Annals of Internal Medicine ORIGINAL RESEARCH

Association of Viral Suppression With Lower AIDS-Defining and Non–AIDS-Defining Cancer Incidence in HIV-Infected Veterans

A Prospective Cohort Study

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Background: Viral suppression is a primary marker of HIV treatment success. Persons with HIV are at increased risk for AIDS-defining cancer (ADC) and several types of non–AIDS-defining cancer (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: Department of Veterans Affairs.

Participants: HIV-positive veterans (n = 42 441) and demographically matched uninfected veterans (n = 104 712) from 1999 to 2015.

Measurements: Standardized cancer incidence rates and Poisson regression rate ratios (RRs; HIV-positive vs. uninfected persons) by viral suppression status (unsuppressed: person-time with HIV RNA levels ≥500 copies/mL; early suppression: initial 2 years with HIV RNA levels <500 copies/mL; long-term suppression: person-time after early suppression with HIV RNA levels <500 copies/mL).

Results: Cancer incidence for HIV-positive versus uninfected persons was highest for unsuppressed persons (RR, 2.35 [95% CI, 2.19 to 2.51]), lower among persons with early suppression (RR, 1.99 [CI, 1.87 to 2.12]), and lowest among persons with long-term suppression (RR, 1.52 [CI, 1.44 to 1.61]). This trend was strongest for ADC (unsuppressed: RR, 22.73 [CI, 19.01 to 27.19]; early suppression: RR, 9.48 [CI, 7.78 to 11.55]; long-term suppression: 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 suppression: RR, 3.42 [CI, 2.95 to 3.97]; long-term suppression: RR, 3.17 [CI, 2.78 to 3.62]), and absent for NADC not caused by viruses.

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

Conclusion: Antiretroviral therapy resulting in long-term viral suppression may contribute to cancer prevention, to a greater degree for ADC than for NADC. Patients with long-term viral suppression still had excess cancer risk.

Primary Funding Source: National Cancer Institute and National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health.

Ann Intern Med. doi:10.7326/M16-2094 **Annals.org**
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This article was published at Annals.org on 12 June 2018.

Antiretroviral therapy (ART) has been associated with reduced AIDS-related and non–AIDS-related morbidity and mortality in persons living with HIV/AIDS (1–3). Nevertheless, HIV-infected (HIV-positive) persons have higher incidence than the general population of many comorbid conditions (4), including AIDS-defining cancer (ADC; that is, Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer) (5–9) and several types of non–AIDS-defining cancer (NADC) (5–7, 9–14). Oncogenic viruses cause ADC and most types of NADC that are more common among HIV-positive persons. These viruses include Kaposi sarcoma–associated herpesvirus, Epstein–Barr virus (non-Hodgkin and Hodgkin lymphoma), human papillomavirus (invasive cervical cancer, anal squamous cell carcinoma [SCC], genital SCC, and some types of oral cavity and pharynx SCC), and hepatitis B and C viruses (hepatocellular carcinoma) (12). Immunodeficiency induced by HIV and elevated prevalence of traditional cancer risk factors, such as smoking and oncogenic virus co-infections, contribute to this increased 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 RNA [21]), improved immune function (as measured by increasing $CD4^+$ T-cell count), and reduced inflammation (18). Randomized controlled trials that examined 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 few cancer outcomes. Observational studies that examined associations between various cumulative measures of viral suppression and cancer risk have mostly focused on 1 or a few specific cancer types or were limited by few outcomes (24–31), and none specifically focused on the effect of sustained viral suppression.

In a large cohort with ample statistical power, we examined whether long-term viral suppression (as measured by sustained periods with low levels of HIV RNA) was associated with reduced cancer risk among HIV-

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positive persons during the modern ART era. We compared cancer risk among HIV-positive persons, stratified by viral suppression status, with that among demographically similar uninfected persons using the incidence rate ratio (RR), a measure of relative risk. We hypothesized that HIV-positive persons with long-term viral suppression would have lower cancer incidence than HIV-positive persons without such suppression, and thus, the RR comparing HIV-positive versus uninfected persons would be greater in unsuppressed HIV-positive persons than in those with long-term suppression.

METHODS

The VACS (Veterans Aging Cohort Study) is a cohort derived from national Department of Veterans Affairs (VA) databases (including data on demographics, vital status, inpatient and outpatient encounters, pharmacy, and laboratory results) (32). VACS enrolls HIV-positive veterans when they begin HIV care in the VA and matches them to 2 uninfected veterans under VA care at that time by age, sex, race/ethnicity, and clinical site. The matched uninfected veterans are assigned the same entry date as the HIV-positive veteran. Institutional review boards at the VA Connecticut Healthcare System and Yale University approved the VACS.

We linked VACS with the VA Central Cancer Registry and the VA Corporate Data Warehouse oncology registry, 2 national databases of patients with cancer who were diagnosed or treated in the VA. We mapped topography and morphology codes from the International Classification of Diseases for Oncology, Third Edition (33), from these databases to specific cancer types, consistent with SEER (Surveillance, Epidemiology, and End Results) 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 (nonvirus NADC), and poorly specified cancer (**Supplement Table 1**, available at Annals.org). We used morphology and detailed topography to divide oral cavity and pharynx, anal, liver, vagina, vulva, and penis cancer into virus NADC versus nonvirus NADC (for example, SCC of the anus is a virus NADC, whereas other morphologic types of anal cancer are nonvirus NADC) (**Supplement Table 1**).

For each HIV-positive person, we classified each day of observation into 1 of 3 HIV viral suppression categories: unsuppressed, early suppression, and long-term suppression. In the VA, HIV-positive persons have an average of 3 laboratory tests for HIV RNA per year. We used midpoint estimation for HIV RNA levels between test results. We extended each result backward either to the midpoint of the interval between the previous and index test results or to 180 days (about 6 months), whichever was reached first, and forward either to the midpoint of the interval between the index and subsequent test results or to 180 days, whichever was first (**Supplement Figure 1**, available at Annals.org) (35). We classified observation time not covered by these extensions, which occurred when more than 360 days elapsed between laboratory results, as "unknown." Finally, we extended each person's first laboratory result for HIV RNA backward 180 days and last result forward 180 days.

