*Clinical Infectious Diseases*

MAJOR ARTICLE

# Risk of Cancer in People With Human Immunodeficiency Virus Experiencing Varying Degrees of Immune Recovery With Sustained Virological Suppression on Antiretroviral Treatment for More Than 2 Years: An International, Multicenter, Observational Cohort

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***Background.*** The impact of long-term virological suppression (VS) and CD4 count recovery on non–AIDS-defining cancers (NADCs) is unclear. We determined whether poor immune recovery was associated with incident cancer risk in people with human immunodeficiency virus (HIV) with VS.

***Methods.*** Participants from the Data-Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) and International Cohort Consortium of Infectious Disease (RESPOND) collaborations in Europe and Australia who achieved ≥2 years of VS on antiretroviral therapy (ART) between December 1999 and December 2022 were included. Follow-up was from baseline (date of VS for 2 years) until the earliest of a first cancer event, virological failure, final follow-up, or administrative censoring date. Multivariable Poisson regression was used to assess associations between cancer incidence (overall, AIDS-defining cancer, NADC, infection-related cancer, infection-unrelated cancer) and time-updated CD4 count stratified by pre-ART nadir CD4 counts.

***Results.*** Overall, 48 343 people with VS were included (median [interquartile range] baseline age, 43 years [37–50]; CD4 count, 540 cells/μL [380–730]; nadir CD4 count, 245 cells/μL [121–394]; 74% male). There were 1933 incident cancers (median follow-up, 6.2 years [2.9–9.5]; incidence rate [IR], 6.43; 95% confidence interval [CI]: 6.15–6.73/1000 person-years). Higher time-updated CD4 count was associated with a reduced risk of overall cancer (adjusted incidence rate ratio for time-updated CD4 count 350–499 cells/μL: 0.45 [95% CI: 0.39–0.51]; 500–749 cells/μL: 0.30 [95% CI: 0.27–0.34]; and ≥750 cells/μL: 0.26 [95% CI: 0.23–0.30] vs <350 cells/μL; $P < .0001$). There was a significant reduction in all cancer risk by higher time-updated CD4 count, regardless of nadir CD4 count, with higher pre-ART nadir CD4 count exhibiting lower risk.

***Conclusions.*** Despite VS on ART for more than 2 years, people with poorer immune recovery experienced a significantly higher incidence of cancer. This highlights the importance of early HIV diagnosis and ART initiation, and appropriate cancer screening strategies for those with poor immune recovery.

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The landscape of morbidity and mortality has evolved in people with human immunodeficiency virus (HIV), shifting from opportunistic infections and cancer associated with immunodeficiency to age-associated conditions such as cardiovascular disease and non–AIDS-defining cancers (NADCs) [1–3]. Many age-associated conditions are associated with immune dysregulation of aging, persistent immune activation and inflammation [4]. This phenomenon is observed in people with HIV who are virologically suppressed on antiretroviral therapy (ART). While the risk of AIDS-defining cancer (ADC) falls with higher CD4 counts, the association with NADC incidence is less clear, especially once individuals have achieved virological suppression (VS) [5, 6]. Persistent immunosuppression (CD4 count <200 cells/μL) is associated with increased long-term mortality and NADC mortality [7], while reduced mortality rates are observed in those with CD4 counts >500 cells/μL [8].

Previous studies have shown that either lack of HIV VS or failure to restore CD4 counts is associated with increased risks of infection-related and infection-unrelated cancers [9, 10]. A low CD4:CD8 ratio, an indicator of immune senescence and activation, has been associated with ADC, NADC, and certain cancers [11, 12]. However, these studies generally included individuals regardless of VS and examined the association between viral load or CD4 counts with cancer risk separately. It is unknown whether incomplete CD4 count recovery with sustained VS is associated with increased risk of NADC.

Using data from the combined RESPOND and D:A:D cohorts with large numbers of people and long-tern follow-up, we assessed whether poor immune recovery despite VS is an independent predictor of incident cancers.

## METHODS

### Study Design

The D:A:D and RESPOND cohorts are prospective, multicohort collaborations from across Europe and Australia that comprise approximately 49 000 people with HIV from 11 cohorts in D:A:D (1999–2016) and 35 000 people with HIV from 17 cohorts in RESPOND (2017 to the present). Data from both cohort studies were merged, with some participants being part of and providing data to both collaborations. For individuals enrolled in both collaborations, data from the D:A:D study were used until the baseline date of rollover into the RESPOND study, after which data were used from RESPOND. Full details of both studies have been published [13, 14]. In both studies, cancer events are documented using study-specific case report forms; prospective events are centrally validated against predefined algorithms by study clinicians at the coordinating center and reviewed by an external oncologist [15].

### Study Population

We included all participants aged ≥18 years with a CD4 count and viral load (VL) available from 1 year prior to and 12 weeks after D:A:D/RESPOND cohort entry (Supplementary Figure 1, exclusion box 1) prior to assessment of eligibility for this study. We excluded participants with no VL after cohort entry or at least 2 years of follow-up for those who were ART-naive at cohort entry. We defined study baseline as the date of the first VL <200 copies/mL after ≥2 years of continuous VS (a minimum of 2 VL measurements within 2 years was required) from the latest of cohort entry or 1 January 2006 in D:A:D and from the latest of local cohort entry or 1 January 2012 in RESPOND. Participants were required to have ≥1 CD4 count available in addition to the baseline measurement, ≥1 CD4 count in the year prior to the cancer event diagnosis, and an average of 1 CD4 count every 2 years of follow-up to the cancer event or last visit (Supplementary Figure 1, exclusion box 2). Individuals with cancers prior to baseline were also excluded.

### Study Exposure and Outcomes

The main exposure of interest was time-updated CD4 count (categorized as <350, 350–499, 500–749, and ≥750 cells/μL). We partitioned follow-up into 6-month intervals to update CD4 counts throughout the study. The primary study outcome was incident cancers overall (excluding precancer dysplasia, nonmelanoma skin cancers, relapse) and incident cancers separately for ADC, NADC, infection-related cancer, infection-unrelated cancer, smoking-related cancer, and obesity-related cancer [11, 15]. These cancer groups are not mutually exclusive since each cancer type could be included in more than 1 category (Supplementary Table 1).

### Statistical Analyses

We summarized baseline participant characteristics by cancer status. Follow-up was from baseline to the first date of a cancer event, virological failure (VL >200 copies/mL), discontinuation of ART for >2 months, or the last cohort date, whichever occurred first. Last cohort date was defined as 6 months after the last clinic visit or cohort administrative censor date (1 February 2016) in D:A:D or final follow-up date or administrative censor date (31 December 2021) in RESPOND. The final follow-up in RESPOND was defined as the latest of the most recent CD4 count, VL measurement, dropout date, or date of death. We excluded participants from RESPOND cohorts with low event reporting, defined as those with an upper 95% confidence interval (CI) for cancer incidence below the overall RESPOND incidence. For participants with sustained VS prior to cohort entry, the baseline date was the date of study entry within the respective cohort.

