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ORIGINAL RESEARCH

The association between hepatitis B virus infection and nonliver malignancies in persons living with HIV: results from the EuroSIDA study

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Abstract

Objectives: The aim of this study was to assess the impact of hepatitis B virus (HBV) infection on non-liver malignancies in people living with HIV (PLWH).

Methods: All persons aged ≥ 18 years with known hepatitis B virus (HBV) surface antigen (HBsAg) status after the latest of 1 January 2001 and enrolment in the EuroSIDA cohort (baseline) were included in the study; persons were categorized as HBV positive or negative using the latest HBsAg test and followed to their first diagnosis of nonliver malignancy or their last visit.

Results: Of 17 485 PLWH included in the study, 1269 (7.2%) were HBV positive at baseline. During 151 766 person-years of follow-up (PYFU), there were 1298 nonliver malignancies, 1199 in those currently HBV negative [incidence rate (IR) 8.42/1000 PYFU; 95% confidence interval (CI) 7.94–8.90/1000 PYFU] and 99 in those HBV positive (IR 10.54/1000 PYFU; 95% CI 8.47–12.62/1000 PYFU). After adjustment for baseline confounders, there was a significantly increased incidence of nonliver malignancies in HBV-positive versus HBV-negative individuals [adjusted incidence rate ratio (aIRR) 1.23; 95% CI 1.00–1.51]. Compared to HBV-negative individuals, HBsAg-positive/HBV-DNA-positive individuals had significantly increased incidences of nonliver malignancies (aIRR 1.37; 95% CI 1.00–1.89) and NHL (aIRR 2.57; 95% CI 1.16–5.68). There was no significant association between HBV and lung or anal cancer.

Conclusions: We found increased rates of nonliver malignancies in HBsAg-positive participants, the increases being most pronounced in those who were HBV DNA positive and for NHL. If confirmed, these results may have implications for increased cancer screening in HIV-positive subjects with chronic HBV infection.

KEYWORDS
HBV DNA, hepatitis B, nonliver cancer

INTRODUCTION

Hepatitis B virus (HBV) infection is common in persons living with HIV (PLWH); approximately 5–20% of PLWH also have HBV infection, with large differences according to region and underlying risk factors [1,2]. Advances in treatment for both HIV and HBV have reduced morbidity and mortality, but rates remain higher in coinfected persons [3–5]. The contribution of malignancies to morbidity and mortality in PLWH has increased since the widespread introduction of antiretroviral therapy (ART) [6,7], possibly attributable to increased life expectancy and aging [8]. The risk of hepatocellular carcinoma (HCC) is increased in HIV/HBV-coinfected persons with cirrhosis [9–11], although the risk is decreased among those treated with tenofovir disoproxil fumarate (TDF) [12]. In persons without HIV infection, an association between HBV infection and nonliver cancers has been demonstrated, including Hodgkin's lymphoma, oral cancer and cancer of the pancreas, ovaries, biliary duct and kidney [13–17], although most studies have been carried out in non-European populations. Further, meta-analyses among persons without HIV infection have suggested an increased rate of non-Hodgkin's lymphoma (NHL) in HBV infection [18], although data among PLWH have been inconsistent [19,20]. The reasons for a potential association between HBV infection, HIV infection and NHL remain unclear but could include chronic ongoing inflammation, B-cell proliferation and the presence of HBV DNA in lymph nodes and NHL tissue [21]. A recent meta-analysis showed that the prevalence of HBV infection was significantly increased among PLWH developing

cancer [22], with a report of an association between HBV infection and anal cancer and anal squamous intraepithelial lesions [23,24].

Studies in PLWH investigating the association between nonliver malignancies and HBV are limited, and typically include small numbers and are underpowered to investigate the association in detail. Furthermore, previous studies lacked information on HBV viraemia or had important confounding variables. The aims of this study were to investigate the association between HBV and all fatal and nonfatal nonliver malignancies in PLWH and to determine the association between antiretrovirals used to treat HIV and HBV infection and nonliver malignancies.

METHODS

The EuroSIDA study

Persons were included from the EuroSIDA study, a large, prospective, observational cohort of almost 23 000 HIV-1-positive patients followed in 100 hospitals in 35 European countries plus Israel and Argentina [25]. Individuals were enrolled in ten cohorts from 1994 onward. At recruitment, in addition to demographic and clinical data, a complete ART history was obtained together with the most recent CD4 cell counts and HIV RNA measurements, as well as all HBV surface antigen (HBsAg) and HBV DNA test results. Data, including clinical data, are collected prospectively at clinical sites and sent to the coordinating centre at yearly intervals. At each follow-up visit, all CD4 cell counts, and HBsAg results measured since last follow-up are collected, together with start and stop dates for antiretroviral drugs. Further information on data collected in EuroSIDA can be found at http://www.chip.dk/Ongoing-Studies/EuroSIDA/About.

