CONCISE COMMUNICATION

Increased risk of anal squamous cell carcinoma in HIV-positive men with prior hepatitis B virus infection

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Objective(s): HIV-positive individuals have elevated rates of anal squamous cell carcinoma (SCC), and sexually transmitted infections with its causative agent, high-risk human papillomavirus, and other oncoviruses including hepatitis B virus (HBV). HBV infection can cause liver cancer, and has been associated with increased risk of some extra-hepatic cancers including biliary tract cancer, pancreatic cancer, and non-Hodgkin lymphoma. Whether HBV is associated with anal SCC risk is unknown.

Design: Prospective study of anal SCC risk in HIV-positive and HIV-negative MSM in the Multicenter AIDS Cohort Study from 1984 to 2014.

Methods: Poisson regression models were used to examine the association between past or current HBV infection (positive tests for HBV core antibodies, surface antigen, and/or DNA) and anal SCC risk.

Results: We observed 53 cases of anal SCC among 5298 participants with 79 334 person-years follow-up. Among HIV-positive men, past or current HBV infection was associated with anal SCC risk in models adjusted for age, $CD4^+$ cell counts, HAART use, and other risk factors [incidence rate ratio (IRR), 95% confidence interval 3.15, 1.27–7.82]. Additional risk factors included immunological parameters 1 and 6 years prior to diagnosis (IRR, 95% confidence interval 2.45, 1.31–4.58 and 2.44, 1.3–4.59 for $CD4^+$ cell counts <500 cells/μl; 2.43, 1.34–4.42 and 2.77, 1.5–5.11 for $CD4^+ : CD8^+$ ratios <0.5, respectively). Among HIV-negative men, IRR for prior HBV and anal SCC risk was similar, but NS due to small number of cases.

Conclusion: HIV-positive MSM with prior HBV infection have increased anal SCC risk. This population may benefit from screening.

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Keywords: anal cancer, cancer epidemiology, cohort studies, hepatitis B virus, HIV, MSM

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Introduction

Hepatitis B virus (HBV) infection is a risk factor for hepatocellular carcinoma (HCC), and is also associated with elevated risk for some other types of cancer including pancreatic cancer [1–5] and non-Hodgkin lymphoma (NHL) [6–9]. The mechanisms by which HBV infection increases risk of some extra-hepatic cancers are unclear. However, its protumorigenic effects raise the possibility it could be an oncogenic cofactor [10–15].

HBV infection rates are high among HIV-infected populations and MSM [16–19]. HIV-infected populations have elevated risk for non-AIDS-defining malignancies (NADMs) linked to infections with oncoviruses such as HBV or hepatitis C (HCC) and high-risk human papilloma virus (hrHPV) (genital, anal, and oropharyngeal cancers) [20–31]. Anal squamous cell carcinoma (SCC) is a NADM caused by hrHPV in more than 90% of cases [32]. Anal hrHPV infections are detected in 30–90% of HIV-positive individuals, with the highest rates among MSM [32–37]. However, other factors are required for tumorigenesis [38]. Known risk for anal SCC factors include multiple sexual partners, immunodeficiencies, and smoking [39–42].

Synergistic syndemic interactions between hrHPV and HBV in promoting high-grade squamous intraepithelial lesions (HSIL) were suggested by a previous study [43]. Furthermore, anal hrHPV is more prevalent among individuals with prior HBV [44] or hepatitis [45]. Here, we evaluated the association between prior HBV infection and anal SCC risk in a prospective cohort of HIV-positive and HIV-negative MSM enrolled in the Multicenter AIDS Cohort Study (MACS).

Methods

Study cohort

This is a nested prospective cohort study in the MACS, an ongoing study established in 1984 that has enrolled 7343 HIV-positive and HIV-negative MSM. Clinical and laboratory data were collected at semiannual visits as described [25,39]. Eligible participants were 5298 MSM aged 30–70 years with at least 5 years of follow-up during 1984–2014 and one or more visits with HBV laboratory test data. Baseline was first visit after age 30 years. Institutional Review Boards at each study site approved the research and all participants provided written informed consent.

Data collection, risk factor classification, and cancer outcomes

The MACS public dataset release 25 was used for analyses. Past or current HBV infection was a time-invariant categorical variable defined by two or more positive lab tests for anti-HBV core antigen (ATHBC), HBV surface antigen (HBSAG), HBV e antigen (HBEAG), or HBV DNA ($n = 2001$), or single positive result for HBSAG ($n = 29$) or HBEAG ($n = 1$) any time following enrollment to study endpoint. Incident cancers were classified as described [25].