Crude and adjusted incidence rates (and 95% CIs) of cancers overall and each cancer group were calculated. We used Poisson regression with robust standard errors to investigate the association between the incidence of cancers and time-updated CD4 count categories, adjusted for potential confounders, chosen a priori. These included sex/gender, race/ethnicity, geographical region, HIV mode of acquisition, hepatitis C infection, hepatitis B infection, body mass index, smoking (never, current, previous, or unknown), hypertension, diabetes, dyslipidemia, a prior non-cancer AIDS event, end-stage liver and kidney disease, cardiovascular disease, or chronic kidney disease, all fixed at baseline to mitigate any potential mediating effects on the time-updated CD4 counts. Age (per 10-year increase) and any exposure to ART were fitted as time-updated variables. In these models, any exposure to ART was defined as a time-updated binary variable.

We stratified results by the following key subgroups: age group, race/ethnicity, and pre-ART nadir CD4 count. We tested interactions between time-updated CD4 count and age (categorized as ≤50, >50 years), sex, and calendar periods (≤2015, >2015) in the fully adjusted model. Tests for interactions were limited to cancers overall to ensure sufficient power. We also conducted subgroup analyses for the association of time-updated CD4 count and cancer risk for sex (male and female), age group (≤50, >50 years), and pre-ART nadir CD4 count (<200, 200–350, >350 cells/μL). Due to collinearity between nadir CD4 count and time-updated CD4 count, both variables were not included in the same multivariable regression model. To explore the association between time-updated CD4 count and cancer risk by baseline immune status, we conducted stratified analyses across nadir CD4 count categories.

We included change in CD4 count (calculated as the change in time-updated CD4 count from baseline CD4 count) as a measure to investigate the association between the extent of immune recovery and cancer risk. We evaluated whether pre-ART nadir CD4 count and change in CD4 count from baseline were associated with cancers overall and subgroups using multivariable Poisson regression adjusting for the same covariates.

#### Sensitivity Analyses

The following sensitivity analyses were conducted: lagging time-updated CD4 count by 6 or 12 months to account for potential reverse causation and CD4 count reductions leading up to a cancer diagnosis, including only centrally validated cancer events, including participants with cancers diagnosed prior to baseline, using time-weighted average of area under time-updated CD4 count measurements curve using the trapezoidal rule [16], and using complete case series analysis excluding participants with missing data on any variables.

All analyses were conducted using Stata/SE 18.0 (StataCorp, LLC, College Station, TX).

## RESULTS

#### Baseline Characteristics

We included 48 343 participants who achieved ≥2 years of VS in analyses from 8 cohorts in D:A:D and 15 cohorts in RESPOND from 37 countries (Supplementary Figure 1). Among them, 22 508 (46.6%) were from D:A:D only and 17 779 (36.8%) were from RESPOND only (8056 [16.7%] were enrolled in both cohorts). At baseline, 74.4% were male, median age was 43 years (interquartile range [IQR], 37–50), median time since HIV diagnosis was 7.4 years (IQR, 3.3–13.5), and median pre-ART nadir CD4 count was 245 cells/μL (IQR, 121–394). Baseline demographic and clinical characteristics were similar between individuals included compared with those excluded in the final analysis (Supplementary Table 2).

A total of 1933 (3.9%) participants developed cancer during follow-up (Table 1). At baseline, participants with cancer were older (median, 50 years [IQR, 44–57] vs 44 years [IQR, 37–50]) and had similar median CD4 counts at baseline (517 cells/μL [IQR, 342–716] vs 540 cells/μL [IQR, 380–730]) but lower median pre-ART nadir CD4 counts (194 cells/μL [IQR, 80–310] vs 242 cells/μL [IQR, 120–390]).

#### Cancer Incidence After 2 Years of Virological Suppression

Over 300 273 person-years of follow-up (PYFU), 1933 (3.9%) participants developed cancer (incidence rate [IR], 6.43 (95% CI: 6.15–6.73)/1000 PYFU) after ≥2 years of VS. The median follow-up duration was 6.2 years (IQR, 2.9–9.5) for the total population, 6.1 years (IQR, 3.0–9.6) for participants without a cancer diagnosis, and 4.2 years (IQR, 1.8–7.1) for those with a cancer diagnosis. There were 258 cases of ADC (0.5%) and 1675 cases of NADC (3.5%), with IRs of 0.86 (95% CI: .76–.97)/1000 PYFU and 5.58 (95% CI: 5.31–5.85)/1000 PYFU. There were 645 infection-related cancers (IR, 2.22 [95% CI: 1.98–2.32]/1000 PYFU) and 1288 infection-unrelated cancers (IR, 4.29 [95% CI: 1.06–4.53]/1000 PYFU). The most common cancers were lung cancer, anal cancer, and prostate cancer, followed by non-Hodgkin lymphoma (NHL) and breast cancer (Supplementary Table 1). The crude IR of cancers overall, cancer groups, and individual cancers are presented in Figure 1, and the stratifications by age at baseline (≤50, 50 years), pre-ART nadir CD4 (<200, 200–350, >350 cells/μL), and race/ethnicity (White, Black, other, unknown) are presented in Tables 2 and 3.

#### Association Between the Recent CD4 Count and Cancer Diagnosis

In multivariable Poisson regression, higher time-updated CD4 count was associated with a reduced risk of development of cancers overall (adjusted incidence rate ratio [aIRR] for time-updated CD4, 350–499 cells/μL: 0.45 [95% CI: .39–.51]; 500–749 cells/μL: 0.30 [95% CI: .27–.34], and ≥750 cells/μL: 0.26 [95% CI: .23–.30] compared with <350 cells/μL, $P < .0001$;

**Table 1. Characteristics of Participants Living With Human Immunodeficiency Virus With or Without Overall Cancer During Follow-up at Analysis Baseline**

