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Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Hepather cohort.

Stanislas Pol, Delphine Bonnet, Virginie Payssan-Sicart, Chloe Pomes, François Bailly, Marjolaine Beaudoin, Dominique Giboz, Kerstin Hartig-Lavie, Marianne Maynard, Eric Billaud, et al.

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3 Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in
4 the French AFEF/ANRS CO22 Hepather cohort
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For Peer Review

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 Sub-Saharan 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

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3 following effective viral suppression with either interferon- α or nucleos(t)idic analogues (15).
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5 The more severe the underlying liver disease, the greater benefit of viral suppression (5-
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7 7,16), while there is a less marked benefit when a resistance mutation develops (17). The
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9 benefit of these treatments is significant histological improvement, resulting in a reduction
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11 of fibrosis over time or even a reversion of cirrhosis, as reported for other viral cirrhoses
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13 (18).

14 Although nucleos(t)idic analogues have been clearly associated with a reduction in
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16 complications (16-17, 19-25), recent meta-analyses of Asian cohort studies suggest that
17
18 tenofovir could be associated with a reduced risk of HCC as well as a lower risk of
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20 decompensated cirrhosis or liver-related deaths compared to entecavir (26-33). The aim of
21
22 our study was to prospectively compare the results of Tenofovir and Entecavir on five
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24 outcomes (HCC, decompensated cirrhosis, liver transplantation, all-causes of death and liver-
25
26 related death) as well as a composite endpoint combining any of these outcomes, in patients
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28 with chronic HBV infection from the Hepather cohort treated with nucleos(t)idic analogues.
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30 **Methods**

31 *Study design and participants*

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34 The ANRS CO22 Hepather cohort «Therapeutic option for hepatitis B and C: a French
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36 cohort», is a national, multicenter, observational cohort study with prospectively collected
37
38 data of patients with hepatitis B or C virus infection that has been previously described (see
39
40 reference 34 for a complete description). The main objectives of this study are to quantify
41
42 the clinical efficacy and safety of new hepatitis treatments in real-life. Between August 6th,
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44 2012 and December 31st, 2015, 14,389 HCV-positive patients and 6249 HBV-infected
45
46 patients were enrolled to be followed up for a median of 7 years. Detailed demographics,
47
48 clinical (including fibrosis staging and history of past treatment) and biological data were
49
50 collected during the inclusion visit on an electronic case-report form. Follow-up included
51
52 systematic visits (once a year) and spontaneous reports for particular events on specific data
53
54 forms (e.g. deaths, HCC, decompensated cirrhosis and the onset of therapy). The study was
55
56 observational and the choice of the NUCs regimen, treatment timing, and screening for HCC
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58 or the progression of fibrosis was left up to the physician, but followed national French
59
60 recommendations based on European Association for the Study of the Liver (EASL)

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

10 We selected all patients with chronic hepatitis B who were treated with TDF or ETV for more
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12 than 6 months at entry or after entry to compare the risk of the occurrence of HCC, other
13
14 liver-related events and death between these two treatments.

15
16 Cirrhosis decompensation corresponded to the occurrence of non-carcinomatous cirrhosis
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18 complications, namely ascites, spontaneous bacterial peritoneal infection variceal bleeding,
19
20 hepatic encephalopathy, by definition HCC free decompensation. Pregnant women or
21
22 immunocompromised patients who were receiving nucleos(t)idic analogues prophylaxis
23
24 were not excluded but correspond to a limited number of patients (not available).

25 HDV and HCV coinfecting patients (n = 243) were excluded. The main analysis excluded
26
27 patients with a past history of HCC, decompensated cirrhosis or liver transplantation.
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29

30 *Outcomes*

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32 Study outcomes were incident HCC, incident decompensated cirrhosis, liver transplantation,
33
34 all-causes death and liver-related death. We also created a composite endpoint combining
35
36 all cause death and HCC, decompensated cirrhosis or liver transplantation, whichever
37
38 occurred first. The causes of death were classified by an adjudication committee including
39
40 two hepatologists (HF, MB) and two methodologists (CD, FC). Adjudication was based on
41
42 medical records, and investigators filled in a specific case report form. Data on incident HCC
43
44 included the number of lesions at diagnosis, the size of the largest nodule, total size,
45
46 diagnostic imaging procedures and treatment. Decompensated cirrhosis was defined as the
47
48 development of ascites, variceal hemorrhage, encephalopathy, and/or jaundice.
49

50 *Predictor variables*

51
52 Potential predictors of a clinical outcome were evaluated at entry in the cohort and included
53
54 age, gender, body mass index (BMI), geographic origin, time since HBV diagnosis, time since
55
56 first treatment, time since the start of treatment with Tenofovir or Entecavir, the start of
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58 being HBV treatment-experienced with Tenofovir or Entecavir, fibrosis score, diabetes,
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60 arterial hypertension, past and current alcohol consumption, biological variables (albumin,

