# Tenofovir alafenamide and tenofovir disoproxil fumarate reduce incidence of hepatocellular carcinoma in patients with chronic hepatitis B


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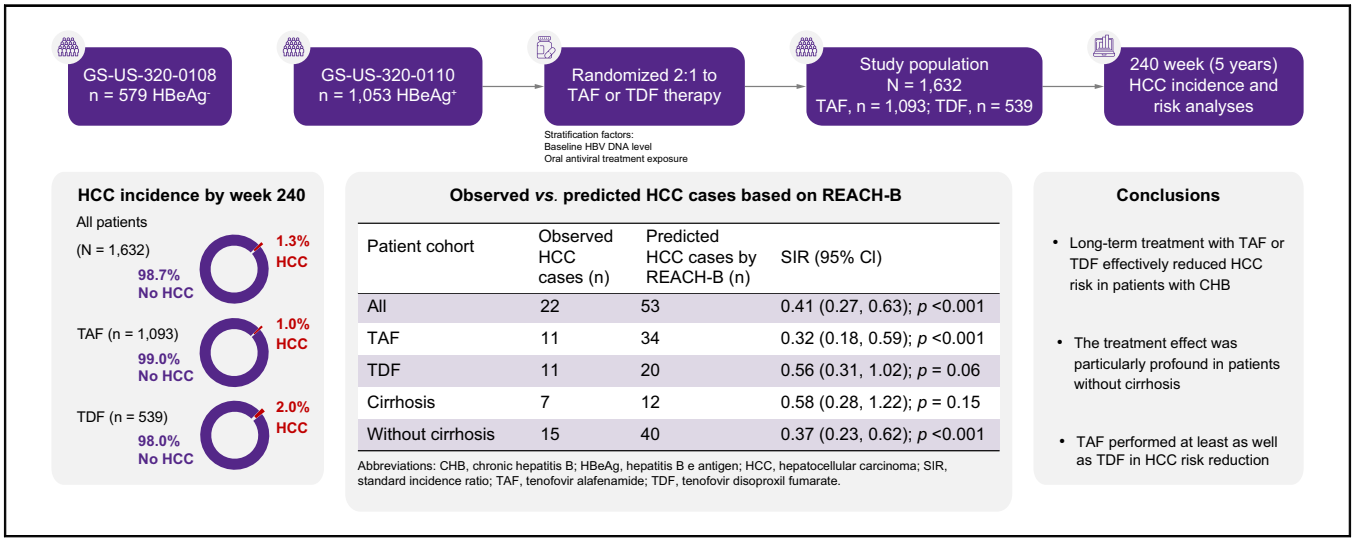
## Graphical abstract




## Highlights

- Three validated models (REACH-B; aMAP; mPAGE-B) were used to predict HCC risk in patients with CHB.
- Treatment with TAF or TDF was associated with a lower HCC risk than that predicted for untreated CHB.
- The difference in observed *vs.* predicted HCC risk was more pronounced with TAF than TDF treatment.
- In patients receiving TAF or TDF, most low-risk patients (by aMAP and mPAGE-B scoring) remained low risk at Week 240 (5 years).
- Antiviral TAF or TDF treatment reduced HCC risk in patients with CHB.

## Impact and implications

Despite the substantial impact of HCC on long-term outcomes of patients with CHB, the differential risk of HCC development among those receiving treatment with TAF *vs.* TDF has not been well elucidated. Using three validated risk prediction models, we found that TAF is at least as effective as TDF in reducing HCC risk in patients with CHB. While TDF is well-studied in the context of HCC risk reduction, our novel findings underscore the effectiveness of TAF as a treatment option for patients with CHB.

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Research article

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# Tenofovir alafenamide and tenofovir disoproxil fumarate reduce incidence of hepatocellular carcinoma in patients with chronic hepatitis B

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**Background & Aims:** Antiviral therapy may attenuate the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). We aimed to explore how tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) affect HCC risk in patients with CHB.

**Methods:** The REACH-B, aMAP, and mPAGE-B models were utilized to assess HCC risk in patients with CHB from two global randomized-controlled trials evaluating the impact of TAF *vs.* TDF treatment. Standard incidence ratios (SIRs) were calculated using data from the REACH-B model as a ratio of observed HCC cases in the TAF- or TDF-treated patients *vs.* predicted HCC cases for untreated historical controls. Proportions of treated patients shifting aMAP and mPAGE-B risk categories between baseline and Week 240 were calculated.

**Results:** Of the 1,632 patients (TAF, n = 1,093; TDF, n = 539) followed for up to 300 weeks, 22 HCC cases developed. Those receiving TAF had an SIR that was lower compared to the SIR of individuals receiving TDF: 0.32 ($p$ <0.001) *vs.* 0.56 ($p$ = 0.06). In the general study population, individuals without cirrhosis at baseline had an SIR that was lower compared to the SIR of individuals with cirrhosis at baseline: 0.37 ($p$ <0.001) *vs.* 0.58 ($p$ = 0.15). Of the patients at low risk of HCC at baseline, the majority (97%) remained low risk by mPAGE-B and aMAP scoring at Week 240. Among those at medium or high risk at baseline, substantial portions shifted to a lower risk category by Week 240 (mPAGE-B: 22% and 42%; aMAP: 39% and 63%, respectively).

**Conclusions:** This evaluation provides evidence that treatment with TAF or TDF can reduce HCC risk in patients with CHB, particularly in patients without cirrhosis.

**Impact and implications:** Despite the substantial impact of HCC on long-term outcomes of patients with CHB, the differential risk of HCC development among those receiving treatment with TAF *vs.* TDF has not been well elucidated. Using three validated risk prediction models, we found that TAF is at least as effective as TDF in reducing HCC risk in patients with CHB. While TDF is well-studied in the context of HCC risk reduction, our novel findings underscore the effectiveness of TAF as a treatment option for patients with CHB.

**Clinical trial numbers:** NCT01940341; NCT02836249; NCT01940471; NCT02836236.



Keywords: REACH-B; aMAP; mPAGE-B; incidence; antiviral therapy.