| Characteristic | | Total (n = 48 343) | | Cancer During Follow-up (n = 1933) | | No Cancer During Follow-up (n = 46 410) | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| Sex/Gender | Male | 36 018 | 74.4 | 1517 | 78.5 | 34 501 | 74.3 |
| | Female | 12 290 | 25.4 | 416 | 21.5 | 11 874 | 25.6 |
| | Transgender | 35 | 0.1 | 0 | 0.0 | 35 | 0.1 |
| Race/Ethnicity | White | 26 846 | 55.4 | 1217 | 63.0 | 25 629 | 55.2 |
| | Black | 3386 | 7.0 | 69 | 3.6 | 3317 | 7.1 |
| | Other | 1603 | 3.3 | 28 | 1.4 | 1575 | 3.4 |
| | Unknown | 16 508 | 34.1 | 619 | 32.0 | 15 889 | 34.2 |
| Geographical region[a] | Western Europe | 18 697 | 38.6 | 861 | 44.5 | 17 836 | 38.4 |
| | Southern Europe | 9251 | 19.1 | 382 | 19.8 | 8869 | 19.1 |
| | Northern Europe | 16 981 | 35.1 | 605 | 31.3 | 16 376 | 35.3 |
| | Eastern Europe | 3414 | 7.0 | 85 | 4.4 | 3329 | 7.2 |
| Mode of HIV acquisition | Men who have sex with men | 22 133 | 45.7 | 863 | 44.6 | 21 270 | 45.8 |
| | Intravenous drug user | 6444 | 13.3 | 355 | 18.4 | 6089 | 13.1 |
| | Heterosexual | 16 806 | 34.7 | 591 | 30.6 | 16 215 | 34.9 |
| | Other | 1069 | 2.2 | 49 | 2.5 | 1020 | 2.2 |
| | Unknown | 1891 | 3.9 | 75 | 3.9 | 1816 | 3.9 |
| Smoking status | Never | 11 944 | 24.7 | 375 | 19.4 | 11 569 | 24.9 |
| | Current | 18 060 | 37.3 | 872 | 45.1 | 17 188 | 37.0 |
| | Previous | 8858 | 18.3 | 404 | 20.9 | 8454 | 18.2 |
| | Unknown | 9481 | 19.6 | 282 | 14.6 | 9199 | 19.8 |
| Body mass index, kg/m$^2$ | <18.5 | 1833 | 3.8 | 105 | 5.4 | 1728 | 3.7 |
| | 18.5 to <25 | 24 879 | 51.4 | 1016 | 52.6 | 23 863 | 51.4 |
| | 25 to <30 | 2850 | 5.9 | 90 | 4.7 | 2760 | 5.9 |
| | >30 | 10 587 | 21.9 | 431 | 22.3 | 10 156 | 21.9 |
| | Unknown | 8194 | 16.9 | 291 | 15.1 | 7903 | 17.0 |
| Prior AIDS | No | 39 666 | 81.9 | 1446 | 74.8 | 38 220 | 82.4 |
| | Yes | 8677 | 17.9 | 487 | 25.2 | 8190 | 17.6 |
| Hepatitis C[b] | No | 3729 | 7.7 | 122 | 6.3 | 3607 | 7.8 |
| | Yes | 42 322 | 87.4 | 1710 | 88.5 | 40 612 | 87.5 |
| | Unknown | 1923 | 4.0 | 104 | 5.4 | 1819 | 3.9 |
| Hepatitis B[c] | No | 4098 | 8.5 | 119 | 6.2 | 3979 | 8.6 |
| | Yes | 36 727 | 75.8 | 1338 | 69.2 | 35 389 | 76.3 |
| | Unknown | 8562 | 17.7 | 518 | 26.8 | 8044 | 17.3 |
| Hypertension[d] | No | 3054 | 6.3 | 77 | 4.0 | 2977 | 6.4 |
| | Yes | 46 864 | 96.8 | 1819 | 94.1 | 45 045 | 97.1 |
| | Unknown | 1479 | 3.1 | 114 | 5.9 | 1365 | 2.9 |
| Diabetes[e] | No | 36 018 | 74.4 | 1517 | 78.5 | 34 501 | 74.3 |
| | Yes | 12 290 | 25.4 | 416 | 21.5 | 11 874 | 25.6 |
| Cardiovascular disease | No | 40 113 | 82.8 | 1673 | 86.5 | 38 440 | 82.8 |
| | Yes | 1125 | 2.3 | 85 | 4.4 | 1040 | 2.2 |
| | Unknown | 7105 | 14.7 | 175 | 9.1 | 6930 | 14.9 |
| Chronic kidney disease[f] | No | 47 520 | 98.1 | 1876 | 97.1 | 45 644 | 98.3 |
| | Yes | 279 | 0.6 | 32 | 1.7 | 247 | 0.5 |
| | Unknown | 544 | 1.1 | 25 | 1.3 | 519 | 1.1 |
| Dyslipidemia[g] | No | 12 635 | 26.1 | 352 | 18.2 | 12 283 | 26.5 |
| | Yes | 35 708 | 73.7 | 1581 | 81.8 | 34 127 | 73.5 |
| Previous exposure to integrase strand transfer inhibitor | | 5177 | 10.7 | 110 | 5.7 | 5067 | 10.9 |
| Previous exposure to protease inhibitor | | 28 602 | 59.1 | 1401 | 72.5 | 27 204 | 58.6 |
| Previous exposure to non-nucleoside reverse transcriptase inhibitor | | 30 731 | 63.4 | 1322 | 68.4 | 29 409 | 63.4 |
| Previous exposure to nucleoside/nucleotide reverse transcriptase inhibitor | | 22 694 | 46.9 | 1131 | 58.5 | 21 563 | 46.5 |

**Table 1. Continued**

| Characteristic | Total (n = 48 343) | | Cancer During Follow-up (n = 1933) | | No Cancer During Follow-up (n = 46 410) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Continuous variables | Median | IQR | Median | IQR | Median | IQR |
| Age, y | 43 | 37–50 | 50 | 44–57 | 44 | 37–50 |
| Nadir CD4 count, cells/μL[h] | 245 | 121–394 | 194 | 80–310 | 242 | 120–390 |
| CD4 count at analysis baseline, cells/μL[h] | 540 | 380–730 | 517 | 342–716 | 540 | 380–730 |
| Duration since HIV diagnosis, y | 7.4 | 3.3–13.5 | 11.0 | 5.1–17.2 | 7.5 | 3.4–13.5 |

Analysis baseline date was the first viral load <200 copies/mL (for more than 2 years) from the latest of study entry or 1 January 2006 for participants in the D:A:D cohort or the latest of local cohort enrollment or 1 January 2012 for participants in the RESPOND cohort.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Due to small numbers, Australia was combined with Northern Europe, and Eastern Central Europe was combined with Eastern Europe.

[b]Hepatitis C was defined by use of anti–hepatitis C virus (HCV) medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA viral load (VL) >615 IU/mL, and/or a positive genotype test.

[c]Hepatitis B was defined by a positive hepatitis B virus (HBV) surface antigen and/or HBV DNA VL >357 IU/mL.

[d]Hypertension was confirmed by use of antihypertensives at any time before baseline or if the most recent systolic or diastolic blood pressure measurement before baseline was higher than 140 or 90 mmHg, respectively.

[e]Diabetes was defined by a reported diagnosis, use of antidiabetic medication, glucose ≥11.1 mmol/L, and/or hemoglobin A1c ≥6.5% or ≥48 mmol/mol.

[f]Chronic kidney disease was defined as 2 consecutive estimated glomerular filtration rate measurements <60 mL/min/1.73 $m^2$ (calculated using the CKD Epidemiology Collaboration, CKD-EPI) measured at least 3 months apart.

[g]Dyslipidemia was defined as total cholesterol >239.4 mg/dL or high-density lipoprotein cholesterol <34.7 mg/dL or triglyceride >203.55 mg/dL or use of lipid-lowering treatments.

[h]CD4 count was taken as the most recent measurements in the 12 months prior to analysis baseline (ie, the date of achieving >2 years of viral suppression). If no measurements were taken prior to analysis baseline, the first measurement within 12 weeks after analysis baseline was used. CD4 nadir was taken as the lowest CD4 cell count prior to antiretroviral therapy initiation.

