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Viral suppression is associated with lower AIDS-defining and non-AIDS-defining cancer incidence in HIV-infected Veterans

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Reproducible Research Statement

Study protocol and statistical code: Available from Dr. Park (lesley.park@stanford.edu).

Data set: We are unable to submit the analytic datasets used in this manuscript because data from the Veterans Health Administration are not permitted to leave VA premises. This limitation is consistent with our past work and with other studies based on VA data.

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Abstract

Background: Viral suppression is a primary marker of HIV treatment success. HIV-infected persons are at increased risk for AIDS-defining cancers (ADC) and several non-AIDS-defining cancers (NADC), some of which are caused by oncogenic viruses.

Objective: To determine whether viral suppression is associated with decreased cancer risk.

Design: Prospective cohort

Setting: Veterans Health Administration

Participants: HIV+ (N = 42,441) and demographically-matched uninfected Veterans (N = 104,712) from 1999–2015

Measurements: Standardized cancer incidence rates (IR) and Poisson regression rate ratios (RR, HIV-infected versus uninfected persons) by viral suppression status (*unsuppressed*: person-time with HIV RNA $\geq$ 500 copies/mL; *early-suppressed*: initial two years with HIV RNA <500 copies/mL; *long-term-suppressed*: person-time after early suppression with HIV RNA <500 copies/mL).

Results: Comparing HIV+ to uninfected persons, unsuppressed persons had the highest overall cancer incidence (RR, 2.35 [95% CI, 2.19 to 2.51]), with lower incidence among early-suppressed (RR, 1.99 [CI, 1.87 to 2.12]), and the lowest incidence among long-term-suppressed (RR, 1.52 [95% CI, 1.44 to 1.61]). This trend was strongest for ADC (unsuppressed RR, 22.73 [CI, 19.01 to 27.19]; early-suppressed RR, 9.48 [CI, 7.78 to 11.55]; long-term-suppressed RR, 2.22 [CI, 1.69 to 2.93]); much weaker for NADC caused by viruses (unsuppressed RR, 3.82 [CI, 3.24 to 4.49]; early-suppressed RR, 3.42 [CI, 2.95 to 3.97]; long-term-suppressed RR, 3.17 [CI, 2.78 to 3.62]); and absent for NADC not caused by viruses.

Limitations: Lower viral suppression thresholds, duration of long-term suppression, and effects of CD4+ and CD8+ T-cell counts were not thoroughly evaluated.

Conclusions: Antiretroviral therapy resulting in long-term viral suppression may contribute to cancer prevention, to a greater degree for ADC than for NADC. Excess cancer risk remained among patients with long-term suppression.

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INTRODUCTION

Antiretroviral therapy (ART) has been associated with reduced AIDS- and non-AIDS-related morbidity and mortality in persons living with HIV/AIDS (1–3). Nevertheless, the incidence of many comorbid conditions remains higher in HIV-infected (HIV+) persons than in the general population (4), including AIDS-defining cancers (ADC; Kaposi sarcoma, non-Hodgkin lymphoma, invasive cervical cancer)) (5–9) as well as several non-AIDS defining cancers (NADC) (5–7, 9–14). ADC, along with most NADC that have elevated incidence among HIV+ persons, are caused by oncogenic viruses, including Kaposi-sarcoma-associated herpesvirus, Epstein Barr virus (non-Hodgkin and Hodgkin lymphoma), human papillomavirus (invasive cervical cancer, anal squamous cell carcinoma [SCC], genital SCCs, and some oral cavity and pharynx SCCs), and hepatitis C and B viruses (hepatocellular carcinoma) (12).

HIV-induced immunodeficiency, along with elevated prevalence of smoking, oncogenic virus co-infections, and other cancer risk factors, contribute to this increased cancer risk (4, 12, 15–19). Furthermore, HIV viral replication may directly contribute to cancer risk through HIV-induced inflammation or immune-senescence (12, 18, 20) or pro-oncogenic effects of secreted HIV-encoded proteins (18).

The benefits of ART include suppressed HIV viral load (as measured by plasma HIV-1 RNA [HIV RNA] (21)), improved immune function (as measured by increasing CD4+ T-cell count [CD4 count]), and reduced inflammation (18). Randomized controlled trials examining the effects of continuous versus interrupted ART (22) and immediate versus deferred ART initiation (23) on cancer risk were limited by low statistical power due to a small number of cancer outcomes. Observational studies examining associations between various cumulative measures of viral suppression and cancer risk have mostly focused on one or a few specific cancer types and/or were limited by a small number of outcomes (24–31), and none specifically focused on the effect of sustained viral suppression.

In the present study, in a large cohort with ample statistical power, we examined whether long-term viral suppression as measured by sustained periods of low HIV RNA was associated with reduced cancer risk among HIV+ during the modern ART era. We compared cancer risk among HIV+ persons, stratified by viral suppression status, to cancer risk among demographically-similar uninfected persons using the incidence rate ratio, a measure of relative risk. We hypothesized that HIV+ persons with long-term viral suppression would have lower cancer incidence compared to HIV+ persons without such suppression, and thus, the relative risk comparing HIV+ versus uninfected persons would be greater in unsuppressed compared to long-term-suppressed HIV+ persons.

