Cutaneous Melanoma Risk among People with HIV in the United States and Canada

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Word Count: 1997  Figure/Table Count: 2 Tables

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Sources of Support: This work was supported by the Intramural Research Program of the National Cancer Institute; National Institutes of Health grants U01AI069918, F31DA037788, G12MD007583, K01AI093197, K23EY013707, K24AI065298, K24AI118591, K24DA000432, KL2TR000421, M01RR000052, N01CP01004, N02CP055504, N02CP91027, P30AI027757, P30AI027763, P30AI027767, P30AI036219, P30AI050410, P30AI094189, P30AI110527, P30MH62246, R01AA016893, R01CA165937, R01DA011602, R01DA012568, R01AG053100, R24AI067039, U01AA013566, U01AA020790, U01AI031834, U01AI034989, U01AI034993, U01AI034994, U01AI035004,
Short Title: Melanoma risk among people with HIV

Abstract

Background: Cutaneous melanoma incidence may be modestly elevated in people with HIV (PWH) versus people without HIV. However, little is known about the relationship of immunosuppression, HIV replication, and antiretroviral treatment (ART) with melanoma risk.

Methods: PWH of white race in the North American AIDS Cohort Collaboration on Research and Design were included. A standardized incidence ratio (SIR) was calculated comparing risk with the white general population, standardizing by age, sex, and calendar period. Associations
between melanoma incidence and current, lagged, and cumulative measures of CD4 count, HIV RNA level, and ART use were estimated with Cox regression, adjusting for established risk factors such as age and annual residential ultraviolet B (UVB) exposure.

**Results:** Eighty melanomas were diagnosed among 33,934 white PWH (incidence=40.75 per 100,000 person-years). Incidence was not elevated compared with the general population (SIR=1.15, 95% confidence interval [95%CI]=0.91-1.43). Higher melanoma incidence was associated with older age (adjusted hazard ratio [aHR] per decade increase=1.50, 95%CI=1.20-1.89) and higher UVB exposure (aHR for exposure ≥35 vs. <35 mW/m²=1.62, 95%CI=0.99-2.65). Current, lagged, and cumulative CD4 and HIV RNA were not associated with melanoma incidence. Melanoma incidence was higher among people ART-treated for a larger proportion of time in the prior 720 days (aHR per 10% increase=1.16, 95%CI=1.03-1.30).

**Conclusions:** These results suggest that HIV-induced immune dysfunction does not influence melanoma development. The association between ART and melanoma risk may be due to increased skin surveillance among PWH engaged in clinical care. Associations with age and UVB confirmed those established in the general population.

**Keywords:** HIV, melanoma, cancer, antiretroviral therapy, CD4 count, HIV viral load
INTRODUCTION

In the combination antiretroviral therapy (ART) era, small elevations in cutaneous melanoma risk have been observed in people with HIV (PWH) compared to people without HIV. But findings have been inconsistent across studies, with some large studies finding no elevation. Compared with uninfected individuals, PWH have melanomas diagnosed at later stages, and have worse survival after melanoma diagnosis. While melanoma risk is increasing in the U.S. general population, age-adjusted incidence rates have not shown an increasing trend in the HIV population. However, the absolute melanoma burden may still increase over time due to aging of the HIV population.

Established risk factors for melanoma include age, fair skin pigmentation, and ultraviolet radiation. Unlike most cancers with elevated risk in PWH, melanoma does not have a known infectious etiology. Melanoma risk is increased among immunosuppressed organ transplant recipients and melanoma is particularly responsive to immunotherapy, suggesting a potential role for immune dysfunction in its development. Among PWH, little is known about the relationship of immunosuppression (as measured by CD4 T-lymphocyte count), plasma HIV RNA viral load, and ART with melanoma risk. We used data from a large, North American cohort collaboration to examine the associations of these HIV-specific characteristics with melanoma incidence.
METHODS

Our study population consisted of adults with HIV from 17 interval and clinical cohorts from the United States and Canada contributing to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) with available data on cancer diagnoses and follow-up during 1996-2009. Participating NA-ACCORD cohorts report demographic and clinical data, including laboratory test results and ART. A standardized protocol was used to ascertain cancer diagnosis information through review of medical records and pathology reports and through linkage to cancer registries. Each participating cohort obtained Institutional Review Board approval.