Statistical analysis

Participants were followed from baseline to first instance of incident cancer, last study visit, or age 70. Poisson regression models were restricted to HIV-positive participants. Factors associated with anal SCC in univariate analyses at P less than 0.2 were entered in the multivariate model, with stepwise backward selection used to retain significant features in the model ($P < 0.05$). Race and HAART use were retained in models as potential confounding factors. Models were sequentially adjusted for additional covariates having known associations with anal SCC risk and/or HBV. Statistical analysis was performed in R version 3.2.4 (R Project for Statistical Computing, Vienna, Austria).

Results

Demographic and behavioral characteristics by HIV and hepatitis B virus infection status

We identified 5298 MSM ages 30–70 enrolled in the MACS during 1984–2010 and contributing 79 334 person-years, with median follow-up of 12 years (Table 1). Thirty-eight percent ($n = 2037$) had past or current HBV infection at endpoint based on positive tests for ATHBC, HBSAG, HBEAG, and/or HBV DNA, of which 87.7% were positive at enrollment and 21% had one or more positive tests for HBSAG, HBEAG, and/or HBV DNA within follow-up. Age at endpoint, follow-up time, and frequencies of anal SCC and other NADMs were higher among participants with past or current HBV in comparison with HBV-negative participants. By contrast, frequencies of HIV-positive participants with ADMs or death were lower among participants with past or current HBV in comparison with HBV-negative participants. More HIV-negative participants with past or current HBV reported more than two sexual or anal receptive partners/6 months in comparison with HBV-negatives, whereas there was no difference by HBV status among only HIV-positive participants.

Immunological and virological characteristics by HIV and hepatitis B virus infection status

$CD4^+$ cell counts and $CD4^+ : CD8^+$ ratios were lower in HIV-positive compared with HIV-negative participants, whereas the relationship of these variables to HBV status varied by HIV status (Table 1). Among HIV-negative participants with past or current HBV, $CD4^+$ cell counts and $CD4^+$ nadirs were lower at 1 year prior to endpoint in comparison with HBV-negative . Among HIV-positive participants with past or current HBV, $CD4^+$ cell counts and $CD4^+ : CD8^+$ ratios were higher, fewer participants had $CD4^+$ cell counts less than 350 cells/μl at

Table 1. Demographic and clinical characteristics of groups by HIV and HBV status.