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

26 27 28 *Statistical analyses*

29
30 The index date was the date a patient first started entecavir or Tenofovir. Survival was
31 calculated for all outcomes as the time between the index date and the date of HCC,
32 decompensated cirrhosis, liver transplantation all-cause deaths, liver-related deaths or
33 composite endpoint, the last-follow-up visit, or July 31, 2019, whichever occurred first.
34 To deal with left-truncation of exposures and take into account a potential selection bias
35 caused by using a prevalent cohort, we estimated delayed entry Cox-models (38). In delayed
36 entry survival analysis, the risk set at a particular time includes only patients who started
37 follow-up prior to that time, and have not yet experienced the outcome or been censored
38 from the study by that time. In Kaplan-Meier curves adjusted for delayed entry, the number
39 at risk may thus increase with time, as some patients will enter in the risk set after a delay
40 corresponding to the time between treatment start (time origin) and start of follow-up
41 (entry in the cohort). To illustrate, a prevalent tenofovir patient who initiated tenofovir 2
42 years before entry in the cohort and with 2 years follow-up will contribute to estimating the
43 survival between 2 and 4 years.

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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

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

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

21 Categorization of continuous covariates was based on clinically relevant previously
22 determined thresholds (all biological parameters) or quartiles limits (age, time since HBV
23 diagnosis). Missing covariate values were handled using indicators for missing data in the
24 multivariate model. All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, North
25 Carolina, USA). A P-value < .05 was considered to be statistically significant.

26 Results

27 One thousand eight hundred and thirty three patients met the eligibility criteria (figure 1).
28 Follow-up information was missing in 33 patients (1.8%). Therefore, follow-up information
29 was available for 1800 (98%) patients (986 tenofovir and 814 Entecavir), who were included
30 in analyses. Most of the patients (1733: 96%) started Tenofovir or Entecavir treatments
31 before their entry in the cohort. The median time between start of Tenofovir or Entecavir
32 treatments and entry in the cohort was approximately 3 years, and only 7% of patients had a
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3 HBV DNA titer > 2000 UI/ml at entry in the cohort. 805 patients were given another
4 treatment before Entecavir or Tenofovir: switches were either related to the evolution from
5 first to second generation nucleos(t)idic analogues, to nucleosides resistance or to
6 intolerance to the previous nucleos(t)idic analogues. Overall 55 (3%) patients changed
7 antiviral therapy over time. 8 (15%) of them switched the first year, 22 (40%) switched the
8 2nd year, 14 (25%) switched the 3rd year and 11 (20%) switched the 4th year.
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16 Baseline demographic, clinical, and laboratory patient characteristics are provided in table 1.
17 Patients were a median of 46.7 years old (IQR 37.1-57.8) and 1263 (70%) were men. Median
18 follow-up was 4.2 years (IQR 3.09-5.06) and was similar between the two groups.
19

20 Patients who received Tenofovir were younger, more frequently women, had a lower
21 prevalence of arterial hypertension or diabetes, had more frequent positive HBe antigen,
22 had a lower prothrombin, creatinine and gamma-glutamyl transpeptidase levels, had a
23 higher alanine aminotransferase and aspartate aminotransferase levels, were more
24 frequently HBV treatment-experienced at the start of treatment (with a longer history of
25 prior HBV treatment) and had had shorter past exposure to current treatment than those
26 who received Entecavir. Geographic origin, alcohol consumption, fibrosis stage and HBV-
27 DNA levels were not different at baseline between the two treatment groups. The balance of
28 baseline characteristics following inverse probability of treatment weighting is presented in
29 supplementary material (supplementary table 1).
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40 21 HCC, 8 decompensated cirrhosis, 2 liver transplantation and 28 all-cause deaths (8 liver-
41 related death) were reported during follow-up (table 2). The incidence rates for the
42 composite endpoint were respectively 4.1 (95%CI 3.0; 5.4) per 1000 person-years (PY) in the
43 Tenofovir group and 5.0 (95%CI 3.3;7.2) per 1000 PY in the Entecavir group, (P=0.20 by
44 comparison of inverse probability of treatment weighting survival curves). Incidence was not
45 different between the Tenofovir and the Entecavir group for HCC (1.8(0.9;3.2) and 1.6
46 (0.7;3.0)), decompensated cirrhosis 0.6 (0.2;1.6) and 0.7 (0.2;1.8)), all-causes deaths 1.7
47 (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
48 for the main analysis (Table 2) like for the patients with cirrhosis at baseline (supplementary
49 tables 2 and 3), the non cirrhotic patients (supplementary tables 4 and 5).
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3 The detailed characteristics of the 21 incident HCC are presented in supplementary table 6.
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5 The number of tumors at diagnosis was lower in the Tenofovir group than in the Entecavir
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7 group. No difference was found in the time between the initiation of Tenofovir or Entecavir
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9 and the occurrence of HCC after nucleos(t)idic analogues initiation, the time between the
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11 last normal imaging test and diagnosis, macroscopic pattern, total nodule size, largest
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13 nodule size or serum α -fetoprotein.