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## Introduction

In 2019, 820,000 deaths occurred due to hepatitis B virus (HBV) infection, mostly attributable to complications such as cirrhosis and hepatocellular carcinoma (HCC).[1] Patients with chronic hepatitis B (CHB) have an estimated lifetime risk of developing HCC ranging from 10–25%, with the risk particularly high for those with cirrhosis;[2] however, the multitude of HCC risk factors in patients with CHB highlights the importance of evaluating HCC risk in patients without cirrhosis as well, especially as early intervention can attenuate the progression to cirrhosis.[3,4]

The identification of treatments effective in reducing HCC risk is needed to promote the long-term health of patients with CHB. Antiviral therapy with nucleot(s)ide analogues (NAs) has been demonstrated to ameliorate risk factors predictive of HCC oncogenesis.[5–10] Further, real-world studies have demonstrated that long-term antiviral treatment is associated with a lower risk of HCC compared to no treatment.[11–14]

In 2016, tenofovir alafenamide (TAF), a novel NA prodrug of tenofovir, was approved for the treatment of CHB by the FDA, joining older NA agents entecavir (ETV) and tenofovir disoproxil fumarate (TDF) as recommended first-line therapies across major treatment guidelines, which have been updated since the approval of TAF.[15–17] TAF was designed to more efficiently deliver the active drug to hepatocytes compared to TDF,[18] and has demonstrated non-inferior efficacy and an improved renal and bone safety profile compared to TDF, as well as a high barrier to resistance.[5,7,8,15,17] Nonetheless, the lack of long-term data on treatment with TAF has left its impact on HCC risk reduction unclear. Two large global randomized-controlled trials exploring TAF treatment in patients with CHB have now reached the 5-year timepoint, providing the opportunity to evaluate the effect of TAF on HCC risk reduction.

The REACH-B, mPAGE-B and aMAP models are three validated prediction tools developed to predict HCC risk in patients with CHB. Each model uses a scoring system based on disease-specific variables and was developed in ethnically and clinically diverse patient populations.[19–21] Given the variability in HCC risk among patients with CHB, predictive models may be leveraged to model the potential risk of HCC if they did not receive treatment.[22]

The objective of this analysis was to explore how long-term treatment with TAF or TDF affects HCC risk in patients with CHB using data from global randomized-controlled trials and three different validated predictive models to assess risk. This study builds on previous work using the REACH-B model by increasing the robustness of this risk assessment through the use of two additional HCC risk models trained and validated in diverse patient populations.[20,21,23]

## Patients and methods

### Study design

This analysis was conducted using data from two phase III, randomized, double-blind (DB), active-controlled trials: GS-US-320-0108 (Study 108) and GS-US-320-0110 (Study 110). Study 108 enrolled 579 hepatitis B e antigen (HBeAg)-negative patients from a global and Chinese cohort (NCT01940341 and NCT02836249, respectively), while Study 110 enrolled 1,053 HBeAg-positive patients from a global and Chinese cohort (NCT01940471 and NCT02836236, respectively). Within both trials, patients were randomized 2:1 to treatment with TAF or TDF, stratified by baseline HBV DNA level and oral antiviral treatment status (treatment-naïve *vs.* treatment-experienced). Included patients had HBV DNA levels ≥20,000 IU/ml, alanine aminotransferase (ALT) levels >60 IU/L for men or >38 IU/L for women, and an estimated glomerular filtration rate by Cockcroft-Gault ≥50 ml/min, with or without compensated cirrhosis. Patients were excluded if they had recent evidence or a history of HCC and if they were coinfected with HIV or hepatitis C or D viruses. More detailed information on the eligibility criteria from the clinical trials has been published previously.[7,8,24] Before enrollment and before any study procedures were carried out, written informed consent was obtained from all patients. The study was approved by the institutional review board or independent ethics committees at all participating sites, as well as the US FDA, and was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

In this analysis, data from both clinical trials were synthesized and used to calculate relevant outcomes. Each trial began with a DB treatment period with patients randomized to receive either 25 mg of TAF or 300 mg of TDF administered daily. The study was designed to randomize participants to a 96-week DB period followed by a 48-week open-label (OL) extension up to Week 144 during which patients in both the TAF and TDF groups crossed over to OL TAF 25 mg once daily at Week 96. Under Protocol Amendment 3 (as requested by the FDA), the crossover from the DB TAF or TDF treatment arm to open-label TAF was changed to Week 144.[25–28] Approximately half of patients, however, had already crossed over to OL TAF at Week 96; the remaining patients crossed over to OL TAF at Week 144. All patients were eligible to continue open-label TAF through Week 384 (*i.e.*, Year 8). In this analysis, patients were followed up for at least 240 weeks or until last visit.[29]

### Study procedures and evaluations

The primary efficacy endpoint was the achievement of HBV DNA <29 IU/ml at Week 48, with ALT normalization as a secondary endpoint. Adherence rate to the study medication was also captured as the number of drug tablets taken divided by the number of tablets prescribed and was calculated separately for the DB and OL phases of the study. Development of HCC was treated as a predefined adverse event.[7,8] Screening and diagnosis of HCC were conducted as per local standards of care. Serum alpha-fetoprotein testing was performed at the screening visit to rule out HCC prior to study entry. With the implementation of the protocol amendment extending study treatment, serial hepatic ultrasonography was conducted every 6 months from Week 96 through the end of study treatment in both studies.[29]

For this *post hoc* analysis, outcomes included the incidence ratios of HCC based on the observed HCC incidence and the incidence predicted by the REACH-B model, and the proportions of patients who shifted HCC risk categories from baseline to Week 240 using the aMAP and mPAGE-B models.

### Statistical analysis

Within the clinical trials, cumulative HCC incidence in each treatment group was compared using the Fisher's exact test. Cumulative incidence curves were plotted by the Kaplan-Meier method and compared using the log-rank test. A sensitivity analysis was conducted excluding patients who developed HCC prior to Week 24 to assess the robustness of the study results when patients with early HCC (*i.e.*, potentially preexisting) were removed. The percentage of patients with HBV DNA <29 IU/ml and ALT normalization (defined as ≤25 U/L for females and ≤35 U/L for males using the 2018 AASLD criteria)[16] assessed by

treatment group and HCC status was calculated and graphed. Adherence rates between treatment arms were compared using the two-sided Wilcoxon rank-sum test.