We defined *viral suppression* as an HIV RNA level less than 500 copies/mL. We classified observation time when HIV RNA levels were 500 copies/mL or greater as *unsuppressed*. We defined *early suppression* as the initial period up to 2 years (720 days) of continuous suppressed observation time. We classified subsequent observation time of continuous suppression after the initial 720 days as *long-term suppression*. We allowed 1 blip with an HIV RNA level up to 1000 copies/mL during a period of early or long-term suppression. When an HIV-positive person became unsuppressed after a period of early or long-term suppression and subsequently became suppressed again, the latter suppressed observation time was classified as early suppression during the initial period up to 720 days (that is, the clock was reset to 0 after each unsuppressed episode). Thus, viral suppression status for a given patient varied with time, and observation time could be distributed among each of the viral suppression categories.

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

Statistical Analysis

For each cancer group or type, we used the direct method to calculate incidence rates (IRs) standardized by age, sex, race/ethnicity, and calendar period for each HIV-positive 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, or unknown), and calendar period (1999 to 2003, 2004 to 2007, 2008 to 2011, or 2012 to 2015). We classified age and calendar period at each day of observation (37).

We used Poisson regression to calculate an RR for each HIV-positive 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 use disorder or dependence, hepatitis C virus infection, and diabetes [39]) (**Supplement Table 2**, available at Annals.org). We used multiple imputation to impute values for

patients with unknown race, hepatitis C virus status, or smoking status (Part 1 of the **Supplement**, available at Annals.org). We used models with a log-link function offset by the natural log of observation time (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* for trend), we used a model with viral suppression or HIV status parameterized as a single ordinal variable (unsuppressed, early suppression, long-term suppression, or uninfected), with a binary term for HIV status that effectively removed the uninfected category from the ordinal variable.

In sensitivity analyses, we explored viral suppression thresholds of 50 versus 500 copies/mL; cut points between early and long-term suppression of 1 versus 2 years; stratification by calendar period; and stratification by baseline nadir $CD4^+$ cell count, baseline $CD4^+$–$CD8^+$ cell count ratio, and time-updated $CD4^+$ cell count (lagged by 180 days to guard against reverse causality) (Part 2 of the **Supplement**). We used midpoint estimation to estimate $CD4^+$ cell counts between laboratory test results.

We used SAS, version 9.4 (SAS Institute), for statistical analyses. We defined statistical significance as *P* less than 0.05 (2-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-positive persons, 3821 developed 4169 cases of cancer (616 ADC, 817 virus NADC, 2683 nonvirus NADC, and 53 poorly specified). Among 104 712 uninfected persons, 7163 developed 7879 cases of cancer (223 ADC, 715 virus NADC, 6850 nonvirus NADC, and 91 poorly specified). The median analytic observation time was 7.4 years for HIV-positive persons and 10.1 years for uninfected persons. Of the 343 150 person-years contributed by HIV-positive persons, 22% were classified as unsuppressed, 27% as early suppression, 37% as long-term suppression, and 14% as unknown, with a median of 20 HIV RNA measurements (interquartile range, 8 to 38 measurements) per person from baseline. Uninfected persons contributed 988 403 person-years.

More than half of HIV-positive persons (62%) achieved long-term viral suppression at some point during follow-up (median duration, 3.0 years [interquartile range, 1.1 to 6.1 years]). Uninfected and HIV-positive persons had similar distributions of age, sex (predominantly male), race/ethnicity, smoking status, and alcohol use disorder or dependence status (**Table**). Persons with HIV had a higher prevalence of chronic hepatitis C virus infection (22% vs. 10%) and lower prevalence of diabetes (21% vs. 34%).

We present results for each cancer group and for each cancer type with at least 30 cases in HIV-positive persons. For nonvirus NADC, however, we present results only for cancer types with at least 30 cases and at least 1 category of HIV-positive viral suppression with significantly decreased or increased cancer risk.

All Cancer

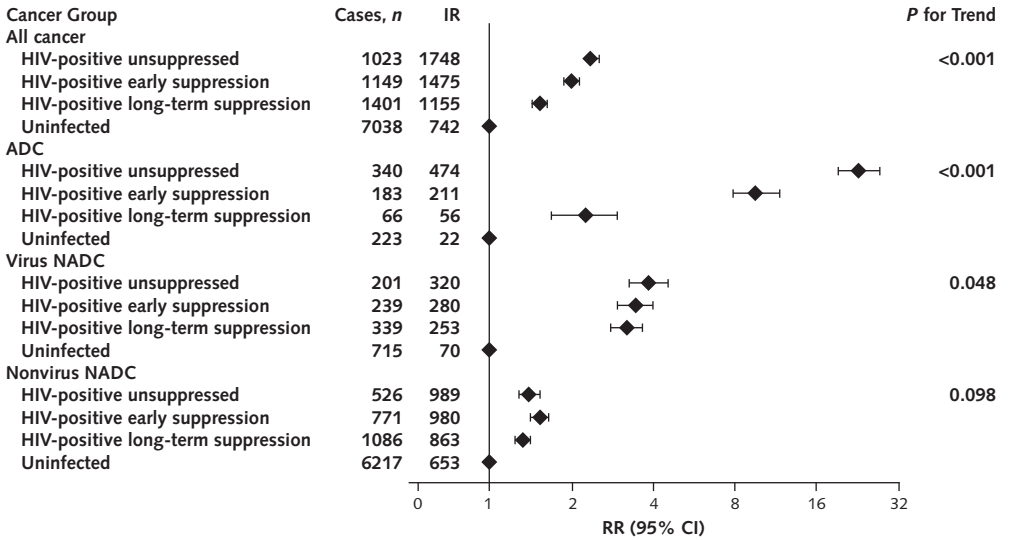
For all cancer, we saw a graded decrease in cancer risk from HIV-positive persons in the unsuppressed state to those with early suppression to those with long-term suppression. The IR decreased from 1748 cases per 100 000 person-years in unsuppressed persons, to 1475 cases per 100 000 person-years in those with early suppression, to 1155 cases per 100 000 person-years in those with long-term suppression, compared with 742 cases per 100 000 person-years among uninfected persons (**Figure 1**). The RR comparing HIV-positive versus

Table. Baseline Characteristics of Patients Who Contributed Observation Time*

Characteristic	HIV-Positive Persons (*n* = 42 441)	Uninfected Persons (*n* = 104 712)
Age		
20–29 y	2577 (6)	5441 (5)
30–39 y	8171 (19)	18 767 (18)
40–49 y	15 992 (38)	39 169 (37)
50–59 y	10 861 (26)	27 524 (26)
60–69 y	4027 (9)	10 822 (10)
≥70 y	813 (2)	2989 (3)
Sex		
Female	1043 (2)	2904 (3)
Male	41 398 (98)	101 808 (97)
Race/ethnicity		
Non-Hispanic white	15 730 (37)	41 428 (40)
Non-Hispanic black	21 673 (51)	49 795 (48)
Hispanic	3406 (8)	8995 (9)
Other	603 (1)	1691 (2)
Unknown	1029 (2)	2803 (3)
Smoking status		
Never	10 853 (26)	29 756 (28)
Ever	28 556 (67)	69 593 (66)
Unknown	3032 (7)	5363 (5)
Alcohol use disorder/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	9343 (22)	10 689 (10)
HCV exposure	2789 (7)	3301 (3)
Never tested in the VA	3241 (8)	26 172 (25)
Diabetes		
No	33 622 (79)	69 197 (66)
Yes	8819 (21)	35 515 (34)

