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Incidence and Risk Factors of Keratinocyte Carcinomas
in the HIV Atlanta Veterans Affairs Cohort Study

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Incidence and Risk Factors of Keratinocyte Carcinomas in the HIV Atlanta Veterans Affairs Cohort Study

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2019

Abstract

Incidence and Risk Factors of Keratinocyte Carcinomas
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By Howa Yeung, M.D.

Keratinocyte carcinomas (KC) – also known as nonmelanoma skin cancers and including basal cell carcinomas and squamous cell carcinomas – represent the most common non-AIDS defining malignancies in the United States in persons living with HIV. There is limited research on KC epidemiology and treatment in persons living with HIV in the United States since KCs are not reportable to cancer registries. This study aimed to 1) estimate the positive predictive value of diagnostic codes in identifying incident cases of KC in VA administrative data, and 2) estimate the associations between incident KC and the immune status, HIV viremia, and duration of HIV diagnosis in persons diagnosed with HIV. Using data from the HIV Atlanta Veterans Affairs (VA) Cohort Study and the VA HIV Clinical Case Registry from 1982 to 2017, we demonstrated modest positive predictive values of ICD-9 and -10 diagnostic codes in ascertaining incident KC cases upon manual electronic medical record review. Among 3,353 veterans with HIV followed for a mean of 8.5 years (median 7.2 years), 227 cases of incident biopsy-confirmed KC cases were identified. 223 cases of KC cases occurred in 680 non-Hispanic White male veterans, with an incidence rate estimated at 29.0 cases per 1,000 person-years. In a multivariable negative binomial model, KC incidence in non-Hispanic White male veterans was associated with older age (incidence rate ratio [IRR] 6.19 for 65 or older versus 18-44, 95% confidence interval [CI]: 0.87-43.98; $P = 0.009$), active follow up status by the end of the study period (IRR 0.22 for inactive versus active follow up; $P = 0.002$), and nadir CD4 lymphocyte count between 50-149 cells/mm^3 (IRR 5.40, 95% CI: 1.55-18.78) or 150-249 cells/mm^3 (IRR 6.12, 95% CI 1.52-24.67; $P = 0.002$]. We demonstrated KC incidence rates greater than 4-fold higher in non-Hispanic White male veterans diagnosed with HIV as compared with previous studies in non-veterans. Early HIV diagnosis and sustained HIV treatment, reduction of ultraviolet radiation exposure, and improved secondary prevention of keratinocyte carcinomas will be required to reduce the high burden of keratinocyte carcinomas in non-Hispanic White male veterans.

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Acknowledgements

To my family and friends who embrace my academic pursuits;

To the advisor who fuels my aspirations – Suephy C. Chen, MD MS;

To the mentors who guide me through the adventures of research – Robert A. Swerlick, MD; Vincent Marconi, MD; Jodie L. Guest, PhD MPH; Patrick S. Sullivan, PhD DVM; Amita Manatunga, PhD; Aaron W. Trammell, MD MSc; Ragini R. Kudchadkar, MD; Michael Goodman, MD MPH; Vin Tangpricha, MD PhD; Jonathan S. Weiss, MD; Brandyn D. Lau, MPH; Junko Takeshita, MD PhD MSCE; & David J. Margolis, MD PhD;

To the team who make it happen – Bridget Bradley, RN FNP CCRC; Cole H. Adler, MPH; Mona Rai, MPH; Rincy Varughese, MS MPH; & Chao Zhang, PhD;

To the veterans with HIV who provided snapshots of their health for this thesis.

This research is supported in part by the Dermatology Foundation and the National Center for Advancing Translational Sciences of the National Institutes of Health, through the Georgia Clinical & Translational Science Alliance, under award number UL1TR002378 and KL2TR002381. The content does not necessarily represent the official views of the National Institutes of Health.

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INTRODUCTION

Skin cancers – including keratinocyte carcinomas and melanomas -- represent the most commonly diagnosed cancers in the United States with increasing incidence, morbidity, and economic burden (1). In 2012, more than 5.4 million cases of keratinocyte carcinoma (KC, including basal cell carcinoma [BCC] and cutaneous squamous cell carcinoma [cSCC]) were diagnosed in 3.3 million people (2). In 2017, 87,110 new cases of melanoma will be diagnosed and lead to 9,730 deaths (3). However, there remains a paucity of research on skin cancer epidemiology since KC are not reportable to cancer registries (4). Persons living with human immunodeficiency virus (HIV) may be particularly vulnerable to develop skin cancers in settings of chronic immunosuppression (5, 6). Recent meta-analyses of available cohort studies suggest that HIV infection may be independently associated with higher KC incidence (7). As more persons living with HIV receive combination antiretroviral therapy (ART), life expectancy has risen and AIDS-related complications have dropped (8). The number of persons living with HIV above age 50 has quadrupled in the past decade, from 101,470 (22.4% of all patients living with HIV) in 2004 to 428,724 (44.9%) in 2014 (9-11). Accordingly, the morbidity and mortality from age-related, non-AIDS defining malignancies have been rising – the most common of which being KC (12-16). The incidence of KC should be evaluated in diverse and aging HIV cohorts to provide new data on clinical, virologic, and immunologic risk factors. Identifying those living with HIV at highest risks for developing KC will be critical for

developing innovative prevention strategies to curb the rise of KC incidence and morbidity in persons living with HIV.

To address these key knowledge gaps in our understanding of risk factors for skin cancer in HIV, this study will leverage the *HIV Atlanta Veterans Affairs Cohort Study (HAVACS),* an existing, prospective, large-scale cohort ongoing since 1982 that has been used to study aging and non-AIDS related malignancies in veterans living with HIV (17). HAVACS is comprised of 4,334 diverse aging veterans with rich, accessible clinical data that will allow the study of skin cancer epidemiology at the intersection of long-term HIV infection, chronic ART, minority status, and aging. We will test the overarching hypothesis that long-term HIV infection accelerates cutaneous carcinogenesis in aging due to chronic immune dysfunction. The specific aims include:

<u>Aim 1:</u> To estimate the positive predictive value of diagnostic codes in identifying incident cases of keratinocyte carcinoma.

<u>Aim 2:</u> To estimate the associations between incident keratinocyte carcinoma and the immune status, HIV viremia, and duration of HIV diagnosis in persons diagnosed with HIV.