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

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

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

35
36 Hazard ratios of Tenofovir vs Entecavir for HCC, decompensated cirrhosis, all-causes deaths,
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38 liver-related deaths and composite endpoint were close to the unity, univariable analysis as
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40 well as multivariable (when feasible) analysis showing that there was no significant
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42 association between treatment and the risk of any of the clinical outcomes in the main
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44 analysis (table 3).

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46 Non liver-related cancers were identified in 3 Tenofovir-treated (incidence rate 0.5/1000 PY
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48 (0.1; 1.3) and 5 Entecavir-treated patients (incidence rate 0.9/1000 PY (0.3; 2.1)) in the main
49
50 analysis. No significant difference was found in the analysis for the incidence of non liver-
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52 related cancers between the 2 groups ($p = 0.35$). The 7 non-liver non-cancer related deaths
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54 were 2 cardiac disorders (acute coronary syndrome, one aortic valve disease), 1
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56 staphylococcal infection, 1 ischemic stroke and 2 renal failures.

57 58 59 **Discussion** 60

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3 In this first large prospective cohort of French patients with chronic HBV infection including
4 patients of European, African as well as Asian origin, the incidence of liver-related events,
5 namely HCC, decompensated cirrhosis, liver transplantation or death was not different
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7 between Tenofovir- and Entecavir-treated patients.
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10 Several prospective and retrospective studies have reported a decreased incidence of HCC in
11 nucleos(t)idic analogues-treated patients with cirrhosis, showing the benefit of HBV viral
12 suppression (16-25, 39). The mechanisms of HBV hepatocarcinogenesis are complex,
13 associating factors related to high viral load or HBV genotypes (15,40), liver regeneration in
14 fibrotic disease, HBV genome integration in the host hepatocyte genome (authorized by a
15 reverse transcription step during viral replication B) with chromosomal rearrangements as
16 well as cis-activation and trans-activation mechanisms (41-42). Nucleos(t)idic analogues-
17 associated viral suppression results in the resolution of fibrosis including biopsy-proven
18 reversal of cirrhosis in more than two thirds of treated patients after five years (18).
19

20 Nucleos(t)idic analogues therapy also decreases the risk of viral hepatocarcinogenesis as it
21 has been prospectively demonstrated in the first prospective randomized trial of lamivudine
22 vs. placebo in patients with significant biopsy-proven extensive fibrosis. Early evidence at 2
23 years showed that lamivudine-treated patients had a lower incidence of HCC than placebo-
24 treated patients and that the occurrence of YMDD mutations reduced this benefit in
25 lamivudine-treated patients (17). These results support the policy of treating all HBV-
26 infected patients with significant fibrosis with the most potent antiviral drugs, namely
27 Tenofovir and Entecavir (4-7), which have proven their efficacy.
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30 Noteworthy is the low rate of HCC in our treated series (around 0.3/year) as compared to
31 other series with figures ranging from 1.5 to 4.4%/year in nucleos(t)idic analogues -treated
32 as compared to 5.2 to 7.7% in untreated cirrhotic patients. These differences are likely
33 related to the rate of patients with cirrhosis (16%) or extensive fibrosis (8%) in our series and
34 to the difference in the duration of nucleos(t)idic analogues -exposure: most of studies
35 included patients since the beginning of the primary line of nucleos(t)idic analogues
36 treatment and compared treated to untreated patients; in our series, half of patients were
37 already treated and a significant rate of patients had a long-term history of nucleos(t)idic
38 analogues treatment before the inclusion in the analysis and viral suppression is associated
39 with a constant decline in the rate of complications, including HCC. In addition, differences
40 may partially be related to the different geographic origin of the patients. We know that
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3 Asian patients are mainly infected at birth, (mother to child transmission), African patients
4 are mainly infected during in early childhood while infection is mainly at the teen age and
5 young adult age in Northern countries (4-7). The duration of infection clearly influences the
6 risk of clinical events in chronic HBV infection and the risk of HCC appears in earlier age in
7 African or Asian than in European patients. In our series, there was no evidence of an impact
8 of the geographical origin on the risk of clinical events (data not shown).
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16 There was no difference in the survival curves between Entecavir and Tenofovir, except for
17 the all-causes mortality or for the composite endpoint in non-cirrhotic patients with a higher
18 rate in Entecavir-treated patients; we assume that these results, despite the inverse
19 probability of treatment weighting analysis, are the consequences of the sub-groups analysis
20 related to the inflation of the 1st species risk (alpha risk of 0.05).
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27 Why would Entecavir be less beneficial, as suggested by Asian studies from Korea, Taiwan
28 and Hong Kong (26-33)?
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30 The differential impact of HBV genotypes on HCC (40) cannot explain this difference. The
31 genotypes in Asia are mainly B and C, and the latter is associated with a higher risk of HCC.
32 Although we did not analyze HBV genotypes in our cohort, the absence of impact of
33 geographical origin on the risk of HCC with nucleos(t)idic analogues excludes this hypothesis.
34
35 Second, Entecavir was associated with the occurrence of malignancies in pre-clinical
36 toxicological studies (www.fda.gov/medwatch). Pulmonary adenomas and carcinomas,
37 hepatocellular adenomas and carcinomas, vascular tumors, glial tumors and cutaneous
38 tumors were observed in mouse and rat animal models exposed to very high doses of
39 Entecavir (approximately 42 times higher than the maximum recommended human dose of
40 1 mg/day in the mouse and 35 times higher in the rat). As a result of the putative
41 carcinogenic risk of Entecavir, France and Sweden refused to participate in registration
42 studies and an observatory prospective study was requested by drug agencies. However,
43 this product has been prescribed for more than 10 years and there are still no convincing
44 signs suggesting any potential carcinogenicity associated with Entecavir: the safety of
45 Entecavir was confirmed in the REALM study with a follow-up of at least 7 years in patients
46 receiving long-term randomized treatment with Entecavir or another nucleos(t)idic
47 analogues, which showed no increase in the occurrence of cancer (43). Thus, an increased
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3 risk of HCC associated with the long-term toxicity of Entecavir per se, appears unlikely. This
4 is also supported by the similar distribution of non-hepatic cancers in both groups, the
5 similar clinical and morphological characteristics of HCC in Tenofovir- and Entecavir-treated
6 patients as well as a similar delay between the initiation of Tenofovir or Entecavir and the
7 occurrence of HCC, the size and number of nodules, the time between the last normal
8 imaging test and the diagnosis of HCC, macroscopic pattern, total nodule size and serum
9 α -fetoprotein levels.