HCV = hepatitis C virus; VA = Department of Veterans Affairs.
* Values are numbers (percentages).
† HCV negative indicates negative HCV antibody test result(s) only, chronic HCV indicates positive HCV RNA test result(s), HCV exposure indicates positive HCV antibody test result(s) but no positive HCV RNA test result(s), and never tested in the VA indicates no HCV laboratory test results available from the VA (some of these patients may have been tested for HCV outside the VA).

Figure 1. Numbers of cancer cases, IRs (per 100 000 person-years), multivariate Poisson regression RRs with 95% CIs by HIV viral suppression status, and *P* values for HIV-positive IR viral suppression trend, for cancer groups.



IRs were standardized by age, sex, race/ethnicity, and calendar period, and RRs were adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol use disorder or dependence, hepatitis C virus infection, and diabetes. The end point for a given patient was the first diagnosis of a cancer type classified in the group. For example, if a person had both non-Hodgkin lymphoma and Kaposi sarcoma, only the first of the 2 diagnoses would contribute to the ADC analysis. ADC = AIDS-defining cancer; IR = standardized incidence rate; nonvirus NADC = non–virus-related non–AIDS-defining cancer; RR = adjusted incidence rate ratio; virus NADC = virus-related non–AIDS-defining cancer.

uninfected persons (adjusted for demographics and cancer risk factors) was highest for unsuppressed persons (RR, 2.35 [95% CI, 2.19 to 2.51]), then those with early suppression (RR, 1.99 [CI, 1.87 to 2.12]), then those with long-term suppression (RR, 1.52 [CI, 1.44 to 1.61]). Of note, the RR remained elevated in persons with long-term suppression.

ADC

Viral suppression IRs decreased sharply for ADC from 474 cases per 100 000 person-years in unsuppressed persons, to 211 cases per 100 000 person-years in those with early suppression, to 56 cases per 100 000 person-years in those with long-term suppression, compared with 22 cases per 100 000 person-years among uninfected persons (**Figure 1**). The RR comparing HIV-positive versus uninfected persons was highest for unsuppressed persons (RR, 22.73 [CI, 19.01 to 27.19]), then those with early suppression (RR, 9.48 [CI, 7.78 to 11.55]), then those with long-term suppression (RR, 2.22 [CI, 1.69 to 2.93]). Even among persons with long-term suppression, 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)]; 65% of this reduction [(22.73 − 9.48)/(22.73 − 2.22)] occurred during early suppression. Patterns were similar for the 2 main ADCs, non-Hodgkin lymphoma and Kaposi sarcoma (**Figure 2**).

Virus NADC

Viral suppression IRs decreased weakly for virus NADC from 320 cases per 100 000 person-years in unsuppressed persons, to 280 cases per 100 000 person-years in those with early suppression, to 253 cases per 100 000 person-years in those with long-term suppression, compared with 70 cases per 100 000 person-years among uninfected persons (**Figure 1**). The RR comparing HIV-positive versus uninfected persons was highest for unsuppressed persons (RR, 3.82 [CI, 3.24 to 4.49]), then those with early suppression (RR, 3.42 [CI, 2.95 to 3.97]), then those with long-term suppression (RR, 3.17 [CI, 2.78 to 3.62]). Even among persons with long-term suppression, the RR remained substantially elevated. Long-term suppression was associated with a 23% reduction in excess risk for virus NADC [(3.82 − 3.17)/(3.82 − 1.00)]; 62% of this reduction [(3.82 − 3.42)/(3.82 − 3.17)] occurred during early suppression. The only cancer type to exhibit a significant decreasing trend in viral suppression IRs was anal SCC (*P* for trend = 0.014) (**Figure 3**). However, the RR remained markedly elevated in patients with long-term suppression (RR, 34.70 [CI, 22.63 to 53.20]).

Nonvirus NADC

For nonvirus NADC, the IR remained essentially the same in unsuppressed persons (989 cases per 100 000 person-years) and those with early suppression (980 cases per 100 000 person-years) and then decreased to 863 cases per 100 000 person-years in those with long-term suppression, compared with 653 cases per 100 000 person-years among uninfected persons (**Figure 1**). After adjustment for demographics and cancer risk factors, the RRs comparing HIV-positive versus uninfected persons did not show a trend, with RRs of 1.40 (CI, 1.28 to 1.53) for unsuppressed patients, 1.53 (CI,

1.42 to 1.65) for patients with early suppression, and 1.32 (CI, 1.24 to 1.41) for those with long-term suppression. Although RRs were substantially lower for nonvirus NADC than for ADC or virus NADC, the RRs for nonvirus NADC were elevated, even among patients with long-term suppression.

Viral suppression IRs decreased from unsuppressed patients to those with early suppression to those with long-term suppression for lung cancer (*P* for trend = 0.003), larynx cancer (*P* for trend = 0.007), melanoma of the skin (*P* for trend = 0.008), and leukemia (*P* for trend < 0.001) (**Figure 4**). Risk was not significantly elevated among persons with long-term suppression for the latter 3 cancer types. Prostate cancer was the only type with an increasing trend in viral suppression IRs (*P* for trend < 0.001). The prostate cancer RR was 0.79 (CI, 0.65 to 0.95) for unsuppressed persons but was elevated for those with early suppression (RR, 1.18 [CI, 1.03 to 1.35]) and long-term suppression (RR, 1.22 [CI, 1.10 to 1.35]).

