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Summary

Background: Chronic hepatitis B virus (HBV) infection results in a high risk of cirrhosis and its complications, cirrhosis decompensation (DC), hepatocellular carcinoma (HCC), liver transplantation (LT), death or any of these outcomes (composite endpoint (CE)). Nucleos(t)idic analogues (NUCs) such as tenofovir (TDF) or entecavir (ETV) are associated with a reduction in these complications. The aim of this study was to compare the impact of TDF and ETV on these outcomes in patients treated for HBV included in the prospective Hepather cohort.

Methods: All patients with HBV infection who had received TDF or ETV for more than 6 months at or after entry in the ANRS CO22 cohort were selected. Patients with HDV and HCV coinfection and prior liver event were excluded. Incidence rates of events were compared using inverse probability of treatment weighting (IPW).

Results: The cohort included 1800 patients (986 TDF and 814 ETV patients). Median follow-up was 4.2 years. The incidences of HCC, DC, LT, ACD, LRD and CE were not different between TDF- (1.8 (0.9;3.2), 0.6 (0.2 ;1.6), 0.2 (0.0;0.8), 1.7 (0.8;3.0), 0.8 (0.2,1.8), and 4.1 (3.0;5.4) per 1000 person-years) and ETV-treated patients (1.6 (0.7;3.0), 0.7 (0.2 ;1.8), 0.2 (0.0;1.0), 3.0 (1.7,4.8), 0.5 (0.1;1.5) and 5.0 (3.3;7.2)) per 1000 person-years, respectively.

Conclusion: The risk of liver-related events or death were not different between tenofovir- and entecavir-treated patients in this large prospective cohort of predominantly no cirrhotic French patients.

Trial registration number: NCT019553458

Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer in the world, representing approximately 7% of all cancer diagnoses or about 850,000 new cases each year (the annual incidence of liver cancer is very close to the number of related deaths per year), and the second leading cause of cancer death (1-3). The incidence is low in Northern Europe, but is higher in Subsaharan Africa or Asia where there is a high incidence of both hepatotropic viruses and mycotoxin exposure. HCC is a complication of cirrhosis in more than 80% of cases, and predominates in men, with a male-to-female ratio of 3. The prevalence of HCC is on the rise due to an increase in its worldwide incidence, improved techniques and diagnostic criteria, the consequences of hepatitis B (HBV) and hepatitis C virus (HCV) infection, and the obesity epidemic generating metabolic non alcoholic fatty liver. Thus, the incidence of HCC is expected to increase in the next 20 years (3).

Cirrhosis is the main risk factor of HCC and about 30 to 35% of patients with cirrhosis develop HCC with an annual risk of 1 to 8% depending on the etiology of cirrhosis (4-8). The consensus recommendations in patients with cirrhosis include a biannual liver ultrasound for the early detection of HCC because the smaller the HCC, the more effective the treatment (4-8).

The association between HBV infection and HCC has been established based on the increased incidence of HCC in areas where the virus is endemic (HBsAg-positive patients or those with anti-HBc antibodies more frequently have HCC than those without viral markers in case-control studies) with a relative risk of 10 to 100 in endemic areas (9). Prospective human studies and animal models of hepadna virus infections (particularly the woodchuck HBV virus) (10) have confirmed the association between HBV infection and HCC. Finally, the incidence of HBV infection has significantly decreased as a result of routine vaccination policies for newborns and adolescents, associated with a decrease in HBV-related morbidity and mortality, mainly cirrhosis and HCC, especially in highly endemic zones (Hong Kong, Singapore, Taiwan, Alaska then China) (11-14). Moreover, the causal link between viral levels, cirrhosis and HCC was clearly established by the Taiwan "Reveal" study (parallel increase in HCC and elevated HBV DNA titres) and by the reduction in the incidence of HCC

following effective viral suppression with either interferon-α or nucleos(t)idic analogues (15). The more severe the underlying liver disease, the greater benefit of viral suppression (5-7,16), while there is a less marked benefit when a resistance mutation develops (17). The benefit of these treatments is significant histological improvement, resulting in a reduction of fibrosis over time or even a reversion of cirrhosis, as reported for other viral cirrhoses (18).

Although nucleos(t)idic analogues have been clearly associated with a reduction in complications (16-17, 19-25), recent meta-analyses of Asian cohort studies suggest that tenofovir could be associated with a reduced risk of HCC as well as a lower risk of decompensated cirrhosis or liver-related deaths compared to entecavir (26-33). The aim of our study was to prospectively compare the results of Tenofovir and Entecavir on five outcomes (HCC, decompensated cirrhosis, liver transplantation, all-causes of death and liver-related death) as well as a composite endpoint combining any of these outcomes, in patients with chronic HBV infection from the Hepather cohort treated with nucleos(t)idic analogues.

Methods

Study design and participants

The ANRS CO22 Hepather cohort «Therapeutic option for hepatitis B and C: a French cohort», is a national, multicenter, observational cohort study with prospectively collected data of patients with hepatitis B or C virus infection that has been previously described (see reference 34 for a complete description). The main objectives of this study are to quantify the clinical efficacy and safety of new hepatitis treatments in real-life. Between August 6th, 2012 and December 31st, 2015, 14,389 HCV-positive patients and 6249 HBV-infected patients were enrolled to be followed up for a median of 7 years. Detailed demographics, clinical (including fibrosis staging and history of past treatment) and biological data were collected during the inclusion visit on an electronic case-report form. Follow-up included systematic visits (once a year) and spontaneous reports for particular events on specific data forms (e.g. deaths, HCC, decompensated cirrhosis and the onset of therapy). The study was observational and the choice of the NUCs regimen, treatment timing, and screening for HCC or the progression of fibrosis was left up to the physician, but followed national French recommendations based on European Association for the Study of the Liver (EASL)

guidelines (5). Written informed consent was obtained from each patient before enrolment. The protocol was performed in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "CPP Ile de France 3" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

We selected all patients with chronic hepatitis B who were treated with TDF or ETV for more than 6 months at entry or after entry to compare the risk of the occurrence of HCC, other liver-related events and death between these two treatments.

Cirrhosis decompensation corresponded to the occurrence of non-carcinomatous cirrhosis complications, namely ascites, spontaneous bacterial peritoneal infection variceal bleeding, hepatic encephalopathy, by definition HCC free decompensation. Pregnant women or immunocompromised patients who were receiving nucleos(t)idic analogues prophylaxis were not excluded but correspond to a limited number of patients (not available).

HDV and HCV coinfected patients (n = 243) were excluded. The main analysis excluded patients with a past history of HCC, decompensated cirrhosis or liver transplantation.

Outcomes

Study outcomes were incident HCC, incident decompensated cirrhosis, liver transplantation, all-causes death and liver-related death. We also created a composite endpoint combining all cause death and HCC, decompensated cirrhosis or liver transplantation, whichever occurred first. The causes of death were classified by an adjudication committee including two hepatologists (HF, MB) and two methodologists (CD, FC). Adjudication was based on medical records, and investigators filled in a specific case report form. Data on incident HCC included the number of lesions at diagnosis, the size of the largest nodule, total size, diagnostic imaging procedures and treatment. Decompensated cirrhosis was defined as the development of ascites, variceal hemorrhage, encephalopathy, and/or jaundice.

Predictor variables

Potential predictors of a clinical outcome were evaluated at entry in the cohort and included age, gender, body mass index (BMI), geographic origin, time since HBV diagnosis, time since first treatment, time since the start of treatment with Tenofovir or Entecavir, the start of being HBV treatment-experienced with Tenofovir or Entecavir, fibrosis score, diabetes, arterial hypertension, past and current alcohol consumption, biological variables (albumin,

aspartate aminotransferase, alanine aminotransferase, gamma glutamyl-transferase, prothrombin time, platelet count, alpha-fetoprotein), and MELD score in patients with a cirrhosis. Patients with a platelet count < 150,000/µL or a prothrombin time < 70%, were considered to have cirrhosis unless specified otherwise (35-36). Fibrosis was evaluated in other patients by liver biopsy or another non-invasive method (liver stiffness measurement (Fibroscan®), Fibrotest®, other non invasive scores) that was performed closest to the date of inclusion, but less than 1 year before and up to 3 months after inclusion. If a recent measurement of fibrosis was not available or in case of discrepancies between non-invasive fibrosis markers, physicians were asked to assess the level of fibrosis based on past fibrosis scores and the patient's history of liver-related comorbidities. The baseline fibrosis score before the start of a nucleos(t)idic analogues treatment remained unknown in eligible patients. Mild fibrosis (F0-F2), severe fibrosis (F3) and cirrhosis (F4) were defined by the Metavir score (37).

