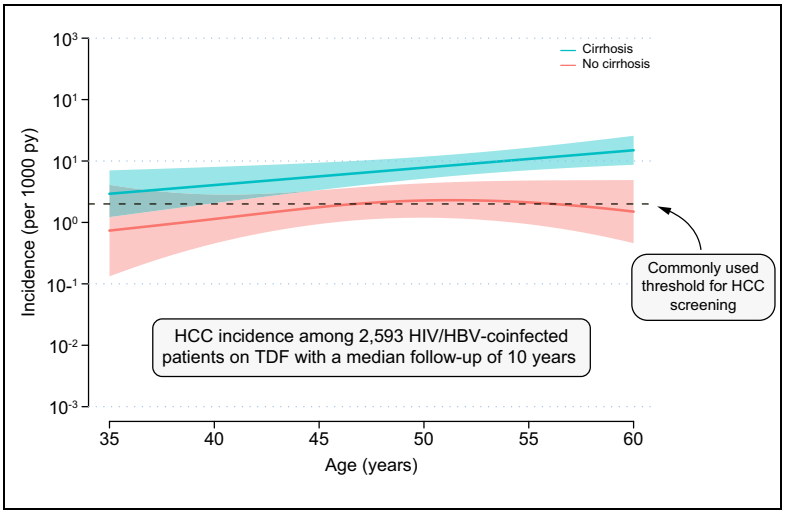
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies

Graphical abstract



Highlights

- Over 32,673 patient-years of follow-up, 60 (1.7%) HIV/HBV-coinfected individuals developed HCC.
- In cirrhotic patients on TDF-containing antiretroviral therapy, the incidence of HCC was 5.90 per 1,000 patient-years.
- In non-cirrhotic patients on TDF-containing antiretroviral therapy, the incidence was 1.17 per 1,000 patient-years.
- HCC incidence stayed below the recognized screening threshold in non-cirrhotics who started TDF when <46 years old.

Authors

Gilles Wandeler, Etienne Mauron, Andrew Atkinson, ..., Didier Neau, Fabrice Bonnet, Andri Rauch

Correspondence

gilles.wandeler@insel.ch
(G. Wandeler)

Lay summary

We investigated the incidence of hepatocellular carcinoma in HIV/hepatitis B virus-coinfected individuals from a large multi-cohort study in Europe. Over 32,673 patient-years, 60 individuals (1.7%) developed hepatocellular carcinoma. The incidence of hepatocellular carcinoma remained low in patients without cirrhosis, who started on tenofovir disoproxil fumarate when aged <46 years old.

http://dx.doi.org/10.1016/j.jhep.2019.03.032
© 2019 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved. J. Hepatol. 2019, 71, 274–280

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies

Gilles Wandeler[1,2,*], Etienne Mauron[1,†], Andrew Atkinson[1,†], Jean-François Dufour[3], David Kraus[1,4], Peter Reiss[5,6,7], Lars Peters[8], François Dabis[9], Jan Fehr[10,11], Enos Bernasconi[12], Marc van der Valk[7], Colette Smit[5], Lars K. Gjærde[8], Jürgen Rockstroh[13], Didier Neau[14], Fabrice Bonnet[9,15], Andri Rauch[1], on behalf of the Swiss HIV Cohort Study, Athena Observational Cohort Study, EuroSIDA, ANRS CO3 Aquitaine Cohort

[1]*Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland;* [2]*Institute of Social and Preventive Medicine, University of Bern, Switzerland;* [3]*University Clinic for Visceral Surgery and Medicine, Bern University Hospital, University of Bern, Switzerland;* [4]*Department of Mathematics and Statistics, Masaryk University, Brno, Czech Republic;* [5]*HIV Monitoring Foundation, Amsterdam, the Netherlands;* [6]*Department of Global Health, Amsterdam University Medical Centers, Location AMC, Amsterdam, the Netherlands;* [7]*Division of Infectious Diseases, Amsterdam University Medical Centers, Location AMC, the Netherlands;* [8]*CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [9]*ISPED, Université Bordeaux, Centre INSERM U1219-Epidémiologie Biostatistique, France;* [10]*Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Switzerland;* [11]*Department of Public Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland;* [12]*Division of Infectious Diseases, Regional Hospital Lugano, Switzerland;* [13]*Department of Medicine I, University Hospital Bonn, Bonn, Germany;* [14]*CHU de Bordeaux, Service de Maladies Infectieuses et Tropicales, Bordeaux, France;* [15]*CHU Bordeaux, Service de Médecine Interne et Maladies Infectieuses, Bordeaux, France*

Background & Aims: Robust data on hepatocellular carcinoma (HCC) incidence among HIV/hepatitis B virus (HBV)-coinfected individuals on antiretroviral therapy (ART) are needed to inform HCC screening strategies. We aimed to evaluate the incidence and risk factors of HCC among HIV/HBV-coinfected individuals on tenofovir disoproxil fumarate (TDF)-containing ART in a large multi-cohort study.