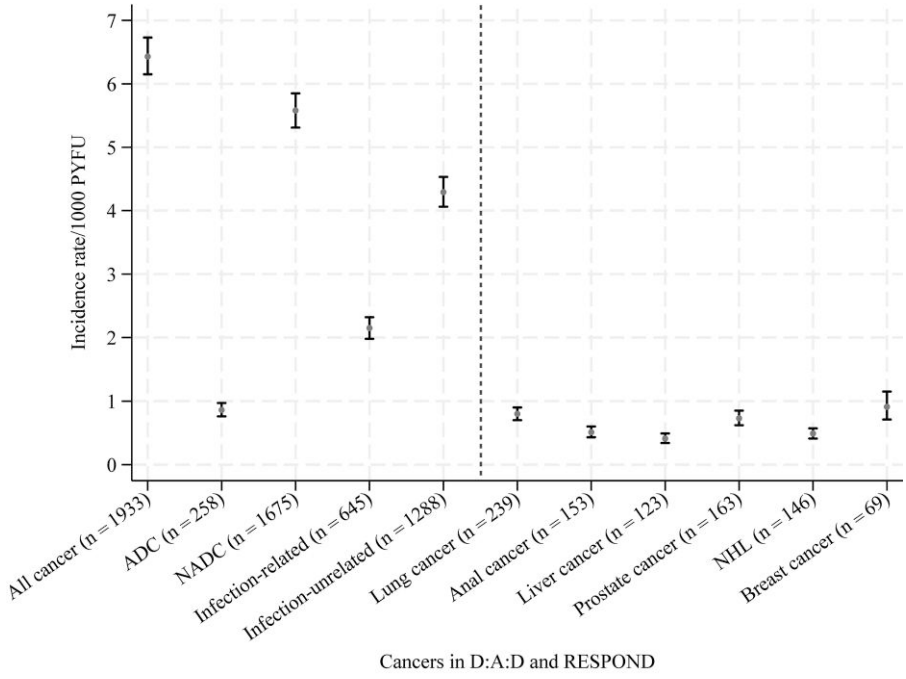


**Figure 1.** Cancer incidence after at least 2 years of virological suppression in D:A:D and RESPOND collaborations. Cancer incidence rates on the left of the dotted line represent the overall cancer and cancer groups, and those to the right are individual cancer types. Abbreviations: ADC, AIDS-defining cancer; NADC, non–AIDS-defining cancer; NHL, non-Hodgkin lymphoma; PYFU, person-years of follow-up.

Figure 2). A test for trend confirmed strong evidence of a linear association between increasing time-updated CD4 count and lower cancer risk ($P$ trend <.001). There were no significant interactions between time-updated CD4 count and age group (categorized as ≤50/>50 years; $P_{interaction} = .24$), sex ($P_{interaction} = .97$), or calendar periods (<2015/≥2015; $P_{interaction} = .40$).

The results remained consistent for ADC ($P < .0001$) and NADC ($P < .0001$), although the strength of the association was less for NADC compared with ADC and for infection-related and infection-unrelated cancers (Figure 2), as well as individual cancers except prostate cancer (Figure 3). The degree of cancer risk reduction with higher time-updated CD4 count was

**Table 2. Crude Incidence Rate of Overall Cancers and Cancer Subgroups**

| | All Cancers | | AIDS-Defining Cancers | | Non–AIDS-Defining Cancers | | Infection-Related Cancers | | Infection-Unrelated Cancers | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Number | Incidence Rate/1000 Person-Years (95% CI) | Number | Incidence Rate/1000 Person-Years (95% CI) | Number | Incidence Rate/1000 Person-Years (95% CI) | Number | Incidence Rate/1000 Person-Years (95% CI) | Number | Incidence Rate/1000 Person-years (95% CI) |
| Overall | 1933 | 6.43 (6.15–6.73) | 258 | 0.86 (.76–.97) | 1675 | 5.58 (5.31–5.85) | 645 | 2.15 (1.98–2.32) | 1288 | 4.29 (1.06–4.53) |
| Sex/Gender | | | | | | | | | | |
| Male | 1517 | 6.76 (6.43–7.11) | 191 | 0.85 (.73–.98) | 1326 | 5.91 (5.60–6.24) | 526 | 2.34 (2.22–2.56) | 991 | 4.42 (4.15–4.70) |
| Female | 416 | 5.48 (4.97–6.03) | 67 | 0.88 (.68–1.12) | 349 | 4.60 (4.12–5.11) | 119 | 1.57 (1.30–1.88) | 297 | 3.91 (3.48–4.38) |
| Age at baseline, y | | | | | | | | | | |
| ≤50 | 946 | 4.24 (3.97–4.52) | 160 | 0.72 (.61–.84) | 786 | 3.52 (3.28–3.78) | 380 | 1.70 (1.54–1.88) | 566 | 2.54 (2.33–2.76) |
| >50 | 987 | 12.7 (12.0–13.6) | 98 | 1.26 (1.19–1.36) | 889 | 12.7 (10.3–12.3) | 265 | 3.42 (3.02–3.86) | 722 | 9.33 (8.66–10.03) |
| Pre-antiretroviral therapy nadir CD4, cells/μL | | | | | | | | | | |
| <200 | 985 | 7.40 (6.95–7.88) | 146 | 1.09 (.93–1.29) | 839 | 6.31 (5.89–6.75) | 357 | 2.68 (2.41–2.98) | 628 | 4.72 (4.36–5.11) |
| 200–350 | 577 | 6.10 (5.61–6.61) | 59 | 0.62 (.47–.80) | 518 | 5.47 (5.01–6.00) | 163 | 1.72 (1.5–2.01) | 414 | 4.37 (3.96–4.82) |
| >350 | 371 | 5.11 (4.60–5.66) | 53 | 0.73 (.55–.96) | 318 | 4.38 (3.91–4.89) | 125 | 1.72 (1.43–2.05) | 246 | 3.39 (2.98–3.84) |
| Race/Ethnicity | | | | | | | | | | |
| White | 1217 | 7.04 (6.65–7.45) | 136 | 0.79 (.66–.93) | 1081 | 6.35 (5.89–6.64) | 377 | 2.18 (1.97–2.41) | 840 | 4.86 (4.54–5.20) |
| Black | 69 | 3.31 (2.57–4.19) | 14 | 0.67 (.37–1.13) | 55 | 2.64 (2.00–3.43) | 23 | 1.10 (.70–1.65) | 46 | 2.21 (1.61–2.94) |
| Other | 28 | 2.74 (1.83–3.97) | 8 | 0.79 (.34–1.54) | 20 | 1.96 (1.19–3.03) | 9 | 0.88 (.40–1.67) | 19 | 1.86 (1.12–2.91) |
| Unknown | 619 | 6.42 (5.93–6.95) | 100 | 1.04 (.84–1.26) | 519 | 5.39 (4.93–5.87) | 236 | 2.45 (2.14–2.78) | 383 | 3.97 (3.59–4.39) |

Cancer groups are not mutually exclusive since each cancer type could be included in more than 1 category.

Abbreviation: CI, confidence interval.

