The association between hepatitis B infection and non-liver malignancies in persons living with HIV: Results from the EuroSIDA study

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Abstract

Background and Aims

Little is known about the impact of hepatitis B virus (HBV) infection on non-liver malignancies in PLWH.

Methods

All persons aged ≥18 with known HBsAg status after the latest of 1 January 2001 and enrolment to the EuroSIDA cohort (baseline) were included; persons were categorised HBV-positive or negative using the latest HBsAg test and followed to their first non-liver malignancy or last visit. Poisson regression assessed the association between current HBV status and non-liver malignancies, anal, lung or non-Hodgkin's lymphoma (NHL).

Results

Of 17485 PLWH included, 1269 (7.2%) were HBV-positive at baseline. During 151766 person-years follow-up (PYFU), there were 1298 non-liver malignancies, 1199 in those currently HBV-negative (incidence rate [IR]=8.42/1000 PYFU; 95% confidence interval [CI]=7.94–8.90) and 99 in those HBV-positive (IR=10.54/1000 PYFU; 95% CI=8.47–12.62). After adjustment for baseline confounders, there was a significantly increased incidence of non-liver malignancies in HBV-positive versus negative individuals (adjusted IRR [aIRR]=1.23; 95% CI 1.00–1.51). Compared to those HBV-negative, HBV-positive/HBV-DNA-positive individuals had a significantly increased incidence of non-liver malignancies (aIRR 1.37; 95% CI 1.00–1.89), and of 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 non-liver malignancies in HBsAg-positive participants, which was most pronounced in those HBV-DNA positive, and for NHL. If confirmed, these results may have implications for increased cancer screening in HIV-positive subjects with chronic HBV.

Background

Hepatitis B virus (HBV) infection is common in persons living with HIV (PLWH); approximately 5-20% of PLWH also have HBV, with large differences according to region and underlying risk factors [1, 2]. Advances in both treatment for PLWH 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[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]. An association between HBV and non-liver cancers has been demonstrated in persons without HIV, including Hodgkin's lymphoma, oral cancer and cancer of the pancreas, ovaries, biliary duct and kidney[13-17]; although studies of largely European individuals are less common. Further, meta-analyses among persons without HIV have suggested an increased rate of non-Hodgkin's lymphoma with HBV infection[18] , although data among PLWH have been inconsistent[19, 20]. The reasons for a potential association between HBV, HIV 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 the prevalence of HBV was significantly increased among PLWH developing cancer[22], with a report of an association between HBV and anal cancer and anal squamous intraepithelial lesions [23, 24].

Data in PLWH investigating the association between non-liver 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 viremia or had important confounding variables. The aims of this study are to investigate the association between HBV and all fatal and non-fatal non-liver malignancies in PLWH and to determine the association between antiretrovirals used to treat HIV and HBV, and non-liver malignancies.

Methods

The EuroSIDA study

Persons were included from the EuroSIDA study, a large prospective observational cohort of almost 23000 HIV-1 positive patients followed in 100 hospitals in 35 European countries plus Israel and Argentina[25]. Individuals were enrolled into 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 hepatitis B surface antigen (HBsAg) test results and HBV-DNA. 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 Committees requirements, this 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 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 Hepatitis B virus surface antigen (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 summarised using simple summary statistics comparing those HBV positive with those HBV negative at baseline. Persons with HCC prior to baseline were excluded, persons with non-liver malignancies at baseline were included and followed to the first unique non-liver malignancy, including both fatal and non-fatal 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 non-liver malignant event. The incidence of non-liver malignancies was calculated according to current HBV status; Poisson regression was used to investigate factors associated with the development of any non-liver malignancy and the three most common non-liver malignancies (anal cancer, non-Hodgkins lymphoma 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, BMI, smoking status, coinfection with hepatitis C (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 was 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. Due to correlation with use of antiretrovirals, we did not additionally adjust for use of antiretroviral treatment. We calculated the percentage of follow-up time since baseline 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 non-liver 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 HBV negative.

All analyses were performed using SAS version 9.4 (Statistical Analysis Software, Cary, NC, USA).