Methods: We included all HIV-infected adults with a positive hepatitis B surface antigen test followed in 4 prospective European cohorts. The primary outcome was the occurrence of HCC. Demographic and clinical information was retrieved from routinely collected data, and liver cirrhosis was defined according to results from liver biopsy or non-invasive measurements. Multivariable Poisson regression was used to assess HCC risk factors.

Results: A total of 3,625 HIV/HBV-coinfected patients were included, of whom 72% had started TDF-containing ART. Over 32,673 patient-years (py), 60 individuals (1.7%) developed an HCC. The incidence of HCC remained stable over time among individuals on TDF, whereas it increased steadily among those not on TDF. Among individuals on TDF, the incidence of HCC was 5.9 per 1,000 py (95% CI 3.60–9.10) in cirrhotics and 1.17 per 1,000 py (0.56–2.14) among non-cirrhotics. Age at initiation of TDF (adjusted incidence rate ratio per 10-year increase: 2.2, 95% CI 1.6–3.0) and the presence of liver cirrhosis (4.5, 2.3–8.9) were predictors of HCC. Among non-cirrhotic individuals, the incidence of HCC was only above the commonly used screening threshold of 2 cases per 1,000 py in patients aged >45 years old at TDF initiation.

Conclusions: Whereas the incidence of HCC was high in cirrhotic HIV/HBV-coinfected individuals, it remained below the HCC screening threshold in patients without cirrhosis who started TDF aged <46 years old.

Lay summary: We investigated the incidence of hepatocellular carcinoma in HIV/hepatitis B virus-coinfected individuals from a large multi-cohort study in Europe. Over 32,673 patient-years, 60 individuals (1.7%) developed hepatocellular carcinoma. The incidence of hepatocellular carcinoma remained low in patients without cirrhosis, who started on tenofovir disoproxil fumarate when aged <46 years old.

© 2019 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Hepatitis B virus (HBV) infection is the most important cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide.[1] In high-income settings, between 5 and 10% of HIV-infected individuals are coinfected with HBV, which is a major cause of severe morbidity and mortality in this population.[2] HIV infection accelerates the progression of HBV-related liver disease and mortality is higher among HIV/HBV-coinfected individuals compared to HBV-monoinfected ones.[3] While the incidence of HBV-related HCC is estimated to range between 0.1 and 0.4% per year among non-cirrhotics and to be above 3% per year among cirrhotics, it is uncertain if the risk of developing HCC is different among HIV/HBV-coinfected individuals.[4] In fact, many factors which have a profound impact on HBV-related HCC incidence, including age, sex, liver cirrhosis, HBV viral load, hepatitis B e antigen (HBeAg) and hepatitis delta virus

Keywords: Hepatitis B infection; HIV infection; Hepatocellular carcinoma; Screening; Antiretroviral; Nucleotide inhibitors; Surveillance.
Received 19 November 2018; received in revised form 2 March 2019; accepted 29 March 2019; available online 6 April 2019
* Corresponding author. Address: Department of Infectious Diseases, Inselspital, 3010 Bern, Switzerland. Tel.: +41 31 632 2525.
E-mail address: gilles.wandeler@insel.ch (G. Wandeler).
† Equal contribution.

(HDV)-coinfection, are distributed differently among HIV-infected individuals compared to HIV-uninfected ones.[5–8]

International guidelines recommend the initiation of tenofovir-containing antiretroviral therapy (ART) in all HIV-infected individuals who are positive for hepatitis B surface antigen (HBsAg). Tenofovir disoproxil fumarate (TDF) is very successful in suppressing HBV replication, independent of HIV infection, although treatment response seems to be slightly delayed in HIV/HBV-coinfected individuals.[8–10] Importantly, no clinically relevant HBV-related resistance to TDF has been described to date.[11] The use of the potent nucleos(t)ide analogs (NAs) TDF and entecavir (ETV) has been associated with a reduced incidence of HCC among HBV-infected patients in Europe and Asia.[12,13] Among 325 cirrhotic HBV-infected patients treated with TDF or ETV, the HCC incidence rate within the first 5 years (3.22% per year) was higher than that beyond 5 years of therapy (1.57% per year), suggesting a potential decrease in HCC risk with long-term suppression of HBV replication.[12] Furthermore, recent data from South Korea suggest that HCC incidence is further decreased, albeit not eliminated, in the event of HBsAg loss during NA therapy, also defined as the functional cure of HBV infection.[14]

HCC surveillance through 6-monthly ultrasound imaging aims at reducing mortality by diagnosing small lesions that are potentially curable by resection, ablation or transplantation,[4,15] Whereas the natural history of hepatitis C virus (HCV)-related HCC is largely driven by liver cirrhosis, HBV-related HCC also develops in non-cirrhotic individuals, which makes surveillance strategies more complex. Current recommendations for HBV-related HCC surveillance are mainly based on incidence estimated in untreated HBV-monoinfected patients. It is generally accepted that screening is cost-effective in sub-populations with an incidence >0.2%/year, such as individuals with cirrhosis, Asian males >40 years, Asian females >50 years and Africans. Among treated HBV-infected Caucasians, the recently established PAGE-B score seems to be particularly helpful in evaluating the risk of HCC and potential indication for HCC screening.[4,16] However, this score has not been evaluated among HIV/HBV-coinfected individuals to date. Furthermore, as the large majority of HIV/HBV-coinfected patients are expected to have a suppressed HBV viral load on a TDF-containing ART, it is unknown if this large patient group would benefit from HCC screening. We explored the long-term incidence of HCC during NA therapy in the largest collaborative study on HIV/HBV-coinfection in Europe to date. In order to inform HCC screening strategies among HIV/HBV-coinfected individuals on TDF-containing ART, we assessed the risk of HCC in sub-populations categorized by age, sex and the presence of liver cirrhosis.