Univariate and multivariate Cox regression models were used to analyze the baseline and on-treatment factors predictive of HCC development. All variables with a $p$ value <0.15 in the univariate Cox regression model were included as candidates in the stepwise selection. In the stepwise selection, variables were entered into and removed from the model in a way that each forward selection step could be followed by one or more backward elimination steps, whereas a chi-square $p$ value from the score test of 0.05 was used as a cut-off for entering and staying in the model. In the end, the final multivariate model was fit by using all variables selected from the stepwise method. Individuals who did not develop HCC during the study were censored at their last study treatment date.

REACH-B, mPAGE-B and aMAP are all multivariate Cox regression models which utilize distinct model input variables and were developed in clinically and ethnically diverse patient populations (Table 1).[19–21] REACH-B was used to calculate the predicted incidence of HCC from baseline to the end of follow-up.[23] Standard incidence ratios (SIRs) were then calculated as a ratio of observed HCC cases over predicted HCC cases, with 95% CIs calculated by Poisson regression. Patients who dropped out were censored on their last date of study treatment; their exposure time was considered from baseline up to the time of censoring.

mPAGE-B and aMAP risk scores were calculated at baseline and up to Week 240 (Table S1; Table S2).[20,21] Shifts in mPAGE-B and aMAP risk categories between baseline and Week 240 were captured as proportions, calculated as the number of patients experiencing each shift divided by the total number of patients with no missing baseline or post-baseline risk scores. Patients who were missing any baseline or post-baseline risk scores were not included. This analysis was performed in the subgroup of patients who went on to develop HCC.

## Results

In total, 1,632 patients were randomized and treated in Studies 108 and 110. The 1,632 patients are comprised of two global studies (n = 1,298)[7,8] and the China cohort (n = 334).[24] One patient in Study 110 was missing aMAP and mPAGE-B records at baseline and was therefore excluded from the analyses. Overall, 155 patients (9.7%) had baseline cirrhosis (defined for this analysis as a FibroTest score of ≥0.75) (Table 2).[30] Patients were mostly male (65.1%), Asian (83.0%), and HBeAg-positive (63.7%).

When comparing baseline characteristics between those initially receiving TAF and those initially receiving TDF, median age was the only baseline characteristic which differed significantly (39 years *vs.* 40 years, respectively; $p$ = 0.02) (Table S3). Furthermore, median adherence rates of antiviral therapy during both the DB and OL phases of the study were similar between patients initially treated with TAF and patients initially treated with TDF (DB: 99.11 *vs.* 98.91, $p$ = 0.12; OL: 98.98 *vs.* 98.90, $p$ = 0.30).

A total of 22 HCC cases occurred during the study, representing a cumulative incidence of 1.3% (1.0% in the TAF group *vs.* 2.0% in the TDF group). The difference in cumulative incidence of HCC was not statistically significant between the two treatment groups ($p$ = 0.08; Fig. 1). Based on the univariate Cox regression model, the following baseline variables were significantly associated with the risk of HCC development: higher baseline Fibrotest score ($p$ <0.001), older age ($p$ <0.001), lower platelets ($p$ <0.001), lower albumin ($p$ <0.001), hypertension ($p$ <0.001), history of alcohol intake ($p$ <0.001), diabetes ($p$ <0.001), cirrhosis ($p$ <0.001), higher BMI ($p$ = 0.02), male sex ($p$ = 0.02), and alcohol intake at baseline ($p$ <0.05) (Table S4). A multivariate model using both baseline and on-treatment predictors found male sex (hazard ratio [HR] 9.46; 95% CI 1.22, 73.07; $p$ = 0.03), increasing age (HR 1.08; 95% CI 1.02, 1.14; $p$ = 0.007), hypertension (HR 4.80; 95% CI 1.79, 12.91; $p$ = 0.002), decreasing baseline platelets (HR 0.98; 95% CI 0.97, 0.99; $p$ <0.001), alcohol intake history (HR 4.58; 95% CI 1.59, 13.21; $p$ = 0.005), and lack of ALT normalization at Week 48 (HR 2.94; 95% CI 1.12, 7.67; $p$ = 0.03) to be predictive of HCC development (Table 3). In the sensitivity analysis excluding patients who developed HCC prior to Week 24, a total of 21 HCC cases occurred. The probability of developing HCC was not statistically different between the two treatment groups (1.0% in the TAF group *vs.* 1.9% in the TDF group; $p$ = 0.14; Fig. S1).

Within the REACH-B analysis, the SIR calculated at the maximum observation time for each patient was 0.41 (95% CI 0.27, 0.63; $p$ <0.001; Fig. 2A), indicating that the observed HCC incidence was 59% lower than expected when compared to the incidence predicted by the REACH-B model. Patients receiving TAF had a numerically lower SIR than those receiving TDF: 0.32 (95% CI 0.18, 0.59; $p$ <0.001; Fig. 2B) *vs.* 0.56 (95% CI 0.31, 1.02; $p$ = 0.06; Fig. 2C), respectively, indicating HCC incidences that were 68% and 44% lower than those predicted by REACH-B, respectively. The SIRs for patients with and without cirrhosis at baseline were 0.58 (95% CI 0.28, 1.22; $p$ = 0.15; Fig. 2D) and 0.37 (95% CI 0.23, 0.62; $p$ <0.001; Fig. 2E), respectively, indicating an HCC incidence 42% and 63% lower than that predicted by REACH-B, respectively.

The proportion of patients with virologic response (HBV DNA <29 IU/ml) over 240 weeks was similar across treatment groups and by HCC development (Fig. S2). However, the rate of ALT normalization was numerically much lower in the patients receiving TDF who developed HCC than in those receiving TAF who developed HCC and those who did not develop HCC (Fig. 3).