Results

Of 23005 persons enrolled in EuroSIDA, 18524 persons had known HBsAg status and prospective follow-up after 1 January 2001. Of these, 17485 persons had a baseline CD4 count and HIV viral load, were aged ≥ 18 years and were not previously diagnosed with HCC. Compared with the 17485 included, the 1039 excluded were younger, men having sex with men (MSM), from Central and Northern Europe compared to Southern Europe and 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) with 96% 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) and a median CD4 of 440/mm^3 (IQR 284–634). The median follow-up was 7.4 years (IQR 4.2–13.5).

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, which was most marked in those HBV-positive. A higher percentage of follow-up among those 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 HBV-negative included TDF/TAF or XTC, compared to 68.5% in those HBV-positive. These differences persisted over follow-up, and by 2019, 87.2% and 91.3% of the follow-up of those HBV-negative or positive included TDF/TAF or XTC containing regimens.

1298 persons developed 1360 non-liver malignancy events during 151766 person-years of follow-up (PYFU); incidence rate [IR] 8.55/1000 PYFU (95% confidence interval [CI] 8.09–9.92). Figure 2 shows the number and crude incidence rates of non-liver malignancies overall and stratified by HBV status prior to the malignancy. In those HBV positive, the crude incidence of any non-liver malignancy was 10.54/1000 PYFU (95% CI 8.46–12.62), compared to 8.42/1000 PYFU (95% CI 7.94–8.90) in those HBV negative. Among those with known malignancy type, anal (188 events), lung (147 events) and NHL (131 events) were the most commonly occurring non-liver malignancies. Figure 2 also shows the number and crude incidence rates of each of the non-liver malignancies occurring in more than 50 persons, stratified by current HBV status. In those with an non-liver malignancy, there were no differences in the distribution of malignancy types between those HBV positive or negative at date of event (p=0.12). The crude incidence of bladder, breast and lung cancer was lower in those currently HBV positive compared to negative, while the incidence of all other non-liver malignancies was similar or higher in those currently HBV positive. Results were consistent when excluding those with chronic hepatitis C.

Table 2 summarises the rates of non-liver malignancies, univariable and multivariable incidence rate ratios (IRR) overall, 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 an non-liver malignancies (IRR 1.25; 95% CI 1.02–1.54). The increased incidence remained significant after adjustment for baseline, age CD4, 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 non-liver malignancies were higher in those currently HBV positive versus those negative (IR 7.35 vs 11.33/100 PYFU), 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 non-liver 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 non-liver malignancies with > 50% of follow-up time treated with TDF/TAF ± XTC (aIRR 0.95; 95% CI 0.59 - 1.53; Table2; p=0.21 test for interaction). All the

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 non-liver malignancies in those currently HBV DNA negative (incidence rate 8.89/1000 PYFU; 95% CI 5.65–12.13) and 40 events in those currently HBV DNA positive (incidence rate 12.16 95% CI 8.39–15.93). The distribution of individual non-liver malignancies was 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 individuals HBV positive, 69.7%). After adjustment for baseline values of age, HIV viral load, CD4 count, baseline date, smoking status and liver fibrosis, those HBV DNA positive had an increased incidence of non-liver malignancies (aIRR 1.37; 95% CI 1.00–1.89; p=0.050) compared to those HBV-negative (Figure 3b). There was no significant differences between those HBV DNA negative and HBV-negative (aIRR 1.09; 95% CI 0.75–1.08, p=0.66).

Anal cancer (188 events), lung cancer (147 events) and non-Hodgkins lymphoma (131 events) were the three most common individual events. Figure 3a shows the univariate and multivariate incidence rate ratio of each of these non-liver malignancies in those currently HBV positive versus those negative. After adjustment, there was a non-significant increased incidence of anal cancer in those 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, 4 in those currently HBV positive). There were no significant differences between those currently HBV positive or negative for non-Hodgkin's lymphoma (aIRR 1.54; 95% CI 0.84–2.04, p=0.16) 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, 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 HBV positive had higher rates of anal cancer when persons were HBV DNA positive 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. There were only 17 events in those with known HBV DNA. For NHL, those HBV-DNA positive had a significantly increased incidence of NHL (aIRR 2.57; 95% CI 1.16–5.68, p=0.020) compared to those HBV negative. In contrast, those HBV DNA negative did not (aIRR 1.23; 95% CI 0.38–3.95, p=0.73), although the wide confidence intervals 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 non-liver malignancies. Furthermore, after adjustment for a range of confounding variables, PLWH with current HBV infection and a positive HBV DNA had higher rates of non-liver malignancies and NHL compared to those with a negative HBV DNA or without a current HBV infection.