	All		HIV-negative		HIV-positive	
	HBV-negative, $n=3261$	Past or current HBV, $n=2037$	HBV-negative, $n=1725$	Past or current HBV, $n=848$	HBV-negative, $n=1536$	Past or current HBV, $n=1189$
Age at baseline (median [IQR])	34 [30, 39]	35 [30, 41]	34 [30, 40]	36 [31, 42]	34 [30, 38]	34 [30, 40]
Age at endpoint (median [IQR])	45 [39, 53]	56 [47, 63]	48 [41, 56]	60 [52, 66]	43 [38, 50]	53 [45, 60]
Cumulative person-years (median [IQR])	11 [7, 13]	20 [12, 28]	11 [9, 17]	24 [12, 30]	9 [6, 12]	14 [11, 27]
Race						
White	2601 (79.8)	1476 (72.5)	1428 (82.8)	690 (81.4)	1173 (76.4)	786 (66.1)
African-American	379 (11.6)	394 (19.3)	188 (10.9)	109 (12.9)	191 (12.4)	285 (24.0)
Other	281 (8.6)	167 (8.2)	109 (6.3)	49 (5.8)	172 (11.2)	118 (9.9)
No. of sexual partners >2/6 months[a]	2159 (66.2)	1474 (72.4)	1036 (60.1)	616 (72.6)	1123 (73.1)	858 (72.2)
No. of anal receptive sexual partners >2/6 months[a]	684 (21.0)	515 (25.3)	150 (8.7)	120 (14.2)	534 (34.8)	395 (33.2)
Tobacco ≥0.5 packs/day[b]	788 (24.2)	469 (23.0)	363 (21.0)	159 (18.8)	425 (27.7)	310 (26.1)
Alcohol >14 drinks/week or bingeing[b]	743 (22.8)	469 (23.0)	360 (20.9)	196 (23.1)	383 (24.9)	273 (23.0)
Marijuana ≥1000 exposures[c]	252 (7.7)	180 (8.8)	88 (5.1)	56 (6.6)	164 (10.7)	124 (10.4)
Poppers ≥1 year of daily or weekly use	729 (22.4)	605 (29.7)	321 (18.6)	239 (28.2)	408 (26.6)	366 (30.8)
Crack cocaine ≥100 exposures[c]	76 (2.3)	111 (5.4)	42 (2.4)	28 (3.3)	34 (2.2)	83 (7.0)
$CD4^+$ cell count (cells/μl) (median [IQR])[d]	–	–	988 [765, 1250]	938 [734, 1183]	291 [88, 567]	489 [272, 703]
$CD4^+$ cell count <350 cells/μl[d]	–	–	6 (0.3)	9 (1.1)	855 (55.7)	399 (33.6)
$CD4^+$ nadir (cells/μl) (median [IQR])[e]	–	–	640 [494, 813]	606 [475, 770]	157 [30, 352]	215 [95, 342]
$CD4^+$:$CD8^+$ ratio (median [IQR])[d]	–	–	1.84 [1.37, 2.48]	1.79 [1.32, 2.35]	0.34 [0.13, 0.70]	0.57 [0.31, 0.88]
$CD4^+$:$CD8^+$ ratio <1[d]	–	–	128 (7.4)	82 (9.7)	1319 (85.9)	964 (81.1)
$CD4^+$:$CD8^+$ ratio nadir (median [IQR])[e]	–	–	1.22 [0.91, 1.61]	1.13 [0.89, 1.48]	0.20 [0.06, 0.41]	0.24 [0.12, 0.42]
HIV viral load >400 copies/ml[d]	–	–	–	–	1048 (73.0)	389 (33.7)
HAART use at endpoint	–	–	–	–	494 (32.2)	911 (76.6)
HBV-active medication use prior to endpoint[f]	375 (11.5)	755 (37.1)	7 (0.4)	30 (3.5)	368 (24.0)	725 (61.0)
HBV past or current						
ATHBC positive[g]	–	2003 (98.3)	–	829 (97.8)	–	1174 (98.7)
HBSAG, HBEAG, and HBV DNA negative[h]	–	1610 (79.0)	–	707 (83.4)	–	903 (75.9)
HBSAG, HBEAG, or HBV DNA positive	–	393 (19.3)	–	122 (14.4)	–	271 (22.8)
ATHBC negative/HBSAG or HBV DNA positive	–	34 (1.7)	–	19 (2.2)	–	15 (1.3)
HCV past or current infection[i]	256 (7.9)	273 (13.4)	67 (3.9)	73 (8.6)	189 (12.3)	200 (16.8)
ADMs[j]	434 (13.3)	152 (7.5)	8 (0.5)	8 (0.9)	426 (27.7)	144 (12.1)
NADMs						
Anal SCC	8 (0.2)	45 (2.2)	2 (0.1)	6 (0.7)	6 (0.4)	39 (3.3)
Liver cancer	3 (0.1)	17 (0.8)	1 (0.1)	6 (0.7)	2 (0.1)	11 (0.9)
Other NADMs[k]	161 (4.9)	182 (8.9)	85 (4.9)	79 (9.3)	76 (4.9)	103 (8.7)
Deaths	445 (13.6)	181 (8.9)	33 (1.9)	22 (2.6)	412 (26.8)	159 (13.4)

Data shown are *n* (%) unless otherwise indicated. ADM, AIDS defining malignancy; ATHBC, antibody to HBV core antigen; HBEAG, HBV e antigen; HBSAG, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NADM, non-AIDS-defining malignancy; SCC, squamous cell carcinoma.

[a]Average over first three visits.

[b]Average over 10 years prior to endpoint.

[c]Total exposures over 10 years prior to endpoint.

[d]Time-updated values lagged 1 year prior to endpoint.

[e]Lowest value between enrollment and study endpoint.

[f]HBV-active medications included lamivudine ($n=952$), tenofovir ($n=618$), emtricitabine ($n=134$), pegylated-interferon or IFN-α ($n=79$), and other ($n=25$) between enrollment and study endpoint.

[g]At least two positive tests, or one positive test in combination with positive test for HBSAG, HBEAG, or HBV DNA any time following enrollment to study endpoint.

[h]Negative = 0 positive tests among subjects with at least 1 value.

[i]At least one positive test for HCV antibodies or HCV RNA any time following enrollment to study endpoint.

[j]Kaposi sarcoma and/or non-Hodgkin lymphoma diagnosed within study period.

[k]All other NADMs (excluding nonmelanoma skin cancers and benign tumors) diagnosed within study period.

1 year prior to endpoint, and HAART or HBV-active medication use was more frequent in comparison with HBV-negative participants (Table 1).

Crude incidence of anal squamous cell carcinoma and other virus-associated cancers

We observed 53 incident cases of anal SCC during follow-up, eight in HIV-negative participants and 45 in HIV-positive participants. Crude incidence rates of anal SCC were higher in participants with past or current HBV regardless of HIV status (Supplemental Digital Content 1, http://links.lww.com/QAD/B386). Past or current HBV was associated with increased risk of anal SCC among HIV-positive participants [crude incidence rate ratio (IRR), 95% confidence interval (CI) 4.92, 2.09–11.63]. Similar IRR was observed among HIV-negative participants (IRR, 95% CI 4.05, 0.82–20.08), but NS due to a low number of cases. Crude incidence rates of liver cancer were higher in participants with vs. without past or current HBV regardless of HIV status. Incidence rates of other NADMs were similar by HBV status (IRRs 1.04–1.27), whereas incidence rates of Kaposi sarcoma and NHL were lower in HIV-positive participants with past or current HBV.