**Table 3. Crude Incidence Rate of Individual Cancers**

| | Lung Cancer | | Anal Cancer | | Liver Cancer | | Prostate Cancer | | Non-Hodgkin Lymphoma | | Breast Cancer | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | Number | Incidence Rate/ 1000 Person-Years (95% CI) | Number | Incidence Rate/ 1000 Person-Years (95% CI) | Number | Incidence Rate/ 1000 Person-Years (95% CI) | Number | Incidence Rate/ 1000 Person-Years (95% CI) | Number | Incidence Rate/ 1000 Person-Years (95% CI) | Number | Incidence Rate/ 1000 Person-Years (95% CI) |
| Overall | 239 | 0.80 (.70–.90) | 153 | 0.51 (.43–.60) | 123 | 0.41 (.34–.49) | 163 | 0.73 (.62–.85) | 146 | 0.49 (.41–.57) | 69 | 0.91 (.71–1.15) |
| Sex/Gender | | | | | | | | | | | | |
| Male | 191 | 0.85 (.74–.98) | 135 | 0.60 (.50–.71) | 105 | 0.47 (.38–.56) | 163 | 0.73 (.62–.85) | 125 | 0.56 (.46–.66) | NA | NA |
| Female | 48 | 0.63 (.47–.84) | 18 | 0.24 (.14–.37) | 18 | 0.24 (.14–.37) | NA | NA | 21 | 0.38 (.17–.42) | 69 | 0.91 (.71–1.15) |
| Age at baseline, y | | | | | | | | | | | | |
| ≤50 | 84 | 0.38 (9.30–.47) | 90 | 0.40 (.32–.50) | 68 | 0.31 (.24–.39) | 18 | 0.11 (.06–.18) | 83 | 0.37 (.30–.46) | 53 | 0.85 (.63–1.11) |
| >50 | 155 | 2.00 (1.70–2.34) | 63 | 0.81 (.62–1.04) | 55 | 0.71 (.54–.92) | 145 | 2.26 (1.91–2.66) | 63 | 0.80 (.63–1.04) | 16 | 1.20 (.69–1.95) |
| Pre-antiretroviral therapy nadir CD4, cells/μL | | | | | | | | | | | | |
| <200 | 124 | 0.93 (.74–1.11) | 84 | 0.63 (.50–.78) | 75 | 0.56 (.44–.71) | 65 | 0.67 (.54–.82) | 89 | 0.67 (.54–1.15) | 29 | 0.80 (.54–1.15) |
| 200–350 | 78 | 0.82 (.65–1.03) | 39 | 0.41 (.29–.56) | 31 | 0.33 (.22–.46) | 57 | 0.80 (.61–1.04) | 31 | 0.33 (.22–.46) | 33 | 1.40 (.96–1.97) |
| >350 | 37 | 0.51 (.36–.70) | 30 | 0.41 (.28–.59) | 17 | 0.23 (.14–.38) | 41 | 0.73 (.52–.98) | 26 | 0.36 (.23–.52) | 14 | 0.87 (.48–1.47) |
| Race/Ethnicity | | | | | | | | | | | | |
| White | 148 | 0.86 (.72–1.01) | 98 | 0.57 (.46–.69) | 84 | 0.49 (.39–.60) | 104 | 0.77 (.63–.93) | 84 | 0.49 (.39–9.60) | 39 | 1.32 (.98–1.74) |
| Black | 1 | 0.05 (.001–.27) | 1 | 0.05 (.001–.27) | 3 | 0.14 (.03–.42) | 2 | 0.10 (.01–.35) | 6 | 0.29 (9.11–.63) | 4 | 0.19 (.05–.49) |
| Other | 5 | 0.49 (.16–1.14) | 0 | 0 | 0 | 0 | 2 | 0.20 (.03–.71) | 4 | 0.39 (.11–1.00) | 3 | 0.29 (.06–.86) |
| Unknown | 85 | 0.88 (.70–1.09) | 54 | 0.56 (.42–.73) | 36 | 0.37 (.26, .52) | 55 | 0.57 (.43, .74) | 52 | 0.54 (.40, .71) | 23 | 0.24 (.15, .36) |

Abbreviation: CI, confidence interval; NA, not applicable.

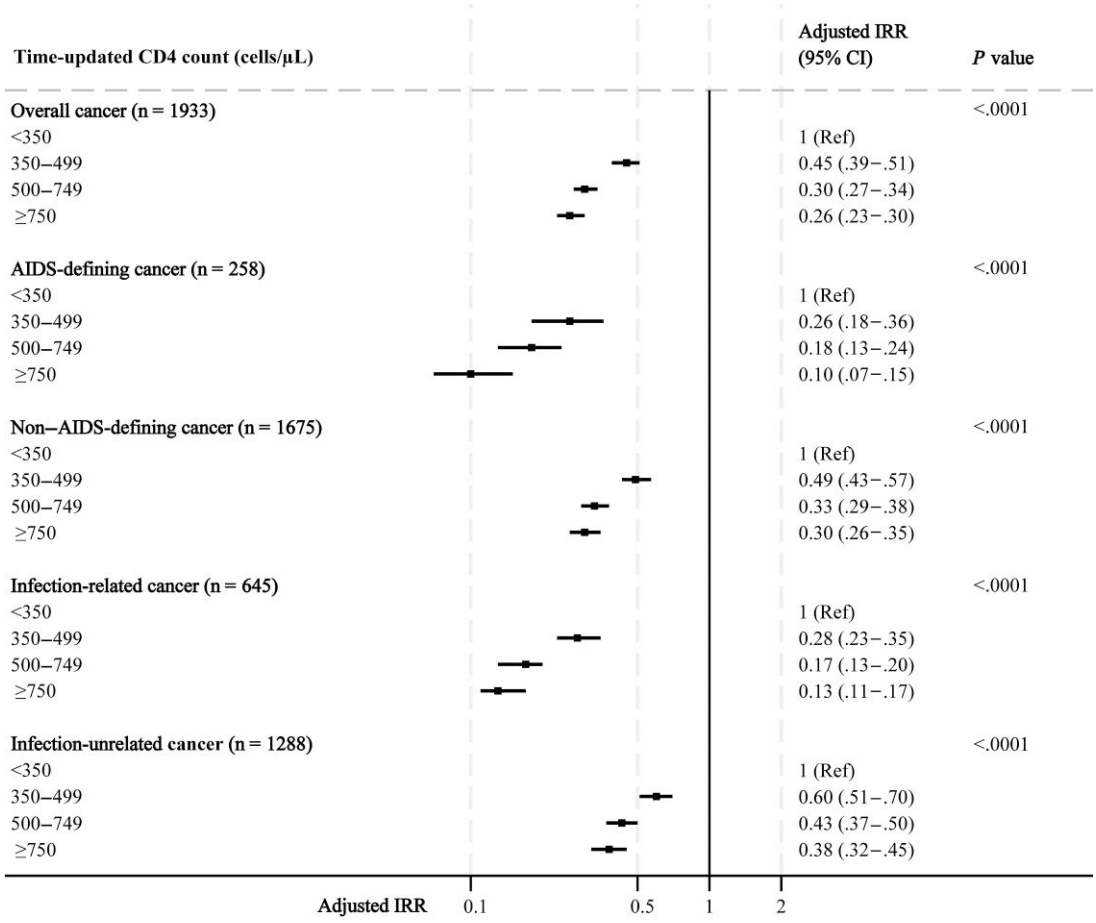


**Figure 2.** Association between time-updated CD4 count and cancers overall and cancer groups. Poisson regression models for cancer overall and cancer groups were adjusted for sex, race/ethnicity, geographical region, human immunodeficiency virus (HIV) transmission risk group, duration since HIV diagnosis, a prior non-cancer AIDS event, hepatitis C virus, hepatitis B virus, body mass index, hypertension, diabetes, cardiovascular disease, chronic kidney disease, and dyslipidemia, all fixed at baseline. Time-updated covariates included age, smoking status, as well as any exposure to integrase strand transfer inhibitors, protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors (as cumulative exposure). Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

greater in infection-related cancer than infection-unrelated cancer, with a time-updated CD4 count ≥750 cells/μL (vs <350) being associated with an almost 90% reduction in infection-related cancers, whereas this reduction was lower (approximately 60%) for infection-unrelated cancers. When ADCs were excluded from the infection-related cancer group (n = 444), time-updated CD4 counts remained associated with cancer incidence (350–499 cells/μL: IRR, 0.30 [95% CI: .22–.39]; 500–749 cells/μL: IRR, 0.15 [95% CI: .11–.20]; and ≥750 cells/μL: IRR, 0.16 [95% CI: .12–.21]) compared with <350 cells/μL.

