HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2019 January 30.

Published in final edited form as:

AIDS. 2019 January 27; 33(1): 145–152. doi:10.1097/QAD.0000000000002059.

Increased risk of anal squamous cell carcinoma in HIV-positive men with prior HBV infection

Jordan Aldersley[a], **David R. Lorenz**[a], **Vikas Misra**[a], **Hajime Uno**[b], and **Dana Gabuzda**[a]

[a]Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[b]Center for Population Science, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Abstract

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 -negative men who have sex with men (MSM) in the Multicenter AIDS Cohort Study from 1984–2014.

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 5,298 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 [CI] 3.15, 1.27–7.82). Additional risk factors included immunological parameters one and six years prior to diagnosis (IRR, 95% CI 2.45, 1.31–4.58 and 2.44, 1.3–4.59 for CD4+ 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 not significant due to small number of cases.

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

Keywords

HIV; hepatitis B virus; anal cancer; MSM; cohort studies; cancer epidemiology

Correspondence to: Dana Gabuzda, MD, Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Center for Life Science 1010, 450 Brookline Avenue, Boston, MA 02215, USA. dana_gabuzda@dfci.harvard.edu.

The authors declare that they have no competing interests

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 pro-tumorigenic effects raise the possibility it could be an oncogenic cofactor [10–15].

HBV infection rates are high among HIV-infected populations and men who have sex with men (MSM) [16–19]. HIV-infected populations have elevated risk for non-AIDS-defining malignancies (NADM) 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 >90% of cases [32]. Anal hrHPV infections are detected in 30–90% of HIV-positive individuals, with 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 -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 7,343 HIV-positive and HIV-negative MSM. Clinical and laboratory data were collected at semiannual visits as described [25, 39]. Eligible participants were 5,298 MSM age 30–70 with at least five years of follow-up during 1984–2014 and one or more visits with HBV laboratory test data. Baseline was first visit after age 30. 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 data set 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

Subjects were followed from baseline to first instance of incident cancer, last study visit, or age 70. Poisson regression models were restricted to HIV-positive subjects. Factors associated with anal SCC in univariate analyses at $p<0.2$ 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 HBV infection status

We identified 5,298 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=2,037) 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 subjects with past or current HBV in comparison to HBV-negative subjects. By contrast, frequencies of HIV-positive subjects with ADMs or death were lower among subjects with past or current HBV in comparison to HBV-negative subjects. More HIV-negative subjects with past or current HBV reported >2 sexual or anal receptive partners/6 months in comparison to HBV-negatives, while there was no difference by HBV status among only HIV-positive subjects.

Immunological and virological characteristics by HIV and HBV infection status

CD4+ cell counts and CD4:CD8 ratios were lower in HIV-positive compared to HIV-negative subjects, while the relationship of these variables to HBV status varied by HIV status (Table 1). Among HIV-negative subjects with past or current HBV, CD4+ counts and CD4+ nadirs were lower at one year prior to endpoint in comparison to HBV-negative subjects. Among HIV-positive subjects with past or current HBV, CD4+ cell counts and CD4:CD8 ratios were higher, fewer subjects had CD4+ counts <350 cells/μl at one year prior to endpoint, and HAART or HBV-active medication use was more frequent in comparison to HBV-negative subjects (Table 1).

Crude incidence of anal SCC and other virus-associated cancers

We observed 53 incident cases of anal SCC during follow-up, 8 in HIV-negative subjects and 45 in HIV-positive subjects. Crude incidence rates of anal SCC were higher in subjects with past or current HBV regardless of HIV status (Supplemental Digital Content 1). Past or current HBV was associated with increased risk of anal SCC among HIV-positive subjects (crude IRR, 95% CI 4.92, 2.09–11.63). Similar IRR was observed among HIV-negative subjects (IRR, 95% CI 4.05, 0.82–20.08), but not significant due to a low number of cases. Crude incidence rates of liver cancer were higher in subjects 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), while incidence rates of KS and NHL were lower in HIV-positive subjects with past or current HBV.