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

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28 It is noteworthy that, by opposition of the studies from Asia, other European studies did not
29 evidence any benefit of Tenofovir in reducing significantly the risk of HCC as compared to
30 Entecavir: results from multicenter European or US cohorts raise similar conclusions (45-46).
31 Our study has several strengths. First, it is a large prospective cohort, including 1800
32 patients, 986 patients in the Tenofovir and 814 patients in the Entecavir groups. Second,
33 patients are well phenotyped allowing to prospectively evaluate the impact of Tenofovir
34 compared to Entecavir on five outcomes (HCC, decompensated cirrhosis, liver
35 transplantation, all-cause deaths, liver-related death, and a composite endpoint combining
36 any of these outcomes, in nucleos(t)idic analogues HBV-treated patients from the Hepather
37 cohort. Third, patients are from different origins, including patients from European, African
38 as well as Asian origin.

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49 This study has several limitations. First, it is not a randomized study and characteristics of
50 the patients between the 2 groups are different: the Entecavir group had worse
51 characteristics than the Tenofovir group regarding the risk of HCC (age, gender, ...) like in
52 other registry cohorts in which the Tenofovir group was usually less severe requiring
53 weighting analysis for the comparisons between the groups, for example in the study from
54 South Korea (27). If we do consider, on the basis of studies from Asia, that Entecavir is
55 associated with an increased risk of HCC as compared to Tenofovir, this worse pattern
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3 should increase the difference between the 2 nucleos(t)idic analogues treatment favoring
4 Tenofovir; this heterogeneity could be considered as reinforcing the message that there is
5 no difference in the risk of HCC between Tenofovir and Entecavir and the heterogeneity is
6 cancelled by the inverse probability of treatment weighting analysis (supplementary table 1)
7 which does not evidence any difference between Tenofovir and Entecavir.
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12 Second, the number of liver-related clinical events was low and the study may have been
13 underpowered to detect a small difference between the two treatment groups, a
14 predominantly no cirrhotic population. Indeed, a post-hoc calculation of the statistical
15 power showed that our study had a 45% power to show a hazards ratio of 0.6 for HCC with
16 our sample size and rates, as reported in another study (27). To increase the statistical
17 power, we used a composite endpoint combining all relevant clinical outcomes but we did
18 not find any significant differences between the groups. If any difference exists between the
19 two groups, it should be limited.
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27 Third, our study selected and evaluated patients who had been receiving Tenofovir or
28 Entecavir for a median of 2.7 years as well as 45% of these patients who had been receiving
29 HBV treatment with nucleotides/nucleosides analogs for even longer at the start of follow-
30 up. Prior HBV treatment is strongly associated with the duration of viral suppression and was
31 adequately controlled using method accounting for left truncation in exposures (39),
32 adjustments or inverse probability of treatment weighting, thus limiting the risk of a
33 selection bias. However, prior treatment may explain our relatively low rates of HCC or other
34 liver-related complications compared to studies focusing on incident Tenofovir or Entecavir
35 users. While the geographical, clinical and pathological profiles of the patients as well as the
36 durations of follow-up were only slightly different for the nucleos(t)idic analogues in our
37 real-life cohort, in the Asian studies the distribution of NUCs and the follow-up durations
38 were imbalanced due to the very early registration of ETV (27). Although a hospital cohort
39 confirmed the results of the registry cohort, several sophisticated statistical methodologies
40 were required to make face-to-face comparisons between Entecavir and Tenofovir.
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52 Finally, another limitation of our study is the “heterogeneity” first in the evaluation of
53 fibrosis (histopathological, biochemical by noninvasive tests or by evaluation of the liver
54 stiffness) and second in the potential kinetics of fibrosis and its ability to reverse but also to
55 progress in a given patient. Fibrosis was mainly based on the physician feeling of the fibrosis
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3 for a given patient. Nevertheless, this uncertainty was equally distributed across the
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5 tenofovir and entecavir arms.