Materials and methods

Study setting

Patients from the following 4 prospective European HIV cohorts were included: The Swiss HIV cohort study (SHCS, www.shcs.ch),[17] EuroSIDA (www.chip.dk/Ongoing-Studies/EuroSIDA/About),[18] Athena Observational Cohort Study (www.hiv-monitoring.nl/english/),[19] and ANRS CO3 Aquitaine Cohort.[20] Detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events, laboratory measurements, viral hepatitis coinfections, and on the full treatment history for HBV and HIV infections were collected using standard protocols at registration and at intervals of 3 to 6 months. Local ethical committees of all participating study sites approved the cohort studies and written or verbal consent was obtained from all participants, as appropriate according to local regulations.

Inclusion criteria, definitions and outcomes

We included all HIV-infected adults with a positive hepatitis B surface antigen (HBsAg) test and a complete ART history available. Patients were categorized according to the HBV-activity of their ART regimen: (i) no active drug, or first generation drugs, such as lamivudine (LAM) or emtricitabine only (referred to as the "no TDF group"); or (ii) second-generation drugs, including TDF and ETV (referred to as the "TDF group", as only 35 patients were on ETV). Patients who did not start TDF at any time-point were grouped together as the incidence of HCC was similar in those on LAM or no HBV therapy, according to preliminary analyses in this patient population.[21] Individual follow-up was measured from the date of inclusion into one of the cohorts until the date of database closure (01.01.2015), HCC diagnosis, death, or loss to follow-up, whichever happened first.

Our primary outcome was the occurrence of HCC at any time-point during follow-up. In all participating cohorts, data on causes of death and confirmation of HCC diagnosis were collected on standardized case-report forms, using information from medical hospitalizations, imaging studies or liver histology from biopsy to inform and validate the diagnosis. Liver cirrhosis was defined primarily according to histology reports from liver biopsies or as a liver stiffness measurement (LSM) >11 kPa.[22] If these 2 measurements were not available, we classified participants into the group with cirrhosis if the AST-to-platelet ratio index (APRI) was >2.0, as recommended by the World Health Organization.[22]

Statistical analyses

We described demographic and clinical characteristics using absolute numbers and proportions, or medians and interquartile ranges (IQR), and compared them between patients in the "TDF group" and those in the "non-TDF group" using Chi-square or Mann-Whitney *U* tests, as appropriate. The incidence of HCC was described for the full population and compared between sub-groups according to the main demographic and clinical characteristics. Non-parametric cumulative hazard plots were used to assess crude risk of HCC across the 2 HBV treatment groups. In order to predict the incidence rate ratio of HCC during therapy for both groups, we fitted a Poisson regression model, stratified by cumulative time on therapy. Individuals could contribute follow-up time to different NAs if they were switched from 1 drug to another.

Among patients on TDF-containing ART, we explored graphically the incidence of HCC according to the presence of liver cirrhosis and the PAGE-B score.[16] The latter is based only on baseline patients' age, sex and platelets, and is a reliable score for prediction of the 5-year HCC risk in Caucasian HBV-infected patients under ETV or TDF. As proposed in the most recent EASL guidelines, we used the PAGE-B score cut-off <10 *vs.* ≥10.[11] We evaluated the association between HCC and potential risk factors, including age, sex, time-updated CD4 cell counts, probable mode of HIV transmission, ethnicity (Caucasian *vs.* non-Caucasian), HCV infection, the respective cohort, cumulative time off TDF (*i.e.* time from inclusion to first initia-

tion of TDF), and liver cirrhosis, using univariable and multivariable Poisson regression analyses. Derived adjusted incidence rate ratios for HCC were shown graphically in a Forest plot. In order to inform HCC screening strategies for HIV/HBV-coinfected individuals starting TDF-containing ART, we predicted the cumulative incidence of HCC in specific population sub-groups in relation to the widely used incidence threshold for HCC screening (2 cases per 1,000 patient-years [py]).[15] The sub-groups were selected according to the results of the multivariable analyses. Where appropriate, generalized additive models were fitted using restricted cubic splines for continuous variables.

HDV infection and HBeAg-positivity have both been associated with a higher incidence of HCC in previous studies.[6,7] To assess the impact of these 2 characteristics on the incidence of HCC, we repeated the main analyses in the cohorts with data available. In order to avoid relevant selection bias, we only included cohorts in which more than 60% of their patients had data available. To further explore potential differences in results between patients infected with HCV and others, we also repeated the analyses after having excluded HIV/HBV/HCV-coinfected individuals. All statistical analyses were performed using R (Version 3.4).