HBV and anal SCC risk in HIV-positive subjects

In univariate models, past or current HBV was associated with increased risk of anal SCC in HIV-positive subjects (IRR, 95% CI 4.92, 2.09–11.63), as was older age and CD4+ counts <500 or CD4:CD8 ratios <0.5 lagged six years prior to endpoint (Supplemental Digital Content 2). The association remained significant in multivariate models adjusted for age, race, HAART use, and CD4+ counts or CD4:CD8 ratios (IRRs, 95% CIs 3.07–3.29, 1.24–7.64 to 1.32–8.23; Table 2). In sub-analyses of either past or current HBV compared to HBV-negative subjects, 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 <500 or CD4:CD8 ratios <0.5 at six years prior to endpoint were associated with increased anal SCC risk in adjusted models (Table 2). CD4+ cell counts <500 or CD4:CD8 ratios <0.5 at one year prior to endpoint were significant only in adjusted models, while nadir values were marginally significant (Supplemental Digital Content 2 and 3 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=0.068–0.16) (Supplemental Digital Content 3), 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 SCC diagnosis

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

DISCUSSION

In this prospective study of 5,298 MSM enrolled in the MACS from 1984–2014, past or current HBV was associated with 3-fold increased risk of anal SCC among HIV-positive subjects, and remained an independent risk factor in models adjusted for age, HAART use, CD4+ counts or CD4:CD8 ratios, and other risk factors. We also confirmed previously reported associations between anal SCC risk and older age, decreased CD4+ counts or CD4:CD8 ratios, and smoking. Together with prior studies demonstrating increased HSIL

among individuals co-infected with anal hrHPV and HBV [43], our findings suggest that HBV may be an oncogenic co-factor for development of anal SCC.

The association between HBV infection and anal SCC occurred primarily in HIV-positive subjects with resolved HBV [46]. In analyses limited to active or chronic HBV, the association between HBV and anal SCC was not significant. Similarly, Hassan *et. al* (2008) found the association between HBV and increased risk of pancreatic cancer was evident in ATHBC-positive, HBSAG-negative individuals [1]. 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 non-hepatic cancers and NHL [1–9]. HBV integrates into host DNA, causing insertional mutagenesis, and encodes the oncoprotein HBx, which targets tumor suppressor and DNA damage repair pathways [10, 12, 13, 15]. With regard to indirect roles in promoting 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+ counts or CD4:CD8 ratios at six 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.

Subjects on HAART had greater risk of anal SCC in comparison to 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 subjects 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Data for this manuscript was obtained by the Multicenter AIDS Cohort Study (MACS) with centers at: Baltimore (U01-AI35042): The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (PI), Jay Bream, Todd Brown, Barbara Crain, Adrian Dobs, Richard Elion, Michelle Estrella, Lisette Johnson-Hill, Sean Leng, Anne Monroe, Cynthia Munro, Michael W. Plankey, Wendy Post, Ned Sacktor, Jennifer Schrack, Chloe Thio; Chicago (U01-AI35039): Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: S.W. (PI), John P. Phair, Sheila Badri, D.G., David Ostrow, Frank J. Palella, Jr., Sudhir Penugonda, Susheel Reddy, Matthew Stephens, Linda Teplin; Los Angeles (U01-AI35040): University of California, UCLA Schools of Public Health and Medicine: Roger Detels (PI), Otoniel Martı´nez-Maza (Co-PI), Aaron Aronow, Peter Anton, Robert Bolan, Elizabeth Breen, Anthony Butch, Shehnaz Hussain, Beth Jamieson, Eric N. Miller, John Oishi, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang; Pittsburgh (U01-AI35041): University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (PI), Lawrence A. Kingsley (Co-PI), James T. Becker, Phalguni Gupta, Kenneth Ho, Susan Koletar, Jeremy J. Martinson, John W. Mellors, Anthony J. Silvestre, Ronald D. Stall; Data Coordinating Center (UM1-AI35043): The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (PI), Gypsyamber D'Souza (Co-PI), Alison Abraham, Keri Althoff, Jennifer Deal, Priya Duggal, Sabina Haberlen, Alvaro Munoz, Derek Ng, Janet Schollenberger, Eric C. Seaberg, Sol Su, Pamela Surkan. Website located at http://www.statepi.jhsph.edu/macs/macs.html.