**Table 1. Predictor variables and population characteristics for REACH-B, mPAGE-B, and aMAP.**

| | Predictor variables | Time horizon | Source populations for training and validation sets |
|---|---|---|---|
| REACH-B[19] | Baseline age, sex, ALT levels, HBeAg status, and HBV DNA levels | Ten years | Asian patients with CHB not on antiviral treatment; included those without cirrhosis for training and a mix of those with and without cirrhosis for validation |
| mPAGE-B[20] | Baseline age, sex, serum albumin levels, and platelet levels | Five years | Asian patients with CHB on antiviral treatment; included those with and without cirrhosis for both training and validation |
| aMAP[21] | Baseline age, sex, ALBI score, and platelet levels | Five years | Asian and Caucasian patients with CHB, hepatitis C, or non-viral hepatitis on antiviral treatment; included those with and without cirrhosis for both training and validation |

ALBI, albumin-bilirubin; ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen.

**Table 2. Baseline characteristics in patients with HCC *vs.* without HCC.**

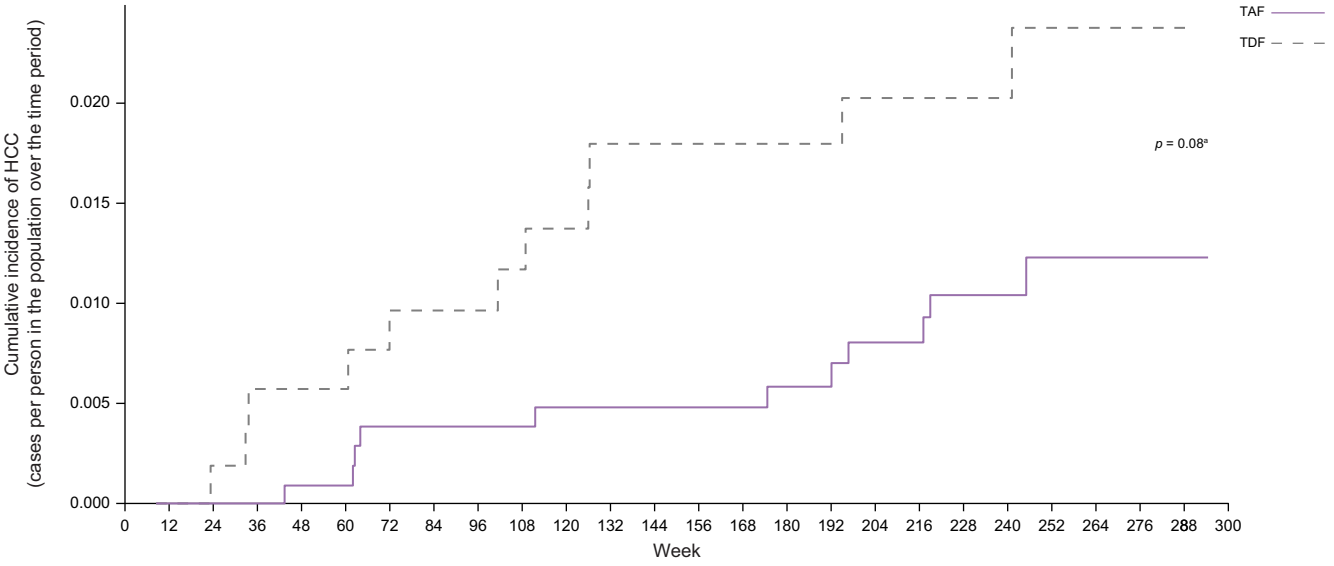
| | Total (N = 1,632) | HCC (n = 22) | No HCC (n = 1,610) |
|---|---|---|---|
| Median age, years (Q1, Q3) | 39 (31, 49) | 53 (48, 59) | 39 (31, 48) |
| Male, n (%) | 1,063 (65.1%) | 20 (90.9%) | 1,043 (64.8%) |
| Asian, n (%) | 1,354 (83.0%) | 21 (95.5%) | 1,333 (82.8%) |
| HBeAg-negative, n (%) | 593 (36.3%) | 11 (50.0%) | 582 (36.1%) |
| Median HBV DNA, $log_{10}$ IU/ml (Q1, Q3) | 7.3 (5.6, 8.2) | 6.4 (5.6, 7.1) | 7.3 (5.6, 8.2) |
| Median ALT, U/L (Q1, Q3) | 82 (55, 131) | 70 (54, 100) | 82 (55, 132) |
| HBV genotype, n (%) | | | |
| A | 85 (5.2%) | 0 | 85 (5.3%) |
| B | 371 (22.7%) | 2 (9.1%) | 369 (22.9%) |
| C | 823 (50.4%) | 17 (77.3%) | 806 (50.1%) |
| D | 331 (20.3%) | 3 (13.6%) | 328 (20.4%) |
| Other | 19 (1.2%) | 0 | 19 (1.2%) |
| Missing | 3 (0.2%) | 0 | 3 (0.2%) |
| Median total bilirubin, μmol/L (Q1, Q3) | 10.3 (8.6, 15.4) | 13.7 (8.6, 15.4) | 10.3 (8.6, 15.4) |
| Median albumin, g/L (Q1, Q3) | 43 (41, 45) | 40 (37, 42) | 43 (41, 45) |
| Diabetes mellitus | | | |
| Yes, n (%) | 112 (6.9%) | 6 (27.3%) | 106 (6.6%) |
| No, n (%) | 1,520 (93.1%) | 16 (72.7%) | 1,504 (93.4%) |
| Median platelet count, $10^3$/μl (Q1, Q3) | 190 (156, 228) | 143 (95, 180) | 191 (157, 229) |
| Median FibroTest score (Q1, Q3) | 0.3 (0.2, 0.5) | 0.6 (0.5, 0.8) | 0.3 (0.2, 0.5) |
| Cirrhosis, n (%) | 155 (9.7%) | 7 (31.8%) | 148 (9.4%) |
| Median eGFR, ml/min (Q1, Q3) | 107.4 (91.8, 126.0) | 110.5 (85.2, 117.0) | 107.4 (91.8, 126.0) |
| Treatment during DB period | | | |
| TAF | 1,093 (67.0%) | 11 (50.0%) | 1,082 (67.2%) |
| TDF | 539 (33.0%) | 11 (50.0%) | 528 (32.8%) |
| Median BMI, $kg/m^2$ (Q1, Q3) | 23.7 (21.2, 26.4) | 25.5 (22.7, 28.0) | 23.7 (21.2, 26.4) |
| HBV risk factors[a] | | | |
| Contaminated needle or IV drug, n (%) | 45 (2.8%) | 0 (0%) | 45 (2.8%) |
| Blood product transfusion, n (%) | 14 (0.9%) | 0 (0%) | 14 (0.9%) |
| Contact with infected individual, n (%) | 86 (5.3%) | 1 (4.5%) | 85 (5.3%) |
| Vertical transmission, n (%) | 366 (22.4%) | 4 (18.2%) | 362 (22.5%) |
| Surgery/operation, n (%) | 46 (2.8%) | 1 (4.5%) | 45 (2.8%) |
| Unknown, n (%) | 1,064 (65.2%) | 15 (68.2%) | 1,049 (65.2%) |
| Other, n (%) | 49 (3.0%) | 1 (4.5%) | 48 (3.0%) |
| Median serum creatinine, mg/dl (Q1, Q3) | 0.83 (0.69, 0.93) | 0.84 (0.75, 0.91) | 0.83 (0.69, 0.93) |
| Median AST, U/L (Q1, Q3) | 52 (37, 84) | 56 (49, 79) | 52 (37, 84) |
| Median INR (Q1, Q3) | 1.0 (1.0, 1.1) | 1.0 (1.0, 1.1) | 1.0 (1.0, 1.1) |
| Hypertension | | | |
| Yes, n (%) | 191 (11.7%) | 9 (40.9%) | 182 (11.3%) |
| No, n (%) | 1,441 (88.3%) | 13 (59.1%) | 1,428 (88.7%) |
| Hyperlipidemia | | | |
| Yes, n (%) | 126 (7.7%) | 4 (18.2%) | 122 (7.6%) |
| No, n (%) | 1,506 (92.3%) | 18 (81.8%) | 1,488 (92.4%) |
| Cardiovascular disease | | | |
| Yes, n (%) | 48 (2.9%) | 1 (4.5%) | 47 (2.9%) |
| No, n (%) | 1,584 (97.1%) | 21 (95.5%) | 1,563 (97.1%) |
| Alcohol intake history | | | |
| Yes, n (%) | 507 (31.1%) | 15 (68.2%) | 492 (30.6%) |
| No, n (%) | 1,125 (68.9%) | 7 (31.8%) | 1,118 (69.4%) |
| Baseline alcohol intake status | | | |
| Yes, n (%) | 268 (16.4%) | 7 (31.8%) | 261 (16.2%) |
| No, n (%) | 1,364 (83.6%) | 15 (68.2%) | 1,349 (83.8%) |