Results

Description of study population and overall HCC incidence

Of the 3,625 HIV/HBV-coinfected individuals included in this study, 2,593 (71.5%) had received TDF or ETV during follow-up. Overall, 40.3% of the cumulative follow-up time was spent on TDF, 30.5% on LAM only and 29.2% on ART without HBV activity. Table 1 compares the main characteristics of patients in the "TDF group" with those of individuals in the "no TDF group". Age and sex distribution were similar across treatment groups, but individuals from the "no TDF group" were more likely to be Caucasian, injection drug users (IDU), and to be HCV-coinfected. Importantly, HIV/HBV-coinfected individuals who never received TDF had a shorter median follow-up time compared to those on TDF (5 *vs.* 9.8 years), and the majority of them had their last follow-up visit before 2009, whereas most patients on TDF were still in care at the time of analyses (Table 1). Over 32,673 py, 60 individuals (1.7%) developed an HCC, resulting in an overall incidence of 1.84 per 1,000 py (95% CI 1.40–2.36). The incidence rate of HCC remained stable over time when patients used TDF (adjusted incidence rate ratio [aIRR] per additional year: 0.95, 95% CI 0.85–1.06, Fig. 1), whereas it increased steadily during the time patients were not on TDF (aIRR: 1.14, 95% CI 1.07–1.21). The relatively constant incidence of HCC during TDF therapy allowed us to assess the long-term HCC risk based on characteristics at the time of TDF initiation.

Incidence of HCC among HIV/HBV-coinfected individuals on TDF and related risk factors

Overall, 2,593 patients had ever received TDF and their median follow-up time was 9.8 years (IQR 5.7–14.5). Eighty-four percent of participants in the "TDF group" were male and 54% were men who have sex with men (MSM) (Table 1). Liver cirrhosis was diagnosed in 24% of patients on TDF. The diagnosis of cirrhosis was made with the use of liver biopsy in 8% of cases, transient elastography in 19% of them, and APRI score in the remainder. Their median CD4 cell count at initiation of TDF was 332 cells/μl (IQR 190–498) and their median age was 37 years (IQR 31–44). Over 3,393 py, 20 cirrhotic individuals on TDF developed HCC (5.90 per 1,000 py, 95% CI 3.60–9.10), whereas the incidence of HCC was 1.17 per 1,000 py (95% CI 0.56–2.14) in non-cirrhotic individuals on TDF. The distribution of HCC cases in patients on TDF according to cirrhosis status and PAGE-B score is shown in Fig. 2. Among non-cirrhotic patients with a PAGE-B score ≥10, the incidence of HCC was 1.3 per 1,000 py, whereas the estimate for non-cirrhotics with a PAGE-B score <10 was 0.8 per 1,000 py. Two non-cirrhotic patients with a PAGE-B score <10 developed an HCC: a 37-year old, non-Caucasian female and a 38-year old Caucasian

Table 1. Demographic and clinical characteristics of patients according to the HBV-activity of their ART regimen (n = 3,625).

	No TDF	TDF	*p* value
	n = 1,032	n = 2,593	
Median age in years (IQR)	35 [29, 42]	37 [31, 44]	0.5
Female sex (%)	179 (17)	414 (16)	0.4
Non-caucasian (%)	136 (13)	588 (23)	<0.001
HIV transmission group (%)			<0.001
Heterosexual	235 (23)	726 (28)	
IDU	289 (28)	299 (12)	
MSM	422 (41)	1401 (54)	
Other	25 (2)	51 (2)	
Missing	*61 (6)*	*116 (4)*	
HCV coinfection (%)	352 (34)	490 (19)	<0.001
Liver cirrhosis (%)	145 (14)	620 (24)	<0.001
Median baseline CD4 count in cells/μl (IQR)	310 (159–503)	332 (190–498)	0.02
Cohort (%)			<0.001
Aquitaine	291 (28)	319 (12)	
Athena	236 (23)	1146 (44)	
EuroSIDA	276 (27)	553 (21)	
SHCS	229 (22)	575 (22)	
Median follow-up in years (IQR)	5.0 (1.9–9.0)	9.8 (5.7–14.5)	<0.001
Calendar year of last visit (IQR)	2008 (2002–2014)	2014 (2014–2015)	<0.001

P value from Chi-square or Mann-Whitney *U* tests. ART, antiretroviral therapy; HCV, hepatitis C virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men; SHCS, Swiss HIV Cohort Study; TDF, tenofovir disoproxil fumarate.