Patient consent statement

Patient informed consent was obtained according to local and/or national ethics committee requirements, and was obtained from each participant before any study-related procedure was performed and in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)–Good Clinical Practice Guidelines. Further information is available at https://www.chip.dk/Portals/0/files/Eurosida/EuroSIDA/EuroSIDA_Protocol_v4_2019JULI05.pdf?ver=2019-10-02-145631-730.

Statistical methods

All PLWH in EuroSIDA aged ≥ 18 years at baseline with a CD4 count and viral load before or up to 6 months after baseline with known HBV status were included. Persons were defined as HBV positive at baseline if they were positive for HBsAg at or before baseline. HBV status was updated during follow-up using the last test result carried forward (negative or positive). Baseline was defined as the latest of enrolment to EuroSIDA, known HBsAg status or 1 January 2001, when prospective collection of malignancies in EuroSIDA began.

Baseline characteristics of participants were summarized using simple summary statistics comparing those who were HBV positive with those who were HBV negative at baseline. Persons with HCC prior to baseline were excluded. Persons with nonliver malignancies at baseline were included and followed to the first unique nonliver malignancy, including both fatal and nonfatal malignancies. Recurrent cancers of the same type were not included as events; for example, an individual with lung cancer at baseline would be eligible for inclusion and could develop prostate cancer during follow-up, but a new diagnosis of lung cancer would not be classified as an event. Metastatic events and basal cell carcinoma were not included as events. Persons were followed to the earliest of last visit or first nonliver malignant event. The incidence of nonliver malignancies was calculated according to current HBV status; Poisson regression was used to investigate factors associated with the development of any nonliver malignancy and the three most common nonliver malignancies (anal cancer, NHL and lung cancer), all of which occurred in > 100 participants. *A priori* we included HBV status as a time-updated variable.

We investigated a wide range of demographic, clinical and laboratory confounders, including age, region of Europe [25], gender, baseline date, HIV exposure group, CD4 count, HIV viral load, body mass index (BMI), smoking status, coinfection with hepatitis C virus (HCV) (including both antibody and HCV RNA data where available) and liver fibrosis, both defined in earlier studies [26]. Comorbidities such as diabetes, hypertension, cardiovascular disease (CVD) and non-AIDS-defining malignancies (NADM; excluding liver cancer) were included as potential confounding variables [27]. Different models were constructed, including all variables listed above (except HBsAg status) as fixed at baseline, and where all variables (excluding NADM, which was part of the endpoint) were allowed to vary over time. Categorical variables included missing data as a missing category. Where models used updated variables, data were included if available during follow-up, reducing the amount of missing data. Use of anti-HBV

drugs was considered in three groups and updated over time. As a consequence of correlation with use of antiretrovirals, we did not additionally adjust for use of ART. We calculated the percentage of follow-up time since baseline during which individuals were treated with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) ± emtricitabine or lamivudine (referred to as XTC). *A priori* we tested for an interaction between anti-HBV treatment and HBV status and the development of nonliver malignancies. These stratified models were adjusted for age, HIV viral load, CD4, baseline date, smoking status and liver fibrosis. In the subset of HBV-positive individuals with measured HBV DNA, we investigated the role of plasma HBV DNA (positive or negative) using similar methodology as for the main analyses, compared to individuals who were HBV negative.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 23 005 persons enrolled in EuroSIDA, 18 524 persons had known HBsAg status and prospective follow-up after 1 January 2001. Of these, 17 485 persons had a baseline CD4 count and HIV viral load, were aged ≥ 18 years and had not been previously diagnosed with HCC. Compared with the 17 485 included in the study, the 1039 excluded were younger and were more likely to be men who have sex with men (MSM), from Central and Northern Europe compared to Southern Europe and to have a later study baseline. Those excluded were more likely to be from East Central or Eastern Europe, to be HCV antibody positive, and to be ART naïve. The median time between CD4 count and baseline was 0.6 months [interquartile range (IQR) 0–2.6 months], with 96% of CD4 counts being within 12 months of baseline. The characteristics of the patients included stratified by baseline HBsAg status are shown in Table 1. At baseline, 1269 (7.2%) were HBV positive with a median age of 41 years (IQR 35–49 years) and a median CD4 count of 440 cells/μL (IQR 284–634 cells/μL). The median follow-up was 7.4 years (IQR 4.2–13.5 years).

As illustrated in Figure 1, there was an increase over time in exposure to HBV-active ART regimens over time in those with and without HBV infection, which was most marked in those who were HBV positive. A higher percentage of follow-up among those who were HBV-positive included treatment with regimens with TDF/TAF ± XTC compared to HBV-negative subjects. For example, in 2002, 63.3% of follow-up in those who were HBV-negative included TDF/TAF or XTC, compared to 68.5% in those who were HBV positive. These differences persisted over follow-up, and by 2019, 87.2% and 91.3% of the follow-up of those who were HBV negative and positive, respectively, included TDF/TAF or XTC-containing regimens.