Cancer incidence data were provided by the following state agencies: Maryland Cancer Registry, Center for Cancer Prevention and Control, Department of Health and Mental Hygiene, Baltimore, MD 21201; Illinois Department of Public Health, Illinois State Cancer Registry; Bureau of Health Statistics & Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania; Ohio Cancer Incidence Surveillance System (OCISS), Ohio Department of Health (ODH), a cancer registry partially supported in the National Program of Cancer Registries at the Centers for Disease Control and Prevention (CDC) through Cooperative Agreement # 5U58DP000795–05; and California Department of Public Health pursuant to California Health and Safety Code Section 103885; CDC's National Program of Cancer Registries, under cooperative agreement 5NU58DP003862–04/DP003862; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the CDC for the funds that support the collection and availability of the cancer registry data. The analyses, findings, interpretations, and conclusions of this report are those of the authors. No endorsement by any of the states providing data, the National Cancer Institute, the CDC, or their Contractors and Subcontractors is intended nor should be inferred. The authors acknowledge Steven Wolinsky, Sukrutha Chettimada, Debjani Guha, and Shibani Mukerji for helpful discussions and Elizabeth Carpelan for assistance with manuscript preparation.

J.A. participated in study design, performed data assembly and statistical analysis, drafted the manuscript, and prepared tables and figures. D.L. and V.M. participated in data parsing, assembly, and analysis. H.U. participated in study design and statistical analysis. D.G. conceived of the study, supervised its design, coordination, assembly, and analysis, and helped write and edit the manuscript. All authors read, participated in editing the manuscript, and approved the final manuscript.

The work was supported by NIH grants to D.G. (R01 DA030985 and DA046203) and in part by NIH funding to the Northwestern University Clinical Research Unit of the MACS (U01-AI35039, with additional co-funding from National Cancer Institute (NCI) and National Institute on Drug Abuse (NIDA)). J.A. was supported in part by NIH T32-AI007386–25. The MACS is funded by the National Institute of Allergy and Infectious Diseases (NIAID; U01-AI35039, U01-AI35040, U01-AI35041, U01-AI35042, and UM1-AI35043), with additional co-funding from the National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), and National Institute of Mental Health (NIMH) at the National Institutes of Health (NIH). MACS data collection is also supported by UL1-TR000424 (JHU CTSA).

Funding: The work was supported by NIH grants to D.G. (R01 DA030985 and R01 DA046203) and in part by NIH funding to the Northwestern University Clinical Research Unit of the MACS (U01-AI35039, with additional co-funding from National Cancer Institute (NCI) and National Institute on Drug Abuse (NIDA). J.A. was supported in part by NIH T32-AI007386–25. The MACS is funded by the National Institute of Allergy and Infectious Diseases (NIAID; U01-AI35039, U01-AI35040, U01-AI35041, U01-AI35042, and UM1-AI35043), with additional co-funding from the National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), and National Institute of Mental Health (NIMH) at the National Institutes of Health (NIH). MACS data collection is also supported by UL1-TR000424 (JHU CTSA).

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. [PubMed: 18824707]
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. [PubMed: 18076042]
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. [PubMed: 19840258]
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. [PubMed: 27821099]
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. [PubMed: 18557716]
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.
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. [PubMed: 17872574]
8. Q. Z, W H, G 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. [PubMed: 26885191]
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. Annals of Internal Medicine 2017,166:9–17. [PubMed: 27750294]
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. [PubMed: 24798001]
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. [PubMed: 22157327]
12. Hai H, Tamori A, Kawada N. Role of hepatitis B virus DNA integration in human hepatocarcinogenesis. World J Gastroenterol 2014,20:6236–6243. [PubMed: 24876744]
13. Neuveut C, Wei Y, Buendia MA. Mechanisms of HBV-related hepatocarcinogenesis. J Hepatol 2010,52:594–604. [PubMed: 20185200]
14. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol 2015,36:265–276. [PubMed: 25797516]
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. [PubMed: 27703150]
16. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006,44:S6–9. [PubMed: 16352363]
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. [PubMed: 26457744]
18. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology 2009,49:S138–145. [PubMed: 19399813]
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. The 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. [PubMed: 19050385]

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. The Lancet HIV 2017,4:e495–e504. [PubMed: 28803888]
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. [PubMed: 17344204]
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. Annals of Internal Medicine 2008,148:728–736. [PubMed: 18490686]
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. [PubMed: 19114688]
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. [PubMed: 20672354]
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. [PubMed: 19741479]
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 2011:101–107. [PubMed: 21486722]
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 2004:1380–1384.
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. [PubMed: 19926961]
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. [PubMed: 21483021]
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. [PubMed: 22291097]
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. [PubMed: 9466522]
33. Critchlow CW, Holmes KK, Wood R, Krueger L, Dunphy C, Vernon D, et al. Association of Human Immunodefiency Virus and Anal Human Papillomavirus Infection Among Homosexual Men. Arch Intern Med 1992:1673–1676. [PubMed: 1323247]
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 1993:43–49. [PubMed: 8382927]
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. Sexually Transmitted Diseases 1995,22:7–14. [PubMed: 7709329]
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. [PubMed: 9677167]
37. Frisch M, Biggar RJ, Goedert JJ. Human Papillomavirus associated cancers in patients with Human Immunodeficiency Virus infection and Aquired Immunodeficiency Syndrome. J Natl Cancer Inst 2000,92:1500–1510. [PubMed: 10995805]
38. Castellsague X, Bosch FX, Nubia M. Environmental co-factors in HPV carcinogenesis. Virus Res 2002:191–199. [PubMed: 12445659]