Statistical analyses

The index date was the date a patient first started entecavir or Tenofovir. Survival was calculated for all outcomes as the time between the index date and the date of HCC, decompensated cirrhosis, liver transplantation all-cause deaths, liver-related deaths or composite endpoint, the last-follow-up visit, or July 31, 2019, whichever occurred first.

To deal with left-truncation of exposures and take into account a potential selection bias caused by using a prevalent cohort, we estimated delayed entry Cox-models (38). In delayed entry survival analysis, the risk set at a particular time includes only patients who started follow-up prior to that time, and have not yet experienced the outcome or been censored from the study by that time. In Kaplan-Meier curves adjusted for delayed entry, the number at risk may thus increase with time, as some patients will enter in the risk set after a delay corresponding to the time between treatment start (time origin) and start of follow-up (entry in the cohort). To illustrate, a prevalent tenofovir patient who initiated tenofovir 2 years before entry in the cohort and with 2 years follow-up will contribute to estimating the survival between 2 and 4 years.

Baseline characteristics were compared using the Mann-Whitney test for quantitative variables or the Fisher's exact test for categorical variables. Incidence rates and 95% confidence intervals were estimated with an exact method based on the Poisson

distribution. The propensity to be receiving Entecavir or Tenofovir at entry in the cohort was estimated by a logistic regression model including covariates evaluated at entry in the cohort with dummy indicators for missing values of a covariate. The logistic regression model included age, gender, geographic origin, body mass index, arterial hypertension, diabetes, fibrosis score, current excessive alcohol consumption, past excessive alcohol consumption, serum albumin level, prothrombin rate, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha fetoprotein (AFP), HBV DNA, time since HBV diagnosis, time since first treatment, time since start of Tenofovir or Entecavir, HBV treatment-naïve at the start of Tenofovir or Entecavir. The inverse probability of treatment weighting (IPW) was used. Stabilized weights were calculated and the balance of baseline covariates was assessed between groups in the weighted sample.

We used a inverse probability of treatment weighting Cox proportional-hazards models and Kaplan-Meier curves adjusted to delayed entry in our primary analysis. Patients whose treatment was changed were censored 6 months after the change was made assuming that exposure to treatment ends 6 months after the change. In secondary analyses, unweighted univariable and multivariable-adjusted delayed-entry Cox proportional-hazards models were also estimated and a departure from the proportionality assumption was checked based on the Schoenfeld's residuals.

Categorization of continuous covariates was based on clinically relevant previously determined thresholds (all biological parameters) or quartiles limits (age, time since HBV diagnosis). Missing covariate values were handled using indicators for missing data in the multivariate model. All analyses were performed with SAS 9·4 (SAS Institute Inc., Cary, North Carolina, USA). A P-value < .05 was considered to be statistically significant.

Results

One thousand eight hundred and thirty three patients met the eligibility criteria (figure 1). Follow-up information was missing in 33 patients (1.8%). Therefore, follow-up information was available for 1800 (98%) patients (986 tenofovir and 814 Entecavir), who were included in analyses. Most of the patients (1733: 96%) started Tenofovir or Entecavir treatments before their entry in the cohort. The median time between start of Tenofovir or Entecavir treatments and entry in the cohort was approximately 3 years, and only 7% of patients had a

HBV DNA titer > 2000 UI/ml at entry in the cohort. 805 patients were given another treatment before Entecavir or Tenofovir: switches were either related to the evolution from first to second generation nucleos(t)idic analogues, to nucleosides resistance or to intolerance to the previous nucleos(t)idic analogues. Overall 55 (3%) patients changed antiviral therapy over time. 8 (15%) of them switched the first year, 22 (40%) switched the 2nd year, 14 (25%) switched the 3rd year and 11 (20%) switched the 4th year.

Baseline demographic, clinical, and laboratory patient characteristics are provided in table 1. Patients were a median of 46.7 years old (IQR 37.1-57.8) and 1263 (70%) were men. Median follow-up was 4.2 years (IQR 3.09-5.06) and was similar between the two groups.
Patients who received Tenofovir were younger, more frequently women, had a lower prevalence of arterial hypertension or diabetes, had more frequent positive HBe antigen, had a lower prothrombin, creatinine and gamma-glutamyl transpeptidase levels, had a higher alanine aminotransferase and aspartate aminotransferase levels, were more frequently HBV treatment-experienced at the start of treatment (with a longer history of prior HBV treatment) and had had shorter past exposure to current treatment than those who received Entecavir. Geographic origin, alcohol consumption, fibrosis stage and HBV-DNA levels were not different at baseline between the two treatment groups. The balance of baseline characteristics following inverse probability of treatment weighting is presented in supplementary material (supplementary table 1).
21 HCC, 8 decompensated cirrhosis, 2 liver transplantation and 28 all-cause deaths (8 liver-related death) were reported during follow-up (table 2). The incidence rates for the composite endpoint were respectively 4.1 (95%CI 3.0; 5.4) per 1000 person-years (PY) in the Tenofovir group and 5.0 (95%CI 3.3;7.2) per 1000 PY in the Entecavir group, (P=0.20 by comparison of inverse probability of treatment weighting survival curves). Incidence was not different between the Tenofovir and the Entecavir group for HCC (1.8(0.9;3.2) and 1.6 (0.7;3.0)), decompensated cirrhosis 0.6 (0.2;1.6) and 0.7 (0.2;1.8)), all-causes deaths 1.7 (0.8;3.0) and 3.0 (1.7; 4.8) or liver-related deaths 0.8 (0.2;1.8) and 0.5 (0.1;1.5), respectively for the main analysis (Table 2) like for the patients with cirrhosis at baseline (supplementary tables 2 and 3), the non cirrhotic patients (supplementary tables 4 and 5).

The detailed characteristics of the 21 incident HCC are presented in supplementary table 6. The number of tumors at diagnosis was lower in the Tenofovir group than in the Entecavir group. No difference was found in the time between the initiation of Tenofovir or Entecavir and the occurrence of HCC after nucleos(t)idic analogues initiation, the time between the last normal imaging test and diagnosis, macroscopic pattern, total nodule size, largest nodule size or serum □-fetoprotein**.**

HCC occurrence was associated with age, arterial hypertension, fibrosis score, past excessive alcohol comsumption, prothrombin rate, platelets count, GGT, bilirubin levels, time since HBV diagnosis and Page-B score (supplementary table 7).

There was no significant difference in survival free of any of the clinical outcomes between the two groups (figure 2).

The survival curves were not different when comparing Tenofovir and Entecavir groups in cirrhotic patients (Supplementary figure 1). In non cirrhotic patients, there was no difference in the survival curves between Entecavir and Tenofovir, except for the all-causes mortality and for the composite endpoint with a higher rate in Entecavir-treated patients (p = 0.01 for both)(Supplementary figure 2).

Hazard ratios of Tenofovir vs Entecavir for HCC, decompensated cirrhosis, all-causes deaths, liver-related deaths and composite endpoint were close to the unity, univariable analysis as well as multivariable (when feasible) analysis showing that there was no significant association between treatment and the risk of any of the clinical outcomes in the main analysis (table 3).