In the adjusted analyses stratified by pre-ART nadir CD4 count levels, associations between time-updated CD4 count (representing amount of immune recovery) and reduced risk for the development of cancers overall, ADC, NADC, infection-related cancer, and infection-unrelated cancer were consistently observed across various pre-ART nadir CD4 count groups (<200, 200–350, >350 cells/μL; *P* values <.0001; Figure 4). The results were consistent with smoking-related and obesity-related cancers (Supplementary Figure 2). It is noteworthy that participants with higher pre-ART nadir CD4 count also exhibited lower cancer risk, despite the observed significant protective associations across all groups (Figure 4).

As an indicator of immune recovery, we further investigated the association between the diagnosis of cancer and changes in CD4 count. In adjusted analyses, we found that an increase in CD4 count (per 50 cells/μL increase) was strongly associated with a reduced risk of incident cancers overall, cancer groups, and individual cancers (Supplementary Table 3). Furthermore, pre-ART nadir CD4 count was only associated with reduced risk of ADC and infection-related cancers but not for cancers overall and other cancer groups such as NADC and smoking- and obesity-related cancers (Supplementary Table 3).

Furthermore, we observed the diminished risk of overall cancers and specific cancer groups associated with higher time-updated CD4 count levels in both male and female subgroups, as well as in age subgroups categorized as ≤50 years and

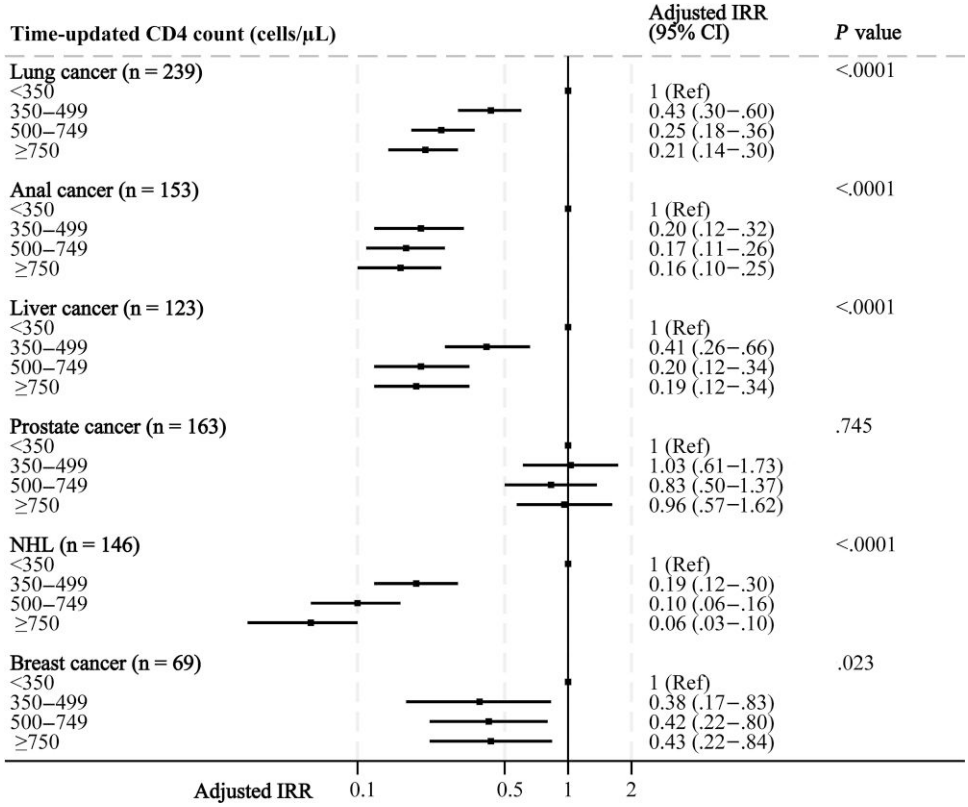


**Figure 3.** Association between time-updated CD4 count and individual cancers. Poisson regression for all individual cancers was adjusted for sex, race/ethnicity, geographical region, human immunodeficiency virus transmission risk group, and a prior non-cancer AIDS event, all fixed at baseline. Time-updated covariates included age and smoking status. Models for liver cancer were additionally adjusted for hepatitis C virus and hepatitis B virus infection. Models for breast cancer included only females, and models for prostate cancer included only males. Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NHL, non-Hodgkin lymphoma.

>50 years (Supplementary Table 5). We examined the relationship between time-updated CD4 count categories and the development of most common individual cancers. The findings were consistent across all cancers assessed, including NHL, lung cancer, liver cancer, breast cancer, and anal cancer, except for prostate cancer ($P = .745$; Figure 5). These associations persisted across pre-ART nadir CD4 count groups for most cancers but only among those with low pre-ART nadir CD4 count ≤200 cells/μL for breast cancer (Figure 5). Notably, the lower pre-ART nadir CD4 count was associated only with NHL but not with other cancers (Supplementary Table 4).

#### Sensitivity Analyses

We conducted a series of sensitivity analyses to evaluate the robustness of our findings. We observed that a time-updated CD4 count lagged by 6 or 12 months was associated with a reduced risk of overall cancers and cancer subgroups and most common cancers, except prostate cancer and breast cancer (Supplementary Tables 6 and 7). The associations between 6-month lagged CD4 and the reduced risk of cancer became weaker compared with the primary analysis. The results from sensitivity analyses remained consistent with the primary analysis across the various analyses (Supplementary Tables 6 and 7).

## DISCUSSION

Using combined data from 2 large multinational HIV cohorts, we found poorer immune recovery despite sustained VS to be associated with an increased incidence of cancers overall, common individual cancers, as well as the following cancer groupings: ADC, NADC, infection-related, infection-unrelated, smoking-related, and obesity-related cancers. The associations remained consistent across various subgroups and sensitivity analyses, including those with low pre-ART nadir CD4 counts. The reduced risk of cancer overall was also observed in participants with CD4 counts ≥750 cells/μL compared with those with CD4 counts 500–749 cells/μL. These findings reinforce the importance of optimal immune recovery on the incidence of cancers in people with HIV.

