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CD4 Cell Count Trends After Common Cancers in People With HIV: A Multicohort Collaboration

Running head: CD4 count trends after cancer in people with HIV

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Abstract

Objective: Whilst cancer is increasingly common in people with HIV insight into immunological outcomes after cancer diagnosis (CaD) is limited. European guidelines recommend opportunistic infection prophylaxis at CD4<200 cells/μL, and during chemo/radiotherapy regardless of CD4 count. We assessed CD4 trends and predictors of post-CaD immunosuppression across common cancers. **Design:** Participants from D:A:D and RESPOND with Kaposi's sarcoma (KS), non-Hodgkin

lymphoma (NHL), lung, anal or prostate cancer and ≥2CD4 measurements at 6-12months post-CaD were included.

Methods: CD4 measurements were evaluated at 6-monthly intervals. Logistic regression models with generalized estimating equations assessed predictors of CD4<200 up to 3 years post-CaD.

Results: Among 1670 individuals (9597 person-years of follow-up, median 5.3 years), 89% were male, median age was 51 years [interquartile range 42-60] and CD4 400 cells/μL [288-590] at CaD. The highest proportion of participants with CD4<200 was at time of CaD for KS (36%), at 6 months post-CaD for NHL and anal cancer (40 and 30%), at 12 months post-CaD for lung (17%) and 18 months post-CaD for prostate cancer (7%). Higher CD4 at CaD was associated with lower odds of CD4<200 post-CaD (200-350: 0.12 [95% confidence interval 0.08-0.16]; 350-500: 0.05 [0.03-0.07]; >500: 0.02 [0.02-0.04], vs <200). Other predictors included disseminated disease, anal cancer, injection drug use as HIV acquisition mode and male gender/sex; age and calendar time were not predictive.

Conclusion: As post-CaD immunosuppression trends varied by several factors including cancer type, and CD4 at CaD, individualized use of opportunistic infection prophylaxis may be considered when regular CD4 monitoring is available.

Keywords: CD4 cell count, cancer, people with HIV, immunosuppression, opportunistic infection prophylaxis

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This work is not under consideration elsewhere.

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INTRODUCTION

Whilst cancer is a major contributor to morbidity and mortality in people with human immunodeficiency virus (HIV) (1–3), insights into trends and factors influencing immunological status after individual cancer diagnosis (CaD) are limited. Moreover, optimal strategies for post-cancer management of people with HIV remain unclear.

Prior studies have shown that people with HIV may experience CD4 count declines even before CaD (4,5). Additionally, a US study based on data from 2000–2011 showed a temporal decline in CD4 counts after CaD with different CD4 trajectories for what was formerly classified as acquired immunodeficiency syndrome (AIDS)- and non-AIDS-defining cancers, without considering individual cancer types (5). Another study using a composite of different cancers in people with HIV,

demonstrated that chemotherapy and/or radiotherapy resulted in a steeper initial decline in CD4 counts and increased mortality compared to other types of cancer treatment (6).

Whilst opportunistic infection prophylaxis (OIP) is universally recommended for people with HIV with CD4 count<200 cells/μL (7–9), guidelines vary for people with HIV and cancer. The European AIDS Clinical Society (EACS) guidelines recommend OIP for all individuals undergoing chemo/radiotherapy regardless of CD4 count (8), whereas International AIDS Society (IAS) recommends individualised strategies based on immune status, cancer type and treatment (10). Identifying groups at high risk of post-CaD severe immunosuppression may help create a more individualized, CD4 count guided OIP approach.

In this analysis we assessed temporal CD4 count trends in people with HIV before and after the most common incident cancers and investigated risk factors associated with severe post-CaD immunosuppression, defined as CD4 count <200 cells/μL.

METHODS

Study design and participants

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study (1999-2016) and International Cohort Consortium of Infectious Diseases (RESPOND) (2017-present) are prospective HIV multi-cohort collaborations from across Europe, the US and Australia. Detailed information has been published elsewhere (11,12). The studies used a similar methodology and collected standardised demographics, clinical and HIV-specific data during routine clinical care. All cancers were reported using study-specific report forms, that were centrally validated according to prespecified criteria (13,14).