Non liver-related cancers were identified in 3 Tenofovir-treated (incidence rate 0.5/1000 PY (0.1; 1.3) and 5 Entecavir-treated patients (incidence rate 0.9/1000 PY (0.3; 2.1)) in the main analysis. No significant difference was found in the analysis for the incidence of non liver-related cancers between the 2 groups (p = 0.35). The 7 non-liver non-cancer related deaths were 2 cardiac disorders (acute coronary syndrome, one aortic valve disease), 1 staphylococcal infection, 1 ischemic stroke and 2 renal failures.

Discussion

In this first large prospective cohort of French patients with chronic HBV infection including patients of European, African as well as Asian origin, the incidence of liver-related events, namely HCC, decompensated cirrhosis, liver transplantation or death was not different between Tenofovir- and Entecavir-treated patients.

Several prospective and retrospective studies have reported a decreased incidence of HCC in nucleos(t)idic analogues-treated patients with cirrhosis, showing the benefit of HBV viral suppression (16-25, 39). The mechanisms of HBV hepatocarcinogenesis are complex, associating factors related to high viral load or HBV genotypes (15,40), liver regeneration in fibrotic disease, HBV genome integration in the host hepatocyte genome (authorized by a reverse transcription step during viral replication B) with chromosomal rearrangements as well as cis-activation and trans-activation mechanisms (41-42). Nucleos(t)idic analogues-associated viral suppression results in the resolution of fibrosis including biopsy-proven reversal of cirrhosis in more than two thirds of treated patients after five years (18). Nucleos(t)idic analogues therapy also decreases the risk of viral hepatocarcinogenesis as it has been prospectively demonstrated in the first prospective randomized trial of lamivudine vs. placebo in patients with significant biopsy-proven extensive fibrosis. Early evidence at 2 years showed that lamivudine-treated patients had a lower incidence of HCC than placebo-treated patients and that the occurrence of YMDD mutations reduced this benefit in lamivudine-treated patients (17). These results support the policy of treating all HBV-infected patients with significant fibrosis with the most potent antiviral drugs, namely Tenofovir and Entecavir (4-7), which have proven their efficacy.

Noteworthy is the low rate of HCC in our treated series (around 0.3/year) as compared to other series with figures ranging from 1.5 to 4.4%/year in nucleos(t)idic analogues -treated as compared to 5.2 to 7.7% in untreated cirrhotic patients. These differences are likely related to the rate of patients with cirrhosis (16%) or extensive fibrosis (8%) in our series and to the difference in the duration of nucleos(t)idic analogues -exposure: most of studies included patients since the beginning of the primary line of nucleos(t)idic analogues treatment and compared treated to untreated patients; in our series, half of patients were already treated and a significant rate of patients had a long-term history of nucleos(t)idic analogues treatment before the inclusion in the analysis and viral suppression is associated with a constant decline in the rate of complications, including HCC. In addition, differences may partially be related to the different geographic origin of the patients. We know that

Asian patients are mainly infected at birth, (mother to child transmission), African patients are mainly infected during in early childhood while infection is mainly at the teen age and young adult age in Northern countries (4-7). The duration of infection clearly influences the risk of clinical events in chronic HBV infection and the risk of HCC appears in earlier age in African or Asian than in European patients. In our series, there was no evidence of an impact of the geographical origin on the risk of clinical events (data not shown).

There was no difference in the survival curves between Entecavir and Tenofovir, except for the all-causes mortality or for the composite endpoint in non-cirrhotic patients with a higher rate in Entecavir-treated patients; we assume that these results, despite the inverse probability of treatment weighting analysis, are the consequences of the sub-groups analysis related to the inflation of the 1st species risk (alpha risk of 0.05).

Why would Entecavir be less beneficial, as suggested by Asian studies from Korea, Taiwan and Hong Kong (26-33)?

The differential impact of HBV genotypes on HCC (40) cannot explain this difference. The genotypes in Asia are mainly B and C, and the latter is associated with a higher risk of HCC. Although we did not analyze HBV genotypes in our cohort, the absence of impact of geographical origin on the risk of HCC with nucleos(t)idic analogues excludes this hypothesis.

Second, Entecavir was associated with the occurrence of malignancies in pre-clinical toxicological studies (www.fda.gov/medwatch). Pulmonary adenomas and carcinomas, hepatocellular adenomas and carcinomas, vascular tumors, glial tumors and cutaneous tumors were observed in mouse and rat animal models exposed to very high doses of Entecavir (approximately 42 times higher than the maximum recommended human dose of 1 mg/day in the mouse and 35 times higher in the rat). As a result of the putative carcinogenic risk of Entecavir, France and Sweden refused to participate in registration studies and an observatory prospective study was requested by drug agencies. However, this product has been prescribed for more than 10 years and there are still no convincing signs suggesting any potential carcinogenicity associated with Entecavir: the safety of Entecavir was confirmed in the REALM study with a follow-up of at least 7 years in patients receiving long-term randomized treatment with Entecavir or another nucleos(t)idic analogues, which showed no increase in the occurrence of cancer (43). Thus, an increased

risk of HCC associated with the long-term toxicity of Entecavir per se, appears unlikely. This is also supported by the similar distribution of non-hepatic cancers in both groups, the similar clinical and morphological characteristics of HCC in Tenofovir- and Entecavir-treated patients as well as a similar delay between the initiation of Tenofovir or Entecavir and the occurrence of HCC, the size and number of nodules, the time between the last normal imaging test and the diagnosis of HCC, macroscopic pattern, total nodule size and serum□□-fetoprotein levels.

Third, although a hypothetically higher rate of virological response in Tenofovir- vs Entecavir-treated patients could explain a higher risk of HCC in the latter, a comparison of effective viral suppression between the second-generation nucleos(t)idic analogues was not clear and the virological response was not an independent risk factor of HCC in the Korean study (27). Finally, it has been recently suggested that nucleotide analogues increase serum interferon □3 levels compared to nucleoside analogues, which could have certain antiproliferative properties (44).

It is noteworthy that, by opposition of the studies from Asia, other European studies did not evidence any benefit of Tenofovir in reducing significantly the risk of HCC as compared to Entecavir: results from multicenter european or US cohorts raise similar conclusions (45-46).

Our study has several strengths. First, it is a large prospective cohort, including 1800 patients, 986 patients in the Tenofovir and 814 patients in the Entecavir groups. Second, patients are well phenotyped allowing to prospectively evaluate the impact of Tenofovir compared to Entecavir on five outcomes (HCC, decompensated cirrhosis, liver transplantation, all-cause deaths, liver-related death, and a composite endpoint combining any of these outcomes, in nucleos(t)idic analogues HBV-treated patients from the Hepather cohort. Third, patients are from different origins, including patients from European, African as well as Asian origin.

This study has several limitations. First, it is not a randomized study and characteristics of the patients between the 2 groups are different: the Entecavir group had worse characteristics than the Tenofovir group regarding the risk of HCC (age, gender, …) like in other registry cohorts in which the Tenofovir group was usually less severe requiring weighting analysis for the comparisons between the groups, for example in the study from South Korea (27). If we do consider, on the basis of studies from Asia, that Entecavir is associated with an increased risk of HCC as compared to Tenofovir, this worse pattern

should increase the difference between the 2 nucleos(t)idic analogues treatment favoring Tenofovir; this heterogeneity could be considered as reinforcing the message that there is no difference in the risk of HCC between Tenofovir and Entecavir and the heterogeneity is cancelled by the inverse probability of treatment weighting analysis (supplementary table 1) which does not evidence any difference between Tenofovir and Entecavir.

Second, the number of liver-related clinical events was low and the study may have been underpowered to detect a small difference between the two treatment groups, a predominantly no cirrhotic population. Indeed, a post-hoc calculation of the statistical power showed that our study had a 45% power to show a hazards ratio of 0.6 for HCC with our sample size and rates, as reported in another study (27). To increase the statistical power, we used a composite endpoint combining all relevant clinical outcomes but we did not find any significant differences between the groups. If any difference exists between the two groups, it should be limited.