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7 In conclusion, this prospective cohort of French patients of different geographical origins
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9 with chronic hepatitis B virus infection, does not support a reduced benefit of entecavir
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11 treatment compared to tenofovir for the incidence of liver-related events in a predominantly
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13 no cirrhotic population.
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5 **Legends to figures**
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8 **Figure 1.** Flow of participants through the study comparing the progression of 1055 patients
9 with hepatitis B virus infection treated with tenofovir (TDF) compared to 885 patients
10 treated by entecavir (ETV) with or without a prior history of hepatocellular carcinoma (HCC)
11 or decompensated cirrhosis (DC).
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17 **Figure 2.** IPW survival curves of hepatocellular carcinoma, decompensated cirrhosis, liver
18 transplantation, death from all causes, liver-related deaths or a composite endpoint
19 corresponding to any of the clinical events in primary analysis in 986 patients with hepatitis
20 B virus infection treated by tenofovir compared to 814 patients treated by entecavir
21 (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).

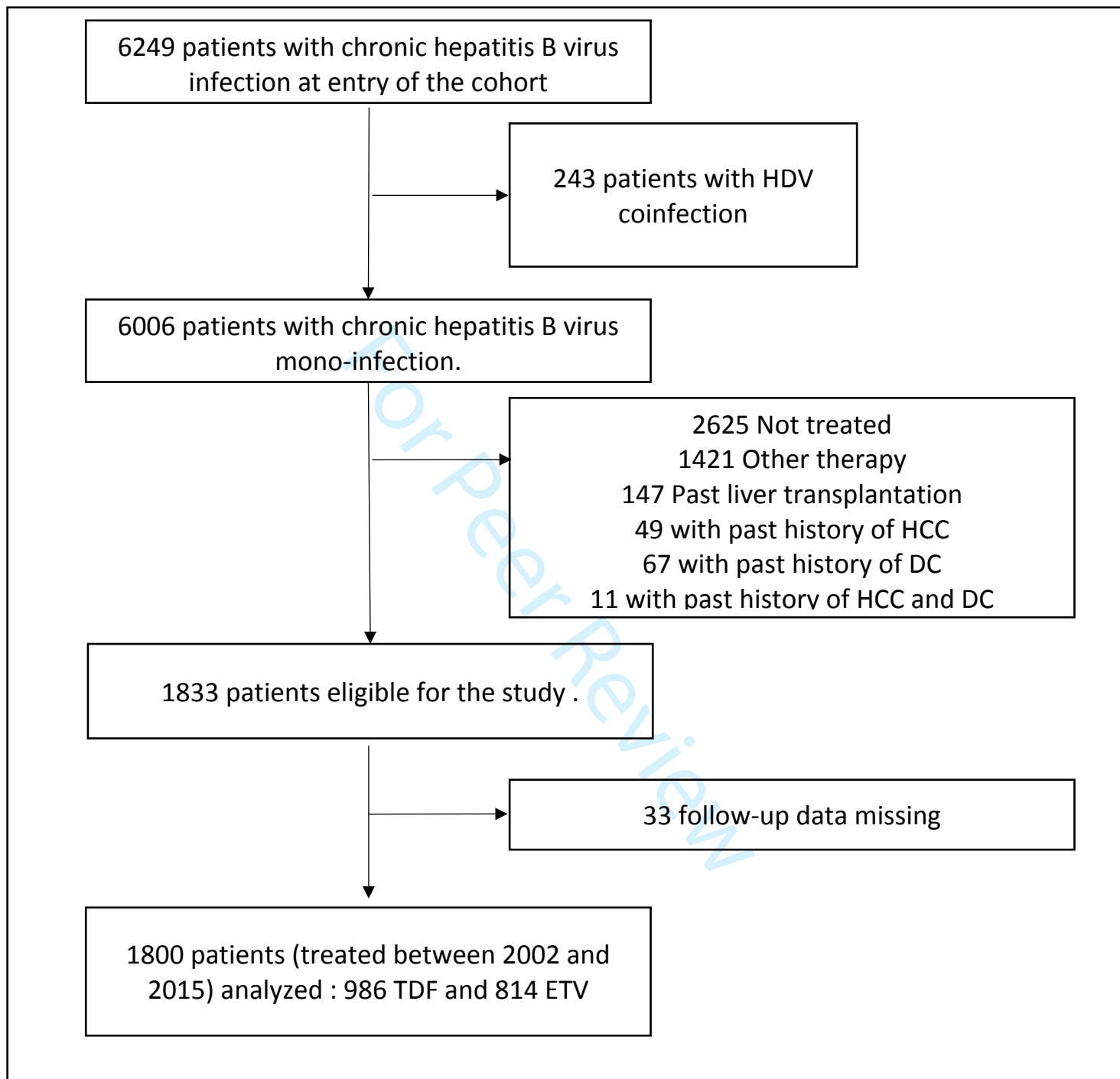


Figure 2. IPW survival curves of hepatocellular carcinoma, cirrhosis decompensation, liver transplantation, all-cause deaths, liver-related deaths or a composite endpoint corresponding to any of the clinical event in primary analysis in 986 hepatitis B virus-infected patients treated by Tenofovir compared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