Analyses were restricted to individuals of non-Hispanic/Latino white race, as only 8 melanoma diagnoses occurred in individuals of other races or ethnicities. At-risk time for melanoma began at the last of: January 1, 1996 (the first year of the highly active antiretroviral therapy era), start of cohort-specific cancer diagnosis ascertainment, 360 days before first CD4 count, or 360 days before first HIV RNA measurement. At-risk time ended at the first of: melanoma diagnosis, death, end of cohort-specific cancer diagnosis ascertainment, 360 days after last CD4 count, or 360 days after last HIV RNA measurement. We excluded individuals with <2 CD4 count or <2 HIV RNA measurements to limit to individuals that were likely more engaged in care and for whom we could capture changes in CD4 and HIV RNA.

CD4 count, HIV RNA, and ART use were considered time-varying characteristics. Values were updated every 30 days using linear interpolation. Furthermore, values for the first CD4 count and HIV RNA measurements were carried backward 360 days, while the last measurements were carried forward 360 days, as described previously. ART use was
categorized as ever vs. never with any time after the initiation of ART considered as ART-exposed. Any use of antiretrovirals, including mono-, dual-, and triple-therapy, was considered ART use, because initial analyses demonstrated similar melanoma incidence rates across different ART use categories.

Melanoma incidence was calculated overall and compared with expected incidence using a standardized incidence ratio (SIR). Expected incidence was based on general population rates for non-Hispanic/Latino whites in strata of age, sex, and calendar period based on data from Surveillance, Epidemiology, and End Results (SEER) program cancer registries. Incidence was also calculated within subgroups stratified by: time-updated CD4 count category, time-updated HIV RNA suppression status (suppression defined as ≤500 copies/ml), time-updated ART status, as well as by sex, transmission risk, time-updated age and calendar period, and average annual ultraviolet B (UVB) exposure based on zip code of residence. Average annual residential UVB exposure was calculated by linking residential zip codes to daily estimates of cloud-adjusted noon-time UVB radiation from a national database, a method that has effectively been used to capture sun exposure in prior studies. Cox regression was used to estimate the associations of these characteristics with melanoma incidence in the HIV population using study follow-up time as the time scale. Associations of time-updated CD4 count, time-updated HIV RNA level, and time-updated ART status with incident melanoma were also estimated after adjusting for sex, time-updated age and calendar year, average annual residential UVB, and cohort.
Lags of 180 days, 360 days, and 720 days (approximately six months, one year, and two years) were considered, in which CD4 count, HIV RNA, and ART use were defined based on the values of these measurements at 6 months, 1 year, and 2 years prior to at-risk time for melanoma diagnosis. These measures allowed evaluation of the influence of these HIV-related factors at earlier time points in the melanoma development process, and provided estimates that are less susceptible to bias from reverse causation.

As values of CD4 count, HIV RNA, or ART use at a single point in time may have limited influence on melanoma risk, we also estimated associations with moving averages of CD4 count and HIV RNA level, and proportions of ART-exposed time, during time-updated 720-day intervals prior to at-risk time for melanoma diagnosis. Moving averages are calculated by averaging the values assigned every 30 days within each 720-day interval. Associations with averages/proportions were also examined with a 180-day lag (associations with averages/proportions during the prior 180-900 days).

RESULTS

The 17 NA-ACCORD cohorts included in this analysis contributed data from 92,620 PWH during 1996-2009. Of these, 15,571 were excluded because they did not have follow-up time as defined above or because they had <2 CD4 count or <2 HIV RNA measurements. Of the remaining population, 43,115 people of non-white race or Hispanic/Latino ethnicity were excluded. The final study population consisted of 33,934 non-Hispanic/Latino individuals of white race.
Of these 33,934 individuals, 92% were male. When follow-up started, 46% had never been exposed to ART, but of these, 77% initiated ART during follow-up. At the start of follow-up, the median age was 42 years (interquartile range [IQR]=35-49) and the median calendar year was 2000 (IQR=1997-2004). The median average annual UVB exposure was 36 mW/m² (IQR=27-47), measures equivalent to exposure in Indianapolis, IN (≈27 mW/m²), San Francisco, CA (≈36 mW/m²), and Las Vegas, NV (≈47 mW/m²).