Third, our study selected and evaluated patients who had been receiving Tenofovir or Entecavir for a median of 2.7 years as well as 45% of these patients who had been receiving HBV treatment with nucleotides/nucleosides analogs for even longer at the start of follow-up. Prior HBV treatment is strongly associated with the duration of viral suppression and was adequately controlled using method accounting for left truncation in exposures (39), adjustments or inverse probability of treatment weighting, thus limiting the risk of a selection bias. However, prior treatment may explain our relatively low rates of HCC or other liver-related complications compared to studies focusing on incident Tenofovir or Entecavir users. While the geographical, clinical and pathological profiles of the patients as well as the durations of follow-up were only slightly different for the nucleos(t)idic analogues in our real-life cohort, in the Asian studies the distribution of NUCs and the follow-up durations were imbalanced due to the very early registration of ETV (27). Although a hospital cohort confirmed the results of the registry cohort, several sophisticated statistical methodologies were required to make face-to-face comparisons between Entecavir and Tenofovir.

Finally, another limitation of our study is the “heterogeneity” first in the evaluation of fibrosis (histopathological, biochemical by noninvasive tests or by evaluation of the liver stiffness) and second in the potential kinetics of fibrosis and its ability to reverse but also to progress in a given patient. Fibrosis was mainly based on the physician feeling of the fibrosis

for a given patient. Nevertheless, this uncertainty was equally distributed across the tenofovir and entecavir arms.

In conclusion, this prospective cohort of French patients of different geographical origins with chronic hepatitis B virus infection, does not support a reduced benefit of entecavir treatment compared to tenofovir for the incidence of liver-related events in a predominantly no cirrhotic population.

Legends to figures

Figure 1. Flow of participants through the study comparing the progression of 1055 patients with hepatitis B virus infection treated with tenofovir (TDF) compared to 885 patients treated by entecavir (ETV) with or without a prior history of hepatocellular carcinoma (HCC) or decompensated cirrhosis (DC).

Figure 2. IPW survival curves of hepatocellular carcinoma, decompensated cirrhosis, liver transplantation, death from all causes, liver-related deaths or a composite endpoint corresponding to any of the clinical events in primary analysis in 986 patients with hepatitis B virus infection treated by tenofovir compared to 814 patients treated by entecavir (number at risk may increase due to delayed entry of patients in the survival analysis).

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Figure 1. Flow of participants through the study comparing the evolution of 986 hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 814 patients treated by Entecavir (ETV) with or without prior history of hepatocellular carcinoma (HCC) or cirrhosis decompensation (DC).

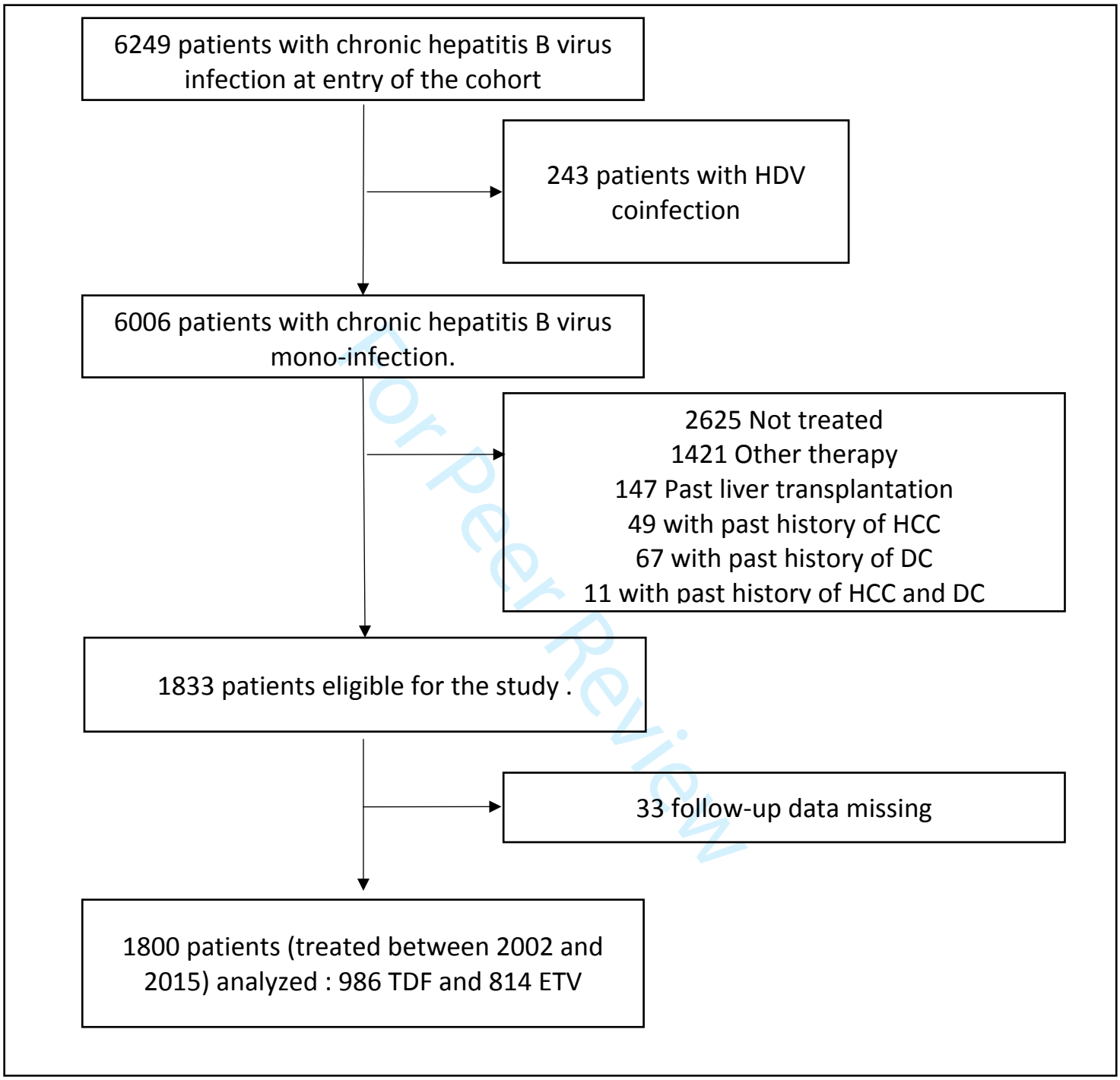


Figure 2. IPW survival curves of hepatocellular carcinoma, cirrhosis decompensation, liver transplantation, all-cause deaths, liver-related deaths or a composite endpoint corresponding to any of the clinical event in primary analysis in 986 hepatitis B virus-infected patients treated by Tenofovir compared to 814 patients treated by Entecavir (number at risk may increase due to delayed entry of patients in the survival analysis).