We found that HBV-infected individuals had a 25% increase in the incidence of non-liver malignancies compared to HBV-uninfected ones, 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 HBV prevalence of coinfection of 5% of 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 HBV DNA positive, suggesting a role of replicating HBV in non-liver 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 currently HBV positive, consistent with previous findings from EuroSIDA[28]. During 2019, 50% of the follow-up among those currently HBV negative were treated with TDF/TAF ± XTC compared to 75% of those currently positive, reflecting current treatment guidelines that all HIV/HBV coinfected persons be treated with TDF or TAF-based antiretrovirals[29]. In 2019, less than 10% of the follow up of those currently HBV positive was not on TDF, TAF or XTC, and the reasons for individuals not using one of these antiretrovirals was not clear. Further, these PLWH may not have clinically relevant levels of HBV DNA[30], which we were unable to investigate further as level of HBV DNA was inconsistently reported.

In persons without HIV, the evidence of a general association between chronic hepatitis B and non-liver malignancies is contradictory. Andersen et al reported a non-significant 10% increased incidence rate of all cancers[31], but other studies have suggested a greater increase of approximately 2-fold higher[17, 32]. Differences between the studies were likely due to differences in study design, population, the proportion with replicating HBV DNA, and whether HCC was included as the study endpoint, given its known association with hepatitis B. Chronic HBV has been associated with increased incidences of digestive system cancers (stomach cancer, colorectal cancer, oral cancer, pancreatic cancer) and lymphoma in Chinese individuals[16, 17]. Unfortunately, we were not powered to look at digestive cancers due to the low number of events. Non-liver malignancies in PLWH are likely to be driven by many competing factors, not only traditional risk factors, but also including 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 non-liver malignancies[36] and the results presented here were consistent when excluding those with chronic hepatitis C coinfection.

Our study suggests there is an increased incidence associated with some, but not all, non-liver malignancies. We considered the three most common malignancies, anal cancer, non-Hodgkin's lymphoma and lung cancer in our study. Previous studies have found an association between HBV infection and non-Hodgkin's lymphoma 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 HBV negative, and no difference between those HBV negative and HBV positive but without replicating HBV DNA. While this analysis was

underpowered, it is consistent with studies showing HBV DNA in non-Hodgkin's lymphoma 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 immunologic response to local antigens caused by HBV[37], or that HBV infection of endothelial cells is 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 non-liver malignancies differed for those with or 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 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 play a role with interactions between HPV and HBV, and high grade squamous intraepithelial lesions 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; 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 generalisable 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 non-liver malignancies. HBV DNA has not been routinely measured for all persons with HBV, and for those positive, we have very limited information on the level of viremia 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 maximise 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 non-liver malignancies in those HBV positive, particularly among those with replicating HBV DNA. Among the 3 most common cancers, there was an increased incidence of NHL in those with replicating HBV DNA. If confirmed, these results may have implications regarding for increased cancer screening in HIV-positive subjects with chronic HBV.

Table 1 Characteristics at baseline

		All		HBV negative		HBV positive	
		N	%	N	%	N	%
All		17485	100.0	16216	92.7	1269	7.3
Gender	Male	12884	73.7	11817	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	15004	85.8	13956	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	14762	84.4	13637	84.1	1125	88.7
HIV VL	<500	11959	68.4	11070	68.3	889	70.1
	>500	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*	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

Table 1 Characteristics at baseline (ctd)

		All		HBV negative		HBV positive	
		N	%	N	%	N	%
All		17485	100.0	16216	92.7	1269	7.3
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
	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	/mm^3	440	284–634	442	288–638	399	251–576
Nadir CD4	/mm^3	179	75–290	180	77–293	148	55–251
Baseline	Mm/yy	03/06	01/01–08/12	04/06	01/01–09/12	09/05	12/03–04/12