Results from this study will inform subsequent studies to derive and validate a novel predictive model for skin cancer risks and targeted screening and secondary prevention interventions based on predicted skin cancer risks in patients living with HIV. Validation of skin cancer ascertainment algorithm will also facilitate research on skin cancer epidemiology using large, existing VA databases. Key results from the study may optimize prevention for skin cancers and ultimately reduce the morbidity of skin cancers in patients aging with HIV.

BACKGROUND

Keratinocyte carcinomas are common and impose significant morbidity.

Keratinocyte carcinomas (KCs) – also known as non-melanoma skin cancers including basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCCs) – represent the most common cancers in the U.S. with increasing incidence, morbidity, and economic burden (1). More than 5.4 million incident KCs were diagnosed in 3.3 million persons in 2012 – an increase of 35% since 2006 (2). The annual KC incidence exceeds 3 times that of all other cancers combined (18). While mortality from BCCs are rare, cSCCs may metastasize and are estimated to cause up to 8,791 deaths per year (19). The annual costs of KC treatment in 2012 was estimated at $4.8 billion (1). In particular, The Veterans Health Administration (VA) cared for 89,465 veterans with KC and 197,041 with KC precursor lesions in 2012, costing $356 million, or approximately 2% of all VA outpatient medical costs.

Most KCs are preventable by reducing ultraviolet radiation exposure and treatable with timely dermatology evaluation at early stages. Given the high burden of skin cancers, *The Surgeon General's Call to Action to Prevent Skin Cancer* was published in 2014 and delineated strategic goals to strengthen research and surveillance to maximize the success of future skin cancer prevention efforts, including to enhance understanding of the burden of skin cancers and to increase research efforts to determine high-risk population groups most likely to benefit from skin cancer screening and early detection (1). Thus, it

is crucial to identify populations disproportionately affected by KCs and their modifiable risk factors to devise targeted interventions.

Expansion of validated research on skin cancer epidemiology is critically needed.

Despite high prevalence and burden demonstrated in sporadic insurance claims studies, KC epidemiology is understudied (4, 20). The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and state-based cancer registries specifically exclude KCs from data collection. This may be partly because of higher case ascertainment burden and lower associated mortality (20). The few existing epidemiologic studies on KCs are based on large population-based surveys and secondary analysis of existing database from insurance claims or electronic medical records (20). The lack of state-based cancer registry data hindered external validation of these databases against the gold standard in cancer case ascertainment (21). Prior studies suggested that the use of International Classification of Diseases, Ninth Revision (ICD-9) codes alone to identify skin cancers in insurance claims data in a private health system and in Veterans Health Administration (VA) data have only modest positive predictive values of 47% and 60%, respectively (20, 22). The predictive values of the International Classification of Diseases, Tenth Revision (ICD-10) codes remain unknown. It is critical to validate KC case ascertainment methods to build capacity for future epidemiologic research. Our proposed research will apply validated skin cancer outcomes to study KC incidence and risk factors in veterans diagnosed with HIV.

The U.S. population living with HIV is growing and aging.

Multiple advances in HIV management have contributed to a substantial increase in the number of persons living with HIV. These include: 1) expanded HIV screening with earlier HIV diagnosis and treatment, 2) development of effective and tolerable ART and its widespread use, and 3) expanded approaches to link and retain HIV patients in healthcare systems (23). Persons living with HIV are surviving and aging: the life expectancy of HIV-positive persons at age 20 and 35 years receiving ART in high-income countries are estimated to be an additional 43.3 years and 32.2 years, respectively (24). Moreover, persons over age 50 continue to experience the same HIV risk factors as younger persons and represented 17% (7,391 cases) of new HIV diagnoses in 2014 (9). Consequently, the number of people living with HIV above the age of 50 in the United States has quadrupled in the past decade, rising from 101,470 (22.4% of all patients living with HIV) in 2004, to 262,595 (33.3%) in 2009, to 428,724 (44.9%) in 2014 (9-11). This aging trend is expected to continue in the next decades, prompting the need to examine the unique and complex health needs of populations living and aging with HIV.

Persons aging with HIV face higher risks of keratinocyte carcinomas.

Older age is associated with increased risks for developing major comorbid diseases in both HIV-positive and HIV-negative persons. As persons age with HIV, multiple factors have been implicated to influence their health trajectories. These include: HIV-related immune dysfunction and chronic persistent inflammation, long-term exposure to antiretroviral agents, other comorbid infections and chronic diseases, and modifiable behavioral risk factors (25-27).

The risks of comorbid diseases may increase not only with age, but also with the duration of HIV diagnosis, HIV viremia, long-term ART exposure, and other factors that may either accelerate the process of aging itself or pose as additional risk factors (28). As a result of increased comorbid disease burden, aging HIV-infected persons exhibit the premature onset of clinical symptoms and syndromes often associated with advanced aging, including multi-morbidity, poly-pharmacy, limited reserve, and physical, cognitive and functional decline (28). Emerging studies suggest that HIV-positive patients face higher risks of age-related comorbid diseases than HIV-negative patients, including ischemic heart disease (29), cerebrovascular disease (30), neurocognitive disorders (31), end-stage renal disease (32), chronic liver disease (33), osteoporotic fractures (34), as well as numerous types of cancers (35, 36). Notably, as more patients receive effective ART, the incidence and mortality from AIDS-defining malignancies have dropped while those of HIV-associated, non-AIDS-defining malignancies (NADMs) have risen, including cancers of the skin, lung, colon, anus, oropharynx, and Hodgkin lymphoma (12-16). NADMs have emerged as the leading non-AIDS cause of death in people with HIV (37). Caring for a population aging with HIV, primary care physicians and HIV specialists increasingly face questions such as: What periodic cancer screening exams need to be offered as part of primary care for HIV-positive patients and when should they start? What are effective strategies to improve cancer screening in HIV-positive patients?

Keratinocyte carcinomas may present with increased frequency or more aggressive course in persons living with HIV and impose significant morbidity (6). BCCs and cSCCs respectively comprised 32% and 12% of all incident NADMs

in a study of 4,144 persons living with HIV (16). Recent meta-analyses of available studies until 2009 suggest that HIV infection may be independently associated with higher KC risks (standardized incidence ratio, 1.95; 95% confidence interval (CI), 2.55-2.98 (7). Recurrence of KC is higher in HIV-positive patients (20.8%; 95% CI, 6.6-32.9%) than HIV-negative patients (2.8%; 95% 1.8-3.7%) five years after definitive treatment (38). Since NADMs overall have increased in aging populations, our proposed study will provide new evidence on the changing incidence of KCs in a cohort of persons aging with HIV.