METHODS

The Veterans Aging Cohort Study (VACS) is a cohort derived from national Veterans Health Administration (VA) databases (e.g., demographic, vital status, inpatient and outpatient encounters, pharmacy, laboratory results) (32). VACS enrolls HIV+ Veterans when they begin HIV care in the VA and matches them to two uninfected Veterans under VA care at

that time by age, sex, race/ethnicity, and the clinical site where they receive care. The matched uninfected Veterans were assigned the same entry date as the HIV+ Veteran. The VA Connecticut Healthcare System and Yale University Institutional Review Boards have approved the VACS.

We linked VACS with the VA Central Cancer Registry and the VA Corporate Data Warehouse Oncology Registry, two national databases of cancer cases diagnosed or treated at the VA. We mapped International Classification of Diseases for Oncology, third edition (33) topography and morphology codes from these databases to specific cancer types, consistent with Surveillance, Epidemiology, and End Results (SEER) recoding algorithms (34). We classified cancer types into the following groupings: all cancer; ADC; NADC caused by oncogenic viruses (virus-NADC); NADC not caused by oncogenic viruses (non-virus-NADC); and poorly specified cancers (Appendix Table 1a). We used morphology and detailed topography to divide oral cavity and pharynx, anal, liver, vagina, vulva, and penis cancer, respectively, into virus-NADC versus non-virus-NADC (Appendix Table 1a; for example, SCC of the anus is a virus-NADC, whereas other morphological types of anal cancer are non-virus-NADC).

For each HIV+ person, we classified each day of observation time into one of three HIV viral suppression categories: 1) unsuppressed, 2) early-suppressed, and 3) long-term-suppressed. HIV+ persons in the VA have an average of three HIV RNA laboratory tests per year. To estimate HIV RNA levels between test results, we used midpoint estimation, extending each HIV RNA test result backward either to the midpoint of the interval between the previous test result and the index test result or 180 days (about one-half year), whichever was reached first, and forward either to the midpoint of the interval between the index test result and the subsequent test result or 180 days, whichever was reached first (Appendix Figure 1a) (35). We classified observation time not covered by these extensions, which occurred when there was a gap greater than 360 days between laboratory results, as “unknown.” Finally, we extended a person’s first HIV RNA laboratory result backward 180 days and last result forward 180 days.

We defined viral suppression as HIV RNA <500 copies/mL. We classified observation time when HIV RNA $\geq$ 500 copies/mL as *unsuppressed*. We defined *early-suppressed* as the initial period up to two years (720 days) of continuous suppressed observation time. We classified subsequent continuous suppressed observation time after the initial 720 days as *long-term-suppressed*. We allowed one blip of HIV RNA up to 1,000 copies/mL during an early-suppressed or long-term-suppressed period. When an HIV+ person became unsuppressed after a period of early-suppression or long-term-suppression, and subsequently became suppressed again, the latter suppressed observation time was classified as early-suppressed during the initial period up to 720 days of suppression (i.e., the suppression clock was set back to zero after each unsuppressed episode). Thus, viral suppression status for a given patient was time-varying, with observation time potentially distributed among each of the viral suppression categories.

We defined baseline as the first HIV RNA laboratory test date for HIV+ persons and VACS entry date for uninfected persons. However, we started observation time at the later of 180

days after baseline (to exclude prevalent cancer cases) or October 1, 1999 (when all covariate information was consistently available). We defined exit date as the earliest of: diagnosis date for the specific cancer group (the first diagnosis of a cancer type classified in the group) or type being analyzed, death date, loss to follow-up date (last VA visit plus 180 days), or September 30, 2015. Although our earliest possible start of observation time was October 1, 1999, we calculated viral suppression status starting with an HIV+ person's earliest HIV RNA laboratory test. Thus, a patient who was virally suppressed continuously from January 1, 1997, for example, would enter observation time on October 1, 1999 as long-term suppressed.

For each cancer group/type, we used the direct method to calculate age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rates (IR) for each HIV+ viral suppression group and for uninfected persons (36). We derived standardization weights from the person-time distribution of the entire VACS by age (5-year groups), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other, unknown), and calendar period (1999–2003, 2004–2007, 2008–2011, 2012–2015). We classified age and calendar period at each day of observation (37).

We used Poisson regression to calculate an incidence rate ratio (RR) for each HIV+ viral suppression group versus uninfected persons, adjusted for time-updated age, sex, race/ethnicity, time-updated calendar-period, and certain cancer risk factors (smoking (38), alcohol abuse/dependence, hepatitis C virus [HCV] infection, and diabetes (39); Appendix Table 1b). We used multiple imputation to impute values for patients with unknown race, HCV, or smoking status (Appendix 1). We used models with a log-link function offset by the natural log of observation time where time was measured in days. Using the model deviance, we checked for, but did not find, overdispersion. We included linear and quadratic continuous age terms in the models. To calculate statistical significance of viral suppression IR trends (P_{trend}), we used a model with viral suppression/HIV status parameterized as a single ordinal variable (unsuppressed, early-suppressed, long-term-suppressed, uninfected), with a binary term for HIV status that effectively removed the uninfected category from the ordinal variable.

In sensitivity analyses, we explored a viral suppression threshold of 50 copies/mL versus 500 copies/mL, an early-suppressed/long-term-suppressed cut-point of one versus two years, stratification by calendar period, and stratification by baseline nadir CD4, baseline CD4:CD8 ratio, and time-updated CD4 count (lagged by 180 days to guard against reverse causality) (Appendix 2). We used midpoint estimation to estimate CD4 counts between laboratory test results.