Cirrhosis was defined as a FibroTest score of ≥0.75.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, double-blind; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IV, intravenous; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a] A patient may fit more than one HBV risk factor category; therefore, percentages add to more than 100%.

For both the mPAGE-B and aMAP models, most patients who were at low or medium risk at baseline either remained in those risk categories or shifted to a lower risk group over the 240 weeks of treatment. Of those who were high risk at baseline, many remained at high risk, but a substantial portion shifted to medium risk by Week 240 (Table 4). A decrease from baseline in mean aMAP and mPAGE-B scores was seen at Week 144 and Week 240 for both treatment groups (Table S5). Of the patients who ultimately developed HCC, the majority remained in the medium- and high-risk aMAP and mPAGE-B groups from baseline to Week 240 (Fig. S3).

## Discussion

The results of this analysis demonstrate that treatment with either TAF or TDF in patients with CHB likely provides a benefit in reducing HCC risk. Using the REACH-B analysis, a low and statistically significant SIR was demonstrated overall, indicating




| | TAF: n = 1,093 | TDF: n = 539 |
|---|---|---|
| Cumulative HCC incidence (%) | 1.0 | 2.0 |
| HCC cases, n[b] | 11 | 11 |
| DB phase, n (%)[c] | 5 (0.5) | 6 (1.1) |
| OL TAF phase, n (%) | 6 (0.5) | 5 (0.7) |
| Median time to HCC onset, wk (Q1, Q3)[d] | 173 (56, 217) | 96 (26, 122) |

**Fig. 1. Observed cumulative HCC incidence in patients who initially received TAF or TDF.** Log-rank test; level of significance: $p = 0.08$. [a]The $p$ value was calculated using the log-rank test [b]$p = 0.11$ (two-sided Fisher's exact test) [c]$p = 0.19$ (two-sided Fisher's exact test) [d]$p = 0.19$ (two-sided Wilcoxon rank-sum test). DB, double-blind; HCC, hepatocellular carcinoma; OL, open-label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**Table 3. Multivariate cox regression model of baseline and on-treatment predictors of HCC.**

| Predictor | Hazard ratio | 95% CI | *p* value[a] |
|---|---|---|---|
| Age (years) | 1.08 | (1.02, 1.14) | 0.007 |
| Sex (male *vs.* female) | 9.46 | (1.22, 73.07) | 0.03 |
| Hypertension (yes *vs.* no) | 4.80 | (1.79, 12.91) | 0.002 |
| Baseline platelets (x$10^3$/μl) | 0.98 | (0.97, 0.99) | <0.001 |
| Alcohol intake history (yes *vs.* no) | 4.58 | (1.59, 13.21) | 0.005 |
| ALT normalization status at Week 48 (no *vs.* yes) | 2.94 | (1.12, 7.67) | 0.03 |

ALT, alanine aminotransferase; HCC, hepatocellular carcinoma.
[a] *p* values were calculated using the chi-square test.

a lower observed HCC incidence than would be expected had patients been left untreated. The group initially treated with TAF maintained a lower HCC incidence across study timepoints compared to the group initially treated with TDF, even within the sensitivity analysis excluding patients who developed HCC before Week 24. Therefore, our results suggest that TAF is at least as effective as TDF in reducing the risk of HCC, and given the improved renal and bone safety profile of TAF compared to TDF, TAF may be the preferred treatment between the two.[5,7,8,31] Both the aMAP and mPAGE-B predictive models for HCC further corroborated that antiviral treatment with TAF or TDF reduces HCC risk, with both models showing a substantial shift in medium- and high-risk baseline groups to a lower risk group following 240 weeks of treatment. All three validated models supported the value of TAF and TDF in reducing HCC risk, highlighting the robustness of this finding.