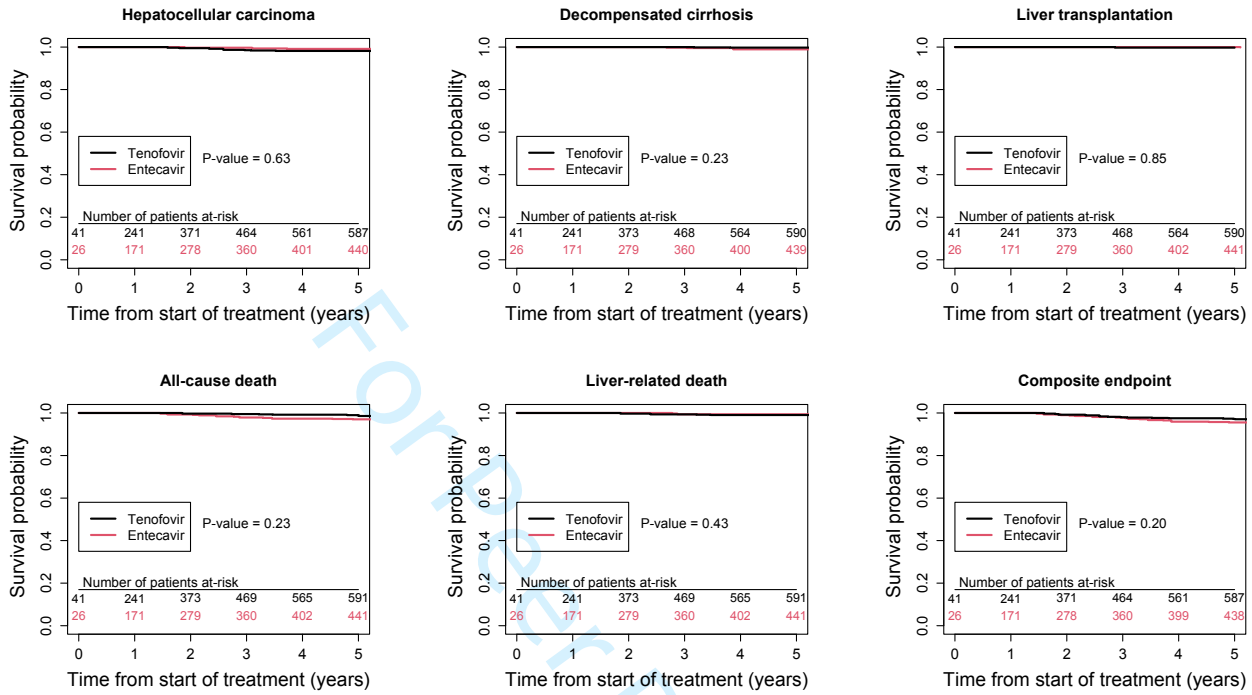


Table 1. Baseline characteristics of 986 hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 814 patients treated by Entecavir (ETV) with or without prior history of hepatocellular carcinoma (HCC) or cirrhosis decompensation (DC).

	All patients (n = 1800)	**Tenofovir (TDF) (n=986)**	**Entecavir (ETV) (n=814)**	**P-value**
Age (Years)				**<.0001**
median (Q1-Q3)	46.7 (37.1-57.8)	44.8 (35.0-56.5)	49.2 (39.7-58.9)	.
Sex				**0.01**
Male	1263 (70%)	666 (68%)	597 (73%)	
Geographic Origin				0.16
Africa	652 (36%)	366 (37%)	286 (35%)	.
Asia	378 (21%)	220 (22%)	158 (19%)	.
Other	171 (10%)	85 (9%)	86 (11%)	.
Europa	599 (33%)	315 (32%)	284 (35%)	
Body mass index (kg/m²)				0.14
median (Q1-Q3)	24.8 (22.3-27.8)	24.7 (22.2-27.6)	25 (22.4-27.8)	.
Missing	18	11	7	.
				.
Body mass index				0.50
<18.5	48 (3%)	28 (3%)	20 (3%)	.
[18.5-25[	881 (49%)	496 (50%)	385 (48%)	.
[25-30[	606 (34%)	319 (33%)	287 (35%)	.
≥30	247 (14%)	132 (14%)	115 (14%)	.
Missing	18	11	7	.
Arterial hypertension	366 (20%)	166 (17%)	200 (26%)	**<.0001**
Diabetes	170 (9%)	77 (8%)	93 (11%)	**0.01**
Fibrosis score				0.79
F0	150 (9%)	79 (8%)	71 (9%)	.
F0/F1	271 (15%)	141 (14%)	130 (16%)	.
F1	291 (16%)	158 (16%)	133 (16%)	.
F1/F2	137 (8%)	71 (7%)	66 (8%)	.
F2	253 (14%)	141 (14%)	112 (14%)	.
F2/F3	24 (2%)	9 (1%)	15 (2%)	.
F3	119 (7%)	64 (7%)	55 (7%)	.
F3/F4	16 (1%)	7 (1%)	9 (1%)	.
F4	159 (9%)	90 (9%)	69 (9%)	.
Missing	380	226	154	.

Fibrosis evaluation method				0.36
Platelet count <150 or PT <70%	79 (4%)	43 (4%)	36 (4%)	.
Liver biopsy	223 (12%)	111 (11%)	112 (14%)	.
Fibroscan	117 (7%)	65 (7%)	52 (6%)	.
Fibrotest	34 (2%)	16 (2%)	18 (2%)	.
Other NI scores	3 (0%)	1 (0%)	2 (0%)	.
Physician evaluation based on patient's history	964 (54%)	524 (53%)	440 (54%)	.
Missing	380	226	154	.
HBeAg				**0.001**
Negative	1390 (77%)	735 (75%)	655 (81%)	
Positive	292 (16%)	186 (19%)	106 (13%)	
Missing	118	65	53	
Past excessive alcohol consumption	183 (10%)	102 (10%)	81 (10%)	0.81
Current excessive alcohol consumption				0.20
Missing	2 (0%)	0 (0%)	2 (0%)	.
	538	284	254	
Smoking	333 (19%)	193 (20%)	140 (17%)	0.20
Missing	1	1	0	.
Albumin (g/L)				0.12
median (Q1-Q3)	43 (40.8-45.8)	43 (41-46)	43 (40.5-45.6)	
Missing	592	331	261	
Prothrombin rate (%)				**0.01**
median (Q1-Q3)	95 (87-100)	94 (86-100)	96 (87-100)	
Missing	360	211	149	
Platelets count (per µL)				0.14
median (Q1-Q3)	206000 (171000-247000)	207000 (174000-248000)	204000 (168000-245000)	
Missing	162	97	65	
Alanine aminotransferase (UI/L)				**<.0001**
median (Q1-Q3)	28 (21-39)	29 (22-41)	26 (19-37)	
Missing	61	34	27	
Aspartate aminotransferase (UI/L)				**<.0001**
median (Q1-Q3)	26 (22-34)	27 (23-35)	25 (21-32)	
Missing	73	42	31	
Alpha fetoprotein (ng/mL)				0.99
median (Q1-Q3)	2.9 (2-4)	2.9 (2-4)	2.8 (2-4)	
Missing	416	236	180	

Creatininemia (mg/L) median (Q1-Q3) Missing	 8.9 (7.6-10.3) 115	 8.9 (7.6-10.1) 59	 9 (7.7-10.6) 56	**0.01** . .
Hemoglobin (g/dL) median (Q1-Q3) Missing	 14.6 (13.4-15.5) 131	 14.6 (13.5-15.5) 81	 14.5 (13.4-15.5) 50	0.27 . .
Gamma-Glutamyl transpeptidase (UI/L) median (Q1-Q3) Missing	 26 (18-41) 192	 25 (17-40) 113	 28 (19-43) 79	**0.001** . .
Bilirubin (µmol/L) median (Q1-Q3) Missing	 9.9 (7-13.6) 234	 9.8 (7-13.8) 134	 9.9 (7-13.6) 100	0.60
Child A B C Missing	 111 (85%) 5(4%) 1 (1%) 58	 62 (96%) 1 (2%) 1 (2%) 33	 49 (92%) 4 (8%) 0 (0%) 25	0.17
HBV-DNA (log_{10} UI/mL) Median Missing	 1.3 (1.2-1.3) 137	 1.3 (1.2-1.3) 83	 1.3 (1.1-1.3) 54	**0.04**
HBV treatment experienced at start of TDF or ETV No Yes	 995 (55%) 805 (45%)	 476 (48%) 510 (52%)	 519 (64%) 295 (36%)	**<.0001** .
NA treatment experienced at entry in the cohort No Yes	 38 (2%) 1762 (98%)	 22 (2%) 964 (98%)	 16 (2%) 798 (98%)	0.70
Duration of past exposure to TDF or ETV (years) median (Q1-Q3)	 2.7 (1.1-4.5)	 2.6 (1-4.2)	 2.9 (1.3-4.8)	**0.0006** .
Time from first HBV treatment (years) median (Q1-Q3) Missing	 4.6 (1.9-9) 48	 5.1 (1.9-10.4) 34	 4.3 (1.8-7.3) 14	**0.0002** . .