There are insufficient current data to determine the extent to which various HIV-related parameters may influence the risk of skin cancer development (7). One study showed that both HIV RNA levels (hazard ratio (HR), 1.75 per $\log_{10}$ copies/mL; 95% CI, 1.42–2.14) and age (HR 1.05, 95% CI 1.01–1.09) predicted KC incidence in 2,234 patients living with HIV (39). Another showed a trend between lower recent CD4 count with incident cSCCs but not BCCs (5). Others did not show significant associations between CD4 count, HIV RNA levels, ART use, and skin cancer risks (40). Our proposed study will provide new data on the clinical, virologic, and immunologic risk factors in patients aging with HIV to identify those at high risks for developing skin cancers.

Skin cancer risk disparities in men who have sex with men

The majority (70%) of persons living with HIV in 2014 are men who have sex with men (MSM). Our preliminary data suggest that MSM may engage in more indoor tanning and less often engage in photoprotective behaviors, both risk factors for skin cancer, more frequently than heterosexual men (41-43).

Using nationally representative data in the 2013 National Health Interview Survey (NHIS), we showed 3.1-fold and 4.5-fold higher odds of any indoor tanning, and 4.8-fold to 6.5-fold higher odds of frequent tanning (≥10 sessions within 12 months) among self-reported gay and bisexual men than heterosexual men, respectively (42). The high magnitude of disparities in indoor tanning prevalence was consistent in multiple studies in MSM (44-46). We also demonstrated significant disparities in skin cancer-related behavioral risk factors in men in same-sex relationships using pooled data from NHIS 2000-2013 (41). Men in same-sex relationships employed less effective photoprotective strategies and tanned indoors more frequently, as compared to men in opposite-sex relationships (41). Potential mediators for indoor tanning among MSM may include elevated body dissatisfaction and body image concerns and increased motives to enhance physical appearance (47, 48), as well as elevated social distress due to perceptions and experiences of victimization, stigma, and discrimination (49). Disparities in skin cancer related behavioral risk factors will likely influence disparities in skin cancer incidence later on in life in MSM, particularly MSM living and aging with HIV.

Implications for skin cancer prevention and public health.

Insufficient data on skin cancer burden and risk stratification in persons aging with HIV pose critical barriers to skin cancer prevention efforts. Consequently current guidelines on caring for persons living with HIV have not included any recommendations on skin cancer risk reduction counseling or screening (50). By better understanding the burden and characteristics of skin cancer development, results from this study will directly translate to improving

clinical care in aging patients living with HIV by informing a subsequent research to 1) derive and validate a novel predictive model for skin cancer risks and 2) develop and evaluate the feasibility of a pilot targeted screening and secondary prevention intervention based on predicted skin cancer risks. Validation of a skin cancer identification algorithm in VA administrative data will also facilitate future research on skin cancer epidemiology using large, existing VA databases. Key results from the study will optimize the primary and secondary prevention for skin cancers and will ultimately reduce the KC-related morbidity and advance the overall health of patients aging with HIV.

To address key knowledge gaps in KC epidemiology in HIV-positive veterans, we conducted a cross-sectional validation study for keratinocyte carcinoma diagnostic coding (Aim 1) and a longitudinal cohort study to determine risk factors for keratinocyte carcinoma incidence (Aim 2), using data from the HIV Atlanta Veterans Affairs Cohort Study (HAVACS) and the Veterans Affairs HIV Clinical Case Registry.

METHODS

Specific Aims

<u>Aim 1:</u> To estimate the positive predictive value of diagnostic codes in identifying incident cases of keratinocyte carcinoma. We will compare keratinocyte carcinoma diagnostic coding against manual review of electronic medical records and pathology reports.

<u>Aim 2:</u> To estimate the associations between incident keratinocyte carcinoma and the immune status, HIV viremia, and duration of HIV diagnosis in persons diagnosed with HIV. We hypothesize that lower current and nadir CD4+ T lymphocyte counts, higher HIV RNA levels, and greater number of years since HIV diagnosis are independently associated with higher incidence rates of keratinocyte carcinoma.

Study Design

This study was approved by the Emory University Institutional Review Board (IRB Protocol #00097558) and Atlanta Veterans Affairs Medical Center (AVAMC) Research and Development Committee (R&D #2017-080688). Results are reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guidelines (51).

HIV Atlanta Veterans Affairs Cohort Study and VA HIV Clinical Case Registry

HAVACS is an ongoing, open, prospective, observational cohort established to identify HIV-positive veterans who have ever sought care at the Atlanta Veterans Affairs Medical Center since 1982 (17). By August 15, 2017,

4,664 HIV-positive veterans have been entered into this cohort database manually by research coordinators and clinicians. Data were prospectively recorded from routine clinic visits and were supplemented with data from the VA Computerized Patient Record System, including demographic characteristics, HIV-related diagnoses, prophylaxis, antiretroviral regimens, clinic and inpatient visits, and laboratory measurements. Over 60% of active HAVACS participants were older than 50 years of age by 2017. The VA HIV Clinical Case Registry provided additional laboratory data, diagnostic codes and procedure codes to supplement HAVACS data. The Clinical Case Registry software compiles lists of local patients at AVAMC with specific conditions, such as HIV, based on Veterans Health Information Systems and Technology Architecture data.

Specific Aim 1: Validation of incident keratinocyte carcinomas

Diagnostic codes of KC were extracted from the HIV Clinical Case Registry from 1982 to 2017 from HAVACS participants. These include ICD-9 codes 173.x and ICD-10 codes C44.x, indicating "other and unspecified malignant neoplasm of skin." Manual chart review was performed for all patients with ≥1 compatible codes from the clinical case registry by a trained data analyst (C.H.A.) and a board-certified dermatologist (H.Y.). Discrepancies were resolved by consensus and, as needed, discussion with a second board-certified dermatologist (S.C.C.). KC cases were considered validated if there was evidence of cSCC or BCC with evidence of biopsy confirmation upon review of the computerized medical records. KCs in mucosal or anogenital sites were excluded. The positive predictive value of ICD-9/-10 diagnostic codes in ascertaining biopsy-confirmed KC upon

manual chart review was calculated, with 95% confidence interval [CI] estimated based on the binomial distribution.

Specific Aim 2: Risk Factors for Keratinocyte Carcinoma

Study Inclusion / Exclusion Criteria

Veterans with a diagnosis of HIV enrolled as part of HAVACS who have sought care at AVAMC with a documented first Infectious Disease Clinic visit date and a subsequent documented follow-up date were included. The beginning of follow up was defined at the first documented Infectious Disease Clinic visit date; the end of follow up was defined at the most recent Infectious Disease clinic visit, documented date of death, documented move to other follow up location outside of AVAMC, or August 15, 2017. We excluded patients who did not have a first documented visit at the Infectious Disease Clinic or did not have documented follow up after the initial visit.