Eighty incident melanoma cases were identified (incidence rate 40.75 per 100,000 person-years). This incidence rate was not elevated when compared with the non-Hispanic/Latino white general population incidence reported by SEER (expected melanoma count=69.6, SIR=1.15, 95%CI=0.91-1.43). Within the HIV population, melanoma incidence was significantly higher among older people (HR per decade increase=1.48, 95%CI=1.20-1.82; Table 1) and people living in areas with an average annual UVB ≥35 mW/m² (HR=1.76, 95%CI=1.08-2.86). In multivariable analyses (Table 1), older age remained significantly associated with melanoma incidence (HR per decade increase=1.50, 95%CI=1.20-1.89), while a borderline-significant increase in incidence was observed with higher average annual UVB (HR=1.62, 95%CI=0.99-2.65). Among the 59% of PWH with transmission risk information, men who have sex with men had the highest melanoma incidence (40.5 per 100,000 person-years), but the elevation compared to other known transmission risk groups was not statistically significant (adjusted HR=1.26, 95%CI=0.47-3.35).

Associations of current CD4 count and HIV RNA level, and prior ART exposure, with melanoma incidence were not statistically significant (Table 1). When CD4 count and HIV RNA measures were considered with a lag or as moving averages, associations remained null.
In the lag analysis, persons with ART exposure at least 720 days prior to at-risk time had significantly higher melanoma incidence than those without exposure prior to that time point (HR=2.27, 95%CI=1.02-5.05), although this association did not remain significant in a multivariable analysis. Likewise, we found persons with a higher proportion of ART-exposed time during the 720 days immediately prior to at-risk time (0-720 days prior) or during the 720 days with a 6-month lag prior to at-risk time (180-900 days prior) had significantly higher melanoma incidence. In multivariable analyses, both associations remained statistically significant (0-720 days prior: HR per 10% increase in proportion of ART use=1.16, 95%CI=1.03-1.30; 180-900 days prior: HR per 10% increase in proportion of ART use=1.14, 95%CI=1.01-1.28).

DISCUSSION

Our study found no clear evidence that melanoma incidence was elevated in PWH, or related to HIV-specific factors, such as CD4 count and HIV RNA level, despite higher incidence of melanoma diagnoses among persons with more ART exposure. Important melanoma risk factors in the general population, such as age and UV exposure, were confirmed in our HIV population. Our general population melanoma risk estimates were not stratified by UVB exposure, which could lead to an inaccurate SIR. However, our SIR estimate of 1.15 is within the bounds of the summary SIR adjusted for ethnicity from the most recent meta-analysis of melanoma risk associated with HIV in the ART era (SIR=1.50, 95%CI=1.12-2.01). Melanoma risk is more strongly elevated in other immunosuppressed populations, such as solid organ and bone marrow transplant recipients.10,11
In those settings, melanoma development may be influenced by population-specific factors, such as UV-sensitizing properties of immunosuppressant medications.\textsuperscript{11,21-23} For many HIV-associated cancers, clear relationships have been identified with HIV-specific characteristics, most frequently inverse associations between CD4 count and risk.\textsuperscript{24} However, most HIV-associated cancers have well-defined viral etiologies\textsuperscript{25} and HIV-associated elevations in risk far higher than that observed for melanoma,\textsuperscript{3,4} indicating a stronger role for HIV-specific factors. In our study, estimated associations of virologic and immunologic status with melanoma risk were not statistically significant and near the null value, even after accounting for possible confounders such as age. This lack of observed associations was consistent across different measurement approaches, including lagged and cumulative exposures. These findings are in line with one prior study that did not identify clear associations between melanoma risk and immunologic or virologic status.\textsuperscript{2} One caveat is that HIV infection can influence biologic processes that may not be well captured by CD4 count and HIV RNA level, including increased immune activation and inflammation.\textsuperscript{26} Associations might also change as the HIV population ages further and immune deficiencies are compounded by immunosenescence.