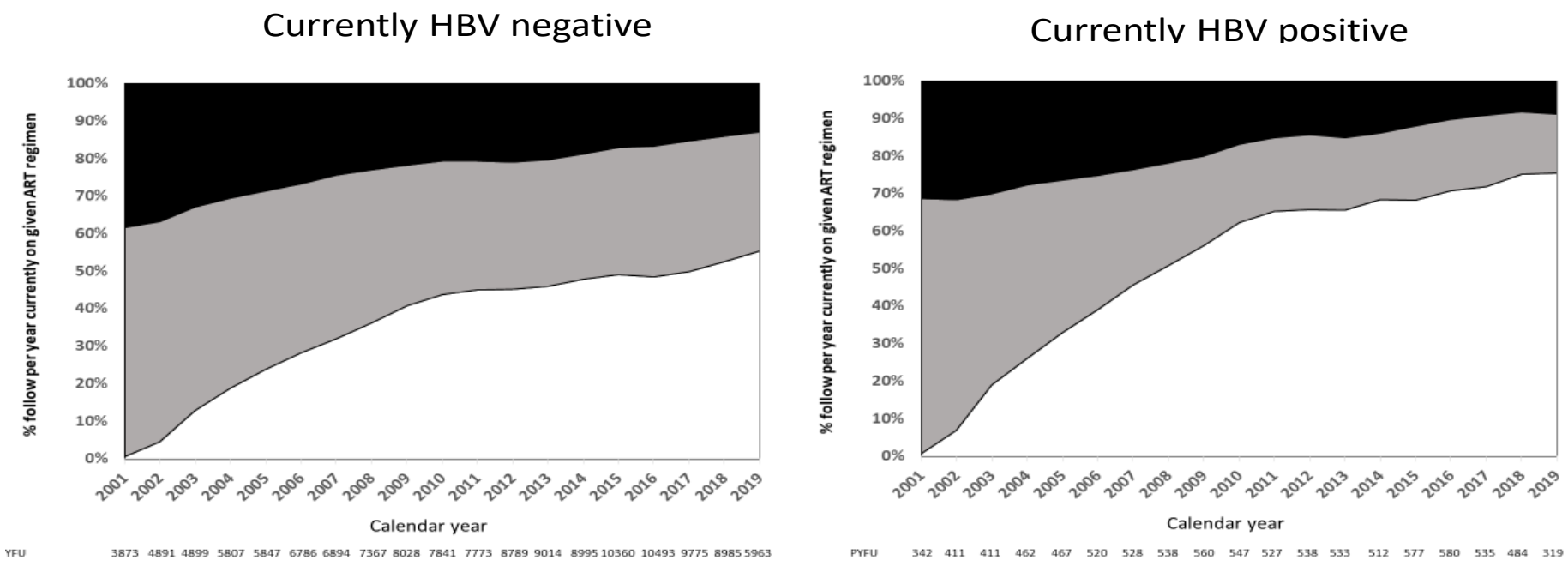
MSM; men having sex with men. IDU; intravenous drug user. ADM; AIDS defining malignancy. NADM; non-AIDS defining malignancy. CVD; cardiovascular disease. ESLD; end stage liver disease. CKD; chronic kidney disease; defined as confirmed (over 3 months) eGFR < 60 ml/min/1.73m^2 where baseline eGFR > 60 or a confirmed 25% decline where baseline eGFR < 60 ml/min/1.73m^2, using the CKDEPI equation. DM; diabetes mellitus. HTN; hypertension. Baseline was defined as the latest of enrolment to EuroSIDA, known HBsAg status or 1 January 2001. *CKD status could be calculated for 15568 at baseline; 14471 HBsAg - and 1097 HBsAg+. Information on aspartate transaminase (AST) and platelet counts were used to calculate the AST to platelet ratio (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 >1 marker was measured priority was given to biopsy, Fibroscan, APRI followed by hyaluronic acid[26]

Table 2 Association between current HBsAg status and non-liver malignancies

		Events	PYFU	Rate/1000 PYFU	95% CI	Univariable			Multivariable		
						IRR	95% CI	P	IRR	95% CI	P
	HBV neg.	1199	142377	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[1]											
0	HBV neg.	503	68394	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	42153	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	31831	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.[1]		1199	142377	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 currently HBV positive and negative, the model was adjusted for gender, region of Europe, ethnicity, HIV exposure group, hepatitis C antibody status, HIV viral load, CD4 and CD4 nadir, baseline date, prior AIDS, cardiovascular disease, chronic kidney disease, hypertension, smoking status, diabetes mellitus, liver fibrosis, BMI, and age (all fixed at baseline). [1]Multivariable model was adjusted for age, HIV viral load, CD4, baseline date, smoking status and fibrosis, all fixed at baseline.