A total of 1298 persons developed 1360 nonliver malignancy events during 151 766 person-years of follow-up (PYFU) [incidence rate (IR) 8.55/1000 PYFU; 95% confidence interval (CI) 8.09–9.92/1000 PYFU]. Figure 2 shows the numbers and crude incidence rates of nonliver malignancies overall and stratified by HBV status prior to the malignancy. In those who were HBV positive, the crude incidence of any nonliver malignancy was 10.54/1000 PYFU (95% CI 8.46–12.62/1000 PYFU), compared to 8.42/1000 PYFU (95% CI 7.94–8.90/1000 PYFU) in those who were HBV negative. Among those with known malignancy type, anal cancer (188 events), lung cancer (147 events) and NHL (131 events) were the most commonly occurring nonliver malignancies. Figure 2 also shows the number and crude incidence rate of each of the nonliver malignancies occurring in > 50 persons, stratified by current HBV status. In those with a nonliver malignancy, there were no differences in the distribution of malignancy types between those who were HBV positive and negative at the date of the event ($P = 0.12$). The crude incidences of bladder, breast and lung cancers were lower in those who were currently HBV positive compared to those who were HBV negative, while the incidences of all other nonliver malignancies were similar or higher in those who were currently HBV positive. Results were consistent when excluding those with chronic hepatitis C.

Table 2 summarizes the rates of nonliver malignancies, univariable and multivariable incidence rate ratios (IRRs) overall and stratified by current HBV status, and the proportion of follow-up time spent on different active HBV regimens. In univariable analyses, those currently HBV positive had a 25% increased incidence of nonliver malignancies (IRR 1.25; 95% CI 1.02–1.54). The increased incidence remained significant after adjustment for baseline, age, CD4 count, HIV viral load, fibrosis and smoking status at baseline [adjusted IRR (aIRR) 1.23; 95% CI 1.00–1.51; Figure 3a]. Among those with zero percentage of their follow-up on TDF/TAF ± XTC, the crude rates of nonliver malignancies were higher in those who were currently HBV positive versus those who were HBV negative (IR 11.33 vs 7.35/1000 PYFU, respectively), a 54% increased incidence before adjustment (IRR 1.54; 95% CI 1.12–2.12). The results were similar after adjustment, with a significantly increased incidence of nonliver malignancies in those with HBV compared to those with no exposure to TDF/TAF ± XTC (aIRR 1.45; 95% CI 1.04–2.01), and no association between HBV status and nonliver malignancies in those with > 50% of follow-up time including treatment with TDF/TAF ± XTC (aIRR 0.95; 95% CI 0.59–1.53; Table 2; $P = 0.21$ in test for interaction). All the

TABLE 1 Characteristics at baseline

	All		HBV negative		HBV positive	
	n	%	*n*	%	*n*	%
All	17 485	100.0	16 216	92.7	1269	7.3
Gender						
Male	12 884	73.7	11 817	72.9	1067	84.1
Female	4601	26.3	4399	27.1	202	15.9
HIV risk						
MSM	6510	37.2	5961	36.8	549	43.3
IDU	4786	27.4	4410	27.2	376	29.6
Heterosexual	5023	28.7	4784	29.5	239	18.8
Other	1166	6.7	1061	6.5	105	8.3
Ethnic						
White	15 004	85.8	13 956	86.1	1048	82.6
Origin						
Other	2481	14.2	2260	13.9	221	17.4
Region						
South	4226	24.2	3950	24.4	276	21.7
Central	4601	26.3	4223	26.0	378	29.8
North	3509	20.1	3235	19.9	274	21.6
Central East	2260	12.9	2106	13.0	154	12.1
East	2305	13.2	2157	13.3	148	11.7
Argentina	584	3.3	545	3.4	39	3.1
HCV status						
Negative	9473	54.2	8815	54.4	658	51.9
Positive	6893	39.4	6397	39.4	496	39.1
Unknown	1119	6.4	1004	6.2	115	9.1
Ever cART						
No	2723	15.6	2579	15.9	144	11.3
Yes	14 762	84.4	13 637	84.1	1125	88.7
HIV VL						
< 500 copies/mL	11 959	68.4	11 070	68.3	889	70.1
> 500 copies/mL	5526	31.6	5146	31.7	380	29.9
Comorbidities						
AIDS	4609	26.4	4226	26.1	383	30.2
ADM	840	4.8	763	4.7	77	6.1
NADM	375	2.1	336	2.1	39	3.1
CVD	401	2.3	374	2.3	27	2.1
ESLD	189	1.1	148	0.9	41	3.2
CKD[a]	201	1.1	189	1.2	12	0.9
DM	761	4.4	718	4.4	43	3.4
HTN	3950	22.6	3673	22.7	277	21.8
Smoking status						
Never	4665	26.7	4356	26.9	309	24.3
Current	9148	52.3	8448	52.1	700	55.2
Previous	1718	9.8	1584	9.8	134	10.6