We included participants ≥18 years, with one of the most commonly occurring cancers in the cohorts (Kaposi's sarcoma [KS], non-Hodgkin lymphoma [NHL], lung, anal, or prostate cancer), who survived at least 6 months after CaD and had ≥2 available CD4 counts within 6-12 months hereafter. Participants with missing gender/sex were excluded. Baseline was defined as the date of diagnosis of the first incident NHL, KS, lung, anal or prostate cancer during the follow-up. We followed participants from baseline until death, last follow-up, or cohort censoring (D:A:D 1Feb2016; RESPOND 31Dec2021). Participants enrolled in both cohorts were included only once, as in prior analyses (15).

Statistical methods

Median CD4 counts were calculated for each cancer using all available data at 6 and 12 months (±3 months) before CaD, at the time of CaD, and at 6 (±3)-monthly intervals up to 3 years after CaD. Additionally, we studied the proportion of participants with CD4<200 cells/μL at the same time points.

Using logistic regression models with generalised estimating equations and robust standard errors, we assessed predictors of CD4<200 cells/μL up to 3 years after CaD. The model was adjusted for ethnicity/race, age, gender/sex, HIV acquisition mode, cancer type (with lung cancer as the reference category due to its poor prognosis), ART status, CD4 count, pre-cancer CD4 nadir, all defined at the

baseline, and calendar year and smoking status as time-updated variables. As cancer stage was only available for anal, lung and prostate cancer, we fitted a separate multivariable regression model restricted to these three cancers, including stage.

In sensitivity analyses, we assessed only those with follow-up data available at every time point, limited the analysis to those ART-experienced and separately to those virally suppressed (VL ≤200 copies/mL) at the baseline, and examined predictors of CD4<200 cells/μL for at <6 months or >6 months after CaD. We assessed the impact of death on our analysis in sensitivity analyses by redefining the outcome as CD4<200 or death and using a Fine-Gray model to treat death as a competing risk of post-CaD severe immunosuppression (16).

Missing data for categorical variables was accounted for using an unknown category in regression models. Analyses were performed using Stata/SE 18.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Among 49,676 D:A:D and 36,790 RESPOND participants, 2,485 had one of the studied cancers. Of these, 815 (32%) were excluded for lacking two CD4 measurements within 6-12 months after CaD (including 338 that did not survive >6 months after CaD).

In total, 1670 participants were included (504 with KS, 390 NHL, 206 lung, 333 anal, 237 prostate cancers), with 9,597 person-years of follow-up (PYFU) after CaD. They were predominantly male (88.7%), white (56.9%) and having acquired HIV as men having sex with men (62.1%, Supplementary Table 1, http://links.lww.com/QAD/D944). Participants with lung, anal and prostate cancers were older (median age 57 years [interquartile range (IQR) 50-63], 52 [46-58], 63 [59-69] respectively), compared to those with KS (43 [36-51]) and NHL (48 [40-55]).

Median follow-up time after CaD was 5.3 years [IQR 2.3-8.4] overall; KS: 7.0 [4.0-9.3], NHL: 5.5 [2.2-8.8], anal: 5.1 [2.6-8.0], prostate: 4.9 [2.8-7.7], lung cancer: 1.7 [0.9-3.9].

Median CD4 count trends before/after CaD

Median CD4 count declined during the 12 months (for KS, NHL and lung cancer) and 6 months (for anal and prostate cancers) preceding CaD. At CaD, median CD4 counts were lowest for KS (294 cells/μL, IQR [105, 474]) and NHL (323 [163, 495]), while remaining >400 cells/μL for lung, anal and prostate cancers. The lowest median CD4 counts for each cancer type occurred at varying time points:: at time of CaD for KS (294 cells/μL [105, 474]), at 6 months after CaD for NHL and anal cancer (228 [127, 370] and 273 [170, 412]), at 12 months after CaD for lung (378 [246, 570]), and at 30 months after CaD for prostate cancer (432 [302, 680]). Thereafter, median CD4 counts generally increased within 24-36 months after CaD (Supplementary Figure 1, http://links.lww.com/QAD/D944**).** In the sensitivity analyses among participants with CD4 measurements at every studied time point (n=468), among ART-experienced (n=1387), and among virally suppressed participants (n=1049) trends were largely similar to the main findings (data not shown). We were unable to assess CD4 trends stratified by type of cancer treatment, as this was unknown for the majority of participants (n on chemotherapy: 101 participants, radiotherapy: 38, chemo and radiotherapy: 55, unknown: 1393).