The results of our analysis reaffirm that TDF therapy is associated with HCC risk reduction and provide long-term evidence for TAF as an effective treatment option, in terms of HCC risk reduction, in patients with CHB.[11,12,23,32] Although initial treatment with TAF produced a highly significant SIR while initial treatment with TDF did not produce a significant SIR, the rollover of TDF-treated patients into OL TAF treatment at Weeks 96 and 144 does not allow for a definitive, direct comparison of the two agents. Moreover, TAF was associated with a higher ALT normalization rate than TDF in our study, which has been reported previously.[5,31] ALT normalization is an established predictor of HCC development,[9] so differences in this outcome between treatment groups

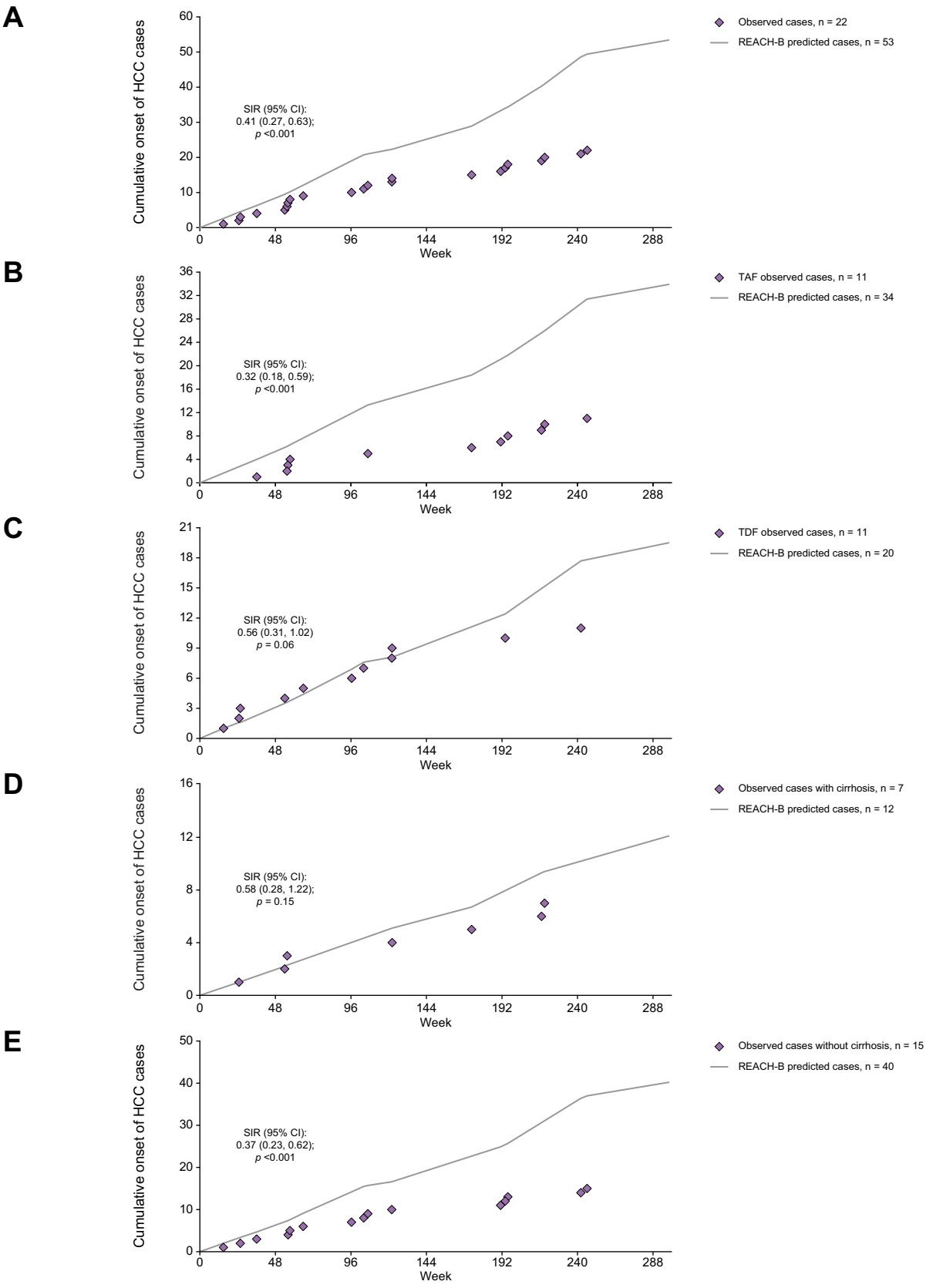



**Fig. 2. Observed HCC cases through Week 240 *vs.* predicted HCC cases based on REACH-B.** (A) All observed HCC cases (95% CIs calculated by Poisson regression for all panels); Level of significance: $p$ <0.001 (Wald test). (B) In patients initially receiving TAF; Level of significance: $p$ <0.001 (Wald test). (C) In patients initially receiving TDF; Level of significance: $p$ = 0.06 (Wald test). (D) In patients with cirrhosis; Level of significance: $p$ = 0.15 (Wald test). (E) In patients without cirrhosis; Level of significance: $p$ <0.001 (Wald test). HCC, hepatocellular carcinoma; SIR, standard incidence ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