Hepatitis B virus and anal squamous cell carcinoma risk in HIV-positive subjects

In univariate models, past or current HBV was associated with increased risk of anal SCC in HIV-positive participants (IRR, 95% CI 4.92, 2.09–11.63), as was older age and $CD4^+$ cell counts less than 500 or $CD4^+ : CD8^+$ ratios less than 0.5 lagged 6 years prior to endpoint (Supplemental Digital Content 2, http://links.lww.com/QAD/B386). The association remained significant in multivariate models adjusted for age, race, HAART use, and $CD4^+$ cell counts or $CD4^+ : CD8^+$ ratios (IRRs, 95% CIs 3.07–3.29, 1.24–7.64 to 1.32–8.23; Table 2). In subanalyses of either past or current HBV compared with HBV-negative participants, only past HBV had a significant association with anal SCC risk (IRRs, 95% CIs 3.39–3.71, 1.32–8.75 to 1.42–9.67; Table 2). Further adjustment for HCV infection, number of sexual partners, tobacco use, or poppers use did not attenuate this association (Table 2). $CD4^+$ cell counts less than 500 or $CD4^+ : CD8^+$ ratios less than 0.5 at 6 years prior to endpoint were associated with increased anal SCC risk in adjusted models (Table 2). $CD4^+$ cell counts less than 500 or $CD4^+ : CD8^+$ ratios less than 0.5 at 1 year prior to endpoint were significant only in adjusted models, whereas nadir values were marginally significant (Supplemental Digital Contents 2 and 3, http://links.lww.com/QAD/B386 and Table 2). A negative association between no HAART use at endpoint and anal SCC risk was significant in unadjusted, but not adjusted models. Older age had a strong association with increased anal SCC risk in adjusted models, tobacco use had a marginally significant association (IRRs 1.60–1.83; $P = 0.068$–0.159) (Supplemental Digital Content 3, http://links.lww.com/QAD/B386), and race, number of sexual partners, HCV infection, or poppers use had no significant associations (Table 2).

Demographic and clinical characteristics of groups by HIV status and anal squamous cell carcinoma diagnosis

We compared characteristics of the cohort stratified by HIV and anal SCC diagnosis (Supplemental Digital Content 4, http://links.lww.com/QAD/B386). Among HIV-positive participants, lab values indicating past HBV infection were more common among anal SCC cases compared with noncases. Similar trends were observed among HIV-negative participants. Anal SCC cases were older at endpoint, with longer follow-up and lower death rates in comparison with noncases among HIV-positive participants, anal SCC cases had lower $CD4^+$ cell counts and $CD4^+ : CD8^+$ ratios lagged 6 years prior to endpoint among HIV-positive participants and lower nadir $CD4^+$ cell counts and nadir $CD4^+ : CD8^+$ ratios compared with noncases in HIV-negative participants. HAART and HBV-active medication use were more common among anal SCC cases compared with noncases.

Discussion

In this prospective study of 5298 MSM enrolled in the MACS from 1984 to 2014, past or current HBV was associated with three-fold increased risk of anal SCC among HIV-positive participants, and remained an independent risk factor in models adjusted for age, HAART use, $CD4^+$ cell counts or $CD4^+ : CD8^+$ ratios, and other risk factors. We also confirmed previously reported associations between anal SCC risk and older age, decreased $CD4^+$ cell counts or $CD4^+ : CD8^+$ ratios, and smoking. Together with prior studies demonstrating increased HSIL among individuals coinfected with anal hrHPV and HBV [43], our findings suggest that HBV may be an oncogenic cofactor for development of anal SCC.

The association between HBV infection and anal SCC occurred primarily in HIV-positive participants with resolved HBV [46]. In analyses limited to active or chronic HBV, the association between HBV and anal SCC was NS. Similarly, Hassan *et al.* [1] found the association between HBV and increased risk of pancreatic cancer was evident in ATHBC-positive, HBSAG-negative individuals. These findings raise the interesting question of how resolved HBV infections might impact cancer risk later in life.

HBV has been associated with elevated risk of several nonhepatic cancers and NHL [1–9]. HBV integrates into host DNA, causing insertional mutagenesis, and encodes the oncogenic hepatitis B X protein, which targets tumor suppressor and DNA damage repair pathways [10,12,13,15]. With regard to indirect roles in promoting

Table 2. Multivariate analysis of risk factors associated with anal squamous cell carcinoma in HIV-positive participants.