Sensitivity Analyses

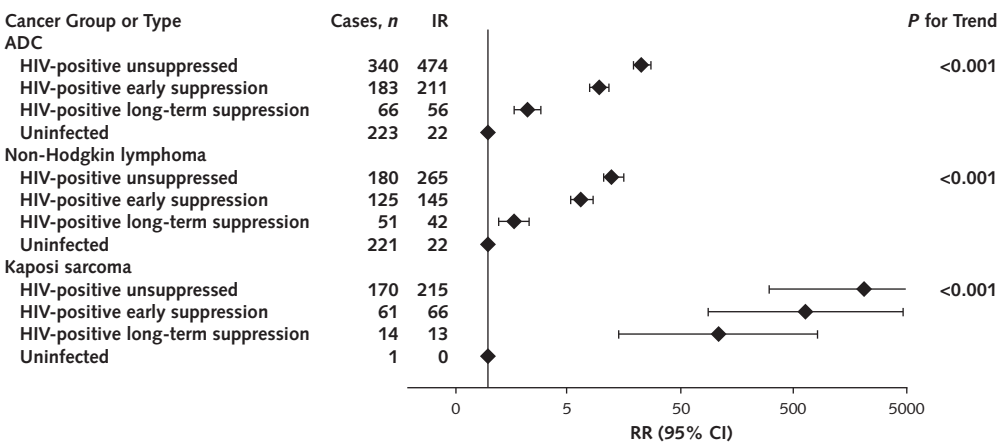
Viral suppression IR trends were similar using viral suppression thresholds of 50 versus 500 copies/mL (**Supplement Figure 2**, available at Annals.org) and using cut points for early versus long-term suppression of 1 versus 2 years (**Supplement Figure 3**, available at Annals.org). Trends did not meaningfully differ by calendar period, except for ADC, for which the trend was weaker in 1999 to 2003 than in later periods (**Supplement Tables 3** and **4**, available at Annals.org). In models for all cancer stratified by baseline nadir $CD4^+$ cell count, viral suppression IRs decreased from unsuppressed patients to those with early suppression to those with long-term suppression in all strata (**Supplement Figure 4**, available at Annals.org). In models for all cancer stratified by baseline $CD4^+$–$CD8^+$ cell count ratio, viral suppression IRs decreased within the lower 2 categories of $CD4^+$–$CD8^+$ cell count ratio (*P* for trend < 0.001) but not within the highest category of 1.0 or greater (**Supplement Figure 5**, available at Annals.org), which included only 8% of all HIV-positive patients with cancer. In models stratified by time-updated $CD4^+$ cell count, viral suppression IRs decreased within each $CD4^+$ cell count stratum for all cancer and ADC but not for virus NADC or nonvirus NADC (**Supplement Figure 6**, available at Annals.org). Furthermore, RRs increased with decreasing $CD4^+$ cell count.

DISCUSSION

In a large cohort of HIV-positive and demographically similar uninfected patients, we comprehensively examined whether long-term viral suppression, the primary objective of ART in HIV-positive persons, was associated with decreased cancer risk. We observed strong trends of decreasing risk across our 3 viral suppression groups (unsuppressed, early suppression, and long-term suppression) for all cancer and ADC, a much weaker trend for virus NADC, and no trend for nonvirus NADC.

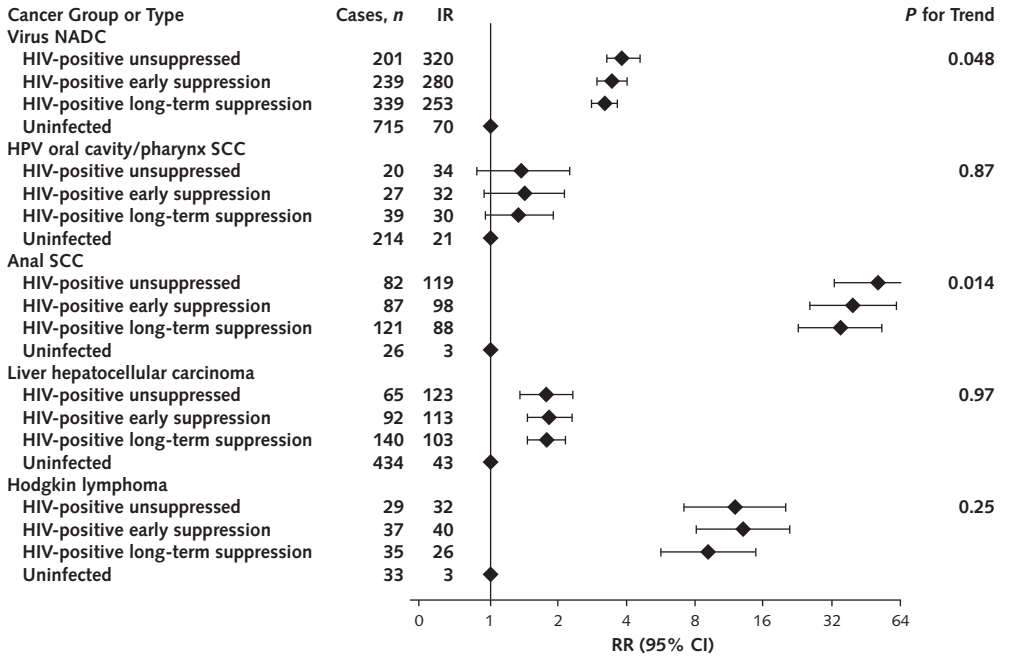
Long-term suppression was associated with a reduction in excess risk of more than 90% for ADC but only 23% for virus NADC. For both of these cancer groups, about three fifths of the risk reduction occurred during early suppression. For ADC, virus NADC, and nonvirus NADC, even long-term suppression did not reduce cancer risk to that among uninfected persons, which indicates ongoing deleterious effects of HIV in-

Figure 2. Numbers of cancer cases, IRs (per 100 000 person-years), multivariate Poisson regression RRs with 95% CIs by HIV viral suppression status, and *P* values for HIV-positive IR viral suppression trend, for ADC.



IRs were standardized by age, sex, race/ethnicity, and calendar period, and RRs were adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol use disorder or dependence, hepatitis C virus infection, and diabetes. For ADC, the end point for a given patient was the first diagnosis of a cancer type classified as ADC, but for an individual cancer type, the end point was the first diagnosis of that cancer type. For example, if a person had both non-Hodgkin lymphoma and Kaposi sarcoma, only the first of the 2 diagnoses would contribute to the ADC analysis, but each diagnosis would contribute to the analysis of non-Hodgkin lymphoma or Kaposi sarcoma, respectively. Because <30 HIV-positive patients had invasive cervical cancer (*n* = 1), it was not included in the figure but was included in the ADC analysis. ADC = AIDS-defining cancer; IR = standardized incidence rate; RR = adjusted incidence rate ratio.

Figure 3. Numbers of cancer cases, IRs (per 100 000 person-years), multivariate Poisson regression RRs with 95% CIs by HIV viral suppression status, and *P* values for HIV-positive IR viral suppression trend, for virus NADC.