We performed statistical analyses using SAS, version 9.4 (SAS Institute). We defined statistical significance as $P < 0.05$ (two-sided).

Role of the Funding Source

This study was funded by the National Institutes of Health, which had no role in data collection, analysis, or interpretation.

RESULTS

Among 42,441 HIV+ persons, 3,821 developed 4,169 incident cancers (616 ADC, 817 virus-NADC, 2,683 non-virus-NADC, 53 poorly specified). Among uninfected persons (N = 104,712), 7,163 developed 7,879 incident cancers (223 ADC, 715 virus-NADC, 6,850 non-virus-NADC, 91 poorly specified). The median analytic observation time was 7.4 years for HIV+ persons and 10.1 years for uninfected persons. Of the 343,150 person-years contributed by HIV+ persons, 22% was classified as unsuppressed, 27% early-suppressed, 37% long-term-suppressed, and 14% unknown, with a median of 20 (IQR, 8–38) HIV RNA measurements per person from baseline. Uninfected persons contributed 988,403 person-years.

Over half of HIV+ persons (62%) achieved long-term viral suppression at some point during follow-up (median duration = 3.0 years [IQR, 1.1–6.1]). HIV+ and uninfected persons had similar distributions of age, sex (predominantly male), race/ethnicity, smoking status, and alcohol abuse/dependence status (Table 1). HIV+ persons had higher prevalence of chronic HCV infection (22% versus 10%) and lower prevalence of diabetes (21% versus 34%).

We present results for each cancer group and for each cancer type with at least 30 HIV+ cases, with the exception of non-virus NADC cancer types, for which we only present results for cancer types with at least 30 cases and with at least one HIV+ viral suppression category with significantly decreased or increased cancer risk.

All cancer

For all cancer, we observed a decreasing viral suppression IR trend (i.e., a graded decrease in cancer risk from unsuppressed to early-suppressed to long-term-suppressed HIV+ persons), with the IR (cases per 100,000 person-years) decreasing from 1,748 in the unsuppressed to 1,475 in the early-suppressed to 1,155 in the long-term-suppressed, compared with 742 among uninfected persons (Figure 1). The RR comparing HIV+ to uninfected persons (adjusted for demographics and cancer risk factors) was highest for unsuppressed (2.35 [95% CI, 2.19 to 2.51]), then early-suppressed (1.99 [CI, 1.87 to 2.12]), then long-term-suppressed (1.52 [CI, 1.44 to 1.61]). Importantly, the RR remained elevated in long-term-suppressed.

ADC

We observed a strong decreasing viral suppression IR trend for ADC, with the IR sharply declining from 474 per 100,000 person-years in the unsuppressed to 211 in the early-suppressed to 56 in the long-term-suppressed, compared with 22 among uninfected persons (Figure 1). The RR comparing HIV+ to uninfected persons was highest for unsuppressed (22.73 [CI, 19.01 to 27.19]), then early-suppressed (9.48 [CI, 7.78 to 11.55]), then long-term-suppressed (2.22 [CI, 1.69 to 2.93]). Even among the long-term-suppressed, the RR remained elevated. With a 100% risk reduction defined as reduction to the uninfected RR reference level of 1.00, long-term-suppression was associated with a 94% reduction in excess ADC risk ($[22.73 - 2.22] / [22.73 - 1.00]$), with 65% of this reduction ($[22.73 - 9.48] /$

[22.73–2.22]) occurring during early suppression. We observed similar patterns for the two main ADCs, non-Hodgkin lymphoma and Kaposi sarcoma (Figure 2).

Virus-NADC

We observed a weak decreasing viral suppression IR trend for virus-NADC, with the IR decreasing from 320 per 100,000 person-years in the unsuppressed to 280 in the early-suppressed to 253 in the long-term-suppressed, compared with 70 among uninfected (Figure 1). The RR comparing HIV+ to uninfected persons was highest for unsuppressed (3.82 [95% CI, 3.24 to 4.49]), then early-suppressed (2.42 [CI, 2.95 to 3.97]), then long-term-suppressed (3.17 [CI, 2.78 to 3.62]). Even among the long-term suppressed, the RR remained substantially elevated. Long-term-suppression was associated with a 23% reduction in excess virus-NADC risk $([3.82-3.17]/[3.82-1.00])$, with 62% of this reduction $([3.82-3.42]/[3.82-3.17])$ occurring during early suppression. The only specific cancer type to exhibit a significant decreasing viral suppression IR trend was anal SCC ($P_{\text{trend}} = 0.014$; Figure 3). However, the RR remained markedly elevated in the long-term suppressed (34.70 [CI, 22.63 to 53.20]).

Non-virus-NADC

For non-virus-NADC, the IR remained essentially the same in the unsuppressed (989 per 100,000 person-years) and early-suppressed (980) and then decreased to 863 in the long-term-suppressed, compared with 653 among uninfected (Figure 1). After adjusting for both demographics and cancer risk factors, the RRs comparing HIV+ to uninfected persons did not show a trend, with RRs of 1.40 (CI, 1.28 to 1.53) for unsuppressed, 1.53 (CI, 1.42 to 1.65) for early-suppressed, and 1.32 (CI, 1.24 to 1.41) for long-term-suppressed. Although the magnitude of the RRs was substantially lower for non-virus-NADC compared with ADC or virus-NADC, the non-virus-NADC RRs were elevated, even among the long-term-suppressed.