There were suggestive associations of increased risk with ART exposure. As effective ART can be a powerful determinant of CD4 count and HIV RNA, this finding seems at odds with the lack of associations with virologic and immunologic status. However, ART use is also an important indicator of engagement in clinical care, and as a result, could likely serve as the strongest indicator of enhanced clinical surveillance for skin cancer (frequent skin examinations and treatment of precancerous lesions). Awareness that cutaneous cancers, especially Kaposi
sarcoma, are more common among HIV patients than other persons\textsuperscript{14,27} may have sensitized clinicians to be more vigilant for skin disease during clinical encounters. In this study, we did not have information on clinical visit frequency or other factors that might help evaluate the influence of increased opportunities for melanoma diagnosis.

NA-ACCORD is one of the largest and most representative cohorts of PWH in the United States and Canada.\textsuperscript{13} Cancer diagnoses were ascertained through standardized protocols, enhancing the reliability and consistency of the data. Despite these strengths, because melanoma is uncommon there was limited statistical power to conduct analyses within some subgroups, such as non-white individuals, who we excluded from the analysis. Also, while we accounted for residential geography, we lacked information on other important determinants of individual UVB exposure, such as time spent outdoors or tanning bed usage. For strong risk factors such as UVB and skin phenotype, a small amount of residual confounding might mask weak effects of HIV-specific risk factors.

In conclusion, we did not identify a significant elevation in melanoma risk in the HIV population compared with the general population, and HIV-specific risk factors, such as CD4 count and HIV RNA level, were not associated with melanoma risk. We found that melanoma is more frequently diagnosed among ART-treated people, possibly resulting from increased surveillance for skin conditions among people engaged in clinical care. Beyond this finding, melanoma risk factors among PWH appear to be the same as those identified in the general population. As such, PWH can be advised to follow prevention practices focused on reducing UVB exposure, as recommended for the general population.
ACKNOWLEDGEMENTS

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was supported by the Intramural Research Program of the National Cancer Institute; National Institutes of Health grants U01AI069918, F31DA037788, G12MD007583, K01AI093197, K23EY013707, K24AI065298, K24AI118591, K24DA000432, KL2TR000421, M01RR000052, N01CP01004, N02CP055504, N02CP91027, P30AI027757, P30AI027763, P30AI027767, P30AI036219, P30AI050410, P30AI094189, P30AI110527, P30MH62246, R01AA016893, R01CA165937, R01DA011602, R01DA012568, R01AG053100, R24AI067039, U01AA013566, U01AA020790, U01AI031834, U01AI034989, U01AI034993, U01AI034994, U01AI035004, U01AI035039, U01AI035040, U01AI035041, U01AI035042, U01AI037613, U01AI037984, U01AI038855, U01AI038858, U01AI042590, U01AI068634, U01AI068636, U01AI069432, U01AI069434, U01AI069439, U01AI069397, U01AI03401, U01AI03408, U01DA03629, U01DA036935, U01HD032632, U10EY008057, U10EY008052, U10EY008067, U24AA020794, U54MD007587, UL1RR024131, UL1TR000004, UL1TR000083, UL1TR000454, UM1AI035043, Z01CP010214 and Z01CP010176; contracts CDC-200-2006-18797 and CDC-200-2015-63931 from the Centers for Disease Control and Prevention, USA; contract 90047713 from the Agency for Healthcare Research and Quality, USA; contract 90051652 from the Health Resources and Services Administration, USA; grants CBR-86906, CBR-94036, HCP-97105 and TGF-96118 from the Canadian Institutes of Health Research, Canada; Ontario Ministry of Health and Long Term Care; and the Government of
Alberta, Canada. Additional support was provided by the National Cancer Institute, National Institute for Mental Health and National Institute on Drug Abuse.

The authors would like to thank all individuals involved with the NA-ACCORD collaboration, including staff, investigators, and patients, for their invaluable contributions to this work.