Figure 1
Use of HBV active regimens over time

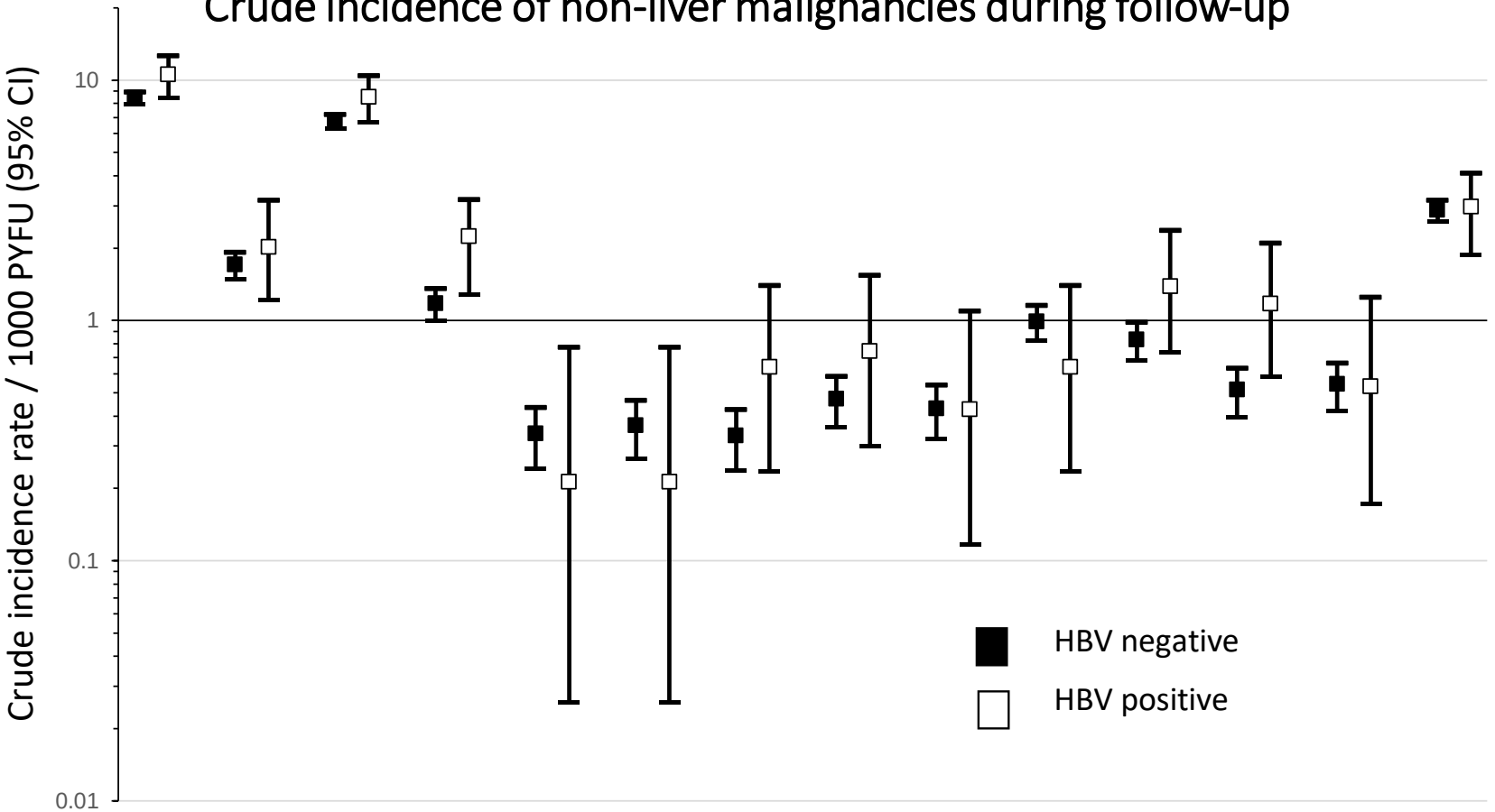


TDF/TAF ± XTC

XTC no TDF/TAF

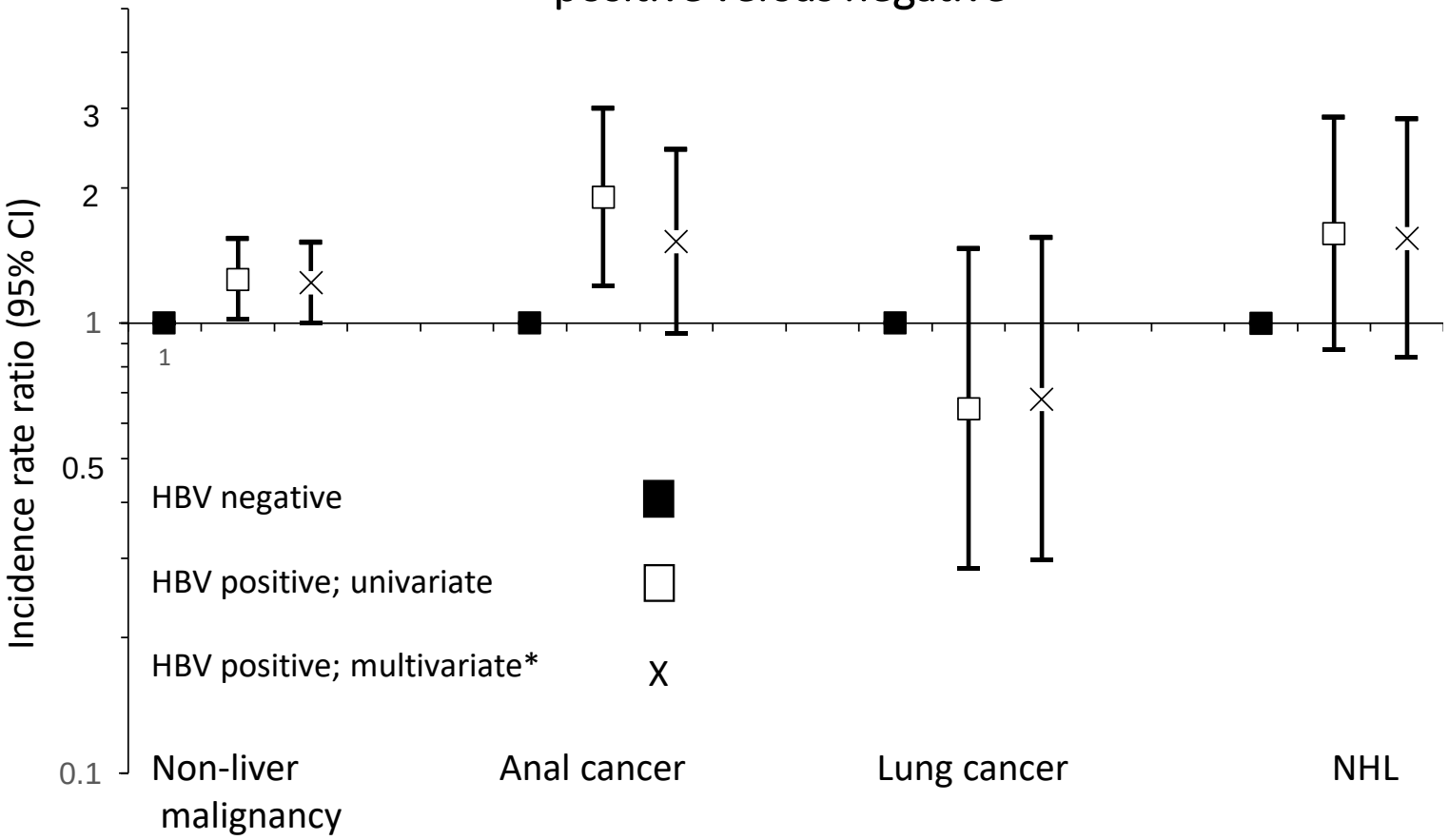
no TDF/TAF/XTC

Figure 2
Crude incidence of non-liver malignancies during follow-up



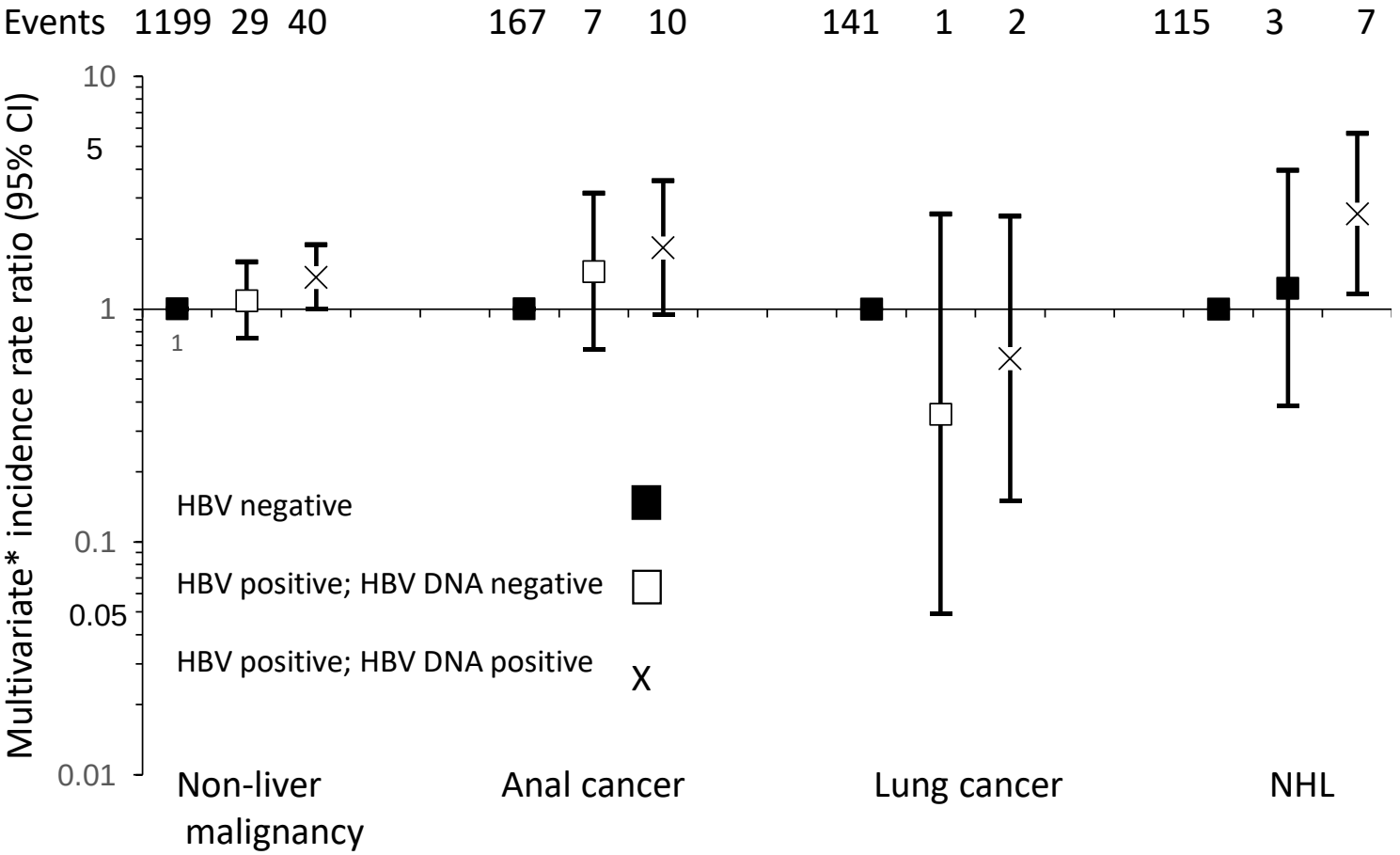
ADM; AIDS defining malignancy. NADM; non-AIDS defining malignancy. ANUS; anal cancer. BLAD, bladder cancer. BRCA; breast cancer. HDL; Hodgkin's lymphoma. HENE; head and neck cancer. KS; Kaposi's sarcoma. Lung; lung cancer. NHL; non-Hodgkin's lymphoma. NS; not specified. PROS; prostate cancer. Other; all other cancers diagnosed in < 50 participants

Figure 3a
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, HIV viral load, fibrosis and smoking status at baseline

Figure 3b
Adjusted incidence rate ratios of non-liver malignancies, anal cancer, lung cancer and non-Hodgkins lymphoma (NHL): Impact of HBV DNA



* Adjusted for baseline, age CD4, HIV viral load, fibrosis and smoking status at baseline

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Conflict 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, AbbVie, outside of 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 (Gilead Sciences, MSD and ViiV Healthcare), outside the submitted work. LP has received travel support from Gilead outside the submitted work.

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Author Statement

JMM proposed the original concept. JMM, AB, JL, GW, LP and AM developed the concept, 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, 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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