	$CD4^+$ variables lagged 1 year				$CD4^+$ variables lagged 6 years			
Multivariate models	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*	IRR (95% CI)	*P*
Model 1								
HBV past or current	3.26 (1.31, 8.16)	**0.011**	3.29 (1.32, 8.23)	**0.011**	3.15 (1.27, 7.82)	**0.013**	3.07 (1.24, 7.64)	**0.016**
Age group: 30–49	Reference		Reference		Reference		Reference	
50–59	4.96 (2.52, 9.75)	**<0.001**	5.1 (2.59, 10.02)	**<0.001**	4.94 (2.51, 9.72)	**<0.001**	5.01 (2.55, 9.85)	**<0.001**
60–70	4.56 (1.81, 11.51)	**0.001**	4.78 (1.90, 12.05)	**<0.001**	4.57 (1.81, 11.53)	**0.001**	4.52 (1.79, 11.42)	**0.001**
Race: Non-African-American	Reference		Reference		Reference		Reference	
African-American	0.99 (0.46, 2.12)	0.973	0.97 (0.45, 2.09)	0.94	0.97 (0.45, 2.09)	0.937	0.95 (0.44, 2.05)	0.905
No HAART use	0.56 (0.19, 1.72)	0.315	0.53 (0.17, 1.61)	0.259	0.71 (0.24, 2.13)	0.539	0.75 (0.25, 2.27)	0.613
$CD4^+$ cell count <500 cells/μl	2.45 (1.31, 4.58)	**0.005**	–		2.44 (1.30, 4.59)	**0.006**	–	
$CD4^+$:$CD8^+$ ratio <0.5	–		2.43 (1.34, 4.42)	**0.004**	–		2.77 (1.50, 5.11)	**0.001**
Model 2								
Past HBV[a]	3.59 (1.38, 9.35)	**0.009**	3.71 (1.42, 9.67)	**0.007**	3.49 (1.35, 9.01)	**0.010**	3.39 (1.32, 8.75)	**0.011**
Age group: 30–49	Reference		Reference		Reference		Reference	
50–59	5.83 (2.77, 12.27)	**<0.001**	6.07 (2.88, 12.77)	**<0.001**	5.84 (2.77, 12.32)	**<0.001**	5.94 (2.82, 12.52)	**<0.001**
60–70	4.10 (1.39, 12.07)	**0.010**	4.37 (1.48, 12.85)	**0.007**	4.10 (1.39, 12.06)	**0.010**	4.10 (1.39, 12.07)	**0.010**
Race: Non-African-American	Reference		Reference		Reference		Reference	
African-American	0.55 (0.19, 1.55)	0.258	0.54 (0.19, 1.53)	0.249	0.54 (0.19, 1.51)	0.240	0.52 (0.19, 1.48)	0.221
No HAART use	0.74 (0.23, 2.35)	0.611	0.66 (0.21, 2.11)	0.486	0.93 (0.30, 2.91)	0.902	0.96 (0.31, 3.01)	0.948
$CD4^+$ cell count <500 cells/μl	2.17 (1.11, 4.23)	**0.023**	–		2.53 (1.28, 5.03)	**0.008**	–	
$CD4^+$:$CD8^+$ ratio <0.5	–		2.62 (1.36, 5.04)	**0.004**	–		2.90 (1.50, 5.62)	**0.002**
Model 3								
Current HBV[b]	1.26 (0.56, 2.83)	0.576	1.19 (0.53, 2.69)	0.671	1.26 (0.56, 2.83)	0.576	1.17 (0.52, 2.64)	0.701
Age group: 30–49	Reference		Reference		Reference		Reference	
50–59	5.40 (2.75, 10.61)	**<0.001**	5.55 (2.82, 10.90)	**<0.001**	5.39 (2.74, 10.59)	**<0.001**	5.48 (2.79, 10.77)	**<0.001**
60–70	5.25 (2.08, 13.24)	**<0.001**	5.47 (2.17, 13.79)	**<0.001**	5.23 (2.07, 13.18)	**<0.001**	5.18 (2.05, 13.06)	**<0.001**
Race: Non-African-American	Reference		Reference		Reference		Reference	
African-American	1.04 (0.48, 2.23)	0.925	1.03 (0.48, 2.22)	0.937	1.03 (0.48, 2.21)	0.947	1.00 (0.47, 2.16)	0.992
No HAART use	0.35 (0.12, 1.01)	0.051	0.32 (0.11, 0.94)	**0.039**	0.45 (0.16, 1.31)	0.143	0.48 (0.17, 1.40)	0.180
$CD4^+$ cell count <500 cells/μl	2.43 (1.30, 4.54)	**0.006**	–		2.46 (1.30, 4.62)	**0.005**	–	
$CD4^+$:$CD8^+$ ratio <0.5	–		2.37 (1.30, 4.34)	**0.005**	–		2.82 (1.53, 5.22)	**<0.001**
Model 1 + HCV[c]								
HBV past or current	3.26 (1.31, 8.16)	**0.011**	3.29 (1.32, 8.22)	**0.011**	3.15 (1.27, 7.82)	**0.013**	3.07 (1.23, 7.63)	**0.016**
Model 1 + no. sexual partners[d]								
HBV past or current	3.26 (1.30, 8.16)	**0.012**	3.29 (1.32, 8.23)	**0.011**	3.15 (1.27, 7.83)	**0.013**	3.06 (1.23, 7.62)	**0.016**
Model 1 + tobacco[e]								
HBV past or current	3.19 (1.28, 7.98)	**0.013**	3.21 (1.29, 8.03)	**0.012**	3.09 (1.25, 7.66)	**0.015**	3.00 (1.21, 7.47)	**0.018**
Model 1 + poppers[f]								
HBV past or current	3.45 (1.38, 8.62)	**0.008**	3.46 (1.39, 8.64)	**0.008**	3.33 (1.34, 8.27)	**0.009**	3.2 (1.29, 7.96)	**0.012**