Time since HBV diagnosis (years)				0.85
median (Q1-Q3)	32.3 (11.6-45.8)	31.5 (13.9-44.2)	33.6 (8.3-46.8)	.
Missing	743	396	347	.
				.
Calendar year of treatment initiation				**0.0001**
median (Q1-Q3)	2011 (2009-2013)	2011 (2009-2013)	2011 (2009 – 2012)	
PAGE-B score				**0.0002**
median (Q1-Q3)	12 (8-16)	12 (8-16)	12 (8-16)	
mean (SD)		11.2 (5.6)	12.4 (5.1)	
Missing	162	97	65	

Table 2. Incidence rates of hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in primary analysis (patients without past history of hepatocellular carcinoma or cirrhotic decompensation) in 986 hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 814 patients treated by Entecavir (ETV).

	Tenofovir		Entecavir	
	n/person year (PY)	Incidence/1000 PY (95%CI)	n/PY	Incidence/1000 PY (95%CI)
HCC	12/6596	1.8 (0.9;3.2)	9/5653	1.6 (0.7;3.0)
DC	4/6612	0.6 (0.2;1.6)	4/5662	0.7 (0.2;1.8)
LT	1/6615	0.2 (0.0;0.8)	1/5668	0.2 (0.0;1.0)
ACD	11/6617	1.7 (0.8;3.0)	17/5668	3.0 (1.7;4.8)
LRD	5/6617	0.8 (0.2;1.8)	3/5668	0.5 (0.1;1.5)
CE	22/6593	4.1 (3.0;5.4)	28/5646	5.0 (3.3;7.2)

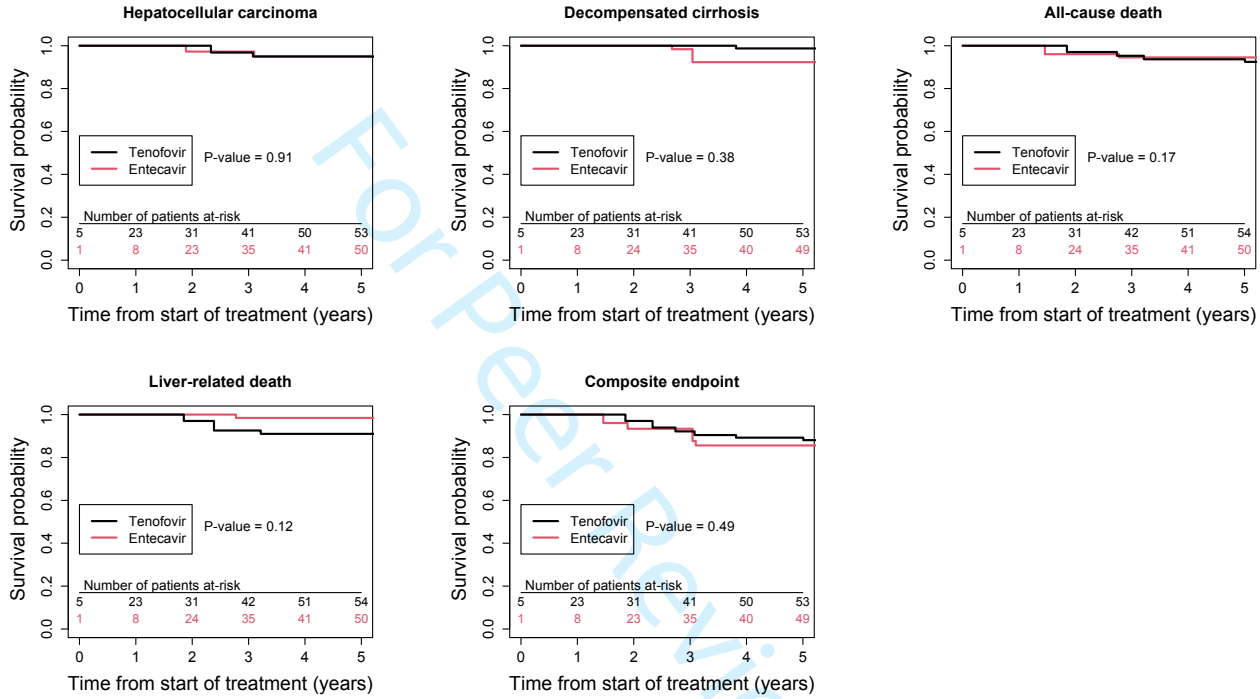
Table 3. Hazard ratios of Tenofovir versus Entecavir for hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in primary analysis set analysis in 986 hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 814 patients treated by Entecavir (ETV) without past history of hepatocellular carcinoma or cirrhotic decompensation.

	IPW analysis HR [95% CI]	Univariable analysis HR [95% CI]	Multivariable analysis HR [95% CI]
HCC	1.24 (0.49 ; 3.13)	1.06 (0.45 ; 2.52)	1.51 (0.58 ; 3.92)
DC	0.44 (0.10 ; 1.90)	0.78 (0.20 ; 3.11)	ND
LT	1.32 (0.07 ; 23.50)	0.76 (0.05 ; 12.54)	ND
ACD	0.63 (0.28 ; 1.44)	0.50 (0.23 ; 1.07)	0.60 (0.25 ; 1.46)
LRD	1.77 (0.40 ; 7.93)	1.37 (0.34 ; 5.53)	ND
CE	0.70 (0.38 ; 1.29)	0.62 (0.35 ; 1.08)	0.66 (0.34 ; 1.28)

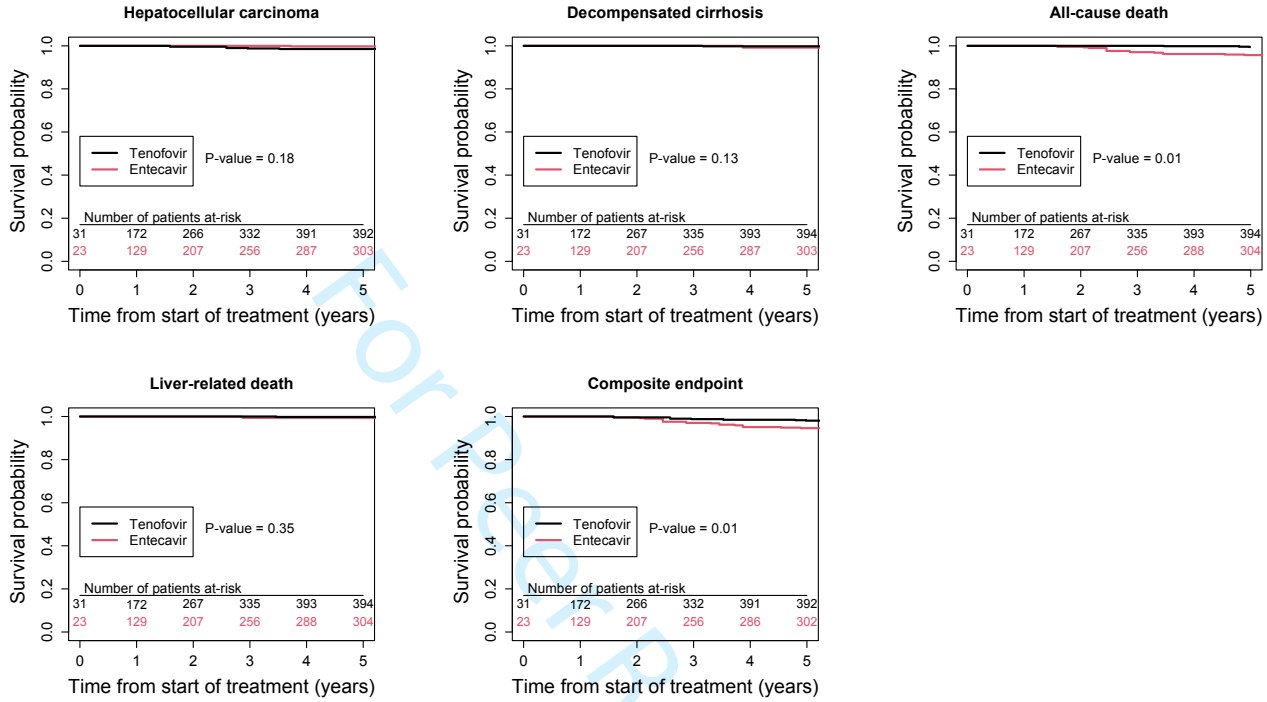
ND = Not done because of insufficient number of events

Supplementary material

Supplementary figure 1. IPW survival curves of hepatocellular carcinoma, cirrhosis decompensation, liver transplantation, all-cause deaths, liver-related deaths or a composite endpoint corresponding to any of the clinical event in primary analysis in 97 cirrhotic (F3/F4 + F4) hepatitis B virus-infected patients treated by Tenofovir compared to 78 patients treated by Entecavir (number at risk may increase due to delayed entry of patients in the survival analysis).