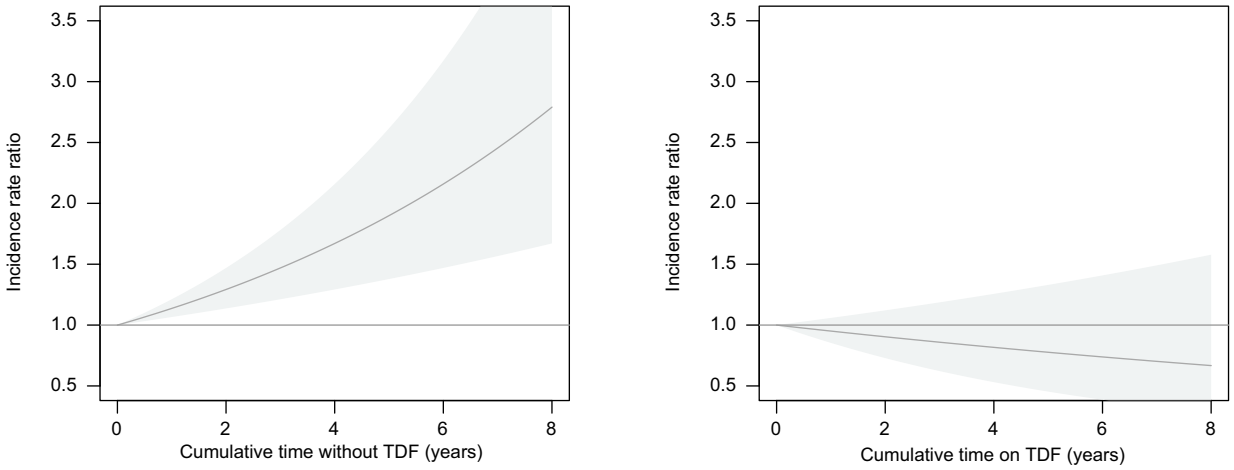


Fig. 1. HCC incidence rate ratio, stratified by cumulative time on HBV therapy regimens. Left panel: without TDF; right panel: with TDF. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

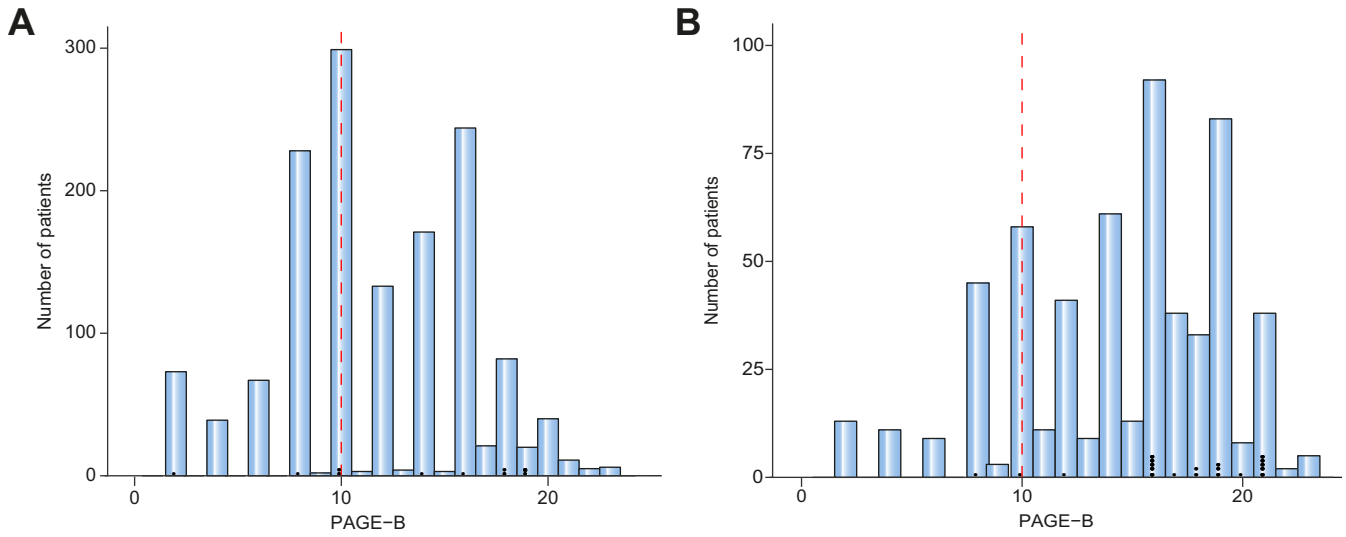


Fig. 2. Distribution of HCC cases among patients on TDF-containing ART, by cirrhosis status and PAGE-B score at TDF start. Dots represent cases of HCC and red dashed line indicates the PAGE-B threshold. (A) Non-cirrhotics (n = 1,479). (B) Cirrhotics (n = 577). ART, antiretroviral therapy; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.

male, both after approximately 5 years of follow-up. At initiation of TDF-containing ART, only age (aIRR per 10-year increase: 2.2, 95% CI 1.6–3.0) and the presence of liver cirrhosis (aIRR: 4.5, 95% CI 2.3–8.9) were significant predictors of the occurrence of HCC (Fig. 3, Table S1). Sex (aIRR: 0.7, 95% CI 0.2–2.4, ref: male) and ethnicity (aIRR: 1.6, 95% CI 0.6–4.6, ref: Caucasian) did not predict HCC incidence.