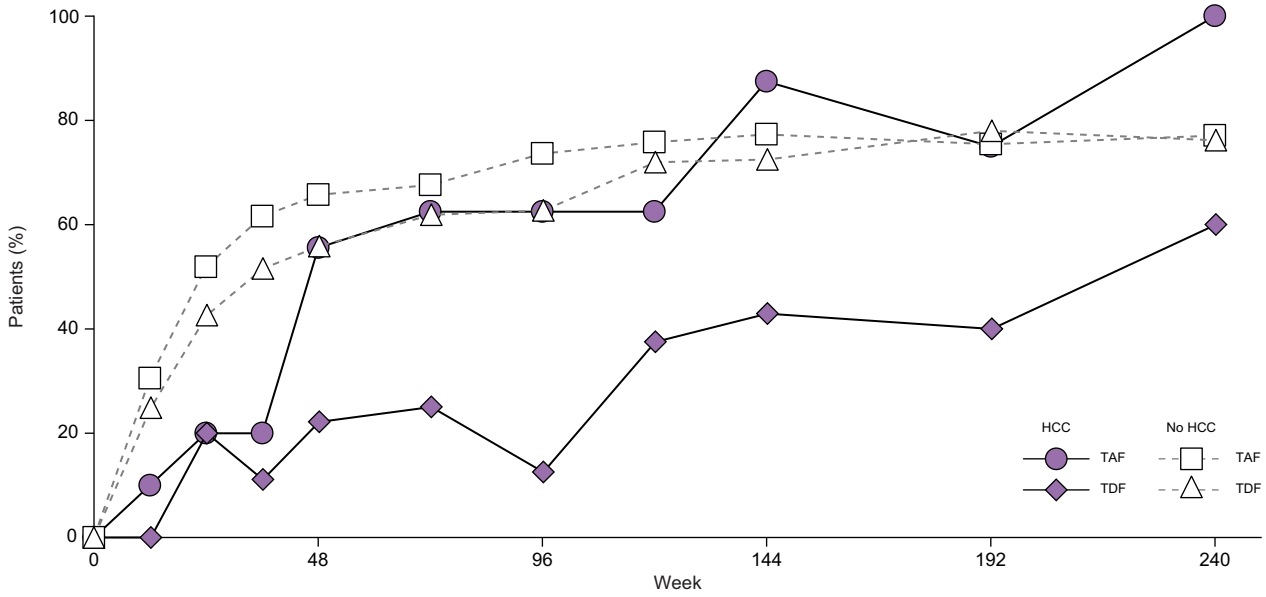



**Fig. 3. ALT normalization over 240 weeks.** ALT normalization is defined using the 2018 AASLD criteria (25 U/L for females and 35 U/L for males). ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**Table 4. aMAP and mPAGE-B risk level shifts at Week 240 by baseline risk level.**

| | Baseline | | | | | |
|---|---|---|---|---|---|---|
| | Low risk | | Medium risk | | High risk | |
| (%)[a] | aMAP, n = 1,033 | mPAGE-B, n = 901 | aMAP, n = 508 | mPAGE-B, n = 588 | aMAP, n = 90 | mPAGE-B, n = 142 |
| **Week 240** | | | | | | |
| Low risk | 97.0% | 97.5% | 39.2% | 21.6% | 4.5% | 0.9% |
| Medium risk | 3.0% | 2.5% | 60.6% | 77.4% | 58.2% | 40.7% |
| High risk | 0% | 0% | 0.2% | 1.0% | 37.3% | 58.3% |
| Missing[b] | 260 | 233 | 87 | 101 | 23 | 34 |

Low risk was defined as an mPAGE-B score ≤8 or an aMAP score <50. Medium risk was defined as an mPAGE-B score ≥9 but ≤12 or an aMAP score ≥50 but ≤60. High risk was defined as an mPAGE-B score of ≥13 or an aMAP score >60.
[a] The denominator for the percentage was the number of patients with non-missing values at both baseline and each post-baseline visit for each baseline category.
[b] The total number of patients with missing data for either the baseline or any post-baseline category.

may partly explain the differences in SIR between TAF and TDF. Furthermore, while not statistically significant, there was a numerical difference in cumulative HCC incidence (1.0% *vs.* 2.0%) and in the median time to the HCC onset (173 weeks *vs.* 96 weeks) between the groups initially treated with TAF and TDF.

Our findings from the cirrhosis subgroup analysis using REACH-B suggest a particular benefit of treatment with TAF or TDF in non-cirrhotic patients, who had a low SIR that was highly significant ($p$ <0.001); for the subgroup of patients with cirrhosis, the SIR was low but did not reach statistical significance ($p$ = 0.15). This difference may be due in part to the small sample size of the group with cirrhosis, use of the FibroTest score to categorize patients at baseline in the absence of liver biopsy, and the fact that REACH-B may underestimate the predicted cases of HCC in patients with cirrhosis as it was developed in patients without cirrhosis. Nevertheless, the highly significant result in the non-cirrhotic subgroup suggests that earlier antiviral treatment in non-cirrhotic patients may be particularly beneficial. This finding is especially important considering the emphasis that has historically been placed on clinical intervention for later stage patients with advanced fibrosis or established cirrhosis.[16]

Evidence on the relationship between HBV integrations, timing of antiviral treatment, and HCC oncogenesis further substantiates the benefit of providing treatment for patients with CHB without cirrhosis for whom treatment is not currently indicated. Péneau *et al.* demonstrated that the number of HBV integrations into the host genome is associated with viral replication in non-tumor liver tissue and poor prognosis in tumors, and thus may be an important aspect of HCC oncogenesis.[33] Consequently, more intense viral suppression, particularly when achieved earlier in the disease course with antiviral therapy, may limit the number of HBV integrations and thereby mitigate the risk of HCC development.[34,35] As newer research highlights a potential advantage to antiviral treatment in the earlier stages of CHB infection, it is important to ensure that treatment guidelines continue to evolve as well, reflecting the treatment course likely to provide the greatest long-term benefit to patients.

A key strength of this study is its use of data from well-designed global randomized-controlled trials with a large sample size (>1,600 patients) and long follow-up time (5 years), allowing for adequate statistical power to analyze the

relationship between TAF and HCC incidence. Other key strengths of this analysis are the consistent findings across three validated prediction models, which were trained and validated in diverse patient populations against a global clinical trial cohort with diverse clinical and demographic characteristics. The mPAGE-B and REACH-B models were validated in Asian patients specifically, and aMAP was validated in both Asian and Caucasian patients, highlighting the particular relevance of the models for patients in this study, the majority of whom were of Asian descent.