IRs were standardized by age, sex, race/ethnicity, and calendar period, and RRs were adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol use disorder or dependence, hepatitis C virus infection, and diabetes. For virus NADC, the end point for a given patient was the first diagnosis of a cancer type classified as virus NADC, but for an individual cancer type, the end point was the first diagnosis of that cancer type. For example, if a person had both Hodgkin lymphoma and anal SCC, only the first of the 2 diagnoses would contribute to the virus NADC analysis, but each diagnosis would contribute to the analysis of Hodgkin lymphoma or anal SCC, respectively. Because <30 HIV-positive patients had penis SCC (n = 17), it was not included in the figure but was included in the virus NADC analysis. No HIV-positive patients had vagina SCC or vulva SCC. HPV = human papillomavirus; IR = standardized incidence rate; RR = adjusted incidence rate ratio; SCC = squamous cell carcinoma; virus NADC = virus-related non–AIDS-defining cancer.

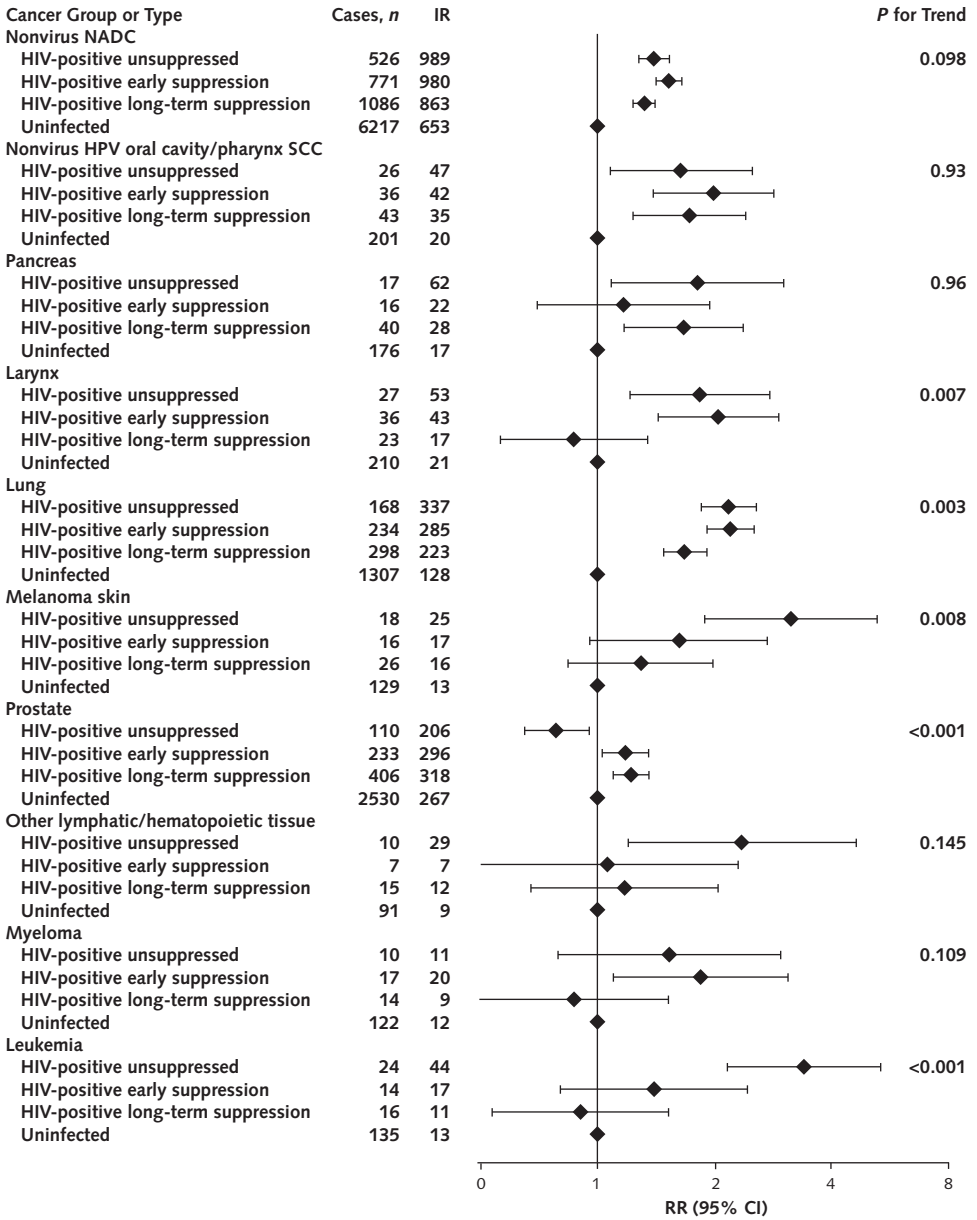
fection in the presence of long-term ART, such as HIV-induced inflammation or immune senescence (12, 18, 20). Nevertheless, our findings suggest that early, sustained ART, which results in long-term viral suppression, prevents cancer, with a marked reduction in ADC risk and a meaningful (but much less pronounced) reduction in virus NADC risk.

Nonvirus NADC is a heterogeneous group of cancer types. Although we did not observe an overall trend in viral suppression IRs, we did observe trends for larynx cancer, lung cancer, melanoma, and leukemia. Thus, long-term suppression may contribute to prevention of these specific cancer types as well.

In the SMART (Strategies for Management of Antiretroviral Therapy) trial (71 cancer cases) (**Supplement Table 5**, available at Annals.org), continuous ART versus treatment interruption was associated with a significantly decreased risk for ADC, but not NADC (22). In the START (Strategic Timing of Antiretroviral Treatment) trial (52 cancer cases), among persons with $CD4^+$ counts greater than 0.500×10^9 cells/L, immediate versus deferred ART initiation was associated with significantly decreased risk for 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 risk for ADC (24), non-Hodgkin lymphoma (24–26), Kaposi sarcoma (27), and anal cancer (28–30), but not liver cancer (30, 31). 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 those of previous observational studies because of 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, but such a mechanism is of considerable interest. An independent inverse association between $CD4^+$ cell count and ADC risk is well-established (12). Evidence also suggests weaker, subtler inverse associations between $CD4^+$ cell count and specific NADC types, especially those caused by viruses (12, 18). Furthermore, because $CD4^+$ cell count is correlated with long-term levels of HIV RNA (41, 42), it might confound and likely mediates the association between viral suppression status and cancer risk. When we stratified by $CD4^+$ cell count, viral suppression IRs still decreased from unsuppressed patients to those with early suppression to those with long-term suppression for all cancer and ADC within each $CD4^+$ cell count

