negative participants.

An important finding in this study was the high HBsAg loss (23% in the bictegravir, emtricitabine, and tenofovir alafenamide group and 14% in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group) and HBsAg seroconversion (9% and 7%) occurring at 96 weeks. HBsAg loss and seroconversion are usually rare; in HBV monoinfection studies, tenofovir alafenamide was associated with HBsAg loss or seroconversion rates of 1% or lower at 96 weeks in either HBeAg-negative or HBeAg-positive individuals.[24] This finding highlights differences in treatment response among people with HIV-1 and HBV coinfection compared with HBV monoinfection, although differences in the study populations should be noted: previous HBV monoinfection studies specifically enrolled individuals with chronic HBV and elevated alanine aminotransferase,[8,9,24] whereas our study enrolled a mixed population, of whom only 44% had elevated alanine aminotransferase concentrations at baseline. Furthermore, the absence of HBsAg quantitation in this study limits the conclusions that can be drawn. A high rate of HBsAg loss and seroconversion in HIV-1 and HBV coinfection might be partly explained by the immune reconstitution hypothesis, in which after initiation of antiretroviral therapy for HIV-1, the immune system begins to reconstitute and the chance of clearing HBsAg increases.[27] However, this does not explain differences between treatment groups, given the similar HIV-1 suppression rates and similar CD4 cell counts and percentages at 48 and 96 weeks. The superiority of tenofovir alafenamide with regard to HBV suppression at 48 weeks might relate to higher intracellular drug concentrations, because tenofovir alafenamide delivers the pharmacologically active tenofovir diphosphate more efficiently into hepatocytes and lymphocytes than tenofovir disoproxil fumarate.[11] This early pharmacokinetic difference, when coupled with an immune boost caused by HIV-1 suppression, might have driven higher rates of HBeAg seroconversion and HBsAg loss in the bictegravir, emtricitabine, and tenofovir alafenamide group.

There could be long-term clinical and societal benefits to achieving HBeAg and HBsAg loss or seroconversion earlier in the treatment course. With HBeAg seroconversion marking a transition to an inactive carrier state, and HBsAg loss representing functional cure, achieving these endpoints quickly might help reduce the risk of progression to liver disease or hepatocellular carcinoma and improve outcomes.[28,29] Furthermore, early and sustained alanine aminotransferase normalisation could confer clinical benefits, since in HBV monoinfection, persistent alanine aminotransferase elevation is an independent factor for the development of hepatic events including hepatocellular carcinoma.[30] Understanding the potential long-term clinical benefits of bictegravir, emtricitabine, and tenofovir alafenamide in HIV-1 and HBV coinfection will be an important area for future investigation.

Our study had limitations. Randomised controlled trials have restrictive populations by design, and the results cannot always be generalised. For example, the population was primarily male and Asian. People with decompensated cirrhosis were excluded, so data cannot be extrapolated to that group. Around 20% of participants were HBeAg negative at baseline (balanced between treatment groups). There is an argument that HBeAg-positive and HBeAg-negative individuals are distinct populations in terms of clinical status, as shown by the

48-week subgroup analysis. Quantitative HBsAg titres were not measured and might have provided useful insights to complement HBV DNA measurements, especially for participants with loss of HBsAg. CD4 cell counts at baseline were also relatively low in the study and might be higher among some people newly diagnosed with HIV and HBV. Although the study was randomised and baseline disease characteristics were balanced between treatment groups, between-group differences, particularly in levels of HBV immune activation, cannot be ruled out. HIV-1 and HBV diagnoses were made simultaneously, thus the duration of HBV infection was unknown, although similar baseline APRI and FIB-4 scores between groups suggest similar disease progression. Although this study spanned almost 2 years, longer observational studies would be required to assess progression to liver disease or risk of hepatocellular carcinoma, or to evaluate fully whether early viral suppression is associated with longer-term effects such as HBeAg or HBsAg loss or alanine aminotransferase normalisation. Future studies investigating predictors of long-term response to treatment could be instrumental in helping to guide therapeutic decisions in the clinic.

In conclusion, this study demonstrated that bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for suppression of HIV-1 RNA levels to less than 50 copies per mL, and superior to dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for suppression of HBV DNA levels to less than 29 IU/mL at 48 weeks. The same endpoints at 96 weeks showed that both regimens had similar efficacy for both measures. Additionally, compared with individuals in the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate group, individuals in the bictegravir, emtricitabine, and tenofovir alafenamide group had higher rates of HBeAg loss and seroconversion over the course of the study. This study provides important clinical data for people with HIV-1 and HBV coinfection. Combined with known benefits in terms of long-term bone and renal measures, our data indicate potential clinical benefits of the single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide for treatment of HIV-1 and HBV coinfection and represent an important step towards defining optimal therapy.

Contributors

HW and HM conceived and designed the study. AA, HL, CLL, C-CH, EK, SK, M-PL, KS, FZ, and TL contributed to the collection of data. AA, HW, JTH, and TL have accessed and verified the underlying data reported. All authors had full access to all study data, contributed to drafting or revising the article, and had final responsibility for the decision to submit for publication.