This study is limited by the smaller sample sizes of certain analyses, restricting statistical power and the ability to detect an effect, particularly given the relatively limited number of HCC cases which developed during this study. Furthermore, HCC was not a predefined endpoint of the study, but rather a predefined adverse event, and thus was not systematically screened for. However, with the protocol amendment to extend treatment, serial (every 6 months) hepatic ultrasonography was implemented in all patients during the OL period (on/after Week 96), which contributed to heightened surveillance for HCC development. While we report numerically lower HCC risk in patients who received TAF compared to those receiving TDF, the lack of a direct comparison between these treatment groups means that further research comparing these treatments is warranted, especially considering the potential role of ALT normalization in HCC risk.

Results from this comprehensive evaluation of data from global phase III randomized trials provide evidence that treatment with TAF or TDF is effective in reducing HCC risk in patients with CHB. The effect on HCC risk was particularly profound in patients without cirrhosis. Our results demonstrate that TAF performs at least as well as TDF in HCC risk reduction. As TDF is well-studied in this context, our findings highlight the value of TAF as an effective treatment option for patients with CHB.

## Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; DB, double-blind; ETV, entecavir; HBeAg, Hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, nucleot(s)ide analogue; OL, open-label; SIRs, standard incidence ratios; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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## Conflict of interest

AJH: There are no financial disclosures for this author. CP: Has served as a speaker for Gilead and received research grants from Gilead. DRS: There are no financial disclosures for this author. EG: Member of scientific advisory boards for AbbVie, Abbott Diagnostics, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Enanta, Gilead Sciences, GSK, Intellia, Janssen, Merck, Novartis, Genentech-Roche, Vaccitech, Ventorx, Vir Bio and Virion Therapeutics. FA: Gilead Sciences employee and stock ownership. HJ: Received grants from: AbbVie, Gilead Sciences, GSK, Janssen, Roche, Vir Biotechnology Inc. Is a consultant for: Aligos, Antios, Arbutus, Eiger, Gilead Sciences, GSK, Janssen, Merck, Roche, VBI Vaccines, Vir Biotechnology Inc., Viroclinics. HC: Has served as an advisor for Aligos, Arbutus, Hepion, Janssen, Gilead, GSK, Roche, Vaccitech, Vir Biotechnology, Virion Therapeutic, and as a speaker for Gilead, Roche, and Mylan. HW: Employee and stockholder for Gilead. JF: Employee and stockholder for Gilead. JK: Consultant for Abbvie, Abbott, Gilead Sciences, Roche and Sysmex. On speaker's bureaus for Abbvie, Bristol-Myers Squibb, Gilead Sciences, and Fujirebio. JH: Has received consulting fee from AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, Roche and received grants from Bristol Myers Squibb and Johnson & Johnson. KA: Aligos, Assembly, Bluejay, BMS, BI, DrugFarm, Gilead, GSK, Janssen, Merck, Roche, Sobi. LJY: Employee of Gilead Sciences and own stock in Gilead Sciences. MB: Has served as an advisor for Abbvie, Arbutus, Assembly, Janssen, Gilead, GSK, Roche, and as a speaker for Gilead and Abbvie. MBr: Speakers Bureau for AbbVie and Gilead. Advisory for AbbVie, Gilead, Janssen, Roche, EISAI-MSD. NI: There are no financial disclosures for this author. QN: Has served as a consultant for BMS, GSK, MSD, and Novartis. SHA: Has acted as advisors and investigator for Gilead, Janssen, AbbVie, Roche, Assembly Biosciences, Arbutus, Brii, Vaccitech, GSK, Inovio, Aligos, Vir Biotechnology, SL Vaxigen, GeneOne Life Science, GreenCross, Yuhan, Samil and Ildong. SF: Has received research support from Gilead. Consultant for Abbvie, Assembly Bio, Janssen, and Gilead. Teacher and speaking for Abbvie and Gilead. SGL: Speakers bureau for Gilead, Janssen, Roche, Sysmex. Advisory board for Gilead, Abbott, Roche, GSK, Janssen, Sysmex, Springbank, Arbutus, Assembly, Grifols, Eisai. Research support from Gilead, Abbott, Roche, Sysmex, Fibronostics, Merck. TTC: There are no financial disclosures for this author. WLC: Member of Advisory Board for Gilead, AbbVie, BMS, Roche, and PharmaEssentia. Speaker for Gilead, AbbVie, BMS, Roche, PharmaEssentia. WKS: Received speaker's fees from Mylan and AstraZeneca, is an advisory board member of Abbott, is an advisory board member and received speaker's fees from AbbVie, and is an advisory board member, received speaker's fees and research funding from Gilead Sciences. YSL: Advisor/consultant/speaker for AbbVie, Assembly Biosciences, Bayer Healthcare, GlaxoSmithKline, Gilead Sciences, Janssen, Olix Pharmaceuticals, Roche, Vaccitech, and Vir Biotechnology; and received grant/research support from Gilead Sciences.

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## Authors' contributions

Substantial contributions to study conception and design: YSL, HLC, SHA, WKS, QN, KA, HLJ, CQP, WLC, NI, SF, DS, MB, AJH, TTC, SGL, FA, JF, HW, LJY, JHK, EG, JH, MB, substantial contributions to analysis and interpretation of the data: YSL, HLC, SHA, WKS, QN, KA, HLJ, CQP, WLC, NI, SF, DS, MB, AJH, TTC, SGL, FA, JF, HW, LJY, JHK, EG, JH, MB, drafting the article or revising it critically for important intellectual content: YSL, HLC, SHA, WKS, QN, KA, HLJ, CQP, WLC, NI, SF, DS, MB, AJH, TTC, SGL, FA, JF, HW, LJY, JHK, EG, JH, MB, final approval of the version of the article to be published: YSL, HLC, SHA, WKS, QN, KA, HLJ, CQP, WLC, NI, SF, DS, MB, AJH, TTC, SGL, FA, JF, LJY, HW, JHK, EG, JH, MB.

## Data availability statement

Gilead Sciences, Inc., shares anonymized 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.

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## Supplementary data

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*Author names in bold designate shared co-first authorship*


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