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REFERENCES


Table 1: Melanoma incidence rates and hazard ratios in 33,934 people with HIV according to selected characteristics, NA-ACCORD, 1996-2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (melanoma cases)</th>
<th>Incidence, per 100,000 p-y (95% CI)</th>
<th>Unadjusted Model HR (95% CI)</th>
<th>Adjusted Model HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>42.4 (33.5-53.0)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>20.5 (4.2-59.9)</td>
<td>0.47 (0.15-1.50)</td>
<td>0.66 (0.20-2.17)</td>
</tr>
<tr>
<td><strong>Transmission risk†</strong></td>
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<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>26</td>
<td>40.5 (26.4-59.3)</td>
<td>1.68 (0.76-3.71)</td>
<td>1.26 (0.47-3.35)</td>
</tr>
<tr>
<td>Other known transmission risk</td>
<td>8</td>
<td>24.0 (10.3-47.2)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td><strong>Time-updated age in years, modeled per decade</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;35</td>
<td>2</td>
<td>8.9 (1.1-32.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>25</td>
<td>37.6 (24.3-55.5)</td>
<td></td>
<td></td>
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<tr>
<td>45-54</td>
<td>29</td>
<td>42.9 (28.7-61.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55+</td>
<td>24</td>
<td>60.5 (38.7-90.0)</td>
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<td><strong>Time-updated calendar year, modeled per year</strong></td>
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<tr>
<td>1996-2000</td>
<td>25</td>
<td>51.6 (33.4-76.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001-2005</td>
<td>32</td>
<td>46.2 (24.7-51.0)</td>
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<tr>
<td>2006+</td>
<td>23</td>
<td>38.8 (24.6-58.2)</td>
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<tr>
<td><strong>Average annual residential UVB ≥35 mW/m²†</strong></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>24</td>
<td>29.3 (18.8-43.6)</td>
<td>Referent</td>
<td>Referent</td>
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<tr>
<td>Yes</td>
<td>51</td>
<td>50.8 (37.8-66.8)</td>
<td>1.76 (1.08-2.86)</td>
<td>1.62 (0.99-2.65)</td>
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<tr>
<td><strong>CD4 cell count, time-updated and modeled per 100 cells/mm³‡</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;200</td>
<td>14</td>
<td>39.9 (21.8-66.9)</td>
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<tr>
<td>200-349</td>
<td>15</td>
<td>35.0 (19.6-57.7)</td>
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<tr>
<td>350+</td>
<td>51</td>
<td>43.1 (32.1-56.7)</td>
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<tr>
<td><strong>Plasma HIV RNA concentration, time-updated and modeled per log₁₀ copies/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>45</td>
<td>38.6 (28.1-51.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>35</td>
<td>43.9 (30.6-61.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ART use, time-updated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never ART-exposed</td>
<td>17</td>
<td>30.7 (17.9-49.2)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Ever ART-exposed</td>
<td>62</td>
<td>48.1 (36.9-61.6)</td>
<td>1.60 (0.94-2.75)</td>
<td>1.45 (0.83-2.55)</td>
</tr>
</tbody>
</table>

*Regression models for each characteristic were adjusted for sex, time-updated age and calendar year (modeled continuously), average annual residential UVB ≥35 mW/m², and cohort.
†Transmission risk information was only available on a subset of 20,164 people.
‡4,764 people (including 5 melanoma cases) were excluded from analyses of average annual UVB because residential information was missing.

For ART analyses, we excluded all person-time occurring after a suppressed HIV RNA value (i.e., ≤500 copies/mL) observed in the absence of reported ART use (6% of person-time excluded). As suppressed HIV RNA is not expected to occur in the absence of ART use, this observation was indicative of potentially missing information on ART initiation.