Previous studies have established associations between low CD4 counts, prolonged immunosuppression, or shorter durations of HIV VS with development of both ADC and NADC [6, 17]. However, we are the first to demonstrate a significant association between poor immune recovery and cancers overall,

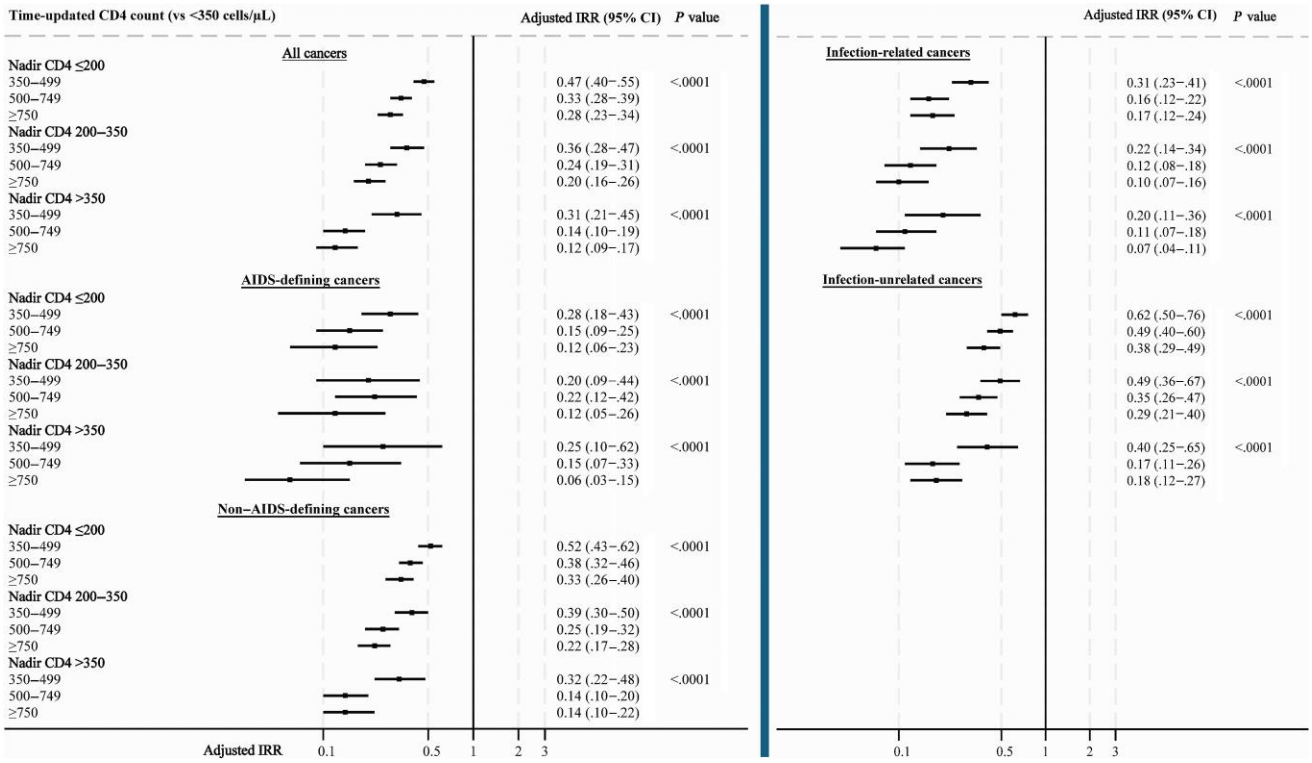


**Figure 4.** Association between time-updated CD4 count and cancers overall and cancer groups stratified by pre–antiretroviral therapy nadir CD4 counts. Poisson regression models for cancer overall and cancer groups were adjusted for sex, race/ethnicity, geographical region, human immunodeficiency virus (HIV) transmission risk group, duration since HIV diagnosis, a prior non-cancer AIDS event, hepatitis C virus, hepatitis B virus, body mass index, hypertension, diabetes, cardiovascular disease, chronic kidney disease, and dyslipidemia, all fixed at baseline. Time-updated covariates included age, smoking status, as well as any exposure to integrase strand transfer inhibitors, protease inhibitors, NRTI- nucleoside/nucleotide reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors; NNRTI-non-NRTI NRTIs, and NNRTIs (as cumulative exposure). Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

encompassing all cancer groups, in people with sustained VS. In addition to the findings from previous studies [11, 18, 19] that have shown a significant increase in the risk of ADC and infection-related cancers with HIV viremia, our study, by exclusively focusing on participants with at least 2 years of VS, offers a robust understanding of the impacts of immune restoration on cancer incidence, unbiased by the influence of unsuppressed HIV VL.

Compared with a prior combined D:A:D/RESPOND analysis of cancer trends, we report a lower incidence rate of ADC (1.94 vs 0.86/1000 PYFU) and infection-related cancers (3.42 vs 2.15/1000 PYFU) due to limiting assessment to participants with sustained VS. However, there were no differences in the incidence rates of NADC between the present and previous studies. This supports findings from previous studies of a greater impact of HIV viremia on ADC and infection-related cancers [17, 20]. However, there is contradictory evidence regarding the impact of HIV viremia on NADC risk. While a recent RESPOND analysis [21 ] and an earlier French study [22] have shown no association between HIV viremia and NADC, results from the Veterans Aging Cohort Study and a population-based study in the United States demonstrated an association between ongoing viral replication and NADC [6, 18]. The latter study also showed that combining HIV VL and CD4 count measures provides a better risk prediction of NADC than either measure alone [6].

When considering the most recent CD4 count prior to cancer diagnosis, a previous study demonstrated a significant, but low magnitude, decline in CD4 count leading up to cancer diagnosis [23]. Another study reported that a meaningful CD4 decline (>15%) occurred in only 6 of 87 cancer cases 6 months prior to cancer diagnosis [24]. This decline may be attributed to reductions in lymphocyte counts during the development of cancer. While our study primarily uses the most recent CD4 count, results were consistent when the analysis used a time-updated CD4 count lagged by 6–12 months. There are also potential limitations in capturing the relationship between immune status and cancer development solely through this measure.

Consistent with previous studies, individuals with lower time-updated CD4 counts appear to be at higher risk of certain common cancers, including lung, anal, liver, NHL, and breast, but not prostate cancer. Other immune measures such as