(Continues)

TABLE 1 (Continued)

	All		HBV negative		HBV positive	
	n	%	*n*	%	*n*	%
Unknown	1954	11.2	1828	11.3	126	9.9
Liver fibrosis						
F0/1	7498	42.9	6788	41.9	710	55.9
F2	531	3.0	484	3.0	47	3.7
F3	268	1.5	245	1.5	23	1.8
F4	601	3.4	518	3.2	83	6.5
Unknown	8587	49.1	8181	50.5	406	32.0
BMI						
< 18	670	3.8	623	3.8	47	3.7
18–25	8468	48.4	7762	47.9	706	55.6
25–30	3064	17.5	2846	17.6	218	17.2
> 30	623	3.6	580	3.6	43	3.4
Unknown	4660	26.7	4405	27.2	255	20.1
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age (years)	41	35–49	41	35–49	41	35–48
CD4 count (cells/μL)	440	284–634	442	288–638	399	251–576
Nadir CD4 count (cells/μL)	179	75–290	180	77–293	148	55–251
Baseline (month/year)	03/06	01/01–08/12	04/06	01/01–09/12	09/05	12/03–04/12

Baseline was defined as the latest of enrolment to EuroSIDA, known hepatitis B virus surface antigen (HBsAg) status and 1 January 2001.

ADM, AIDS-defining malignancy; BMI, body mass index; cART, combination antiretroviral therapy; CKD, chronic kidney disease, defined as confirmed (over 3 months) estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 where baseline eGFR > 60 mL/min/1.73 m^2, or a confirmed 25% decline where baseline eGFR < 60 mL/min/1.73 m^2, using the Chronic Kidney Disease Epidemiology Collaboration equation; CVD, cardiovascular disease; DM, diabetes mellitus; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; IDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men; NADM, non-AIDS-defining malignancy; VL, viral load.

[a]CKD status could be calculated for 15 568 individuals at baseline; 14 471 HBsAg negative and 1097 HBsAg positive. Information on aspartate transaminase (AST) and platelet counts was used to calculate the AST to platelet ratio index (APRI). Hyaluronic acid was available for a small subset. The most recent fibrosis marker measured prior to baseline was used to define fibrosis stage and where more than one marker was measured priority was given to biopsy, Fibroscan, APRI followed by hyaluronic acid [26].

results shown in Table 2 were similar when using current values for factors that changed over time or when excluding persons with any malignancy at baseline. There was no interaction between HIV viral load and current HBV status ($P = 0.72$), indicating that the increased rate seen in those currently HBV positive was similar regardless of HIV viral load suppression.

We investigated further the role of HBV DNA in persons with this measured; the results are also shown in Table 2 and Figure 3b. Among 931 persons currently HBV positive with HBV DNA measured at least once, there were 29 nonliver malignancies in those currently HBV DNA negative (IR 8.89/1000 PYFU; 95% CI 5.65–12.13) and 40 events in those currently HBV DNA positive (IR 12.16; 95% CI 8.39–15.93). The distributions of individual nonliver malignancies were similar to those seen overall, with no differences according to HBV status or whether HBV DNA was positive or negative ($P = 0.17$), although it is worth noting the smaller number of events in those with HBV DNA data (69 of 99 events in HBV-positive individuals; 69.7%). After adjustment for baseline values of age, HIV viral load, CD4 count, baseline date, smoking status and liver fibrosis, those who were HBV DNA positive had an increased incidence of nonliver malignancies (aIRR 1.37; 95% CI 1.00–1.89; $P = 0.050$) compared to those who were HBVnegative (Figure 3b). There was no significant difference between those who were HBV DNA negative and HBV negative (aIRR 1.09; 95% CI 0.75–1.08; $P = 0.66$).