Exposures of Interest

Exposures of interest included the most recent CD4 lymphocyte count (categorized as <200, 200-499, or ≥500 cells/μL), nadir CD4 lymphocyte count throughout the follow up period (<50, 50-149, 150-249, ≥250 cells/μL), most recent plasma HIV RNA level (<50, 50-9,999, >10,000 copies/mL), and duration of known HIV diagnosis defined as the years between the age of HIV diagnosis and age at the end of follow up (<10, 10-19, ≥20 years). Many of these categories were consistent with those used in prior studies (5). Nadir CD4 lymphocyte count categories and duration of known HIV diagnosis, which were empirically

determined since this study cohort had lower nadir CD4 counts and longer follow up time than prior reported data.

Covariates

Covariates examined included age at HAVACS enrollment; follow up status (active (last seen in clinic within past 2 years), died, lost to follow up (last seen in clinic more than 2 years ago), or moved); initial ART class (naïve, 1 nucleoside reverse transcriptase inhibitor (nRTI), 2 nRTIs, or combination ART); any history of AIDS diagnosis by 1993 criteria; and HIV transmission risk factors (MSM, heterosexual, intravenous drug use, and other/unknown).

Outcome Validation

Validated incident KC diagnoses from non-mucosal and non-anogenital sites with documented biopsy confirmation, derived from Specific Aim 1, were used as the outcome. Incidence rates of KC were determined by the number of incident KC cases per 1,000 person-years of follow up time.

Sample Size and Power Considerations

Power determination for Aim 1 was determined based on the entire cohort with 2% incidence of skin cancer (based on prior study of non-Hispanic White patients) to identify 433 cases of skin cancers and provide the positive predictive value (PPV) with 95% CI of ±3.8% assuming an observed PPV of 80%. However, given racial/ethnic diversity in our study population, the observed KC rates were lower in our study results which may limit statistical power and precision of PPV estimates. We used existing HAVACS data for Aim 2 and sample size determination was not conducted *a priori*.

Statistical Analysis

Incidence rates of KC were estimated using negative binomial regression models and presented as the number of new cases per 1,000 person-years (PY) of follow up. Negative binomial models were chosen over Poisson regression models given significant overdispersion, with variance of the incidence rate exceeding its mean. We restricted analysis and multivariable modeling to non-Hispanic White male veterans (NHWM) since the majority of the outcomes occurred in this sub-population. The initial model adjusted for covariates associated with KC incidence with $P < 0.25$. Backward stepwise selection approach was applied to reach a parsimonious model with significant covariates with $P < 0.05$. First-order product interaction terms were tested using chunk likelihood ratio test. Alternatively, all exposures of interests were included in an *a priori* model. Model selection was also guided by the Akaike Information Criterion. Model goodness of fit was examined based on Pearson's χ^2. Secondary analyses were conducted using BCC and cSCC as separate outcomes. Significance level was defined at $\alpha = 0.05$ in 2-sided tests.

RESULTS

Aim 1: Validation of Incident Keratinocyte Carcinomas

Within the HAVACS cohort of 4,664 patients, 101 patients had at least 1 diagnostic code compatible with KC, of whom 55 had a total of 227 unique biopsy-confirmed KCs upon manual chart review. Among the 227 biopsy-confirmed KCs, 147 (65%) were BCCs and 80 (35%) were cSCCs. Thus, the positive predictive value of ≥1 KC diagnostic code in predicting having ≥1 biopsy-confirmed KC was 54% (95% CI, 44%-64%).

Conversely, 46 patients with ≥1 KC diagnostic codes did not have biopsy-confirmed incident KC, with a false positive rate of 45% (95% CI, 36%-56%). Among them, 14 patients (30%) had anal cancers; 6 (13%) had benign skin conditions, including one each of psoriasis, epidermoid cyst, lipodystrophy, trichoepithelioma, and two keloids; 5 (11%) had Kaposi sarcoma; 5 (11%) had a history of KC only without an incident case notable within our chart review; 3 (7%) had penile cancer; 3 (7%) had lung cancer; 1 (2%) had a borderline atypical squamous lesion; 1 (2%) had tongue cancer; 1 (2%) had vocal cord cancer; and 7 (15%) had missing relevant chart data.

Aim 2: Risk Factors for Keratinocyte Carcinomas

Among 4,664 patients within HAVACS, we included 3,353 patients who had a non-zero follow up time in the AVAMC infectious disease clinic (Figure 1). Demographic characteristics of the study population are shown in Table 1. The majority of the cohort were male (96.7%) and non-Hispanic African American/Black (77.1%). NHWM, who have the highest KC risks, represented

20.3% of the cohort. Mean (standard deviation [SD]) age at the first infectious disease clinic visit was 43.8 ± 11.0 years for the study cohort and 45.0 ± 11.6 years for NHWM. For the full study cohort, the mean follow-up time was 8.5 ± 6.4 years (mean ± SD) and the median follow-up time was 7.2 ± 10.0 years (median ± interquartile range [IQR]). For NHWM, the mean follow up time was 9.7 ± 6.8 years (mean ± SD) and the median follow-up time was 8.8 ± 10.3 years (median ± IQR). By the end of follow up, 45.5% of the study cohort and 37.1% of NHWM remain active in HAVACS.

Among the full cohort and NHWM, respectively, 52.0% and 74.0% were men who have sex with men; 42.7% and 55.9% had HIV diagnosed prior to 1996; and 50.6% and 41.8% received combination ART as their first treatment; 45.6% and 44.9% had a recent CD4 lymphocyte count of ≥500 cells/mm^3; 48.2% and 44.6% had undetectable HIV viral load with plasma HIV-1 RNA ≤50 copies/mL; 61.9% and 64.7% had a history of AIDS diagnosis by the 1993 criteria, and 18.6 and 10.6% had known hepatitis C co-infection.

Incidence rates of keratinocyte carcinomas

Fifty-one participants (1.5%) had at least 1 biopsy-confirmed KCs, totaling 227 lesions, with 0.07 ± 0.90 (mean ± SD) incident KCs diagnosed among 3,353 participants. The majority (47/51, 92.2%) of incident KCs were diagnosed in NHWM, with 0.33 ± 1.98 (mean ± SD) incident KCs diagnosed among 680 NHWM.