There were decreasing viral suppression IR trends for lung cancer ($P_{\text{trend}} = 0.003$), larynx cancer ($P_{\text{trend}} = 0.007$), melanoma of the skin ($P_{\text{trend}} = 0.008$), and leukemia ($P_{\text{trend}} < 0.001$) (Figure 4). Risk was not significantly elevated among the long-term suppressed for the latter three cancer types. Prostate cancer was the only cancer type with an increasing viral suppression IR trend ($P_{\text{trend}} < 0.001$). The prostate cancer RR was 0.79 (CI, 0.65 to 0.95) for the unsuppressed, but was elevated for early-suppressed (RR, 1.18 [CI, 1.03 to 1.35]) and long-term-suppressed (RR, 1.22 [CI, 1.10 to 1.35]).

Sensitivity analyses

Viral suppression IR trends were similar using a viral suppression threshold of 50 copies/mL versus 500 copies/mL (Appendix Figure 2a) and using a cut-point for early-suppressed versus long-term suppressed of one year versus two years (Appendix Figure 2b). Viral suppression IR trends did not meaningfully differ by calendar period, except for ADC, for which the trend was weaker in 1999–2003 compared with later calendar periods (Appendix Tables 2a and 2b). In models for all cancer stratified by baseline nadir CD4 count, we observed decreasing viral suppression IR trends in all strata (Appendix Figure 2c). In models for all cancer stratified by baseline CD4:CD8 ratio, we found decreasing viral

suppression IR trends in the lower two CD4:CD8 ratio categories ($P_{\text{trend}} < 0.001$), but not in the highest CD4:CD8 ratio category of ≥ 1.0 (Appendix Figure 2d), which included only 8% of all HIV+ cancer cases. In models stratified by time-updated CD4 count, we observed decreasing viral suppression IR trends within each CD4 stratum for all cancer and ADC, but not for virus-NADC or non-virus-NADC (Appendix Figure 2e). Furthermore, RRs increased with decreasing CD4 count.

DISCUSSION

In a large cohort of HIV+ and demographically-similar uninfected patients, we comprehensively examined whether long-term viral suppression, the primary objective of ART in HIV+ persons, was associated with decreased cancer risk. We observed strong trends of decreasing cancer risk across our three viral suppression groups (unsuppressed, early-suppressed, long-term-suppressed) for all cancer and ADC, with a much weaker trend for virus-NADC, and no trend for non-virus-NADC.

Long-term-suppression was associated with a >90% reduction in excess ADC risk, but only a one-fifth reduction in excess virus-NADC risk. For both of these cancer groups, about three-fifths of the reduction of excess risk occurred during early suppression. For ADC, virus-NADC, and non-virus-NADC, even long-term suppression did not reduce cancer risk to that among uninfected, indicating ongoing deleterious effects of HIV infection in the presence of long-term ART, such as HIV-induced inflammation or immune-senescence (12, 18, 20). Nevertheless, our findings suggest that early and sustained ART, which results in long-term viral suppression, may play a role in cancer prevention, with a marked reduction in ADC risk as well as a meaningful, but much less pronounced, reduction in virus-NADC risk.

Non-virus-NADC is a very heterogeneous group of cancers. Although we did not observe an overall viral suppression IR trends, we did observe trends for specific cancer types: larynx cancer, lung cancer, melanoma, and leukemia. Thus, long-term suppression may contribute to prevention of these specific cancer types as well.

In the Strategies for Management of Antiretroviral Therapy trial (71 cancers, Appendix Table 3a), continuous ART (versus treatment interruption) was associated with a significant decreased risk of ADC, but not NADC (22). In the Strategic Timing of Antiretroviral Treatment trial (52 cancers), among persons with CD4 count >500 cells/mL, immediate ART initiation (versus deferred initiation) was associated with significant decreased risk of all cancer, infection-related cancer (mostly ADC), and Kaposi sarcoma (23, 40). Consistent with our results, previous observational studies found various cumulative measures of viral suppression to be associated with ADC (24), non-Hodgkin lymphoma (24–26), Kaposi sarcoma (27), and anal cancer (28–30) risk, but not liver cancer (30, 31) risk. Inconsistent with our results, some studies found associations for Hodgkin lymphoma (30), but not for non-Hodgkin lymphoma (29), Kaposi sarcoma (29), or lung cancer (29). However, our results are not strictly comparable to previous observational studies due to different measures of viral suppression and different multivariate adjustment covariates.

We aimed to determine the relationship between sustained viral suppression and cancer risk, regardless of biological mechanism. Nevertheless, the mechanism underlying the association between viral suppression and decreased cancer risk is of considerable interest. An independent inverse association between CD4 count and ADC risk is well-established (12). In addition, evidence suggests weaker, subtler inverse associations between CD4 count and specific NADC types, especially those caused by viruses (12, 18). Furthermore, since CD4 count is correlated with long-term HIV RNA levels (41, 42), CD4 count might confound and likely mediates the association between viral suppression status and cancer risk. When we stratified by CD4 count, decreasing viral suppression IR trends persisted for all cancer and ADC within each CD4 stratum, but did not persist for virus-NADC. However, these results are difficult to interpret because of reduced statistical power within strata and because distinguishing between confounding and mediation is challenging. Beneficial effects of viral suppression on cancer risk over and above its beneficial effect on CD4 count could include reduced (if not ideal) levels of inflammation, lessened immune-senescence (12, 18, 20), or decreased presence of pro-oncogenic HIV-encoded proteins (18, 43–50).