Poisson regression models: *P* values calculated using Wald's test, bold indicates *P* less than 0.05. All HIV-positive participants are included ($n = 2725$). CI, confidence interval; HBEAG, HBV e antigen; HBSAG, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IRR, incidence rate ratio.

[a]Participants with at least two positive ATHBC test results compared with HBV-negative participants.

[b]Participants with at least one positive HBSAG, HBEAG, or HBV DNA test result compared with HBV-negative participants.

[c]Positive tests for HCV antibodies or HCV RNA prior to endpoint compared with participants with negative tests, restricted to participants with available tests ($n = 2653$).

[d]More than two sexual partners/6 months compared with two partners or less/6 months, average over first three visits.

[e]At least 0.5 packs/day compared with less than 0.5 packs/day, average over 10 years prior to endpoint. Supplemental Digital Content 3, http://links.lww.com/QAD/B386 shows full models including tobacco use.

[f]At least 1 year of daily or weekly use compared with monthly, less than monthly, or no use within follow-up.

risk of anal SCC, HBV induces inflammation and T-cell exhaustion [11,14] and cirrhosis can lead to immune dysregulation and $CD4^+$ lymphopenia [47–49]. However, immunological effects of resolved HBV infections are unknown. We found a significant association between low $CD4^+$ cell counts or $CD4^+$:$CD8^+$ ratios at 6 years prior to endpoint and anal SCC risk, consistent with [50]. Further studies are warranted to determine if resolved HBV is associated with immunological effects that impact later risk of cancers.

Participants on HAART had greater risk of anal SCC in comparison with those not on HAART, consistent with [39,50]. AIDS-related deaths are a competing risk and HAART prolongs life expectancy, allowing more time during which precursor lesions can progress to anal cancers [39,40,50–52].

We acknowledge limitations of our study. Lack of data related to hrHPV infection precluded modeling its role in anal SCC carcinogenesis. Our study was limited to mostly white MSM in a cohort at high risk of acquiring HIV, HBV, and HPV, with high rates of smoking and substance use, limiting applicability of our findings to the general population. HIV-positive participants with past or current HBV were slightly older, with more HAART and HBV-active medication use, better immunological profiles, and lower death rates. However, a case–control analysis in

which each anal SCC case was matched to 10 controls based on recruitment wave, age at enrollment, race, HIV-infection status, smoking, follow-up, and calendar year at endpoint supported all of our main conclusions (data not shown).