Using data from the study cohort of 3,353 veterans, the incidence rate of KC was estimated at 6.5 KCs per 1,000 PY (95% CI: 4.3-9.7). Higher KC incidence

rate was observed in older age groups. Incidence rates of KC for patients with age at the first infectious disease clinic between 18-44 years were 3.1 per 1,000 PY (95% CI: 1.8-5.2), those with age 45-54 years were 8.1 per 1,000 PY (95% CI: 4.0-16.3), those with age 55-64 years were 14.1 per 1,000 PY (95% CI: 5.3-37.7), and those with age ≥65 years were 22.6 per 1,000 PY (95% CI: 3.2-159.2, overall P = 0.009). All 227 lesions were diagnosed in male veterans. The vast majority, with 223 (98.2%) lesions, were diagnosed in NHWM and 4 (1.8%) were diagnosed in non-Hispanic African American / Black males. We thus restricted further analyses to NHWM only. The incidence rate of KC in NHWM was estimated at 29.0 KCs per 1,000 PY (95% CI: 19.0-44.4).

Risk factors of keratinocyte carcinomas in NHWM

Bivariate analyses comparing KC incidence rates in NHWM by exposures of interest and covariates are shown in Table 2. Higher KC incidence rates were associated with older age at first infectious disease clinic visit. Incidence rates of KC for NHWM with age at the first infectious disease clinic between 18-44 years were 14.2 per 1,000 PY (95% CI: 8.0-25.2), those with age 45-54 years were 36.7 per 1,000 PY (95% CI: 17.0-79.1), those with age 55-64 years were 59.1 per 1,000 PY (95% CI: 21.8-160.7), and those with age ≥65 years were 66.1 per 1,000 PY (95% CI: 12.1-361.8, overall P = 0.03). No significant associations were found between higher KC incidence rates and nadir CD4 count, a history of AIDS diagnosis (P = 0.14), or follow up status (P = 0.16). However, these covariates were included in the initial multivariable model based on our model selection methods.

Notably, active follow up status was itself associated with recent CD4 count ≥500 cells/mm3 (63.5% vs. 32.7%); higher CD4 nadir (nadir CD4 <50 cells/mm3, 18.4% vs. 27.3%; nadir CD4 ≥250 cells/mm3, 38.2% vs. 27.1%); lower recent viral load (plasma HIV-1 RNA <50 copies/mL, 79.3% vs. 26.8%); less likely to be diagnosed with AIDS (54.8% vs. 70.6%); lower risks of known hepatitis C co-infection (6.8% vs. 12.9%); higher likelihood of receiving combination ART as the initial HIV treatment (52.8% vs. 35.3%); more recent HIV diagnosis (HIV diagnosed prior to 1996 40.4% vs. 66.0%; 2006 onward, 26.4% vs. 5.0%), and more likely to have known vitamin D deficiency (known vitamin D deficient, 48.8% vs. 5.1%; vitamin D level unknown 85.8% vs. 13.1%), as compared with inactive follow up status (each $P < 0.05$). No difference in age at the first infectious disease visit was noted by current follow up status ($P = 0.43$).

Results from a multivariable negative binomial model of KC incidence are shown in Table 3. Higher KC incidence rates were significantly associated with older age group at enrollment, active follow up status, and nadir CD4 count between 50-249 cells/mm3 (each $P < 0.001$). Compared to those with age at enrollment of 18-44 years, those with age 45-54 years had an incidence rate ratio [IRR] of 4.42 (95% CI: 1.57-12.48), those with age 55-64 years had an IRR of 10.5 (95% CI: 2.99-36.91), and those with age ≥65 years had an IRR of 8.47 (95% CI: 1.38-52.12), after adjusting for current follow up status and nadir CD4 count. Compared to those who remained active at the end of follow up period, those who were not active had an IRR of 0.22 (95% CI: 0.09-0.55) after adjusting for age at enrollment and nadir CD4 count. Compared to those who had nadir CD4 count

≥250 cells/mm^3, those who had a nadir CD4 count of 50-149 cells/mm^3 had an IRR of 5.49 (95% CI: 1.72-17.49) and those who had a nadir CD4 count of 150-249 cells/mm^3 had an IRR of 5.96 (95% CI: 1.69-20.99) after adjusting for age at enrollment and follow up status. First-order product interaction terms between these variables were not significant.

A sensitivity analysis was conducted adjusting for all exposures of interest *a priori* demonstrated similar results (data not shown). Stratifying the models by using BCC and cSCC incidence rates as separate outcomes similar trends emerged showing that higher BCC and cSCC incidence in older age group, active follow up status, and nadir CD4 between 50-249 cells/mm^3 (Table 4).

DISCUSSION / CONCLUSIONS

KC case ascertainment using ICD-9 and ICD-10 diagnostic codes was only modestly predictive of a biopsy-confirmed incident KC case upon manual chart review, confirming a need for validation of case definition in future KC epidemiology studies using VA administrative data. High incidence of biopsy-confirmed KC was shown among veterans diagnosed with HIV at the Atlanta VA Medical Center. Among non-Hispanic White male veterans diagnosed with HIV, we found 4.3 to over 20-fold higher rates of KC as compared with previously reported incidence in non-Hispanic White persons diagnosed with HIV. Higher KC incidence – including both BCC and cSCC – was demonstrated among those in older age groups, those alive and actively followed up at the end of the study period, and those with a nadir CD4 count between 50-249 cells/mm^3.

The use of ≥1 ICD-9 or ICD-10 diagnostic codes had a modest positive predictive value of 54% to ascertain biopsy-confirmed incident KC, demonstrating the limited use of diagnosis codes alone for case ascertainment in future epidemiologic studies to estimate KC incidence. Notably, anal cancer and Kaposi sarcoma – two common malignancies in persons living with HIV – were the two most common diagnoses that were miscoded as KC. Thus, the use of diagnosis codes only may be subject to misclassification bias for studies on KC, anal cancer, and Kaposi sarcoma. Because manual chart review and case confirmation is tedious and time-consuming, important future work will assess whether the use of different combinations of diagnostic codes, along with Current Procedural Terminology codes for skin biopsies and skin cancer treatments, or

with exclusion of known anal cancer or Kaposi sarcoma diagnoses, improves KC case ascertainment.