Prostate cancer, which is commonly diagnosed in an asymptomatic phase by prostate-specific antigen screening, was the only cancer type with higher incidence in virally-suppressed versus unsuppressed persons. Prior meta-analyses, which included studies from the pre-ART era, reported a 30% decreased risk of prostate cancer in HIV+ men compared with the general population (13, 51), consistent with our finding of a 20% decreased risk among unsuppressed compared with uninfected men. Since persons with a short life expectancy and many comorbidities, such as HIV+ patients in the pre-ART era, may be less likely to be screened, it has been hypothesized that this decreased risk is due to a lower rate of screening among HIV+ men (13, 52–55). With the advent of ART and the resultant dramatic increase in life expectancy among virally-suppressed persons, it is possible that screening rates have increased among these persons, explaining our results. However, one study found that screening differences could not explain lower prostate cancer risk in HIV+ compared to uninfected men during the ART era (53).

A major strength of this investigation was the use of a large national cohort of HIV+ and demographically-similar uninfected persons followed over a 16-year period in the modern ART-era, and thus sufficient cancer events to comprehensively explore the relationship between viral suppression and cancer risk. A limitation was the estimation of time-updated HIV RNA levels, which required assumptions about how HIV RNA levels change between laboratory result dates. Furthermore, since VA sites adopted progressively more sensitive HIV RNA assays over calendar time, encompassing the entire 1999–2015 period in our analysis necessitated using a high threshold (500 copies/mL) to define viral suppression. Our investigation assessed the relationship between current viral suppression status and cancer risk, and thus did not account for patients' entire viral suppression status histories. Prior studies used various cumulative measures of viral suppression, but did not take uninterrupted suppression into account.

Another limitation was the possibility of selection bias due to exclusion of HIV+ observation time with unknown viral suppression status. Since VACS is predominantly male, we were underpowered to generalize our results to women; in particular, we only observed

one invasive cervical cancer. Finally, despite the large number of statistical tests, we did not adjust for multiple comparisons.

Using a large cohort of HIV+ Veterans, we classified observation time by viral suppression status and calculated cancer risk compared with demographically-similar uninfected Veterans. We observed cancer risk to be highest in the unsuppressed, lower in the early-suppressed, lower still in the long-term-suppressed, and lowest in the uninfected for all cancer, ADC, non-virus-NADC, and several cancer types. Our findings suggest that early and sustained ART, which results in long-term viral suppression, may contribute to cancer prevention, with a marked risk reduction for ADC, a much more modest risk reduction for virus-NADC, and possible risk reductions for certain non-virus-NADC cancer types. However, excess cancer risk remained among the long-term suppressed. Future research should extend our sensitivity analyses to perform more detailed examinations of using a viral suppression threshold <500 copies/mL; whether cancer risk continues to decrease with longer durations of long-term suppression; and the role of CD4 count and CD4:CD8 ratio.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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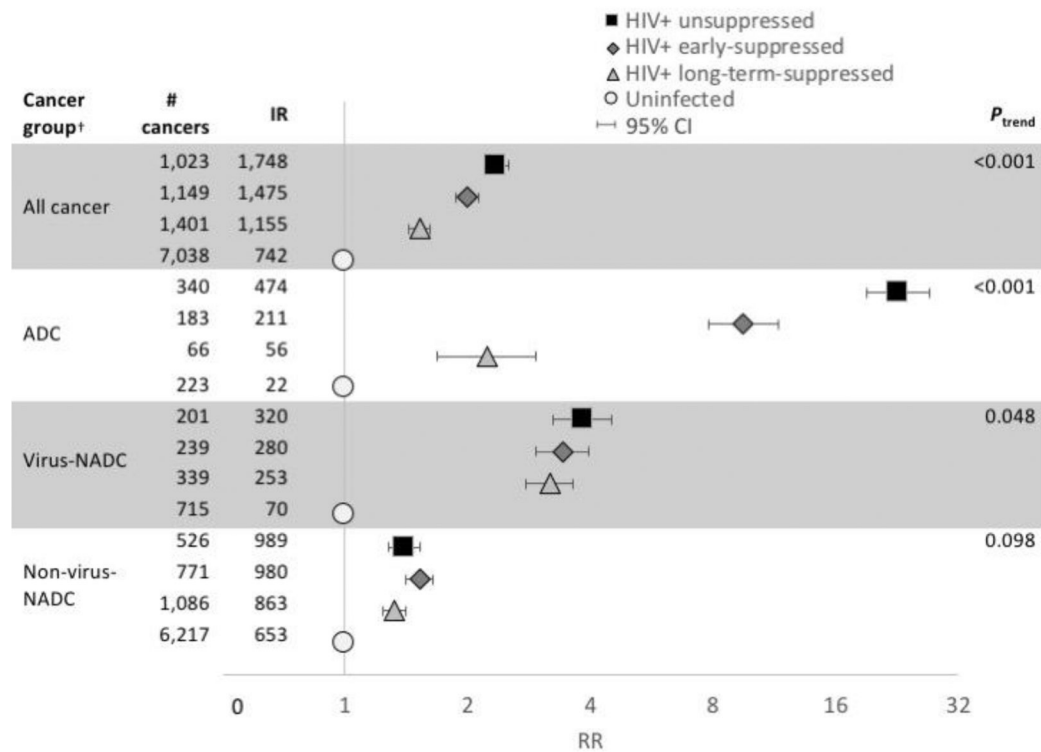


Figure 1. Numbers of cancer cases, IRs (per 100,000 personRRs* with 95% CI by HIV viral suppression status, and P cancer groups†

ADC = AIDS-defining cancer; IR = age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rate; non-virus-NADC = non-virus-related non-AIDS-defining cancer; RR = adjusted incidence rate ratio; virus-NADC = virus-related non-AIDS-defining cancer; 95% CI = 95% confidence interval.

*Adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol abuse/dependence, hepatitis C virus infection, and diabetes.

†For cancer group analyses, the endpoint for a given subject was the first diagnosis of a cancer type classified in the group. For example, if a person had both a non-Hodgkin lymphoma and Kaposi sarcoma diagnosis, only the first of the two diagnoses would contribute to the ADC analysis.

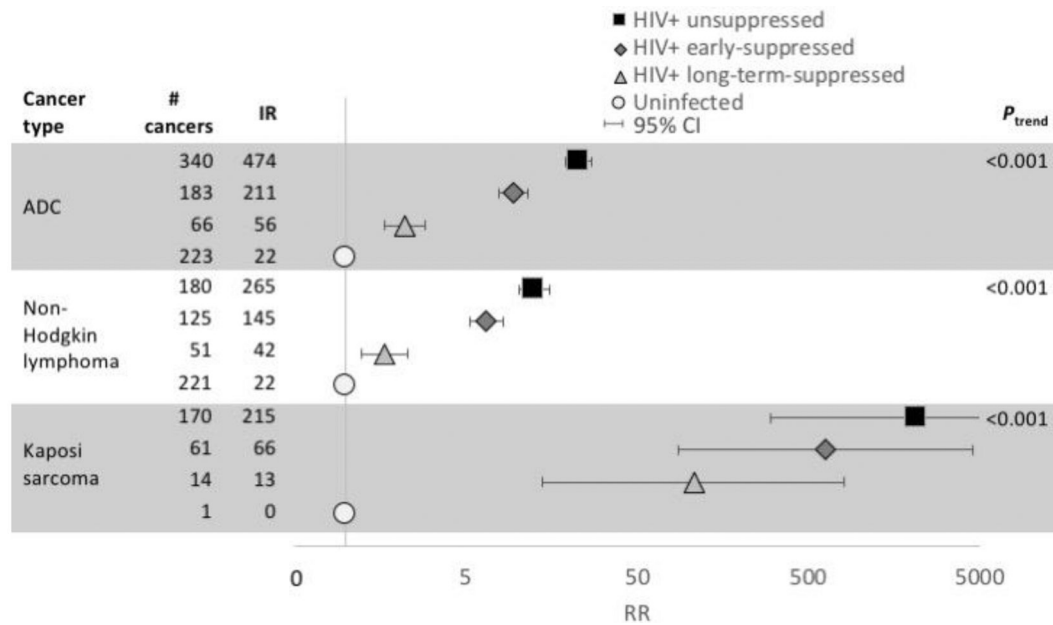


Figure 2. Numbers of cancer cases, IRs (per 100,000 person-RRs* with 95% CI by HIV viral suppression status, and *P* ADC†

ADC = AIDS-defining cancer; IR = age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rate; RR = adjusted incidence rate ratio; 95% CI = 95% confidence interval.

*Adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol abuse/dependence, hepatitis C virus infection, and diabetes.

†For ADC (cancer group), the endpoint for a given subject was the first diagnosis of a cancer type classified as ADC. For example, if a person had both a non-Hodgkin lymphoma and Kaposi sarcoma diagnosis, only the first of the two diagnoses would contribute to the ADC analysis, but both diagnoses would contribute to each specific cancer type analysis. The following cancer type (and number of HIV+ cancer cases) with less than 30 HIV+ cancer cases were not included in the figure, but were included in the ADC analysis: invasive cervical (1).