In conclusion, this study demonstrates a significant association between prior HBV infection and increased anal SCC risk independent of age, HAART use, and immunological parameters. These results have implications regarding potential benefits of anal SCC screening in HIV-negative and HIV-positive MSM with prior HBV, and suggest that HBV vaccination in at-risk populations has the potential to improve anal cancer prevention.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hassan MM, Li D, El-Deeb AS, Wolff RA, Bondy ML, Davila M, *et al*. **Association between hepatitis B virus and pancreatic cancer.** *J Clin Oncol* 2008; **26**:4557–4562.
2. Hsing AW, Zhang M, Rashid A, McGlynn KA, Wang BS, Niwa S, *et al*. **Hepatitis B and C virus infection and the risk of biliary tract cancer: a population-based study in China.** *Int J Cancer* 2008; **122**:1849–1853.
3. Iloeje UH, Yang HI, Jen CL, Su J, Wang LY, You SL, *et al*. **Risk of pancreatic cancer in chronic hepatitis B virus infection: data from the REVEAL-HBV cohort study.** *Liver Int* 2010; **30**:423–429.
4. Kamiza AB, Su FH, Wang WC, Sung FC, Chang SN, Yeh CC. **Chronic hepatitis infection is associated with extrahepatic cancer development: a nationwide population-based study in Taiwan.** *BMC Cancer* 2016; **16**:861.
5. Lee TY, Lee SS, Jung SW, Jeon SH, Yun SC, Oh HC, *et al*. **Hepatitis B virus infection and intrahepatic cholangiocarcinoma in Korea: a case–control study.** *Am J Gastroenterol* 2008; **103**:1716–1720.
6. Li M, Gan Y, Fan C, Yuan H, Zhang X, Shen Y, *et al*. **Hepatitis B virus and risk of non-Hodgkin lymphoma: an updated meta-analysis of 58 studies.** *J Viral Hepat* 2018; **25**:894–903.
7. Persico E, De Renzo A, La Mura V, Bruno S, Masarone M, Torella R, *et al*. **Occult hepatitis B virus infection in patients with non-Hodgkin lymphoma: the need for early diagnosis in anti-Hbc positive patients.** *Gut* 2007; **56**:1470–1471.
8. Qi Z, Wang H, Gao G. **Association of risk of non-Hodgkin's lymphoma with hepatitis B virus infection: a meta-analysis.** *Int J Clin Exp Med* 2015; **8**:22167–22174.
9. Wang Q, De Luca A, Smith C, Zangerle R, Sambatakou H, Bonnet F, *et al*. **Chronic hepatitis B and C virus infection and risk for non-Hodgkin lymphoma in HIV-infected patients: a cohort study.** *Ann Intern Med* 2017; **166**:9–17.
10. Ahn SM, Jang SJ, Shim JH, Kim D, Hong SM, Sung CO, *et al*. **Genomic portrait of resectable hepatocellular carcinomas: implications of RB1 and FGF19 aberrations for patient stratification.** *Hepatology* 2014; **60**:1972–1982.
11. Bertoletti A, Ferrari C. **Innate and adaptive immune responses in chronic hepatitis B virus infections: towards restoration of immune control of viral infection.** *Gut* 2012; **61**:1754–1764.
12. Hai H, Tamori A, Kawada N. **Role of hepatitis B virus DNA integration in human hepatocarcinogenesis.** *World J Gastroenterol* 2014; **20**:6236–6243.
13. Neuveut C, Wei Y, Buendia MA. **Mechanisms of HBV-related hepatocarcinogenesis.** *J Hepatol* 2010; **52**:594–604.
14. Pauken KE, Wherry EJ. **Overcoming T cell exhaustion in infection and cancer.** *Trends Immunol* 2015; **36**:265–276.
15. Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y, *et al*. **Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma.** *Nat Commun* 2016; **7**:12992.
16. Alter MJ. **Epidemiology of viral hepatitis and HIV co-infection.** *J Hepatol* 2006; **44**:S6–S9.
17. Falade-Nwulia O, Seaberg EC, Snider AE, Rinaldo CR, Phair J, Witt MD, *et al*. **Incident hepatitis B virus infection in HIV-infected and HIV-uninfected men who have sex with men from pre-HAART to HAART periods: a cohort study.** *Ann Intern Med* 2015; **163**:673–680.
18. Thio CL. **Hepatitis B and human immunodeficiency virus co-infection.** *Hepatology* 2009; **49**:S138–S145.
19. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. **Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013.** *Lancet* 2015; **386**:1546–1555.
20. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, *et al*. **Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study.** *AIDS* 2009; **23**:41–50.
21. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. **Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study.** *Lancet HIV* 2017; **4**:e495–e504.
22. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. **The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS.** *Am J Epidemiol* 2007; **165**:1143–1153.
23. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, *et al*. **Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003.** *Ann Intern Med* 2008; **148**:728–736.
24. Powles T, Robinson D, Stebbing J, Shamash J, Nelson M, Gazzard B, *et al*. **Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection.** *J Clin Oncol* 2009; **27**:884–890.
25. Seaberg EC, Wiley D, Martinez-Maza O, Chmiel JS, Kingsley L, Tang Y, *et al*. **Cancer incidence in the Multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007.** *Cancer* 2010; **116**:5507–5516.
26. Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, *et al*. **HIV infection and the risk of cancers with and without a known infectious cause.** *AIDS* 2009; **23**:2337–2345.
27. Vogel M, Friedrich O, Luchters G, Holleczek B, Wasmuth JC, Anadol E, *et al*. **Cancer risk in HIV-infected individuals on HAART is largely attributed to oncogenic infections and state of immunocompetence.** *Eur J Med Res* 2011; **16**:101–107.
28. Bedimo R, Chen RY, Accortt NA, Raper JL, Linn C, Allison JJ, *et al*. **Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002.** *Clin Infect Dis* 2004; **39**:1380–1384.
29. Crum-Cianflone NF, Hullsiek KH, Marconi VC, Ganesan A, Weintrob A, Barthel RV, *et al*. **Anal cancers among HIV-infected persons: HAART is not slowing rising incidence.** *AIDS* 2010; **24**:535–543.
30. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, *et al*. **Cancer burden in the HIV-infected population in the United States.** *J Natl Cancer Inst* 2011; **103**:753–762.
31. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, *et al*. **Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America.** *Clin Infect Dis* 2012; **54**:1026–1034.
32. Palefsky JM, Holly EA, Ralston ML, Jay N. **Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men.** *J Infect Dis* 1998; **177**:361–367.
33. Critchlow CW, Holmes KK, Wood R, Krueger L, Dunphy C, Vernon D, *et al*. **Association of human immunodeficiency virus and anal human papillomavirus infection among homosexual men.** *Arch Intern Med* 1992; **152**:1673–1676.
34. Kiviat NB, Critchlow CW, Holmes KK, Kuypers J, Sayer J, Dunphy C, *et al*. **Association of anal dysplasia and human papillomavirus with immunosuppression and HIV infection among homosexual men.** *AIDS* 1993; **7**:43–49.
35. Breese PL, Judson FN, Penley KA, Douglas JM Jr. **Anal human papillomavirus among homosexual and bisexual men: prevalence of type specific infection and association with human immunodeficiency virus.** *Sex Transm Dis* 1995; **22**:7–14.
36. Critchlow CW, Hawes SE, Kuypers JM, Goldbaum GM, Holmes KK, Surawicz CM, *et al*. **Effect of HIV infection on the natural history of anal human papillomavirus infection.** *AIDS* 1998; **12**:1177–1184.
37. Frisch M, Biggar RJ, Goedert JJ. **Human papillomavirus associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome.** *J Natl Cancer Inst* 2000; **92**:1500–1510.
38. Castellsague X, Bosch FX, Nubia M. **Environmental co-factors in HPV carcinogenesis.** *Virus Res* 2002; **89**:191–199.
39. D'Souza G, Wiley DJ, Li X, Chmiel JS, Margolick JB, Cranston RD, *et al*. **Incidence and epidemiology of anal cancer in the Multicenter AIDS Cohort Study.** *J Acquir Immune Defic Syndr* 2008; **48**:491–499.
40. Piketty C, Selinger-Leneman H, Grabar S, Duvivier C, Bonmarchand M, Abramowitz L, *et al*. **Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy.** *AIDS* 2008; **22**:1203–1211.