Proportion of participants with CD4<200 cells/μL after CaD and associated risk factors

Consistent with the median CD4 trends, we found that the highest proportion of participants with CD4<200 was at CaD for KS (36%), at 6 months after CaD for NHL and anal (40 and 30%), 12 months after lung (17%), and 18 months after for prostate cancer (8%) **(Figure 1).**

In adjusted analyses higher CD4 counts at CaD were strongly associated with lower odds of CD4<200 cells/μL after CaD. Other key risk factors for CD4<200 cells/μL after CaD were anal cancer (vs lung cancer), disseminated disease, being male, and having intravenous drug use (IDU) as HIV acquisition mode **(Figure 2)**. Predictors were similar when stratified by time period (at <6 months or >6 months after CaD) and when including death as a competing risk (data not shown).

The incidence of AIDS-events after CaD was generally low (lung: n=16, incidence rate/1000 PYFU 29.4 (95% CI 16.8–47.7), NHL: n=50, 24.1 (17.9–31.7), KS: n=69, 21.9 (17.0–27.7), anal: n=18, 9.8 (5.8–15.5), prostate cancer: n=7, 5.3 (2.1–10.8)). The most common OIs were esophageal candidiasis (n=35) and cytomegalovirus disease (n=20), while pneumocystis jiroveci pneumonia was rare (n=12).

DISCUSSION

This is the first multinational cohort study, investigating CD4 count trends, and predictors for severe immunosuppression following diagnosis of the most common individual cancers in people with HIV.

We found that risk of post-CaD immunosuppression depended on cancer type, disseminated disease, male gender/sex and IDU as HIV acquisition mode. As expected, a higher CD4 count at CaD was a key protective factor against severe post-CaD immunosuppression. In contrast, neither age nor ethnicity/race or calendar year were significant predictors of CD4 decline, consistent with previous studies (5,6). Whilst we did not specifically investigate the uptake of OIP, we assessed predictors that allow identification of those at highest risk of severe post-CaD immunosuppression – the primary indication for OIP. We also showed that only 8-40% of people with HIV and common cancers develop immunosuppression at a level indicative of OIP, suggesting that with access to close CD4 count monitoring an individualized approach to use of OIP in cancer may be considered.

The proportion of participants with severe post-CaD immunosuppression varied by cancer type: those with KS had the highest proportion with CD4<200 cells/μL at time of CaD, likely due to the simultaneous diagnosis of KS and HIV, and subsequent CD4 counts recovery following ART initiation. Similarly, the highest proportion of ART-naïve participants at CaD was in those with KS, and the increasing CD4 counts after CaD reflecting ART initiation. In contrast, among participants with NHL, anal, and lung cancer, the proportion experiencing severe immunosuppression increased during the first 6–12 months after CaD, likely reflecting the impact of both cancer itself and its treatment, especially chemotherapy and radiotherapy (6,17–19).

Prior analyses from RESPOND and others showed high rates of disseminated disease and mortality after lung cancer in people with HIV (20–23). Despite fewer participants with lung cancer had CD4 count measurements during follow-up and documented low CD4 after CaD compared to those with anal cancer, they still experienced higher rates of AIDS-events. Since OIP was unavailable, we

speculate this may be partly explained by more aggressive treatment for lung cancer. Similarly, we are unable to clarify if the low rates of pneumocystis jiroveci pneumonia post-CaD were related to OIP and/or the high proportion of people maintaining CD4 count >200 cells/μL after CaD.

A prior study showed that CD4 count at CaD predicted the magnitude of treatment-related immune decline across a composite of cancers (6). Although we were not able to assess the impact of different cancer treatments, the study size allowed to investigate the trends and predictors after individual cancers with similar observations of immune status at CaD being the most significant protective factor against post-CaD severe immunosuppression. Whilst we did not identify a specific CD4 threshold at CaD at which the risk of severe post-CaD immunosuppression risk increases, participants with CD4 200-350 cells/μL at CaD had lower odds of post-CaD CD4<200 compared to those with a CD4<200 cells/μL. Conversely, disseminated cancer stage was an additional risk factor for severe post-CaD immunosuppression, potentially mediated by cancer treatment intensity, as in the general population, (24) as was male gender/sex, consistent with prior studies and likely reflecting biological differences in immune response (25,26).