Compared to prior estimates in non-Hispanic white persons living with HIV, our KC incidence rate estimate in NHWM veterans was substantially higher at 29.0 cases per 1,000 PY (5, 40, 52, 53). In a cohort of 4,490 non-Hispanic White U.S. military personnel seen in U.S. military HIV clinics in 1986-2006, incidence rates of KC ranged from 3.1 to 6.7 cases per 1,000 PY (40). In a cohort of 6,560 non-Hispanic White adult enrollees of Kaiser Permanente Northern California in 1985-2007, incidence rate of KC was estimated at 5.4 cases per 1,000 PY (5). In a cohort of 9,429 Swiss aged 16 or above in 1985-2007, incidence rates of KC ranged from 0.36 to 0.87 cases per 1,000 PY (52). In a cohort of 4,280 Danes aged 16 or above in 1996-2014, incidence rate of KC was estimated at 2.93 cases per 1,000 PY (53).

The substantially higher incidence of KC in HIV-infected veterans noted in our study, as compared with HIV-infected civilians, possible reflects the high levels of sun exposure and high KC burden among all veterans, regardless of HIV status (54). While the incidence rate of KC among HIV-uninfected veterans, to our knowledge, has not been determined, high prevalence of KC and its risk factors have been demonstrated (54, 55). For example, a survey of 212 veterans returning from deployment to Iraq or Afghanistan in Operations Enduring Freedom and Operation Iraqi Freedom missions showed that 77% reported spending ≥4 hours daily working in the bright sun and 64% reported ≥75% of their day working in the bright sun (56). While the majority wore sun-protective headgear and sunglasses, 70-85% left their face, neck, and arms/hands

unprotected from the sun (56). Only 28% reported routine use of sunscreen and 42% reported not being made aware of skin cancer risks by the military (56).

Higher KC incidence was noted to be independently associated with older age at the first infectious disease clinic visit, nadir CD4 count, and active follow up status. Nadir CD4 count was the only HIV biomarker that remained a significant predictor of KC incidence after adjusting for age and current follow up status. A non-linear relationship was noted with higher KC incidence among patients with nadir CD4 count between 50-249 cells/mm^3, as compared with <50 cells/mm^3 or ≥250 cells/mm^3. These results contrast with prior studies that showed lower nadir CD4 count, when modeled as a linear continuous variable, was associated with higher risk of cSCC but not BCC (53). The association in our model was adjusted for follow up status, which in our cohort was a marker of patients with healthier and more immune competent cohort, as compared to those who died or who were lost to follow up. While we did not formally perform a competing risk analysis, we hypothesize that the unexpectedly low KC incidence among patients with very low nadir CD4 count <50 cells/mm^3 may be secondary to HIV-related complications or other competing risks that reduced KC incidence or diagnosis. Future studies should consider potential non-linear associations between KC incidence and HIV-related biomarkers such as nadir CD4 count.

Our study did not demonstrate association between KC incidence with recent CD4 count or HIV viral load, unlike results from a prior cohort of Kaiser Permanente enrollees (5). However, one study of military personnel diagnosed with HIV also showed that neither CD4 count nor HIV viral load – both at the time of HIV diagnosis and time-updated estimates – were predictive of KC

incidence after adjustment for age and race/ethnicity (40). Another showed that recent CD4 count was not associated with KC incidence (53). Consistent with others' results, the prior use of combination ART (5, 40) and the number of years known to be HIV positive (5) were not significant predictors of KC incidence.

Given the high burden of KC among NHWM veterans diagnosed with HIV, particularly among those with advanced immunosuppression as indicated by lower nadir CD4 count, KC risk reduction counseling to reduce ultraviolet radiation exposure is warranted (57). In addition, early HIV diagnosis, early ART initiation, and ART adherence will be important to avoid lower CD4 nadir associated with higher KC incidence and/or HIV/AIDS-related complications. Future research will be required to weigh whether the burden of KC in NWHM veterans diagnosed with HIV or specific high-risk subpopulations will benefit from skin cancer screening.

The strengths of this study include the use of prospectively collected demographic data from HAVACS and VA Clinical Case Registry, including data on nadir CD4 count, HIV transmission risk factors, and ARV regimen, as well as biopsy-confirmed KC outcomes confirmed by dermatologist chart review. HAVACS study cohort also had a mean follow up time of 9.7 years, which is the longer than all other existing studies that ranged from 3.3 to 7.5 years.

Limitations of this study include a smaller sample size limited to a single VA medical center. Similar to other KC studies in HIV, this secondary analysis of existing data lack information on ultraviolet radiation exposure and other known behavior risk factors. In addition, there may be potential information bias in outcome ascertainment since the VA computerized patient record system was

adopted by the Atlanta VA Dermatology clinic only after 2001-2002. Lastly, our model restricted to NHWM veterans limits generalizability to female, Hispanic, or non-White persons and non-veterans.

Future directions of this research will include to: 1) compare KC incidence in HIV-positive veterans compared with age-, sex-, and race/ethnicity-matched HIV-negative veterans; 2) determine the association between HIV biomarkers with location, histologic patterns, and treatment selection for KC and KC precursor lesions; and 3) extend current study findings using the Veterans Aging Cohort Study-Virtual Cohort (VACS-VC) to examine the incidence, risk factors, and treatment of KC and KC precursor lesions on a national level.

In non-Hispanic White male veterans diagnosed with HIV, we found 4.3 to over 20-fold risk as compared with previously reported incidence in non-Hispanic White persons diagnosed with HIV. Older age, active follow up status, and nadir CD4 count between 50-249 cells/mm^3 is associated with higher incidence rate of keratinocyte carcinoma. Early HIV diagnosis and sustained HIV treatment, reduction of ultraviolet radiation exposure, and improved secondary prevention of keratinocyte carcinomas will be required to reduce the disproportionately high burden of keratinocyte carcinomas in non-Hispanic White male veterans.

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TABLES / FIGURES

Figure 1

Participants flow diagram.