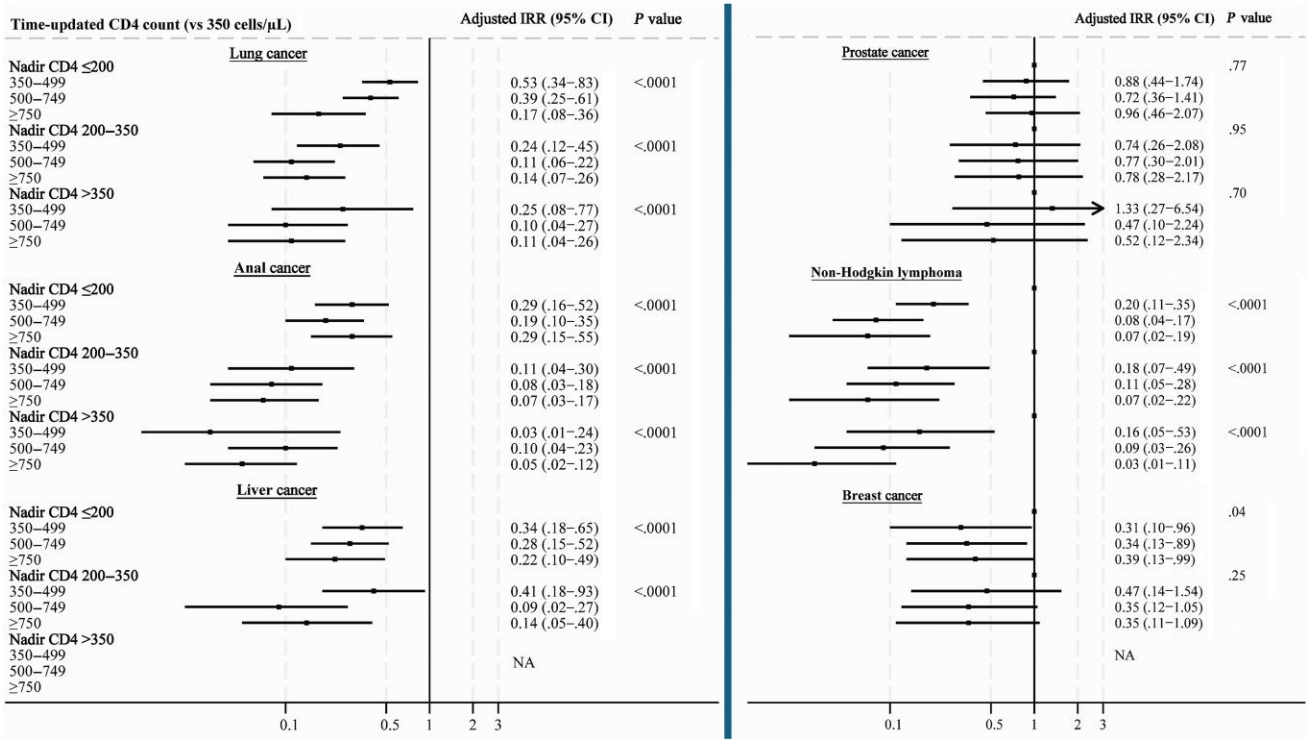


**Figure 5.** Association between time-updated CD4 count and individual cancers stratified by pre–antiretroviral therapy nadir CD4 counts. Poisson regression for all individual cancers was adjusted for sex, race/ethnicity, geographical region, human immunodeficiency virus transmission risk group, and a prior non-cancer AIDS event, all fixed at baseline. Time-updated covariates included age and smoking status. Models for liver cancer were additionally adjusted for hepatitis C virus and hepatitis B virus infection. Models for breast cancer included only females, and models for prostate cancer included only males. Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

cumulative duration of immunosuppression (CD4 count <200 cells/μL) or lower nadir CD4 counts have been associated with an increased risk of both ADC and NADC [21, 22, 25]. In our study, a lower pre-ART nadir CD4 count was only associated with an increased risk of ADC and some infection-related cancers but not NADC and other cancer groups, suggesting a potential underlying mechanism specific to these cancer categories, possibly related to immune dysregulation and excess inflammation during the early untreated stages of HIV infection [26 ].

Our study has several limitations including a relatively young cohort population and a median 6 years of follow-up. Most study participants were from Europe and Australia, which may limit the generalizability to other regions. CD8 counts were largely missing in the D:A:D cohort, making the inclusion of CD4:CD8 ratio in assessing the relationship between poor immune recovery and cancer risk unfeasible. In addition, we did not have information on cancer screening or family history. It also remains challenging to identify a single indicator that can comprehensively capture immune recovery after ART initiation. Despite these limitations, our findings, which demonstrate an association between a normalized immune response and a lower risk of cancer, remain robust across various measures of CD4 count.

## CONCLUSIONS

In this large cohort study that integrated data from the D:A:D/RESPOND collaborations, individuals with suboptimal immune recovery experienced an increased risk of incident cancers despite achieving durable VS. This highlights the critical importance of diagnosing HIV at the earliest opportunity, promptly initiating ART to ensure optimal immune recovery and sustained cancer risk reduction, and ensuring people with poor immune recovery despite effective ART undergo appropriate cancer screening strategies.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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D:A:D

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***Author Contributions.*** J. F. H., K. P., W. M. H., C. A. S., L. R., and L. G. proposed and developed the research question. W. M. H. wrote the first draft of the manuscript and performed the statistical analysis. J. F. H. and K. P. reviewed and edited the first draft. W. M. H. and K. P. accessed and verified the data. J. F. H., W. M. H., L. G., C. A. S., M. C., A. E., C. D., F. W. N. M. W., C. M., A. d A. M., A. C., J. M. M., M. v. d. V., F. B., C. P., M. S., R. M., M. S., N. J., A. T., J. T., F. P. R., V. V., L. A. Y., L. R., and K. P. contributed to the study design, interpretation of the data, and revision of the manuscript. All authors contributed substantially to the interpretation of the results and drafting of the manuscript, including critically reviewing or approving the final version of the manuscript.

***Disclaimer.*** The findings and conclusions presented here are solely the responsibility of the authors and do not necessarily represent the official views of any of the listed institutions or funders.

***Role of the funding source.*** Per RESPOND governance, funders of the study were also academic collaborators; employees or associates could be included as coauthors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof) were not in a position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

***Data sharing.*** The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk). For guidelines on how to submit research concepts, see the RESPOND governance and procedures at https://chip.dk/Portals/0/files/RESPOND/WIs/RESPOND governance and procedures_v7.1__2024JUN10_approved.pdf?ver=2024-07-08-151902-690×tamp=1720444746607. The secretariat will direct the proposal to the relevant

Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group that consists of the proposers (up to 3 people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center will be established. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definitions can be found at https://chip.dk/Portals/0/files/RESPOND/Study documents/RESPOND_EuroSIDA_SOP_Electronic_Version_7.0.pdf?ver=2023-07-18-150155-957&timestamp=1689685440820. For any inquiries regarding data sharing, please contact the RESPOND secretariat by email (respond.rigshospitalet@regionh.dk).

***Ethics statement.*** Participants are consented to share data with RESPOND according to local requirements. Participants were pseudonymized at enrollment by being assigned a unique identifier by the participating cohort before data transfer to the main RESPOND database. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approval was obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating center in Copenhagen, Denmark, in accordance with current legislation and under approval by the Danish Data Protection Agency (approval 2012-58-0004, RH-2018-15, 26/1/2018) under the EU General Data Protection Regulation (2016/679).

All participating cohorts followed local or national guidelines or regulations regarding patient consent and ethical review. Of the countries with participating cohorts, only Australia and Switzerland require specific ethical approval for the entire D:A:D cohort in addition to that required for their national cohorts (the Australian HIV Observational Database and the Swiss HIV Cohort Study). France (Nice and Aquitaine cohorts), Italy (ICONA Cohort), and Belgium (Brussels Saint-Pierre Cohort) do not require specific ethical approval more than that required for the individual cohorts, and the Netherlands (AIDS Therapy in the Netherlands project) does not require any specific ethical approval because data are provided as part of HIV care. For the EuroSIDA study, which includes data from the Barcelona Antiretroviral Surveillance Study and Swedish Cohorts, among participants from many European countries, each participating site has a contractual obligation to ensure that data collection and sharing are done in accordance with national legislation. Each site's principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

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