Declaration of interests

AA received grants and honoraria from Gilead Sciences; speaker honoraria from ViiV Healthcare and GlaxoSmithKline; and grants, speaker honoraria, and consulting fees from Viatris. C-CH has received grants and speaker honoraria from Gilead Sciences. TL has received speaker honoraria from Perkin Elmer, Gilead Sciences, and GlaxoSmithKline; travel expenses from Gilead Sciences, GlaxoSmithKline, and Sansure Biotech. SR, MLDA, HW, JTH, and HM are employees and stockholders of Gilead Sciences. JMB is an employee and stockholder of Gilead Sciences, and has received grants from the National Institutes of Health, outside of the present work. All other authors declare no competing interests.

Data sharing

Gilead Sciences shares anonymised individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com. The full clinical trial protocol and statistical analysis plan are available in the appendix (p 49).

Acknowledgments

This study was sponsored by Gilead Sciences. We thank the ALLIANCE study participants, all participating investigators and support staff, and the Gilead Sciences study staff, including Caleb Marceau (HBV clinical virology support), Hui (Cindy) Liu (biostatistics support), John Flaherty, Frida Abramov (HBV scientific support), and Priyanka Arora (clinical pharmacology support). Writing assistance was provided by Jennifer King and Anne Errichelli (Aspire Scientific Limited) on behalf of Gilead Sciences.

References

1 Platt L, French CE, McGowan CR, et al. Prevalence and burden of HBV co-infection among people living with HIV: a global systematic review and meta-analysis. *J Viral Hepat* 2020; **27:** 294–315.
2 Singh KP, Crane M, Audsley J, Avihingsanon A, Sasadeusz J, Lewin SR. HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment. *AIDS* 2017; **31:** 2035–52.
3 Vinikoor MJ, Sinkala E, Chilengi R, et al. Impact of antiretroviral therapy on liver fibrosis among human immunodeficiency virus-infected adults with and without HBV coinfection in Zambia. *Clin Infect Dis* 2017; **64:** 1343–49.
4 Cheng Z, Lin P, Cheng N. HBV/HIV coinfection: impact on the development and clinical treatment of liver diseases. *Front Med* 2021; **8:** 713981.
5 Boyd A, Dezanet LNC, Lacombe K. Functional cure of hepatitis B virus infection in individuals with HIV-coinfection: a literature review. *Viruses* 2021; **13:** 1341.
6 WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. July 16, 2021. https://www.who.int/publications/i/item/9789240031593 (accessed March 30, 2022).
7 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv (accessed June 28, 2022).
8 Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; **1:** 196–206.
9 Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; **1:** 185–95.
10 Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008; **359:** 2442–55.
11 Di Perri G. Tenofovir alafenamide (TAF) clinical pharmacology. *Infez Med* 2021; **29:** 526–29.
12 Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr* 2016; **73:** 294–98.
13 Benhamou Y, Fleury H, Trimoulet P, et al. Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology* 2006; **43:** 548–55.

14 Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017; **390:** 2063–72.

15 Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017; **390:** 2073–82.

16 Surial B, Béguelin C, Chave JP, et al. Brief report: Switching from TDF to TAF in HIV/HBV-coinfected individuals with renal dysfunction-a prospective cohort study. *J Acquir Immune Defic Syndr* 2020; **85:** 227–32.

17 Sarowar A, Coffin CS, Fung S, et al. Brief report: effect of antiretroviral switch from tenofovir disoproxil fumarate to tenofovir alafenamide on alanine aminotransferase, lipid profiles, and renal function in HIV/HBV-coinfected individuals in a nationwide Canadian study. *J Acquir Immune Defic Syndr* 2022; **91:** 368–72.

18 Rockstroh J, Sax PE, Daar E, et al. High HBV and HIV suppression with treatment of HIV/HBV coinfection in B/F/TAF studies. Conference on Retroviruses and Opportunistic Infections; March 4–7, 2018. Boston, MA, USA (abstr 618).

19 Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; **6:** e355–63.

20 Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV* 2020; **7:** e389–400.

21 Clay PG, Yuet WC, Moecklinghoff CH, et al. A meta-analysis comparing 48-week treatment outcomes of single and multi-tablet antiretroviral regimens for the treatment of people living with HIV. *AIDS Res Ther* 2018; **15:** 17.

22 US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry. 2015. https://www.fda.gov/media/86284/download (accessed March 23, 2023).

23 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67:** 1560–99.

24 Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* 2018; **68:** 672–81.

25 Maurer W, Hothorn L, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In: Vollmar J, ed. Biometrie in der Chemisch-Pharmazeutischen Industrie. Stuttgart: Fischer Verlag, 1995: 3–18.

26 Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. *PLoS One* 2013; **8:** e68152.

27 van Bremen K, Hoffmann C, Mauss S, et al. Obstacles to HBV functional cure: late presentation in HIV and its impact on HBV seroconversion in HIV/HBV coinfection. *Liver Int* 2020; **40:** 2978–81.

28 Liaw YF. HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B. *Hepatol Int* 2009; **3:** 425–33.

29 Moini M, Fung S. HBsAg loss as a treatment endpoint for chronic HBV infection: HBV cure. *Viruses* 2022; **14:** 657.

30 Wong GL, Chan HL, Tse YK, et al. Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B. *J Hepatol* 2018; **69:** 793–802.