Supplementary figure 2. IPW survival curves of hepatocellular carcinoma, cirrhosis decompensation, liver transplantation, all-cause deaths, liver-related deaths or a composite endpoint corresponding to any of the clinical event in primary analysis in 663 non-cirrhotic (F0+F0/F1+F1+F1/F2+F2+F2/F3/F3) hepatitis B virus-infected patients treated by Tenofovir compared to 582 non-cirrhotic patients treated by Entecavir (number at risk may increase due to delayed entry of patients in the survival analysis).



Supplementary Table 1. Balance of baseline covariates after use of IPW according to Tenofovir (TDF) and Entecavir (ETV) groups.

	TDF	ETV	P-value	Standardized difference (%)
Age (Years)				
Mean (sd)	45.4 (13.7)	46.6 (13.2)	0.11	-6
Sex				
Male (%)	70.4	70.3	0.96	0.3
Geographic origin (%)			0.99	1.0
Africa	36.5	36.3		
Asia	20.9	21.4		
Europa	32.9	32.9		
Other	9.7	9.5		
Body mass index (kg/m^2)				
Mean (sd)	25.2 (4.6)	25.2 (4.4)	0.90	1.3
Arterial hypertension (%)	20.4	20.1	0.89	0.7
Diabetes (%)	9.6	9.3	0.85	0.9
Fibrosis (%)			0.62	10
F0	10.1	10.8		
F0/F1	18.6	18.9		
F1	20.5	21.9		
F1/F2	9.8	9.4		
F2	18.8	16.3		
F2/F3	1.2	2.1		
F3	9.1	8.0		
F3/F4	0.7	1.6		
F4	11.3	11.1		
Fibrosis evaluation method (%)			0.71	9.0
Platelet count <150 or PT<70%	5.9	5.5		
Liver biopsy	14.4	17.4		
Fibroscan	8.3	7.6		

Fibrotest Other NI scores Physician evaluation based on patient's history	2.1 0.1 69.3	2.3 0.2 66.9		
Past excessive alcohol consumption (%)	10.3	10.8	0.77	-2.0
Current excessive alcohol consumption (%)	0.0	0.2	0.90	-6.0
Smoking (%)	19.4	18.1	0.48	3.0
Albumin (%) <30 g/L ≥ 30 g/L	 33.8 66.2	 33.8 66.2	0.99	0.1
Prothrombin time (%) ≤70 (%) >70 (%)	 5.1 95.0	 5.2 94.8	0.91	-7.0
Platelets (%) <150000 per µL ≥150000 per µL	 14.1 85.9	 14.6 85.4	0.79	1.3
Alanine aminotransferase (%) ≤ 40 UI/L > 40 UI/L	 76.1 23.9	 76.6 23.4	0.81	1.2
Aspartate aminotransferase (%) ≤ 40 UI/L > 40 UI/L	 87.4 12.6	 87.3 12.7	0.96	0.3
Alpha fetoprotein (%) <5.5 ng/mL ≥5. 5 ng/mL	 87.0 13.9	 86.8 13.2	0.94	1.3
Creatininemia (mg/L) Mean (sd)	 23.8 (389.9)	 26.4 (349.1)	0.74	-0.7
Hemoglobin (g/dL) Mean (sd)	 14.4 (1.5)	 14.3 (1.5)	0.26	8.0

Gamma-glutamyl-transpeptidase (UI/L) Mean (sd)	36.7 (45.4)	44.5 (112.5)	0.12	-10
HBV-DNA (UI/mL) (%) <20 [20-2000[≥2000	 26.9 64.4 8.7	 26.5 65.7 7.9	0.87	3.0
HBV treatment experienced at start of TDF or ETV (%) No Yes	 57.3 42.7	 56.4 43.6	0.77	1.4
Duration of past exposure to TDF or ETV (years) Mean (sd)	3.0 (2.1)	3.0 (2.1)	0.74	1.3
Time from first HBV treatment (years) (%) <2 [2-8[≥8	 29.2 43.9 26.9	 28.7 44.0 27.4	0.97	0.8
Time since HBV diagnosis (years) Mean (sd)	30.7 (19.0)	31.5 (19.4)	0.56	-2.2

Supplementary Table 2. Incidence rates of hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in main analysis in 97 cirrhotic (F3/F4, F4) hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 78 cirrhotic patients treated by Entecavir (ETV).

	Tenofovir		Entecavir	
	n/ person year (PY)	**Incidence/1000 PY 95%CI)**	**n/PY**	**Incidence/1000 PY (95%CI)**
HCC	4/633	6.3 (1.7;16.2)	5/569	8.8 (2.9;20.5)
DC	2/635	3.2 (0.4;11.4)	2/570	3.5 (0.4;12.7)
LT	1/637	1.6 (0.0;8.7)	0/574	0.0 (0.0;6.4)
ACD	6/639	9.4 (3.4;20.4)	4/574	7.0 (1.9;17.8)
LRD	4/639	6.3 (1.7;16.0)	1/574	1.7 (0.0;9.7)
CE	11/630	17.5 (8.7;31.2)	9/565	15.9 (7.3;30.3)

Supplementary Table 3. Hazard ratios of Tenofovir versus Entecavir for hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in primary analysis set analysis in cirrhotic (F3/F4, F4) hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to patients treated by Entecavir (ETV).

	IPW analysis HR [95% CI]	**Univariable analysis HR [95% CI]**	**Multivariable analysis HR [95% CI]**
HCC	1.09 (0.27 ; 4.44)	0.70 (0.19 ; 2.62)	ND
DC	0.43 (0.06 ; 2.89)	0.85 (0.13 ; 5.69)	ND
ACD	2.79 (0.77 ; 10.14)	1.24 (0.35 ; 4.36)	ND
LRD	7.05 (0.83 ; 59.65)	3.38 (0.41 ; 27.86)	ND
CE	1.38 (0.51 ; 3.71)	1.01 (0.42 ; 2.44)	ND

ND : not done because of insufficient number of events

Supplementary Table 4. Incidence rates of hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in main analysis in 663 non-cirrhotic (F0, F0/F1, F1, F1/F2, F2, F2/F3, F3) hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 582 non-cirrhotic patients treated by Entecavir (ETV).

	Tenofovir		**Entecavir**	
	n/ person year (PY)	**Incidence/1000 PY 95%CI)**	**n/PY**	**Incidence/1000 PY (95%CI)**
HCC	6/4349	1.4 (0.5;3.0)	2/4031	0.5 (0.1;1.8)
DC	1/4360	0.2 (0.0;1.3)	2/4032	0.5 (0.1;1.8)
LT	0/4360	0.0 (0;0.8)	1/4034	0.2 (0.0;1.4)
ACD	3/4360	0.7 (0.1;2.0)	12/4034	3.0 (1.5;5.2)
LRD	1/4360	0.2 (0.0;1.3)	2/4034	0.5 (0.1;1.8)
CE	8/4349	1.8 (0.8;3.6)	16/4029	4.0 (2.3;6.4)

Supplementary Table 5. Hazard ratios of Tenofovir versus Entecavir for hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in primary analysis set analysis in non-cirrhotic (F0, F0/F1, F1, F1/F2, F2, F2/3, F3) hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to patients treated by Entecavir (ETV).