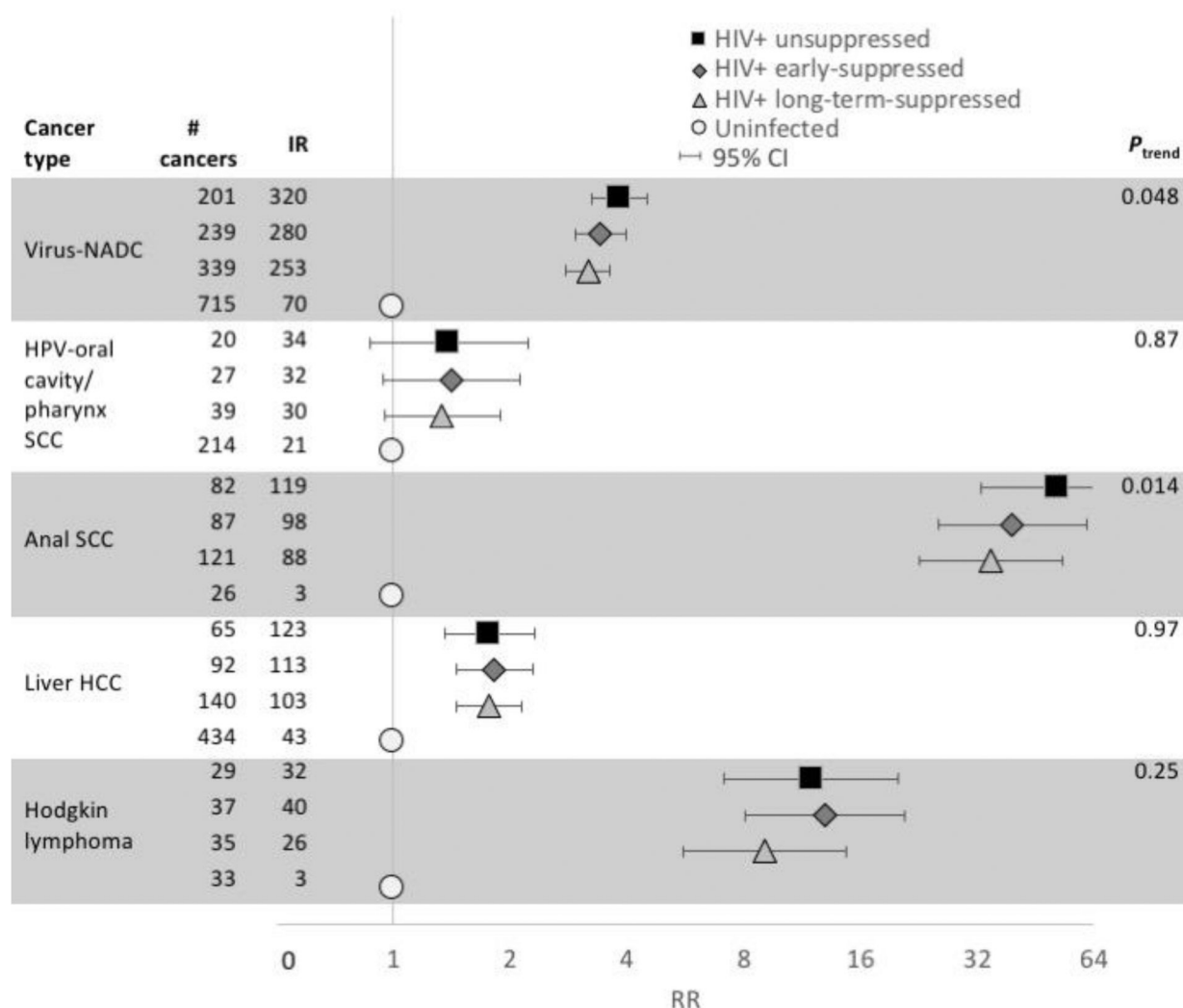


Figure 3. Numbers of cancer cases, IRs (per 100,000 person-years)* with 95% CI by HIV viral suppression status, and P virus-NADC†

HCC = hepatocellular carcinoma; HPV = human papillomavirus; IR = age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rate; RR = adjusted incidence rate ratio; SCC = squamous cell carcinoma; virus-NADC = virus-related non-AIDS-defining cancer; 95% CI = 95% confidence interval.

*Adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol abuse/dependence, hepatitis C virus infection, and diabetes.

†For virus-NADC (cancer group), the endpoint for a given subject was the first diagnosis of a cancer type classified as virus-NADC. For example, if a person had both Hodgkin lymphoma and anal SCC, only the first of the two diagnoses would contribute to the virus-NADC analysis, but both diagnoses would contribute to each specific cancer type analysis. The following cancer types (and numbers of HIV+ cancer cases) with less than 30 HIV+ cancer cases were not included in the figure, but were included in the virus-NADC analysis: penis SCC (17). The following cancer types had no HIV+ cases: vagina SCC; vulva SCC.