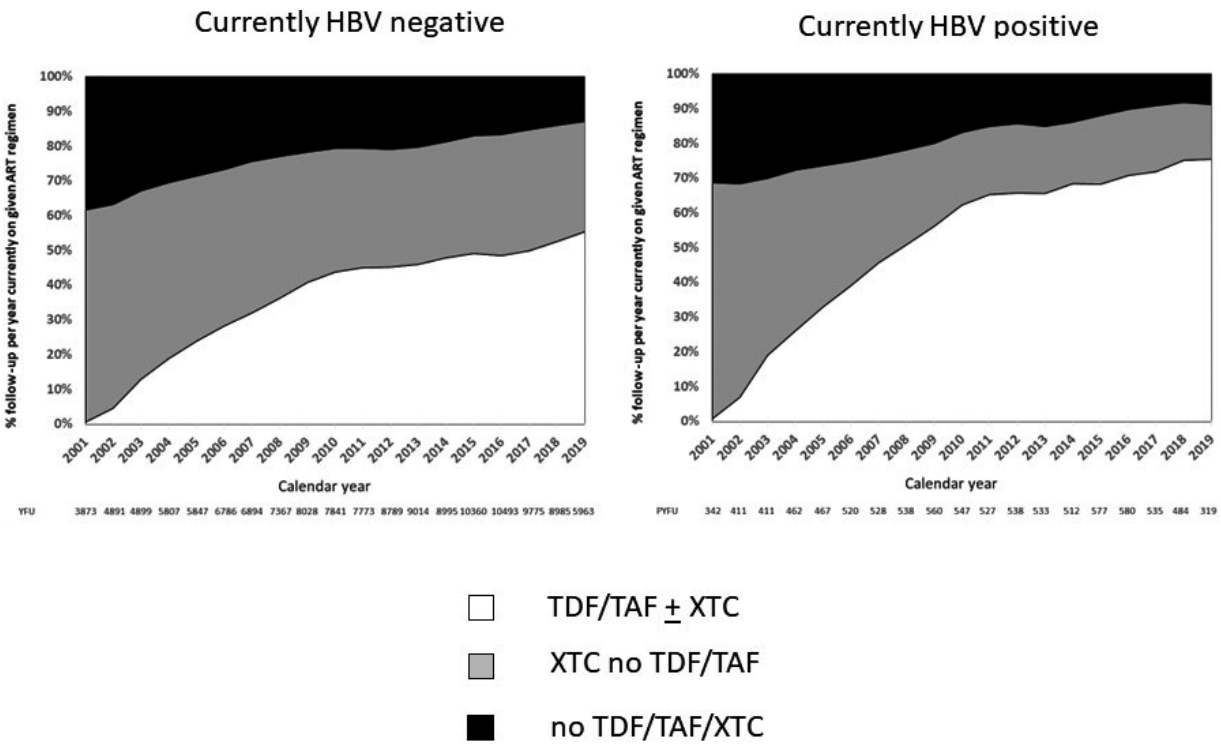

FIGURE 1 Use of HBV active regimens over time. ART, antiretroviral therapy; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; XTC, emtricitabine or lamivudine

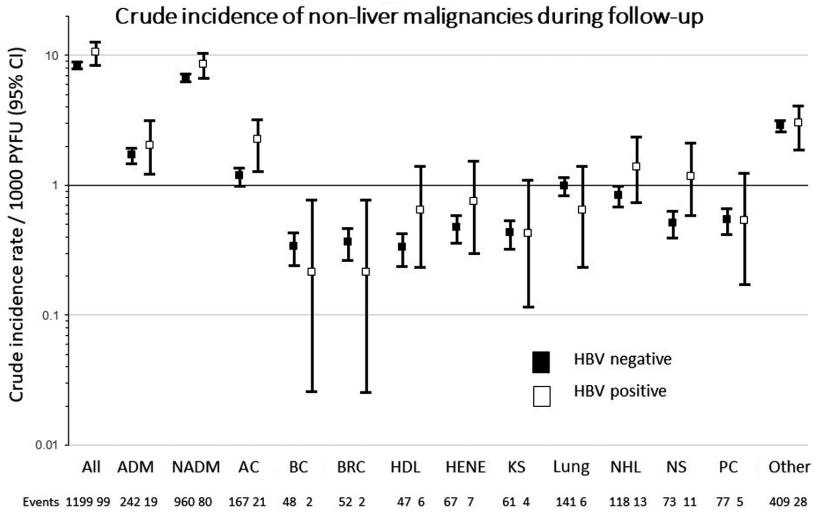

FIGURE 2 Crude incidence of non-liver malignancies during follow-up. ADM, AIDS-defining malignancy; NADM, non-AIDS-defining malignancy; AC, anal cancer; BC, bladder cancer; BRC, breast cancer; HDL, Hodgkin's lymphoma; HENE, head and neck cancer; KS, Kaposi's sarcoma; NHL, non-Hodgkin's lymphoma; NS, not specified; PC, prostate cancer; Other, all other cancers diagnosed in < 50 participants

Anal cancer (188 events), lung cancer (147 events) and NHL (131 events) were the three most common individual events. Figure 3a shows the univariate and multivariate IRR of each of these nonliver malignancies in those who were currently HBV positive versus those who were HBV negative. After adjustment, there was a nonsignificant increased incidence of anal cancer in those who were currently HBV positive (aIRR 1.52; 95% CI 0.95–2.43; $P = 0.082$). This finding was weaker in MSM (aIRR 1.23; 95% CI 0.72–2.10; $P = 0.45$) than in other HIV exposure groups combined (aIRR 1.57; 95% CI 0.55–4.48; $P = 0.40$), albeit with limited events in non-MSM (42 in total; four in those currently HBV positive). There were no significant differences between those who were currently HBV positive and HBV negative for NHL (aIRR 1.54; 95% CI 0.84–2.04, $P = 0.16$)