As HCC incidence remains approximately constant during follow-up on TDF-containing ART (Fig. 1), we predicted the risk of developing an HCC after initiation of TDF-containing ART for patients with and without cirrhosis, across the age spectrum at the time of starting TDF (Fig. 4). In patients with cirrhosis, the incidence was above 2 cases per 1,000 py across the age span. However, among patients without cirrhosis, the HCC screening threshold was only crossed in patients aged >45 years at initiation of TDF-containing ART. However, the 95% CI included estimates above the incidence of 2 cases per 1,000 py for all ages at TDF initiation.

Sensitivity analyses

In an analysis of 1,035 patients on TDF with HDV serology results available from the SHCS and EuroSIDA, including 130 (12.6%) with a positive anti-HDV test, we observed that 6 (4.6%) HIV/HBV/HDV-coinfected patients experienced an event of HCC, whereas 11 (1.2%) had an HCC event in the HDV-negative group ($p = 0.01$). In multivariable analyses, HDV infection was not significantly associated with HCC (aIRR: 2.53, 95% CI 0.76–8.46, $p = 0.13$). Furthermore, among 1,571 patients with available data on HBeAg in the Aquitaine and Athena cohorts, 19/821 (2.3%) HBeAg-positive individuals developed an HCC, whereas 6/750 (0.8%) HBeAg-negative did. HBeAg and HCC were not associated in multivariable analyses (aIRR: 2.17, 95% CI 0.85–5.58, $p = 0.11$). Finally, after the exclusion of 490 HCV-coinfected individuals on TDF, we found an incidence of HCC of 3.83 (95% CI 2.19–6.21) per 1,000 py in the cirrhosis group and 0.74 (95% CI 0.38–1.29) in the non-cirrhotic group. The association between liver cirrhosis and HCC remained similar

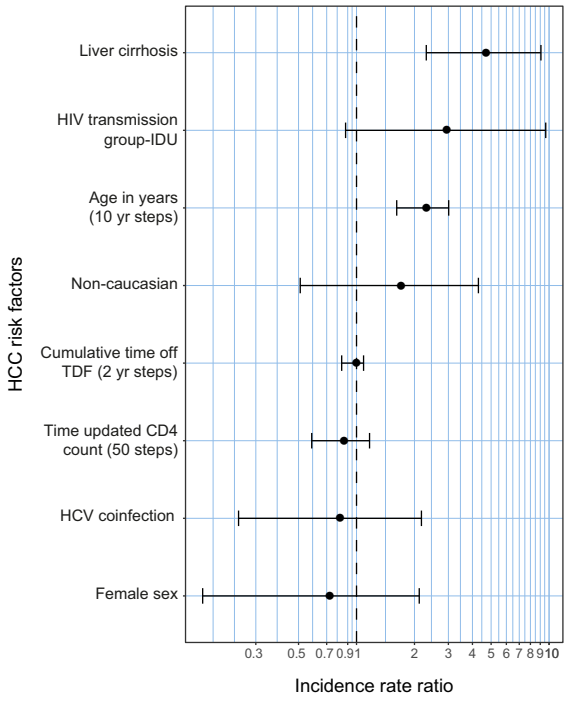


Fig. 3. Multivariate adjusted incidence rate ratios of HCC in patients on TDF during follow-up, based on characteristics at initiation of TDF (n = 2,473). HCC, hepatocellular carcinoma; HCV, hepatitis C virus; TDF, tenofovir disoproxil fumarate.

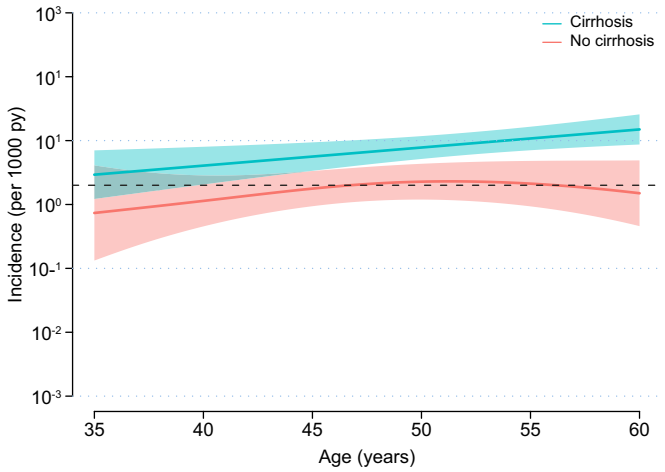


Fig. 4. Adjusted incidence of hepatocellular carcinoma among HIV/HBV coinfected individuals at initiation of TDF-containing ART (n = 2,537). Dotted line represents the recommended screening threshold; shaded area represents the 95% CI. Independent variables: restricted cubic spline fitted for age, cirrhosis, time-updated CD4 and interaction terms between age and cirrhosis, and CD4 and cirrhosis. ART, antiretroviral therapy; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

to the original analysis in the whole study population (aIRR: 5.44, 95% CI 2.45–12.08).