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 AIDS 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. [PubMed: 18525266]
41. Reekie J, Kosa C, Engsig F, Monforte A, Wiercinska-Drapalo A, Domingo P, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer 2010,116:5306–5315. [PubMed: 20661911]
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. The 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. [PubMed: 29179876]
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. [PubMed: 21148496]
45. Frisch M, Glimelius B, van den Brule AJC, Wohlfahrt J, M MCJL, Walboomers JMM, et al. Sexually Transmitted Infection as a Cause of Anal Cancer. NEJM 1997,337:1350–1358. [PubMed: 9358129]
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. [PubMed: 23090927]
47. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014,61:1385–1396. [PubMed: 25135860]
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. [PubMed: 17205454]
49. Sipeki N, Antal-Szalmas P, Lakatos PL, Papp M. Immune dysfunction in cirrhosis. World J Gastroenterol 2014,20:2564–2577. [PubMed: 24627592]
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. [PubMed: 23900553]
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. Sexually Transmitted Diseases 2005,32:314–320. [PubMed: 15849533]
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. [PubMed: 14743072]

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 [TQR])	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 pack/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+ count (cells/μl) (median [IQR])[d]	-	-	988 [765, 1250]	938 [734, 1183]	291 [88, 567]	489 [272, 703]
CD4+ count <350 (cells/μl)[d]	-	-	6 (0.3)	9 (1.1)	855 (55.7)	399 (33.6)
CD4+ nadir (cells/μl) (median [1QR])[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)

AIDS. Author manuscript; available in PMC 2019 January 30.

	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)**
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; HAART, highly active anti-retroviral therapy; 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-IFN or IFN-α (n=79), and other (n=25) between enrollment and study endpoint.

[g] At least 2 positive tests, or 1 positive test in combination with positive test for HBSAG, HBEAG, or HBVDNA any time following enrollment to study endpoint.

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

[i] At least 1 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 non-melanoma skin cancers and benign tumors) diagnosed within study period.

AIDS. Author manuscript; available in PMC 2019 January 30.

Table 2.

Multivariate analysis of risk factors associated with anal SCC in HIV-positive subjects.

Multivariate Models	CD4 variables lagged 1 year				CD4 variables lagged 6 years			
	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 (1.9, 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 (1.3, 4.59)	**0.006**	-	
CD4:CD8 ratio <0.5	-		2.43 (1.34, 4.42)	**0.004**	-		2.77 (1.5, 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**	4.1 (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+ 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)	0.573	1.19 (0.53, 2.69)	0.671	1.26 (0.56, 2.83)	0.586	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, 13.23)	**<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

Multivariate Models	CD4 variables lagged 1 year				CD4 variables lagged 6 years			
	IRR (95%CI)	*p*	IRR (95%CI)	*p*	IRR (95%CI)	*p*	IRR (95%CI)	*p*
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, 1.4)	0.180
CD4+ count <500 cells/μl	2.43 (1.3, 4.54)	**0.006**	-		2.46 (1.30, 4.62)	**0.005**	-	
CD4:CD8 ratio <0.5	-		2.37 (1.3, 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 $p < 0.05$. All HIV-positive subjects are included (n = 2725).

CI, confidence interval; HAART, highly active anti-retroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IRR, incidence rate ratio.

[a] Subjects with at least 2 positive ATHBC test results compared to HBV-negative subjects.

[b] Subjects with at least 1 positive HBSAG, HBEAG, or HBVDNA test result compared to HBV-negative subjects.

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

[d] >2 sexual partners/6 months compared with ≤2 partners/6 months, average over first three visits.

[e] ≥0.5 pack/day compared with <0.5 packs/day, average over 10 years prior to endpoint. Supplemental Digital Content 3 shows full models including tobacco use.

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