TABLE 2 Association between current hepatitis B virus (HBV) surface antigen (HBsAg) status and nonliver malignancies

						Univariable			Multivariable		
		Events	PYFU	Rate/1000 PYFU	95% CI	IRR	95% CI	*P*	IRR	95% CI	*P*
	HBV neg.	1199	142 377	8.42	7.94–8.90	1.00			1.00		
	HBV pos.	99	9389	10.54	8.47–12.62	1.25	1.02–1.54	0.032	1.23	1.00 – 1.51	0.046
% FU time on TDF/TAF ± XTC[a]											
0	HBV neg.	503	68 394	7.35	6.71–8.00	1.00			1.00		
	HBV pos.	41	3620	11.33	7.86–14.79	1.54	1.12–2.12	0.0078	1.45	1.04–2.01	0.026
1–50	HBV neg.	367	42 153	8.71	7.82–9.60	1.00			1.00		
	HBV pos.	39	3837	10.16	6.97–13.35	1.17	0.84–1.62	0.36	1.15	0.82–1.62	0.40
> 50	HBV neg.	329	31 831	10.34	9.22–11.45	1.00			1.00		
	HBV pos.	19	1932	9.84	5.92–15.36	0.95	0.60–1.51	0.83	0.95	0.59–1.53	0.84
HBV neg.[a]		1199	142 377	8.42	7.94–8.90	1.00			1.00		
HBV pos.	HBV DNA neg.	29	3262	8.89	5.65–12.13	1.06	0.73–1.53	0.77	1.09	0.75–1.58	0.66
HBV pos.	HBV DNA pos.	40	3290	12.16	8.39–15.93	1.44	1.05–1.98	0.020	1.37	1.00–1.89	0.050

Three separate multivariable models are shown. For the comparison of those who were currently HBV positive and negative, the model was adjusted for gender, region of Europe, ethnicity, HIV exposure group, hepatitis C virus antibody status, HIV viral load, CD4 count, CD4 count nadir, baseline date, prior AIDS, cardiovascular disease, chronic kidney disease, hypertension, smoking status, diabetes mellitus, liver fibrosis, body mass index and age (all fixed at baseline).

CI, confidence interval; FU, follow-up; IRR, incidence rate ratio; PYFU, person-years of follow-up; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; XTC, emtricitabine or lamivudine.

[a]The multivariable model was adjusted for age, HIV viral load, CD4 count, baseline date, smoking status and fibrosis, all fixed at baseline.