41. Reekie J, Kosa C, Engsig F, Monforte A, Wiercinska-Drapalo A, Domingo P, *et al*. **Relationship between current level of immunodeficiency and nonacquired immunodeficiency syndrome-defining malignancies.** *Cancer* 2010; **116**:5306–5315.
42. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. **Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.** *Lancet* 2007; **370**:59–67.
43. McCloskey JC, Martin Kast W, Flexman JP, McCallum D, French MA, Phillips M. **Syndemic synergy of HPV and other sexually transmitted pathogens in the development of high-grade anal squamous intraepithelial lesions.** *Papillomavirus Res* 2017; **4**:90–98.
44. Nyitray AG, Carvalho da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, *et al*. **Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study.** *J Infect Dis* 2011; **203**:49–57.
45. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, *et al*. **Sexually transmitted infection as a cause of anal cancer.** *N Engl J Med* 1997; **337**:1350–1358.
46. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. **Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the Multicenter AIDS Cohort Study.** *Clin Infect Dis* 2013; **56**:606–612.
47. Albillos A, Lario M, Alvarez-Mon M. **Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance.** *J Hepatol* 2014; **61**:1385–1396.
48. McGovern BH, Golan Y, Lopez M, Pratt D, Lawton A, Moore G, *et al*. **The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients.** *Clin Infect Dis* 2007; **44**: 431–437.
49. Sipeki N, Antal-Szalmas P, Lakatos PL, Papp M. **Immune dysfunction in cirrhosis.** *World J Gastroenterol* 2014; **20**:2564–2577.
50. Bertisch B, Franceschi S, Lise M, Vernazza P, Keiser O, Schoni-Affolter F, *et al*. **Risk factors for anal cancer in persons infected with HIV: a nested case–control study in the Swiss HIV Cohort Study.** *Am J Epidemiol* 2013; **178**:877–884.
51. Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. **Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy.** *Sex Transm Dis* 2005; **32**:314–320.
52. Piketty C, Darragh TM, Heard I, Da Costa M, Bruneval P, Kazatchkine MD, *et al*. **High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy.** *Sex Transm Dis* 2004; **31**:96–99.