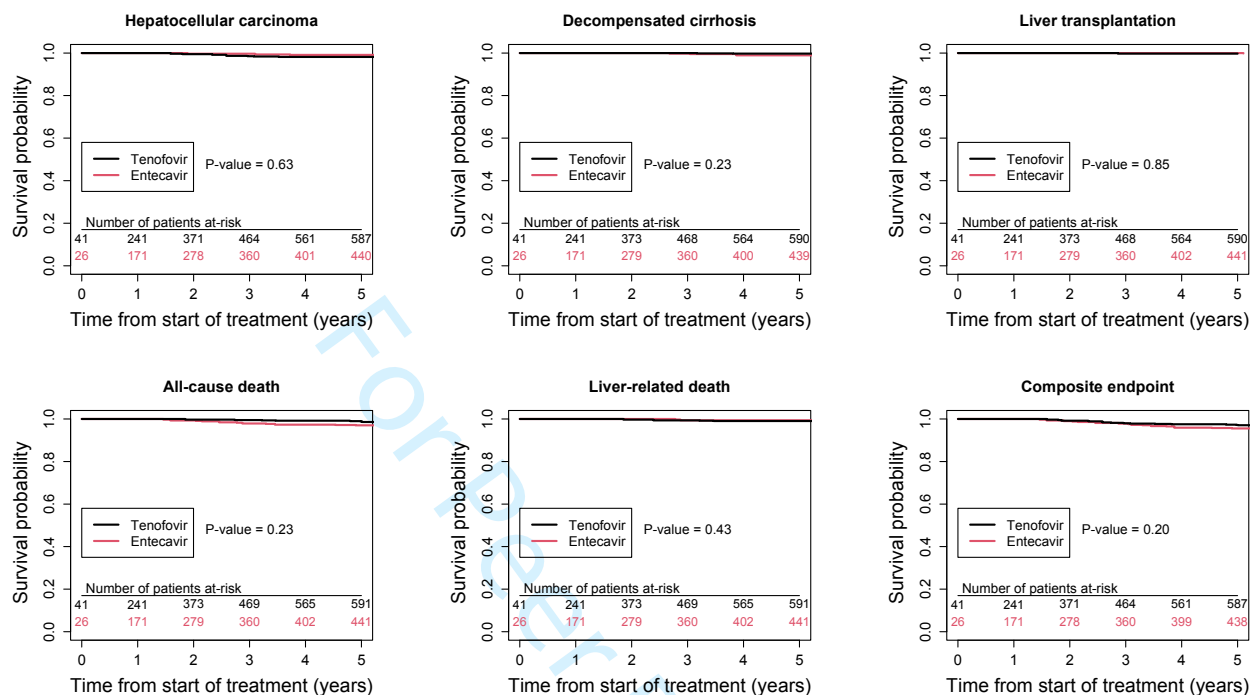


Table 1. Baseline characteristics of 986 hepatitis B virus-infected patients treated by Tenofovir (TDF) compared to 814 patients treated by Entecavir (ETV) with or without prior history of hepatocellular carcinoma (HCC) or cirrhosis decompensation (DC).

| | All patients (n = 1800) | Tenofovir (TDF) (n=986) | Entecavir (ETV) (n=814) | P-value |
|--|------------------------------------|--|--|-----------------------|
| Age (Years) median (Q1-Q3) | 46.7 (37.1-57.8) | 44.8 (35.0-56.5) | 49.2 (39.7-58.9) | <.0001 . |
| Sex Male | 1263 (70%) | 666 (68%) | 597 (73%) | 0.01 |
| 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) median (Q1-Q3) Missing | 24.8 (22.3-27.8) 18 | 24.7 (22.2-27.6) 11 | 25 (22.4-27.8) 7 | 0.14 . . |
| 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%) | . |
| Missing | 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 (log₁₀ 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 | |

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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) |