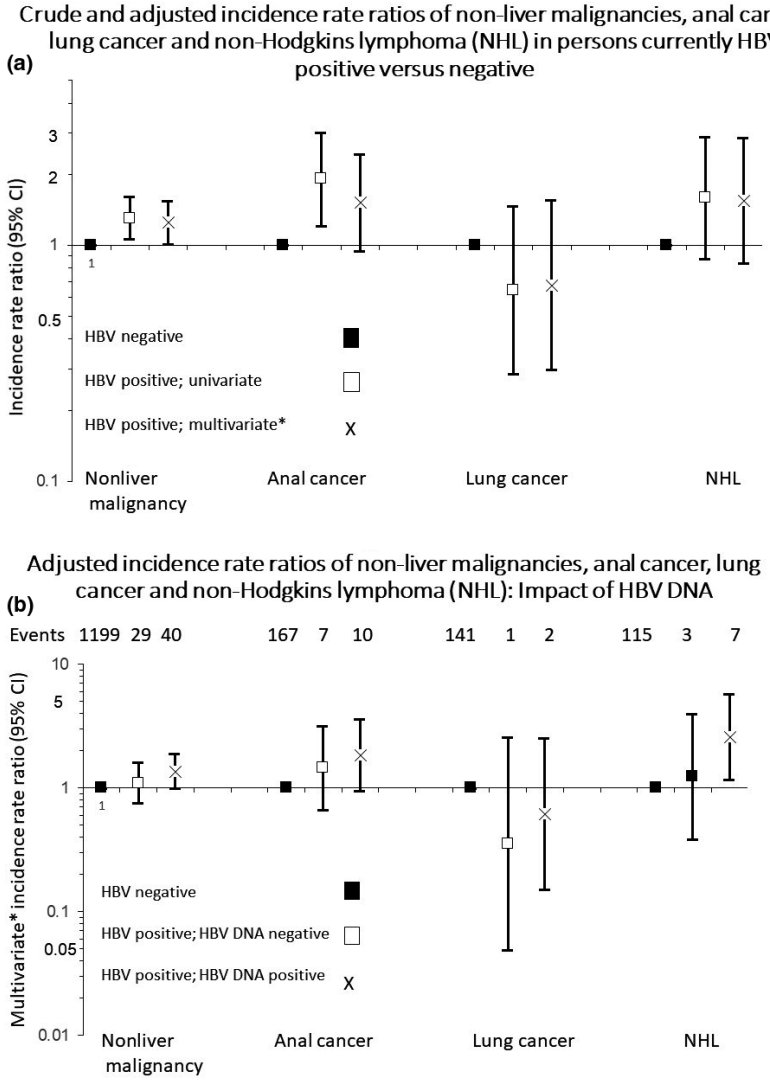

FIGURE 3 Crude and adjusted incidence rate ratios of non-liver malignancies, anal cancer, lung cancer and non-Hodgkins lymphoma (NHL) in persons currently HBV positive versus negative. *Adjusted for baseline, age, CD4 count, HIV viral load, fibrosis and smoking status at baseline. CI, confidence interval; NHL, non-Hodgkin's lymphoma

or lung cancer (aIRR 0.68; 95% CI 0.30–1.55; $P = 0.36$). There was no evidence that the association between current HBV status and lung cancer differed according to baseline smoking status ($P = 0.71$ in test for interaction). In a further exploratory analysis, shown in Figure 3b, we considered the role of HBV DNA in those with available data. For anal cancer, those who were HBV DNA positive had higher rates of anal cancer compared to those HBV-negative (aIRR 1.84; 95% CI 0.95–3.55, P=0.072). The same was not seen for those HBV DNA negative compared to HBV negative (aIRR 1.45; 95% CI 0.67–3.14, P=0.35), although note that neither of these results were statistically significant and had wide overlapping confidence intervals. In contrast, those who were HBV DNA negative did not (aIRR 1.23; 95% CI 0.38–3.95; $P = 0.73$), although the wide CIs seen did not rule out a large difference.

DISCUSSION

This European cohort study of over 17 000 PLWH and almost 150 000 PYFU in individuals with known HBV status showed an association between current HBV infection, as determined by HBsAg status, and development of nonliver malignancies. Furthermore, after adjustment for a range of confounding variables, PLWH with current HBV infection and a positive HBV DNA had higher rates of nonliver malignancies and NHL compared to those with negative HBV DNA or without current HBV infection.

We found that HBV-infected individuals had a 25% increase in the incidence of nonliver malignancies compared to HBV-uninfected individuals, and this finding was similar in those with and without HIV viral suppression. Data from similar studies in PLWH are scarce. In a study investigating the prevalence of malignancy risk factors, Parks

et al. reported a prevalence of HBV infection of 5% in those with HIV/AIDS compared to 0.3% in the US adult population, although this study did not directly address risk factors for development of malignancies [22]. In our study, the increased incidence was mainly in those who were HBV DNA positive, suggesting a role of replicating HBV in nonliver malignancies [1]. We found a significant increase over time in the percentage of persons treated with TDF/TAF ± XTC in all included individuals, most marked in those who were currently HBV positive, consistent with previous findings from EuroSIDA [28]. During 2019, 50% of the follow-up among those who were currently HBV negative included treatment with TDF/TAF ± XTC compared to 75% for those who were currently positive, reflecting current treatment guidelines recommending that all HIV/HBV-coinfected persons be treated with TDF or TAF-based antiretrovirals [29]. In 2019, < 10% of the follow-up of those who were currently HBV positive was not on TDF, TAF or XTC, and the reasons for individuals not using one of these antiretrovirals were not clear. Further, these PLWH may not have had clinically relevant levels of HBV DNA [30], which we were unable to investigate further as the level of HBV DNA was inconsistently reported.

In persons without HIV infection, the evidence of a general association between chronic hepatitis B and nonliver malignancies is contradictory. Andersen *et al*. reported a nonsignificant 10% increased IR of all cancers [31], but other studies have suggested a greater increase of approximately 2-fold higher [17,32]. Differences between the studies were probably attributable to differences in study design, population and the proportion with replicating HBV DNA, and whether HCC was included as the study endpoint, given its known association with hepatitis B. Chronic HBV infection has been associated with increased incidences of digestive system cancers (stomach, colorectal, oral and pancreatic cancers) and lymphoma in Chinese individuals [16,17]. Unfortunately, our study was not powered to look at digestive cancers because of the low number of events. Nonliver malignancies in PLWH are likely to be driven by many competing factors, not only traditional risk factors, but also, for example, viral coinfections, HIV-specific factors such as a direct oncogenic effect of HIV-activated inflammation [33,34] and impaired immune surveillance of pre-cancerous and cancerous cells [35]. Previous EuroSIDA work demonstrated no association between chronic hepatitis C and nonliver malignancies [36], and the results presented here were consistent when excluding those with chronic HCV coinfection.