Discussion

We present HCC incidence estimates from the largest collaborative analysis, to date, of HIV/HBV-coinfected individuals on currently recommended first-line NAs. Among over 2,500 patients on TDF or ETV, the incidence of HCC was 5.9 per 1,000 py in cirrhotic patients and 1.2 per 1,000 py among those without cirrhosis. After the initiation of TDF, the incidence of HCC remained stable over time, suggesting that an assessment of HCC risk at TDF start would be adequate to inform long-term individual HCC screening strategies. Our results show that HIV/HBV-coinfected patients without cirrhosis, starting TDF-containing ART when aged <46 years old, remain at an HCC risk below 2 per 1,000 py, which is generally accepted as the threshold below which screening is not recommended. However, our findings highlight the need to better understand HCC risk factors in non-cirrhotic patients as the risk of HCC was not zero in this category, even in patients with a low risk based on the PAGE-B score. Our results also provide estimates for individualized decisions on HCC screening in non-cirrhotics.

In our study, the incidence of HCC remained stable during TDF therapy, in line with the results from a large multi-center European study of HBV-monoinfected individuals.[12] In contrast, incidence in those without TDF increased steadily over time. Our results justify the approach of evaluating the HCC risk at the time of initiation of potent NA therapy, and to decide on a surveillance strategy based on this assessment. Papatheodoridis *et al.* showed a clear decrease in HCC incidence after 5 years of NA therapy among patients with liver cirrhosis. Unfortunately, we were unable to explore the presence of such a trend in our cohort of HIV/HBV-coinfected individuals due to the limited number of events.

As expected, the incidence of HCC among cirrhotic patients was above 2 cases per 1,000 py, independently of age at TDF start. In comparison, HCC incidence among non-cirrhotics was lower, even though the upper margin of the confidence interval was above the proposed screening threshold in all age groups. In the absence of cirrhosis, HCC risk seems to be driven by specific risk factors, including age at TDF start. In a multi-country cohort of HBV-monoinfected Caucasians, age was an important risk factor of HCC overall, while male sex was a significant predictor in non-cirrhotics only.[23] Several specificities of our study population may explain some of the differences between our results and those from cohorts of HBV-monoinfected individuals, including the absence of an association between sex and HCC. Our study only included HIV-infected individuals, one-half of whom were MSM with generally good access to health-care services. Furthermore, >20% of our patients were of non-Caucasian origin. As the epidemiology of HCC is expected to be different in this sub-population, especially if exposed to other risk factors such as aflatoxin, longitudinal data from HCC screening programs from sub-Saharan Africa are urgently needed.[24]

As HCC screening is costly and can lead to unnecessary interventions, low-risk groups in which surveillance is not necessary need to be defined. The PAGE-B score, recently developed in a European multi-country cohort study and based on age, sex and platelet count, was shown to perform well in selecting patients with low risk for HCC.[16] Among patients with a score <10, the cumulative incidence of HCC was 0%, both in the derivation and the validation datasets. As a consequence, this score was integrated into decision algorithms for recommendations on HCC surveillance in HBV-monoinfected populations without cirrhosis.[4] In our study, 2 non-cirrhotic patients with a low PAGE-B score (<10), including 1 Caucasian, developed an HCC after approximately 5 years of follow-up. Although the numbers are low, these findings contrast with data from HBV-monoinfected cohorts. Previous experience with validating

predictive scores derived from HBV-monoinfected cohorts has shown that similar proficiency can generally not be expected in HIV-infected populations. For instance, non-invasive scores used to predict liver fibrosis among HBV-infected individuals were not shown to be adaptable to HIV-infected populations.[25] In order to achieve a decent risk stratification of HIV/HBV-coinfected populations, a thorough assessment of the proficiency of the PAGE-B score in this population is essential, and the potential development of another score, better adapted to this specific patient population must be evaluated.

We provide robust estimates on HCC incidence from a large, multi-country study of HIV/HBV-coinfected individuals in Europe. As current recommendations for HBV-related HCC screening are based on estimates from HBV-monoinfected populations, our data will inform clinical monitoring strategies for HIV/HBV-coinfected patients and shape future research questions in the field. Unfortunately, we did not have access to systematically measured HBV DNA values during TDF-containing ART. Although previous studies have shown high rates of HBV suppression on TDF-containing ART, we cannot exclude that a small proportion of patients had a sustained viral replication, a well-known risk factor for the development of HCC.[10,26,27] The limited availability of data on HDV infection, as well as on HBeAg serology, was an additional limitation of our study, as both markers are drivers of HCC and liver-related mortality among HBV-infected patients.[6,7] However, in sensitivity analyses limited to cohorts with data available, we did not find significant associations between these markers and HCC. Finally, although it would have been important to analyze the risk of HCC in specific subpopulations of non-cirrhotics to guide HCC surveillance strategies, our sample size and number of events were low, especially in certain patient groups such as women and individuals of African origin.