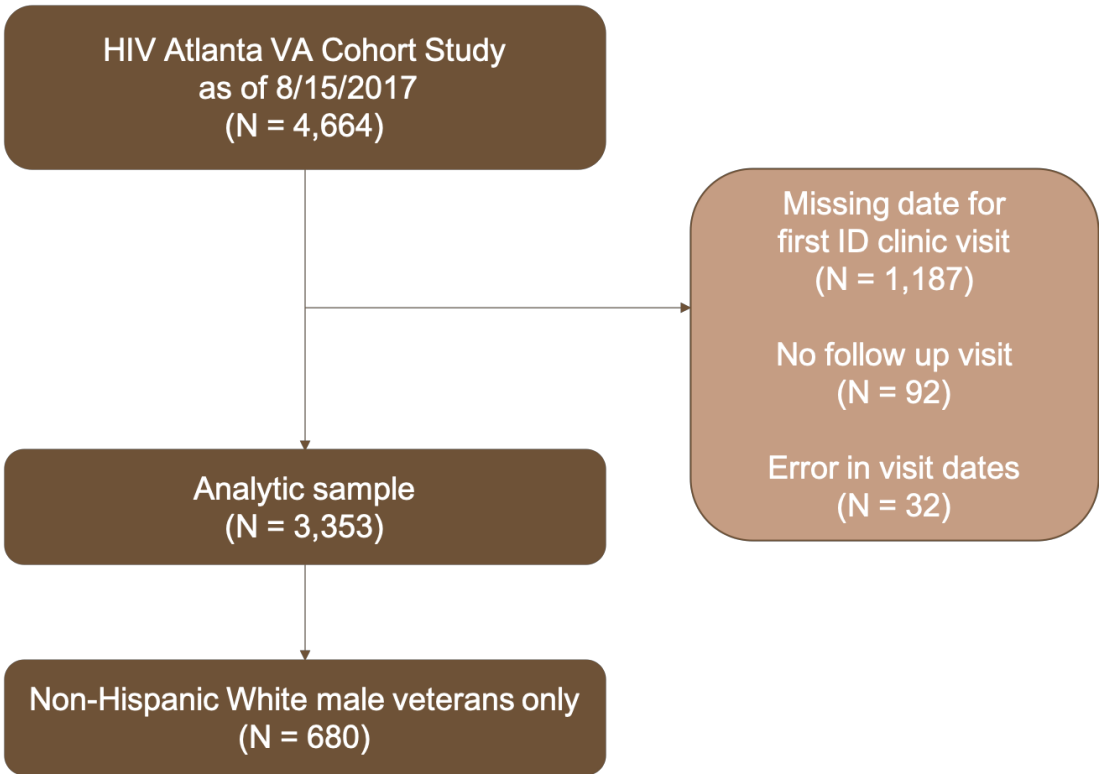

Table 1

Demographics of study participants.

	Cohort sample (N = 3,353)	**Non-Hispanic White males (N = 680)**
Age at Enrollment, years		
Mean (SD)	43.8 (11.0)	45.0 (11.6)
Median (IQR)	43.4 (15.8)	44.0 (16.9)
18-44	1,879 (56.0)	361 (53.1)
45-54	930 (27.7)	182 (26.8)
55-64	430 (12.8)	99 (14.6)
65+	114 (3.4)	38 (5.6)
Sex		
Male	3,243 (96.7)	680 (100.0)
Female	110 (3.3)	0 (0.0)
Race / Ethnicity		
Non-Hispanic Caucasian/White	687 (20.5)	680 (100.0)
Non-Hispanic African American/Black	2,584 (77.1)	0 (0.0)
Hispanic	43 (1.3)	0 (0.0)
Other or Unknown	39 (1.2)	0 (0.0)
Follow Up Time, years		
Mean (SD)	8.5 (6.4)	9.7 (6.8)
Median (IQR)	7.2 (10.0)	8.8 (10.3)
Total person-years	28,346	6,600
Current Follow Up Status		
Active	1,526 (45.5)	252 (37.1)
Died	857 (25.6)	207 (30.4)
Other (Moved, Lost to Follow Up)	970 (28.9)	221 (32.5)
Year of Known HIV Diagnosis		
Missing	163 (4.9)	18 (2.7)
Prior to 1996	1,430 (42.7)	370 (55.9)
1996-2000	638 (19.0)	121 (18.3)
2001-2005	487 (14.5)	77 (11.6)
2006 onward	635 (18.9)	76 (11.5)
Duration of HIV diagnosis, years		
Missing	170 (5.1)	22 (3.2)
<10	897 (26.8)	143 (21.0)
10-19	1,261 (37.6)	257 (37.8)
20+	1,025 (30.6)	258 (37.9)

Primary HIV risk factor		
Men who have sex with men	1,744 (52.0)	503 (74.0)
Heterosexual	239 (7.1)	23 (3.4)
Intravenous drug use	462 (13.8)	39 (5.7)
Unknown / other	908 (27.1)	115 (16.9)
First antiretroviral treatment		
Naïve	245 (7.3)	37 (5.4)
One nRTI alone	587 (17.5)	183 (26.9)
Two nRTIs alone	254 (7.6)	70 (10.3)
Combination ARV	1,695 (50.6)	284 (41.8)
Other	572 (17.1)	106 (15.6)
Recent CD4 Count (cells/mm^3)		
Missing	13 (0.4)	2 (0.2)
<200	758 (22.6)	152 (22.4)
200-499	1,052 (31.4)	221 (32.5)
≥500	1,530 (45.6)	305 (44.9)
Nadir CD4 Count (cells/mm^3)		
Missing	172 (5.1)	37 (5.4)
<50	856 (25.5)	156 (22.9)
50-149	630 (18.8)	154 (22.7)
150-249	587 (17.5)	134 (19.7)
≥250	1,108 (33.1)	199 (29.3)
Recent Plasma HIV-1 RNA (copies/mL)		
Missing	154 (4.6)	41 (6.0)
≤50	1,615 (48.2)	303 (44.6)
50-9,999	920 (27.4)	207 (30.4)
≥10,000	664 (19.8)	129 (19.0)
History of AIDS diagnosis	2,078 (61.9)	440 (64.7)
HBsAg status		
Positive	241 (7.2)	52 (7.7)
Negative	45 (1.6)	3 (0.4)
Missing	3058 (91.2)	625 (91.9)
Anti-HCV antibody status		
Positive	625 (18.6)	72 (10.6)
Negative	19 (0.6)	4 (0.6)
Missing	2709 (80.8)	604 (88.8)
Recent Vitamin D status		
Normal	774 (23.1)	65 (9.6)
Insufficient	418 (12.5)	70 (10.2)
Deficient	525 (15.7)	145 (21.3)
Missing	1,585 (48.8)	400 (58.8)

Abbreviations: SD, standard deviation; IQR, interquartile range; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus

Values were presented as mean and SD for continuous variables and as proportions for discrete variables

Table 2

Incidence rate estimates of keratinocyte carcinomas in non-Hispanic White male veterans diagnosed with HIV.