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



IRs were standardized by age, sex, race/ethnicity, and calendar period, and RRs were adjusted for time-updated age, sex, race/ethnicity, time-updated calendar period, smoking, alcohol use disorder or dependence, hepatitis C virus infection, and diabetes. For nonvirus NADC, the end point for a given patient was the first diagnosis of a cancer type classified as nonvirus NADC, but for an individual cancer type, the end point was the first diagnosis of that cancer type. For example, if a person had both lung cancer and prostate cancer, only the first of the 2 diagnoses would contribute to the virus NADC analysis, but each diagnosis would contribute to the analysis of lung cancer or prostate cancer, respectively. The following cancer types with <30 diagnoses among HIV-positive patients were not included in the figure but were included in the nonvirus NADC analysis: oral cavity and pharynx non-SCC (n = 9); small intestine (n = 4); anal nonSCC (n = 5); liver nonhepatocellular carcinoma (n = 12); biliary tract (n = 16); retroperitoneum and peritoneum, nonmesothelioma (n = 1); other digestive organs (n = 3); nose, nasal cavity, and middle ear (n = 12); pleura (n = 2); trachea, mediastinum, and other respiratory organs (n = 1); bone and joint (n = 2); soft issue, including heart (n = 21); nonepithelial skin (n = 9); female breast (n = 10); male breast (n = 5); testis (n = 10); other male genital organs (n = 4); other urinary organs (n = 6); eye and orbit (n = 3); brain and nervous system (n = 9); thyroid (n = 25); other endocrine, including thymus (n = 1); and mesothelioma (n = 4). The following cancer types did not have any HIV-positive viral suppression categories with significantly elevated cancer risk and were not included in the figure, but were included in the nonvirus NADC analysis: esophagus (n = 51), stomach (n = 32), colorectal (n = 155), urinary bladder (n = 62), and kidney and renal pelvis (n = 115). No HIV-positive patients had corpus or uterine cancer, ovarian cancer, vagina nonSCC, vulva nonSCC, cancer of other female genital organs, or penis nonSCC. We used sex-specific weights to calculate prostate cancer IRs. HPV = human papillomavirus; IR = standardized incidence rate; nonvirus NADC = non–virus-related non–AIDS-defining cancer; RR = adjusted incidence rate ratio; SCC = squamous cell carcinoma.

stratum, but not for virus NADC. However, these results are difficult to interpret because statistical power is reduced within strata and because distinguishing between confounding and mediation is challenging. Beneficial effects of viral suppression on cancer risk over and above its effect on $CD4^+$ cell 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 is commonly diagnosed in an asymptomatic phase by prostate-specific antigen screening and was the only cancer type with higher incidence in virally suppressed than unsuppressed persons. Prior meta-analyses, which included studies from the pre-ART era, reported a 30% decreased risk for prostate cancer in HIV-positive men compared with the general population (13, 51), consistent with our finding of a 20% decreased risk among unsuppressed versus uninfected men. Because persons with a short life expectancy and many comorbid conditions, such as HIV-positive patients in the pre-ART era, may be less likely to be screened, this decreased risk might be due to a lower rate of screening among HIV-positive men (13, 52–55). With the advent of ART and the resultant dramatic increase in life expectancy among virally suppressed persons, screening rates may have increased in this group, explaining our results. However, 1 study found that screening differences could not explain the lower risk for prostate cancer in HIV-positive than uninfected men during the ART era (53).

A major strength of this investigation was the use of a large national cohort of HIV-positive and demographically similar uninfected persons followed over 16 years in the modern ART era, which gave us sufficient cancer events to comprehensively explore the relationship between viral suppression and cancer risk. A limitation was the estimation of time-updated levels of HIV RNA, which required assumptions about how these levels change between laboratory result dates. Furthermore, because VA sites adopted progressively more sensitive assays for HIV RNA over time, we had to define viral suppression using a high threshold (500 copies/mL) to encompass the entire 1999–2015 period in our analysis. Our investigation assessed the relationship between current viral suppression status and cancer risk and thus did not account for each patient's entire history of viral suppression status. Prior studies used various cumulative measures of viral suppression but did not take uninterrupted suppression into account. Selection bias is also possible due to exclusion of HIV-positive observation time with unknown viral suppression status. Because the VACS cohort is predominantly male, we were underpowered to generalize our results to women; in particular, we observed only 1 case of invasive cervical cancer. Finally, despite the large number of statistical tests, we did not adjust for multiple comparisons.

Using a large cohort of HIV-positive veterans, we classified observation time by viral suppression status and calculated cancer risk compared with demographically similar uninfected veterans. Cancer risk was highest in the unsuppressed state, lower in early suppression, lower still in long-term suppression, and lowest in uninfected patients for all cancer, ADC, virus NADC, and several cancer types. Our findings suggest that early, 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 reduction for virus NADC, and possible reductions for certain types of nonvirus NADC. However, excess cancer risk remained among patients with long-term suppression. Future research should extend our sensitivity analyses to examine in more detail viral suppression thresholds less than 500 copies/mL, whether cancer risk continues to decrease with longer durations of long-term suppression, and the role of $CD4^+$ cell count and $CD4^+$–$CD8^+$ cell count ratio.

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Acknowledgment: The authors thank the VA Central Cancer Registry for linking the VACS with the Registry database and providing a data set containing the linked records; this study would not have been possible without its generous assistance. They also thank Dr. Margaret May for her biostatistical consulting and advice and the reviewers and editors who have contributed significantly with their thoughtful questions and critiques; the peer-review process has been valuable in the preparation of this work.

Financial Support: By the VA and by grants U01-AA020790, U24-AA020794, and U10-AA013566 from the National Institute on Alcohol Abuse and Alcoholism; T32-MH020031 and P30-MH062294 from the National Institute of Mental Health; U01-A1069918 from the National Institute of Allergy and Infectious Diseases; F31-CA180775, R01-CA165937, and R01-CA173754 from the National Cancer Institute; and 3T32-DK007217 from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH).

Disclosures: Dr. Park reports grants from the National Cancer Institute, National Institute of Diabetes and Digestive and Kid-

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Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Park (e-mail, lesley.park@stanford.edu). *Data set:* The analytic data sets used are not permitted to leave VA premises. This limitation is consistent with the authors' past work and with other studies based on VA data.