Our study suggests there is an increased incidence associated with some non-liver malignancies, but not all. We considered the three most common malignancies, anal cancer, NHL and lung cancer, in our study. Previous studies have found an association between HBV infection and NHL in PLWH, and, while we found an increased incidence, it was not significant in multivariate analyses. In further exploratory analyses, there was a significantly increased incidence after adjustment in those who were HBV DNA positive compared to those who were HBV negative, and no difference between those who were HBV negative and HBV positive but without replicating HBV DNA. While this analysis was underpowered, its findings are consistent with those of studies showing HBV DNA in NHL tissue in PLWH [21]. There are several suggested mechanisms for an increase in those with HBV DNA, including chronic stimulation of B cells [18], an immunological response to local antigens caused by HBV [37], or HBV infection of endothelial cells being associated with release of tumour growth factors which stimulate cell proliferation [38]. We found no association between HBV status and lung cancer, even after adjustment for smoking status, and no evidence that the association between smoking status and nonliver malignancies differed between those with and without HBV infection.

We also found an increased incidence of anal cancer in our study; this finding was not statistically significant and the estimate was somewhat lower than the three-fold increased risk identified in the Multicenter AIDS Cohort Study in PLWH [23,24]. The association was stronger in the exploratory analysis among those who were HBV positive with replicating virus, suggesting a role of HBV and HBV DNA as an oncogenic cofactor for development of anal cancer in PLWH. Why this would occur in anal cancer and not in other malignancy types is currently unknown, but synergy with human papilloma virus (HPV) might be involved, with interactions occurring between HPV, HBV and high-grade squamous intraepithelial lesions being one possible explanation [23]. Unfortunately, EuroSIDA does not routinely collect data on HPV coinfection.

There are some limitations to our study to note. EuroSIDA does not routinely collect information on alcohol use. We used the last HBsAg status carried forward to determine HBV positivity; the frequency of HBsAg testing reported to EuroSIDA varied over time and has become more frequent in later calendar years. Other methods such as determining chronic HBV status by two consecutive HBsAg positive tests over a set period of time would more precisely define chronic HBV coinfection. However, this definition would be difficult to implement in EuroSIDA and would result in many PLWH being excluded from analyses, and the results would not be generalizable to the vast majority of individuals tested for HBsAg. EuroSIDA does not routinely collect information on Epstein–Barr virus, HPV or cytomegalovirus positivity, which may differ between those with and without HBV infection and which in turn may be associated with nonliver malignancies. HBV DNA has not been routinely

measured for all persons with HBV infection, and for those who were positive, we have very limited information on the level of viraemia, which was inconsistently reported. It would be very relevant to investigate further among those with HBV DNA whether the associations were stronger in those with higher levels of HBV DNA. We included persons with a prior malignancy to maximize power; our results were consistent throughout if persons with a prior malignancy were excluded. The strengths of our study are the large sample size with extensive follow-up, as well as data on HBV DNA in a proportion of PLWH, and information on many confounding variables, such as smoking status. Despite these strengths, unmeasured or unknown confounding cannot be ruled out.

To conclude, overall there was an increased incidence of nonliver malignancies in those who were HBV positive, particularly among those with replicating HBV DNA. Among the three most common cancers, there was an increased incidence of NHL in those with replicating HBV DNA. If confirmed, these results may have implications regarding increased cancer screening in HIV-positive subjects with chronic HBV infection.

CONFLICTS OF INTEREST

AM has received honoraria, speaker fees, travel support and/or consultancy funds from ViiV, Gilead and Eiland and Bonnin PC outside the submitted work. JMM has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare outside the submitted work. GW has received travel support and research grants from Gilead Sciences, ViiV and AbbVie outside the submitted work. JML has received consulting honoraria and/or research grants from ViiV Healthcare, Gilead Sciences and Janssen-Cilag outside the submitted work. CD has received consultancies, speaker honoraria and travel grants from Gilead Sciences, MSD and ViiV Healthcare outside the submitted work. LP has received travel support from Gilead outside the submitted work. AB, KvB, MB, JM, MC, FM, CUF, BK, EB, EK, PD, AZ, JPV, OD, AnM and TB report no conflicts of interest.

AUTHOR CONTRIBUTIONS

JMM proposed the original concept. JMM, AB, JL, GW, LP and AM developed the concept and the statistical analysis plan and reviewed all data. AM performed the statistical analyses and wrote the first draft of the manuscript. JMM, GW, JML, AB, KvB, MB, JM, MC, FM, CD, CUF, BK, EB, EK, PD, AZ, JPV, OD, AnM and TB provided data. All authors reviewed and commented on the draft manuscripts and provided input and feedback. AM and JMM contributed equally to the project. AM and LP verified the data on which the study is based.

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APPENDIX 1
EUROSIDA Study Group

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Odessa Region AIDS Center, Odessa, Ukraine.
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