N = 680	**Incident KCs**	**Incidence rate per 1,000 PY in non-Hispanic White males (95% CI)**	***Overall P***
Non-Hispanic White Males with HIV	223	29.0 (19.0 – 44.4)	N/A
Age at Enrollment, years			
18-44	69	14.2 (8.0 – 25.2)	0.03
45-54	72	36.7 (17.0 – 79.1)	
55-64	66	59.1 (21.8 – 160.7)	
65+	16	66.1 (12.1 – 361.8)	
Current Follow Up Status			
Active	129	40.4 (20.9 – 77.9)	0.16
Not Active (Died, Moved, LTF, Other)	94	21.7 (12.5 – 37.8)	
Year of Known HIV Diagnosis			
Prior to 1996	117	25.3 (14.4 – 44.7)	0.47
1996-2000	35	20.1 (7.5 – 53.6)	
2001-2005	57	59.7 (18.6 – 192.1)	
2006 onward	13	31.9 (8.9 – 114.6)	
Duration of HIV diagnosis, years			
<10	13	22.7 (7.4-69.4)	0.49
10-20	115	40.1 (20.3-79.2)	
≥20	94	23.5 (11.9-46.3)	
Primary HIV risk factor			
Men who have sex with men	162	28.5 (17.4 – 46.5)	0.71
Heterosexual	26	72.9 (8.7 – 610.7)	
Intravenous drug use	16	32.6 (5.9 – 181.5)	
Unknown / other	19	20.4 (6.8 – 60.6)	
First antiretroviral treatment (%)			
Naïve	1	3.9 (0.2-64.7)	0.45
One nRTI alone	86	32.5 (15.1-70.1)	
Two nRTIs alone	11	12.8 (3.3-50.3)	
Combination ARV	108	35.8 (19.0-67.4)	
Other	17	21.8 (6.8 – 70.3)	

Recent CD4 Count (cells/mm^3)			
<200	50	24.2 (9.6 – 61.3)	0.71
200-499	84	36.5 (17.4– 76.8)	
>500	88	25.6 (13.5 – 48.5)	
Nadir CD4 Count (cells/mm^3)			
<50	26	14.5 (5.8 – 36.3)	0.08
50-149	113	52.2 (23.0– 118.5)	
150-249	55	41.3 (16.6 – 102.5)	
≥250+	27	14.9 (6.5 – 34.3)	
Recent Plasma HIV-1 RNA (copies/mL)			
≤50	157	40.0 (22.1 – 72.5)	0.32
50-9,999	30	19.9 (8.6 – 45.0)	
≥10,000	35	21.7 (8.3 – 56.9)	
History of AIDS (1993 criteria)			
No	38	17.2 (8.0 – 37.1)	0.14
Yes	185	35.0 (21.0 – 58.3)	
HBsAg status			
Positive	13	21.8 (4.5 – 105.1)	0.71
Negative / Unknown	210	29.6 (19.1 – 46.1)	
Anti-HCV antibody status			
Positive	28	29.8 (8.3 – 106.5)	0.97
Negative / Unknown	195	29.0 (18.4 – 45.4)	
Recent Vitamin D status			
Normal	41	54.9 (15.4 – 195.2)	0.48
Insufficient	37	41.2 (11.9 – 142.9)	
Deficient	63	30.6 (12.9 – 73.0)	
Unknown	82	21.3 (12.0 – 38.0)	

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus

Overall *P* values denote likelihood ratio tests of the hypothesis that the incidence rate of keratinocyte carcinoma does not differ across subjects in all listed categories of the categorical variable, after controlling for all other listed variables.

Table 3

Multivariable negative binomial regression model of keratinocyte carcinoma risk factors.

	Incidence rate ratios (95% CI)	***P***	**Overall *P***
Age at Enrollment, years			<0.001
18-44	[ref.]		
45-54	4.42 (1.57 – 12.48)	0.005	
55-64	10.5 (2.99 – 36.91)	<0.001	
≥65	8.47 (1.38 – 52.12)	0.02	
Current Follow Up Status			<0.001
Active	[ref.]		
Not Active (Died, Moved, LTF, Other)	0.22 (0.09 – 0.55)	0.001	
Nadir CD4 Count (cells/mm^3)			<0.001
<50	0.61 (0.15 – 2.38)	0.47	
50-149	5.49 (1.72 – 17.49)	0.004	
150-249	5.96 (1.69 – 20.99)	0.005	
≥250	[ref.]		

P values denote Wald tests of the hypothesis that the incidence rate for subjects in the specific category equals that for subjects in the reference category, after controlling for all other listed variables. Overall *P* values denote likelihood ratio tests of the hypothesis that the incidence rate of keratinocyte carcinoma does not differ across subjects in all listed categories of the categorical variable, after controlling for all other listed variables.

Table 4

Sensitivity analyses with multivariable negative binomial regression models of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) incidence rates.

Risk factors for incident BCCs	**Incidence rate ratios (95% CI)**	***P***	**Overall *P***
Age at Enrollment, years			0.009
18-44	[ref.]		
45-54	3.64 (1.19 – 11.13)	0.02	
55-64	7.07 (1.87 – 26.79)	0.004	
65+	6.19 (0.87 – 43.98)	0.07	
Current Follow Up Status			0.002
Active	[ref.]		
Not Active (Died, Moved, LTF, Other)	0.22 (0.08 – 0.58)	0.003	
Nadir CD4 Count (cells/mm^3)			0.002
<50	0.63 (0.14 – 2.88)	0.54	
50-149	5.4 (1.55 – 18.78)	0.008	
150-249	6.12 (1.52 – 24.67)	0.01	
≥250	[ref.]		

Risk factors for incident cSCCs	**Incidence rate ratios (95% CI)**	***P***	**Overall *P***
Age at Enrollment, years			<0.001
18-44	[ref.]		
45-54	4.95 (1.40 – 17.54)	0.01	
55-64	14.45 (3.41 – 61.10)	<0.001	
65+	13.35 (1.50 – 118.69)	0.02	
Current Follow Up Status			
Active	[ref.]		0.05
Not Active (Died, Moved, LTF, Other)	0.35 (0.12 – 1.04)	0.06	
Nadir CD4 Count (cells/mm^3)			0.05
<50	0.95 (0.19 – 4.71)	0.95	
50-149	4.86 (1.19 – 19.79)	0.02	
150-249	3.95 (0.80 – 19.38)	0.09	
≥250	[ref.]		

P values denote Wald tests of the hypothesis that the incidence rate for subjects in the specific category equals that for subjects in the reference category, after

controlling for all other listed variables. Overall *P* values denote likelihood ratio tests of the hypothesis that the incidence rate of keratinocyte carcinoma does not differ across subjects in all listed categories of the categorical variable, after controlling for all other listed variables.