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References

1. **Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, et al; CASCADE Collaboration.** Changes in the risk of death after HIV seroconversion compared with mortality in the general population. JAMA. 2008;300:51-9. [PMID: 18594040] doi:10.1001/jama.300.1.51

2. **Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al; EuroSIDA study group.** Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003;362:22-9. [PMID: 12853195]

3. **Moore RD, Gebo KA, Lucas GM, Keruly JC.** Rate of comorbidities not related to HIV infection or AIDS among HIV-infected patients, by CD4 cell count and HAART use status. Clin Infect Dis. 2008;47:1102-4. [PMID: 18781885] doi:10.1086/592115

4. **Deeks SG, Phillips AN.** HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ. 2009;338:a3172. [PMID: 19171560] doi:10.1136/bmj.a3172

5. **Park LS, Tate JP, Sigel K, Rimland D, Crothers K, Gibert C, et al.** Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997-2012. AIDS. 2016;30:1795-806. [PMID: 27064994] doi:10.1097/QAD.0000000000001112

6. **Silverberg MJ, Chao C, Leyden WA, Xu L, Tang B, Horberg MA, et al.** HIV infection and the risk of cancers with and without a known infectious cause. AIDS. 2009;23:2337-45. [PMID: 19741479] doi:10.1097/QAD.0b013e3283319184

7. **Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al; Swiss HIV Cohort Study.** Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer. 2010;103:416-22. [PMID: 20588274] doi:10.1038/sj.bjc.6605756

8. **Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, et al; French Hospital Database on HIV–ANRS CO4 Cohort.** Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. Clin Infect Dis. 2013;57:1638-47. [PMID: 23899679] doi:10.1093/cid/cit497

9. **Silverberg MJ, Lau B, Achenbach CJ, Jing Y, Althoff KN, D'Souza G, et al; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS.** Cumulative incidence of cancer among persons with HIV in North America: a cohort study. Ann Intern Med. 2015;163:507-18. [PMID: 26436616] doi:10.7326/M14-2768

10. **Park LS, Tate JP, Rodriguez-Barradas MC, Rimland D, Goetz MB, Gibert C, et al.** Cancer incidence in HIV-infected versus uninfected veterans: comparison of cancer registry and ICD-9 code diagnoses. J AIDS Clin Res. 2014;5:1000318. [PMID: 25580366]

11. **Calabresi A, Ferraresi A, Festa A, Scarcella C, Donato F, Vassallo F, et al; Brescia HIV Cancer Study Group.** Incidence of AIDS-defining cancers and virus-related and non-virus-related non-AIDS-defining cancers among HIV-infected patients compared with the general population in a large health district of Northern Italy, 1999-2009. HIV Med. 2013;14:481-90. [PMID: 23560682] doi:10.1111/hiv.12034

12. **Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC.** HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol. 2012;24:506-16. [PMID: 22759737]

13. **Shiels MS, Cole SR, Kirk GD, Poole C.** A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009;52:611-22. [PMID: 19770804] doi:10.1097/QAI.0b013e3181b327ca

14. **Simard EP, Pfeiffer RM, Engels EA.** Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med. 2010;170:1337-45. [PMID: 20696958] doi:10.1001/archinternmed.2010.253

15. **Park LS, Hernández-Ramírez RU, Silverberg MJ, Crothers K, Dubrow R.** Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. AIDS. 2016;30:273-91. [PMID: 26691548] doi:10.1097/QAD.0000000000000922

16. **Grulich AE, Jin F, Poynten IM, Vajdic CM.** HIV, cancer, and aging. Sex Health. 2011;8:521-5. [PMID: 22127038] doi:10.1071/SH11048

17. **Engels EA.** Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities [Editorial]. AIDS. 2009;23:875-85. [PMID: 19349851] doi:10.1097/QAD.0b013e328329216a

18. **Borges AH, Dubrow R, Silverberg MJ.** Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk. Curr Opin HIV AIDS. 2014;9:34-40. [PMID: 24225382] doi:10.1097/COH.0000000000000025

19. **Rubinstein PG, Aboulafia DM, Zloza A.** Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges [Editorial]. AIDS. 2014;28:453-65. [PMID: 24401642] doi:10.1097/QAD.0000000000000071

20. **Borges ÁH, Silverberg MJ, Wentworth D, Grulich AE, Fätkenheuer G, Mitsuyasu R, et al; INSIGHT SMART.** Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers. AIDS. 2013;27:1433-41. [PMID: 23945504] doi:10.1097/QAD.0b013e32835f6b0c

21. **Volberding PA, Deeks SG.** Antiretroviral therapy and management of HIV infection. Lancet. 2010;376:49-62. [PMID: 20609987] doi:10.1016/S0140-6736(10)60676-9

22. **Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, et al.** Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS. 2007;21:1957-63. [PMID: 17721103]

23. **Borges ÁH, Neuhaus J, Babiker AG, Henry K, Jain MK, Palfreeman A, et al; INSIGHT START Study Group.** Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection. Clin Infect Dis. 2016;63:1668-76. [PMID: 27609756]

24. **Bruyand M, Thiébaut R, Lawson-Ayayi S, Joly P, Sasco AJ, Mercié P, et al; Groupe d'Epidémiologie Clinique du SIDA en Aquitaine (GECSA).** Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recher-