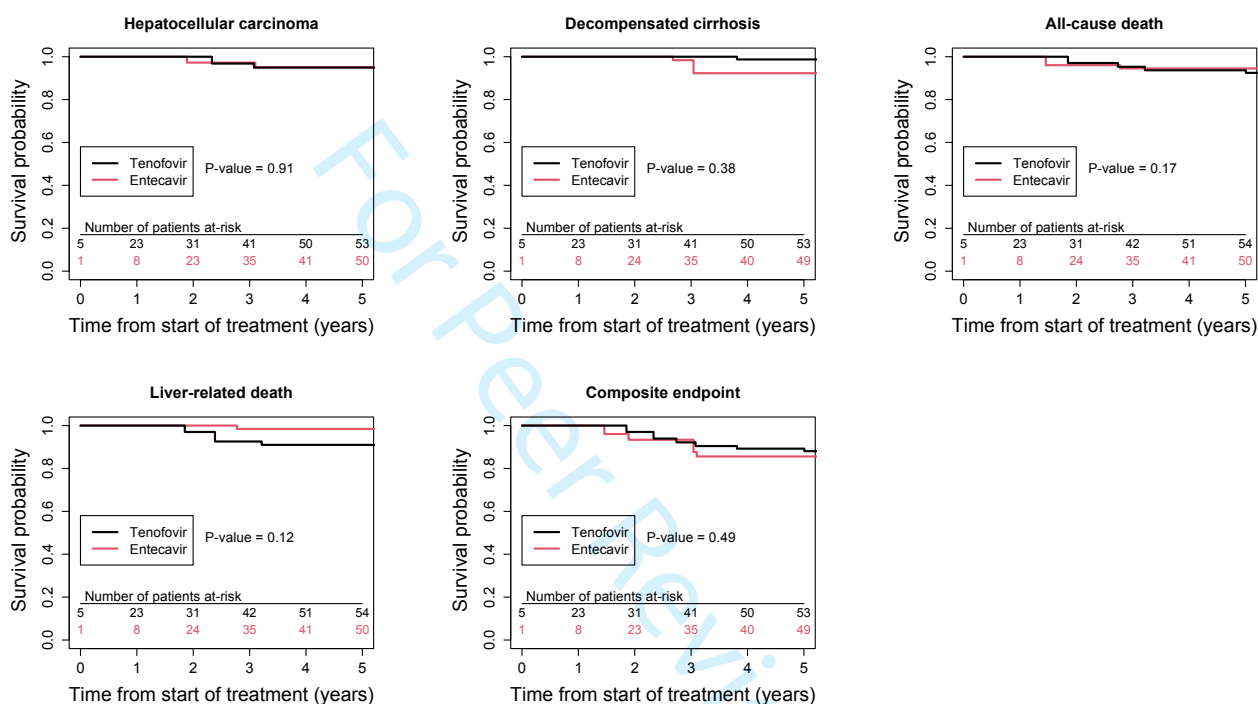
Table 3. Hazard ratios of Tenofovir versus Entecavir for hepatocellular carcinoma (HCC), cirrhosis decompensation (DC), liver transplantation (LT), all-cause deaths (ACD), liver-related deaths (LRD), or a composite endpoint (CE) corresponding to any of the clinical event in primary analysis set analysis 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) |

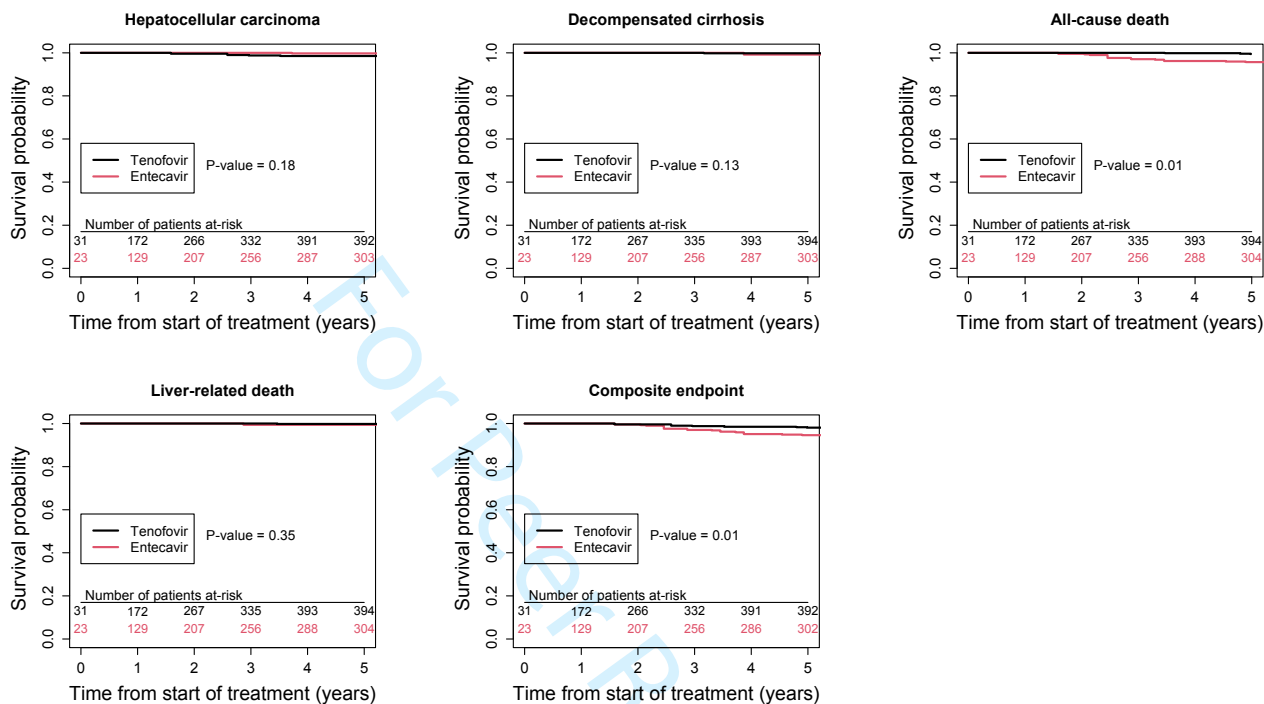
ND = Not done because of insufficient number of events