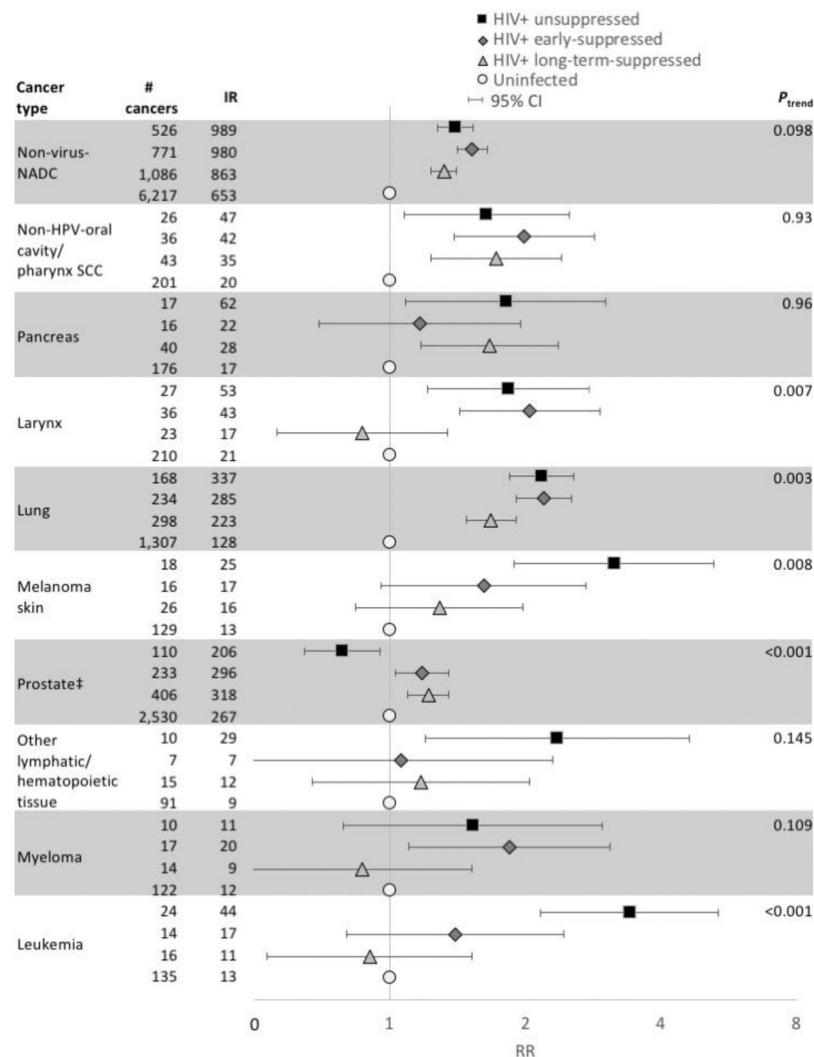


Figure 4. Numbers of cancer cases, IRs (per 100,000 person-years), multivariate Poisson regression values for HIV+ IR viral suppression trend, for RRs* with 95% CI by HIV viral suppression status, and P non-virus-NADC†

HPV = human papillomavirus; IR = age-, sex-, race/ethnicity-, and calendar-period-standardized incidence rate; non-virus-NADC = non-virus-related non-AIDS-defining cancer; RR = adjusted incidence rate ratio; SCC = squamous cell carcinoma; 95% CI = 95% confidence interval.

*Adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol abuse/dependence, hepatitis C virus infection, and diabetes.

† For non-virus-NADC (cancer group), the endpoint for a given subject was the first diagnosis of a cancer type classified as non-virus-NADC. For example, if a person had both lung cancer and prostate cancer, only the first of the two diagnoses would contribute to the virus-NADC analysis, but both diagnoses would contribute to each specific cancer type analysis. The following cancer types (and numbers of HIV+ cancer cases) with less than 30 HIV+ cancer cases were not included in the figure, but were included in the non-virus-NADC analysis: oral cavity and pharynx non-SCC (9); small intestine (4); anal non-SCC (5); liver non-hepatocellular carcinoma (12); biliary tract (16); retroperitoneum and

peritoneum, nonmesothelioma (1); other digestive organs (3); nose, nasal cavity, and middle ear (12); pleura (2); trachea, mediastinum, and other respiratory organ (1); bone and joint (2); soft issue including heart (21); nonepithelial skin (9); female breast (10); male breast (5); testis (10); other male genital organs (4); other urinary organ (6); eye and orbit (3); brain and nervous system (9); thyroid (25); other endocrine including thymus (1); and mesothelioma (4). The following cancer types (and numbers of HIV+ cancer cases) did not have any HIV+ viral suppression categories with significantly elevated cancer risk and were not included in the figure, but were included in the non-virus-NADC analysis: esophagus (51); stomach (32); colorectal (155); urinary bladder (62); kidney and renal pelvis (115). The following cancer types had no HIV+ cases: corpus or uterus; ovary; vagina non-SCC; vulva non-SCC; other female genital organs; and penis non-SCC.

‡We used sex-specific weights to calculate prostate cancer IRs.

Table 1.

Baseline characteristics of patients who contributed observation time

		HIV+persons		Uninfected persons	
		N = 42,441		N = 104,712	
		N	(%)	N	(%)
Age (years)					
	20–29	2,577	(6)	5,441	(5)
	30–39	8,171	(19)	18,767	(18)
	40–49	15,992	(38)	39,169	(38)
	50–59	10,861	(26)	27,524	(26)
	60–69	4,027	(9)	10,822	(10)
	≥ 70	813	(2)	2,989	(3)
Sex					
	Female	1,043	(2)	2,904	(3)
	Male	41,398	(98)	101,808	(97)
Race/ethnicity					
	Non-Hispanic white	15,730	(39)	41,428	(40)
	Non-Hispanic black	21,673	(49)	49,795	(47)
	Hispanic	3,406	(8)	8,995	(8)
	Other	603	(1)	1,691	(2)
	Unknown	1,029	(2)	2,803	(3)
Smoking status					
	Never	10,853	(26)	29,756	(28)
	Ever	28,556	(67)	69,593	(66)
	Unknown	3,032	(7)	5,363	(5)
Alcohol abuse/dependence					
	No	27,643	(65)	68,763	(66)
	Yes	14,798	(35)	35,949	(34)
HCV status *					
	HCV negative	27,068	(64)	64,550	(62)
	Chronic HCV	9,343	(22)	10,689	(10)
	HCV exposure	2,789	(7)	3,301	(3)
	Never tested in the VA	3,241	(8)	26,172	(25)
Diabetes					
	No	33,622	(79)	69,197	(66)
	Yes	8,819	(21)	35,515	(34)

HCV = hepatitis C virus

* Definitions: HCV negative, negative HCV antibody test result(s) only; Chronic HCV, positive HCV RNA test; HCV exposure, positive HCV antibody test, but negative or unknown HCV RNA test; Never tested in the VA, no HCV laboratory test results available from the VA (it is possible that some of these patients were tested for HCV outside the VA)