	IPW analysis **HR [95% CI]**	**Univariable analysis** **HR [95% CI]**	**Multivariable analysis HR [95% CI]**
HCC	3.30 (0.65 ; 16.63)	2.58 (0.56 ; 11.84)	ND
DC	0.13 (0.01 ; 1.51)	0.42 (0.04 ; 4.38)	ND
LT	ND	ND	ND
ACD	0.15 (0.04 ; 0.55)	0.20 (0.06 ; 0.70)	ND
LRD	0.27 (0.02 ; 3.09)	0.46 (0.05 ; 4.45)	ND
CE	0.34 (0.14 ; 0.87)	0.41 (0.18 ; 0.96)	ND

ND : not done because of insufficient number of events

Supplementary Table 6. Characteristics of hepatocellular carcinoma according to exposure to Tenofovir (TDF) and Entecavir (ETV).

Characteristics	TDF (n=12)	ETV (n=9)	P-value
Time between initiation of TDF or ETV and occurrence (years)	4.0 ± 1.8	5.8 ± 2.6	0.39
Missing	0	0	
Time between last normal evaluation and first abnormal evaluation (years)	1.1 ± 1.1	0.7 ± 0.8	0·55
Missing	*3*	*4*	
Time between first abnormal evaluation and diagnosis(years)	1.6 ± 3.0	1.0 ± 1.9	0·86
Missing	*2*	*3*	
Time between last normal evaluation and diagnosis(years)	1.2 ± 1.0	0.7 ± 0.8	0·32
Missing	*3*	*4*	
Macroscopic pattern			
Infiltrative	0 (0%)	0 (0%)	---
Nodular	11 (100%)	6 (100%)	
Missing	*1*	*3*	
In nodular patterns:			
Number of tumors at diagnosis	1.0 ± 0.0	2.3 ± 2.3	**0·01**
Missing	*1*	*3*	
Largest nodule size (in mm)	24.8 ± 18.7	32.6 ± 28.0	0·69
Missing	*1*	*3*	
Total nodule size (in mm)	24.8 ± 18.7	51.6 ± 42.3	0·21
Missing	*1*	*3*	
Alpha fetoprotein (in log(ng/mL))			
at entry	1.4 ± 0.9	1·0 ± 0·4	0.77
missing	*2*	*2*	
at diagnosis	1·3 ± 0.9	3.5 ± 4.0	0.12
missing	*5*	*3*	
Liver biopsy at diagnosis	4 (36%)	4 (67%)	0.33
missing	*1*	*3*	
Grade (WHO)			1.00
Well differentiated	2 (50%)	1 (33%)	
Moderately differentiated	2 (50%)	2 (67%)	
Poorly differentiated/Undifferentiated	0 (0%)	0 (0%)	
Cholangiocarcinoma	0 (0%)	0 (0%)	
Not interpretable	0 (0%)	0 (0%)	
Others	0 (0%)	0 (0%)	
Missing	8	6	

Supplementary table 7. Baseline characteristics of 21 hepatitis B virus-infected patients with hepatocellular carcinoma (HCC^+) and 1779 without hepatocellular carcinoma (HCC^-).

	HCC^+ (n=21)	**HCC^- (n=1779)**	**P-value**
Age (years) median (Q1-Q3)	58.6 (51.9-64.8)	46.5 (37.0-57.6)	**0.001** .
Sex Male	18 (86%)	1245 (70%)	0.12
Geographic Origin			0.13
Africa	5 (24%)	647 (36%)	.
Asia	3 (14%)	375 (21%)	.
Other	5 (24%)	166 (9%)	.
Europa	8 (38%)	591 (33%)	
Body mass index (kg/m^2)			0.52
median (Q1-Q3)	24.9 (23.9-28.4)	24.8 (22.3-27.8)	.
Missing	0	18	. .
Arterial hypertension	9 (43%)	357 (20%)	**0.02**
Diabetes	1 (5%)	169 (10%)	0.71
Fibrosis score			**<0.0001**
F0	0 (0%)	150 (11%)	.
F0/F1	0 (0%)	271 (19%)	.
F1	1 (6%)	290 (21%)	.
F1/F2	0 (0%)	137 (10%)	.
F2	2 (12%)	251 (18%)	.
F2/F3	1 (6%)	23 (2%)	.
F3	4 (24%)	115 (8%)	.
F3/F4	1 (6%)	15 (1%)	.
F4	8 (47%)	151 (11%)	.
Missing	4	376	.

Fibrosis evaluation method			**0.01**
Platelet count <150 or PT <70%	5 (29%)	74 (5%)	.
Liver biopsy	4 (24%)	219 (16%)	.
Fibroscan	0 (0%)	117 (8%)	.
Fibrotest	0 (0%)	34 (2%)	.
Other NI scores	0 (0%)	3 (0%)	.
Physician evaluation based on patient's history	8 (47%)	956 (68%)	.
Missing	4	376	.
HBeAg			0.77
Negative	17 (81%)	1373 (83%)	
Positive	4 (19%)	288 (17%)	
Missing	0	118	
Past excessive alcohol consumption	5 (24%)	178 (10%)	**0.05**
Current excessive alcohol consumption	0 (0%)	2 (0%)	1.00
Missing	6	532	.
Smoking	5 (24%)	328 (18%)	0.57
Missing	0	1	.
Albumin (g/L)			0.93
median (Q1-Q3)	42.6 (40.8-46)	43.1 (40.8-45.8)	
Missing	2	590	
Prothrombin rate (%)			**0.04**
median (Q1-Q3)	90 (79-96)	95 (87-100)	
Missing	0	360	
Platelets count (per µL)			**0.04**
median (Q1-Q3)	187000 (144000-207000)	207000 (171000-247000)	
Missing	1	161	
Alanine aminotransferase (UI/L)			0.84
median (Q1-Q3)	29 (23-37)	28 (21-39)	
Missing	0	61	
Aspartate aminotransferase (UI/L)			0.13
median (Q1-Q3)	32.5 (23.5-40)	26 (22-33)	
Missing	1	72	

Alpha fetoprotein (ng/mL) median (Q1-Q3) Missing	 2.5 (2-3.9) 3	 2.9 (2-4) 413	0.99
Creatininemia (mg/L) median (Q1-Q3) Missing	 9.5 (8.9-11.2) 1	 8.9 (7.6-10.3) 114	0.06 . . .
Hemoglobin (g/dL) median (Q1-Q3) Missing	 14.9 (13.5-15.8) 1	 14.6 (13.4-15.5) 130	0.54 . . .
Gamma-Glutamyl transpeptidase (UI/L) median (Q1-Q3) Missing	 52 (34-82) 1	 26 (18-41) 191	**<0.0001** . . .
Bilirubin (µmol/L) median (Q1-Q3) Missing	 14.6 (8.7-19) 1	 9.7 (7-13.6) 233	**0.01**
Child A B C Missing	 8 (100%) 0 (0%) 0 (0%) 1	 103 (95%) 5 (5%) 1 (0%) 57	1.00
HBV-DNA (log_{10} UI/mL) Median Missing	 1.3 (1.3-1.3) 2	 1.3 (1.1-1.3) 135	0.27
HBV treatment experienced at start of TDF or ETV No Yes	 13 (62%) 8 (38%)	 982 (55%) 797 (45%)	0.54 . .
NA treatment experienced at entry in the cohort No Yes	 1 (5%) 20 (95%)	 37 (2%) 1742 (98%)	0.40
Duration of past exposure to TDF or ETV (years) median (Q1-Q3)	 1.6 (0.8-3.6)	 2.7 (1.1-4.5)	0.22 . .

Time from first HBV treatment (years) median (Q1-Q3) Missing	 4.4 (1.5-9.0) 1	 4.6 (1.8-9.0) 47	0.85 . . .
Time since HBV diagnosis (years) median (Q1-Q3) Missing	 48.7 (27.2-58.7) 7	 32.2 (11.3-45.6) 736	**0.04** . . .
Calendar year of treatment initiation median (Q1-Q3)	 2012 (2010-2013)	 2011 (2009 – 2013)	0.25
PAGE-B score median (Q1-Q3) Missing	 18 (13-20) 1	 12 (8-16) 161	**<0.0001**