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/m²) | | | | |
| 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 | 2.1 | 2.3 | | |
| Other NI scores | 0.1 | 0.2 | | |
| Physician evaluation based on patient's history | 69.3 | 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 (%) | | | 0.99 | 0.1 |
| <30 g/L | 33.8 | 33.8 | | |
| ≥ 30 g/L | 66.2 | 66.2 | | |
| Prothrombin time (%) | | | 0.91 | -7.0 |
| ≤70 (%) | 5.1 | 5.2 | | |
| >70 (%) | 95.0 | 94.8 | | |
| Platelets (%) | | | 0.79 | 1.3 |
| <150000 per μL | 14.1 | 14.6 | | |
| ≥150000 per μL | 85.9 | 85.4 | | |
| Alanine aminotransferase (%) | | | 0.81 | 1.2 |
| ≤ 40 UI/L | 76.1 | 76.6 | | |
| > 40 UI/L | 23.9 | 23.4 | | |
| Aspartate aminotransferase (%) | | | 0.96 | 0.3 |
| ≤ 40 UI/L | 87.4 | 87.3 | | |
| > 40 UI/L | 12.6 | 12.7 | | |
| Alpha fetoprotein (%) | | | 0.94 | 1.3 |
| <5.5 ng/mL | 87.0 | 86.8 | | |
| ≥5.5 ng/mL | 13.9 | 13.2 | | |
| 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) (%) | | | 0.87 | 3.0 |
| <20 | 26.9 | 26.5 | | |
| [20-2000[| 64.4 | 65.7 | | |
| ≥2000 | 8.7 | 7.9 | | |
| HBV treatment experienced at start of TDF or ETV (%) | | | 0.77 | 1.4 |
| No | 57.3 | 56.4 | | |
| Yes | 42.7 | 43.6 | | |
| 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) (%) | | | 0.97 | 0.8 |
| <2 | 29.2 | 28.7 | | |
| [2-8[| 43.9 | 44.0 | | |
| ≥8 | 26.9 | 27.4 | | |
| Time since HBV diagnosis (years) | | | 0.56 | |
| Mean (sd) | 30.7 (19.0) | 31.5 (19.4) | | -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/m²) median (Q1-Q3) Missing | 24.9 (23.9-28.4) 0 | 24.8 (22.3-27.8) 18 | 0.52 . . |
| 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 | | | 1.00 |
| Missing | 0 (0%) | 2 (0%) | . |
| 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) | | | 0.99 |
| median (Q1-Q3) | 2.5 (2-3.9) | 2.9 (2-4) | |
| Missing | 3 | 413 | |
| Creatininemia (mg/L) | | | 0.06 |
| median (Q1-Q3) | 9.5 (8.9-11.2) | 8.9 (7.6-10.3) | . |
| Missing | 1 | 114 | . |
| | | | . |
| Hemoglobin (g/dL) | | | 0.54 |
| median (Q1-Q3) | 14.9 (13.5-15.8) | 14.6 (13.4-15.5) | . |
| Missing | 1 | 130 | . |
| | | | . |
| Gamma-Glutamyl transpeptidase (UI/L) | | | <0.0001 |
| median (Q1-Q3) | 52 (34-82) | 26 (18-41) | . |
| Missing | 1 | 191 | . |
| | | | . |
| Bilirubin (µmol/L) | | | 0.01 |
| median (Q1-Q3) | 14.6 (8.7-19) | 9.7 (7-13.6) | |
| Missing | 1 | 233 | |
| Child | | | 1.00 |
| A | 8 (100%) | 103 (95%) | |
| B | 0 (0%) | 5 (5%) | |
| C | 0 (0%) | 1 (0%) | |
| Missing | 1 | 57 | |
| HBV-DNA (log₁₀ UI/mL) | | | 0.27 |
| Median | 1.3 (1.3-1.3) | 1.3 (1.1-1.3) | |
| Missing | 2 | 135 | |
| HBV treatment experienced at start of TDF or ETV | | | 0.54 |
| No | 13 (62%) | 982 (55%) | . |
| Yes | 8 (38%) | 797 (45%) | . |
| NA treatment experienced at entry in the cohort | | | 0.40 |
| No | 1 (5%) | 37 (2%) | |
| Yes | 20 (95%) | 1742 (98%) | |
| Duration of past exposure to TDF or ETV (years) | | | 0.22 |
| median (Q1-Q3) | 1.6 (0.8-3.6) | 2.7 (1.1-4.5) | . |
| | | | . |

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