ART=antiretroviral treatment, CI=confidence interval, HR=hazard ratio, NA-ACCORD=North American AIDS Cohort Collaboration on Research and Design, p-y=person-years, UVB=ultraviolet B exposure

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Table 2: Associations between current, lagged, and cumulative measures of CD4 count, HIV RNA level, and ART use in relation to melanoma incidence among people with HIV, NA-ACCORD, 1996-2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted Model HR (95% CI)</th>
<th>Adjusted Model HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, per 100 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lag</td>
<td>0.99 (0.91-1.07)</td>
<td>1.00 (0.92-1.09)</td>
</tr>
<tr>
<td>Lagged 180 days</td>
<td>1.00 (0.91-1.09)</td>
<td>1.01 (0.92-1.11)</td>
</tr>
<tr>
<td>Lagged 360 days</td>
<td>0.99 (0.90-1.09)</td>
<td>1.00 (0.91-1.11)</td>
</tr>
<tr>
<td>Lagged 720 days</td>
<td>0.98 (0.88-1.09)</td>
<td>0.98 (0.88-1.09)</td>
</tr>
<tr>
<td>Average over 0-720 days</td>
<td>0.99 (0.89-1.11)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>Average over 180-900 days</td>
<td>1.01 (0.90-1.13)</td>
<td>1.01 (0.90-1.13)</td>
</tr>
<tr>
<td>Plasma HIV RNA, per log₁₀ copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lag</td>
<td>0.99 (0.82-1.20)</td>
<td>1.08 (0.90-1.32)</td>
</tr>
<tr>
<td>Lagged 180 days</td>
<td>0.99 (0.80-1.22)</td>
<td>1.10 (0.89-1.37)</td>
</tr>
<tr>
<td>Lagged 360 days</td>
<td>1.03 (0.83-1.27)</td>
<td>1.12 (0.90-1.40)</td>
</tr>
<tr>
<td>Lagged 720 days</td>
<td>1.04 (0.82-1.32)</td>
<td>1.12 (0.87-1.43)</td>
</tr>
<tr>
<td>Average over 0-720 days</td>
<td>1.00 (0.76-1.32)</td>
<td>1.11 (0.83-1.47)</td>
</tr>
<tr>
<td>Average over 180-900 days</td>
<td>1.01 (0.75-1.34)</td>
<td>1.13 (0.84-1.55)</td>
</tr>
<tr>
<td>Ever ART-exposed† (ref.=never ART-exposed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lag</td>
<td>1.60 (0.94-2.75)</td>
<td>1.45 (0.83-2.55)</td>
</tr>
<tr>
<td>Lagged 180 days</td>
<td>1.80 (0.96-3.38)</td>
<td>1.65 (0.85-3.20)</td>
</tr>
<tr>
<td>Lagged 360 days</td>
<td>1.31 (0.72-2.39)</td>
<td>1.20 (0.64-2.25)</td>
</tr>
<tr>
<td>Lagged 720 days</td>
<td>2.27 (1.02-5.05)</td>
<td>2.29 (0.96-5.46)</td>
</tr>
<tr>
<td>Proportion of time on ART† over prior 0-720 days, per 10% increase</td>
<td>1.14 (1.03-1.27)</td>
<td>1.16 (1.03-1.30)</td>
</tr>
<tr>
<td>Proportion of time on ART† over prior 180-900 days, per 10% increase</td>
<td>1.13 (1.01-1.25)</td>
<td>1.14 (1.01-1.28)</td>
</tr>
</tbody>
</table>

The number of melanoma cases included in each analysis were: no lag N=80, lagged 180 days N=67, lagged 360 days N=62, lagged 720 days N=50, 0-720 days cumulative measures N=50, 180-900 days cumulative measures N=45.

*Regression models for each characteristic were adjusted for sex, time-updated age and calendar year (modeled continuously), average annual residential UVB ≥ 35 mW/m², and cohort. 4,764 people (including 5 melanoma cases) were excluded from the adjusted models because residential information to calculate average annual UVB was missing.

†For ART analyses, we excluded all person-time occurring after a suppressed HIV RNA value (i.e., ≤ 500 copies/mL) observed in the absence of reported ART use (6% of person-time excluded). As suppressed HIV RNA is not expected to occur in the absence of ART use, this observation was indicative of potential missing information on ART initiation.

ART=antiretroviral treatment, CI=confidence interval, HR=hazard ratio, NA-ACCORD=North American AIDS Cohort Collaboration on Research and Design