che sur le Sida (ANRS) CO3 Aquitaine Cohort. Clin Infect Dis. 2009; 49:1109-16. [PMID: 19705973] doi:10.1086/605594
25. **Engels EA, Pfeiffer RM, Landgren O, Moore RD.** Immunologic and virologic predictors of AIDS-related non-Hodgkin lymphoma in the highly active antiretroviral therapy era. J Acquir Immune Defic Syndr. 2010;54:78-84. [PMID: 20418723] doi:10.1097/01.qai.0000371677.48743.8d
26. **Zoufaly A, Stellbrink HJ, Heiden MA, Kollan C, Hoffmann C, van Lunzen J, et al; ClinSurv Study Group.** Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. J Infect Dis. 2009;200:79-87. [PMID: 19476437] doi:10.1086/599313
27. **Dubrow R, Qin L, Lin H, Hernández-Ramírez RU, Neugebauer RS, Leyden W, et al; North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS.** Association of CD4+ T-cell count, HIV-1 RNA viral load, and antiretroviral therapy with Kaposi sarcoma risk among HIV-infected persons in the United States and Canada. J Acquir Immune Defic Syndr. 2017;75:382-90. [PMID: 28394855] doi:10.1097/QAI.0000000000001394
28. **Chiao EY, Hartman CM, El-Serag HB, Giordano TP.** The impact of HIV viral control on the incidence of HIV-associated anal cancer. J Acquir Immune Defic Syndr. 2013;63:631-8. [PMID: 23614995] doi:10.1097/QAI.0b013e3182968fa7
29. **Guiguet M, Boué F, Cadranel J, Lang JM, Rosenthal E, Costagliola D; Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort.** Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009;10:1152-9. [PMID: 19818686] doi:10.1016/S1470-2045(09)70282-7
30. **Kowalkowski MA, Day RS, Du XL, Chan W, Chiao EY.** Cumulative HIV viremia and non-AIDS-defining malignancies among a sample of HIV-infected male veterans. J Acquir Immune Defic Syndr. 2014;67:204-11. [PMID: 25078536] doi:10.1097/QAI.0000000000000289
31. **Kramer JR, Kowalkowski MA, Duan Z, Chiao EY.** The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection. J Acquir Immune Defic Syndr. 2015;68:456-62. [PMID: 25559606] doi:10.1097/QAI.0000000000000494
32. **Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, et al.** Development and verification of a "virtual" cohort using the National VA Health Information System. Med Care. 2006;44:S25-30. [PMID: 16849965]
33. **Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al, eds.** International Classification of Diseases for Oncology. 3rd ed. Geneva: World Health Organization; 2000.
34. **National Cancer Institute.** Surveillance, Epidemiology, and End Results Program: Site Recode ICD-O-3/WHO 2008 Definition. Accessed at http://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html on 2 February 2018.
35. **Kranzer K, Lewis JJ, White RG, Glynn JR, Lawn SD, Middelkoop K, et al.** Antiretroviral treatment cohort analysis using time-updated CD4 counts: assessment of bias with different analytic methods. PLoS One. 2011;6:e27763. [PMID: 22114687] doi:10.1371/journal.pone.0027763
36. **Boyle P, Parkin DM.** Cancer registration: principles and methods. Statistical methods for registries. IARC Sci Publ. 1991:126-58. [PMID: 1894318]
37. **Wood J, Richardson D, Wing S.** A simple program to create exact person-time data in cohort analyses. Int J Epidemiol. 1997;26:395-9. [PMID: 9169176]
38. **McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, et al.** Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. Nicotine Tob Res. 2011;13:1233-9. [PMID: 21911825] doi:10.1093/ntr/ntr206
39. **Butt AA, McGinnis K, Rodriguez-Barradas MC, Crystal S, Simberkoff M, Goetz MB, et al; Veterans Aging Cohort Study.** HIV infection and the risk of diabetes mellitus. AIDS. 2009;23:1227-34. [PMID: 19444074] doi:10.1097/QAD.0b013e32832bd7af
40. **Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al; INSIGHT START Study Group.** Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373:795-807. [PMID: 26192873] doi:10.1056/NEJMoa1506816
41. **Wright ST, Petoumenos K, Boyd M, Carr A, Downing S, O'Connor CC, et al; Australian HIV Observational Database study group.** Ageing and long-term CD4 cell count trends in HIV-positive patients with 5 years or more combination antiretroviral therapy experience. HIV Med. 2013;14:208-16. [PMID: 23036045] doi:10.1111/j.1468-1293.2012.01053.x
42. **Mocroft A, Phillips AN, Ledergerber B, Smith C, Bogner JR, Lacombe K, et al; EuroSIDA Study Group.** Estimated average annual rate of change of CD4(+) T-cell counts in patients on combination antiretroviral therapy. Antivir Ther. 2010;15:563-70. [PMID: 20587849] doi:10.3851/IMP1559
43. **Altavilla G, Caputo A, Lanfredi M, Piola C, Barbanti-Brodano G, Corallini A.** Enhancement of chemical hepatocarcinogenesis by the HIV-1 *tat* gene. Am J Pathol. 2000;157:1081-9. [PMID: 11021811]
44. **Amini S, Khalili K, Sawaya BE.** Effect of HIV-1 Vpr on cell cycle regulators. DNA Cell Biol. 2004;23:249-60. [PMID: 15142382]
45. **Corallini A, Campioni D, Rossi C, Albini A, Possati L, Rusnati M, et al.** Promotion of tumour metastases and induction of angiogenesis by native HIV-1 Tat protein from BK virus/tat transgenic mice. AIDS. 1996;10:701-10. [PMID: 8805860]
46. **Harrod R, Nacsa J, Van Lint C, Hansen J, Karpova T, McNally J, et al.** Human immunodeficiency virus type-1 Tat/co-activator acetyltransferase interactions inhibit p53Lys-320 acetylation and p53-responsive transcription. J Biol Chem. 2003;278:12310-8. [PMID: 12501250]
47. **Nunnari G, Smith JA, Daniel R.** HIV-1 Tat and AIDS-associated cancer: targeting the cellular anti-cancer barrier? J Exp Clin Cancer Res. 2008;27:3. [PMID: 18577246] doi:10.1186/1756-9966-27-3
48. **Vogel J, Cepeda M, Enk A, Ngo L, Jay G.** The HIV tat gene is a promoter of epidermal skin tumors. Int J Oncol. 1995;7:727-33. [PMID: 21552895]
49. **Wang X, Singh S, Jung HY, Yang G, Jun S, Sastry KJ, et al.** HIV-1 Vpr protein inhibits telomerase activity via the EDD-DDB1-VPRBP E3 ligase complex. J Biol Chem. 2013;288:15474-80. [PMID: 23612978] doi:10.1074/jbc.M112.416735
50. **Zhou F, Xue M, Qin D, Zhu X, Wang C, Zhu J, et al.** HIV-1 Tat promotes Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6-induced angiogenesis and tumorigenesis by regulating PI3K/PTEN/AKT/GSK-3β signaling pathway. PLoS One. 2013;8:e53145. [PMID: 23301033] doi:10.1371/journal.pone.0053145
51. **Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM.** Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370:59-67. [PMID: 17617273]
52. **Biggar RJ, Kirby KA, Atkinson J, McNeel TS, Engels E; AIDS Cancer Match Study Group.** Cancer risk in elderly persons with HIV/AIDS. J Acquir Immune Defic Syndr. 2004;36:861-8. [PMID: 15213571]
53. **Marcus JL, Chao CR, Leyden WA, Xu L, Klein DB, Horberg MA, et al.** Prostate cancer incidence and prostate-specific antigen testing among HIV-positive and HIV-negative men. J Acquir Immune Defic Syndr. 2014;66:495-502. [PMID: 24820107] doi:10.1097/QAI.0000000000000202
54. **Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al; Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators.** Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148:728-36. [PMID: 18490686]
55. **Shiels MS, Goedert JJ, Moore RD, Platz EA, Engels EA.** Reduced risk of prostate cancer in U.S. men with AIDS. Cancer Epidemiol Biomarkers Prev. 2010;19:2910-5. [PMID: 20837717] doi:10.1158/1055-9965.EPI-10-0741

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