Conclusions

As most HIV/HBV-coinfected individuals currently in care in high-income countries are non-cirrhotic with a suppressed HBV viral load on a TDF-containing regimen, it is of major importance to have reliable HCC incidence estimates to guide HCC surveillance. Our data suggest that the incidence of HCC is low in this group of patients, especially if TDF is initiated early during the course of disease. However, HCC events still occur in these patients and it will be important to further assess risk factors and derive predictive scores for HCC, tailored to HIV/HBV-coinfected populations.

Financial support

EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n° 260694. Current support includes unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Gilead Sciences. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 148522). The study is also supported by a grant [grant number DNRF126] from the Danish National Research Foundation and by the International Cohort Consortium of Infectious Disease (RESPOND).

The ATHENA cohort is managed by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment.

This work was performed within the framework of the SHCS, supported by the Swiss National Science Foundation (SNF grant number 177499, SHCS project number 751), by the SHCS Research Foundation and the SHCS Association. Further funding was obtained from the NEAT-ID Foundation. GW was supported by a Professorship (PP00P3_176944) from the Swiss National Science Foundation. The funders had no role in study design, data collection and analysis, decision to publish.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

GW and AR conceived and designed the study. DK and AA performed the statistical analyses. GW, EM and AR wrote the first draft of the manuscript. All authors contributed to the acquisition and interpretation of the data, critically revised the paper and approved its final version.

Acknowledgments

We thank the participating patients, physicians and study nurses for excellent patient care, the data- and the coordination center for continuous support. The members of the SHCS are: Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.032.

References

[1] WHO. Global hepatitis report 2017. Geneva: World Health Organization; 2017.
[2] Wandeler G, Gsponer T, Bihl F, Bernasconi E, Cavassini M, Kovari H, et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. J Infect Dis 2013;208:1454–1458.
[3] Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, Moschidis Z, Sypsa V, Zavitsanos X, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis 2009;48:1763–1771.

[4] European Association for the Study of the Liver, Electronic address eee, European Association for the Study of the L. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[5] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
[6] Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–174.
[7] Beguelin C, Moradpour D, Sahli R, Suter-Riniker F, Luthi A, Cavassini M, et al. Hepatitis delta-associated mortality in HIV/HBV-coinfected patients. J Hepatol 2017;66:297–303.
[8] Piroth L, Pol S, Lacombe K, Miailhes P, Rami A, Rey D, et al. Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. J Hepatol 2010;53:1006–1012.
[9] Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, et al. Efficacy of tenofovir disoproxil fumarate at 240 weeks in patients with chronic hepatitis B with high baseline viral load. Hepatology 2013.
[10] Price H, Dunn D, Pillay D, Bani-Sadr F, de Vries-Sluijs T, Jain MK, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS ONE 2013;8 e68152.
[11] European Association for the Study of the Liver, Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–398.
[12] Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444–1453.
[13] Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98–107.
[14] Kim GA, Lim YS, An J, Lee D, Shim JH, Kim KM, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014;63:1325–1332.
[15] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.
[16] Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800–806.
[17] Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Gunthard HF, et al. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol 2010;39:1179–1189.
[18] Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003;362:22–29.
[19] Boender T, Smit C, Sighem A. AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. BMJ Open 2018. https://doi.org/10.1136/bmjopen-2018-022516 e022516.
[20] Collin A, Le Marec F, Vandenhende MA, Lazaro E, Duffau P, Cazanave C, et al. Incidence and risk factors for severe bacterial infections in people living with HIV. ANRS CO3 Aquitaine Cohort, 2000-2012. PLoS ONE 2016;11 e0152970.
[21] Wandeler G, Kraus D, Reiss P, Peters L, Dabis F, Fehr J, et al. Tenofovir and the incidence of hepatocellular carcinoma in HIV/HBV-coinfected persons. 23rd Conference on Retroviruses and Opportunistic Infections (CROI), Boston, 22.-25. February, 2016.
[22] WHO. World. Health organization. guidelines for the prevention, care and treatment of persons with chronic hepatitis B. Infection 2015.
[23] Papatheodoridis GV, Dalekos GN, Yurdaydin C, Buti M, Goulis J, Arends P, et al. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. J Hepatol 2015;62:363–370.
[24] Yang JD, Gyedu A, Afihene MY, Duduyemi BM, Micah E, Kingham TP, et al. Hepatocellular carcinoma occurs at an earlier age in Africans, particularly in association with chronic hepatitis B. Am J Gastroenterol 2015;110:1629–1631.
[25] Stockdale AJ, Phillips RO, Geretti AM, Group HS. The gamma-glutamyl transpeptidase to platelet ratio (GPR) shows poor correlation with transient elastography measurements of liver fibrosis in HIV-positive patients with chronic hepatitis B in West Africa. Response to: 'The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa' by Lemoine et al.. Gut 2016;65:882–884.
[26] de Vries-Sluijs TE, Reijnders JG, Hansen BE, Zaaijer HL, Prins JM, Pas SD, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. Gastroenterology 2010;139:1934–1941.
[27] Boyd A, Gozlan J, Maylin S, Delaugerre C, Peytavin G, Girard PM, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology 2014;60:497–507.