The main limitations of this study were incomplete cancer treatment data (unavailable for 83% of participants) and a lack of OIP data. Even with the combined large size of D:A:D and RESPOND we were underpowered to use cancer-specific models and instead used pooled models for assessment of predictors. Regular post-CaD CD4 monitoring was missing for 19% of participants, either because monitoring was unsystematic or occurred elsewhere and the data were not available. Finally, our findings predominantly present outcomes in participants who survived >6months after CaD and had ≥2 available CD4 data. Our findings warrant additional investigations on OIP use in individual cancers to confirm the suggested CD4 guided risk approach.

In conclusion, CD4 trends after CaD in people with HIV who survived >6 months differ by several factors including CD4 count at CaD, cancer type, stage and gender/sex. Between 8-40% participants experienced severe post-CaD immunosuppression. Provided close CD4 count monitoring is feasible, our results may help in defining lower-risk groups for post-CaD immunosuppression and support a more individualized CD4 count guided strategy for OIP use in people with HIV and cancer.

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Institutional Review Board Statement

The study was conducted in accordance with the Declara-tion of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of all participating centres as per local and national requirements.

Authors contribution

AT, supervised by JL, LR, LP and LG, conceived the idea and developed the project proposal and a statistical analysis plan. All authors reviewed the proposal and analysis plan. LG performed the statistical analysis, which was reviewed by all authors. AT developed the first draft of the manuscript and revised the subsequent drafts. AT, LR, LP and LG reviewed all versions of the manuscript and interpreted the data. PD, PET, AE, CM, CMus, FW, AC, CL, ACas, KP, CS, AB, WES, JL, ASH, CC, AA, KG, HG, AM and LY contributed to the interpretation of data and reviewed the final draft of the manuscript.

Conflicts of Interest

Individual Conflicts of Interest statements for all authors will be submitted separately to the journal as required. HG, AM, LY are employees of ViiV Healthcare, Gilead Sciences and MSD, respectively.

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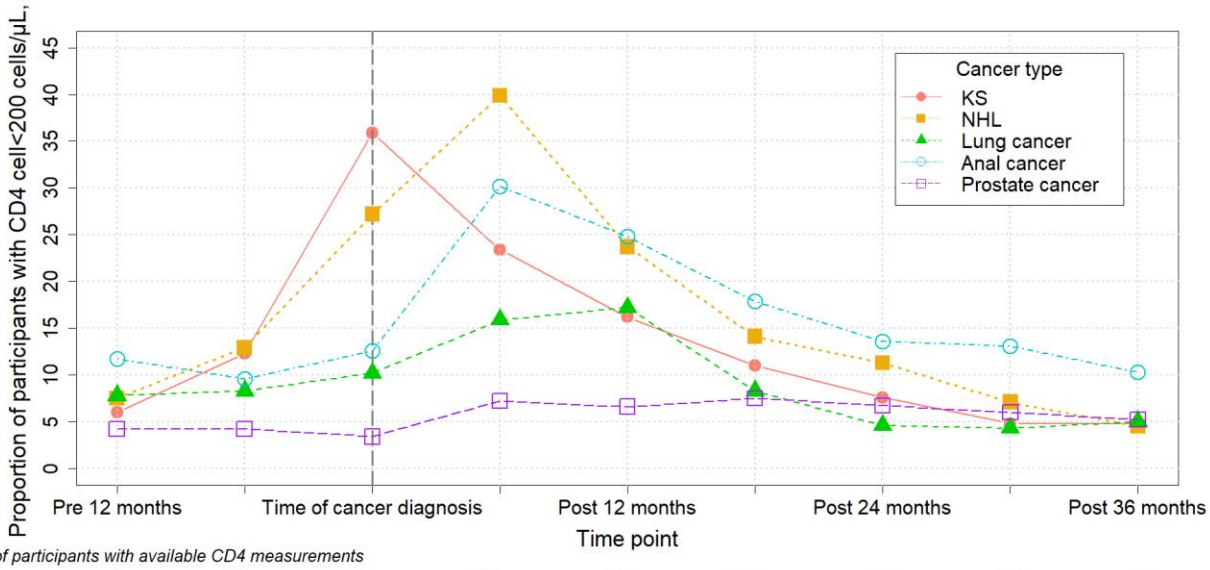
Figure 1. Proportion* of participants with CD4 count <200 cells/µL over time pre/post cancer diagnosis



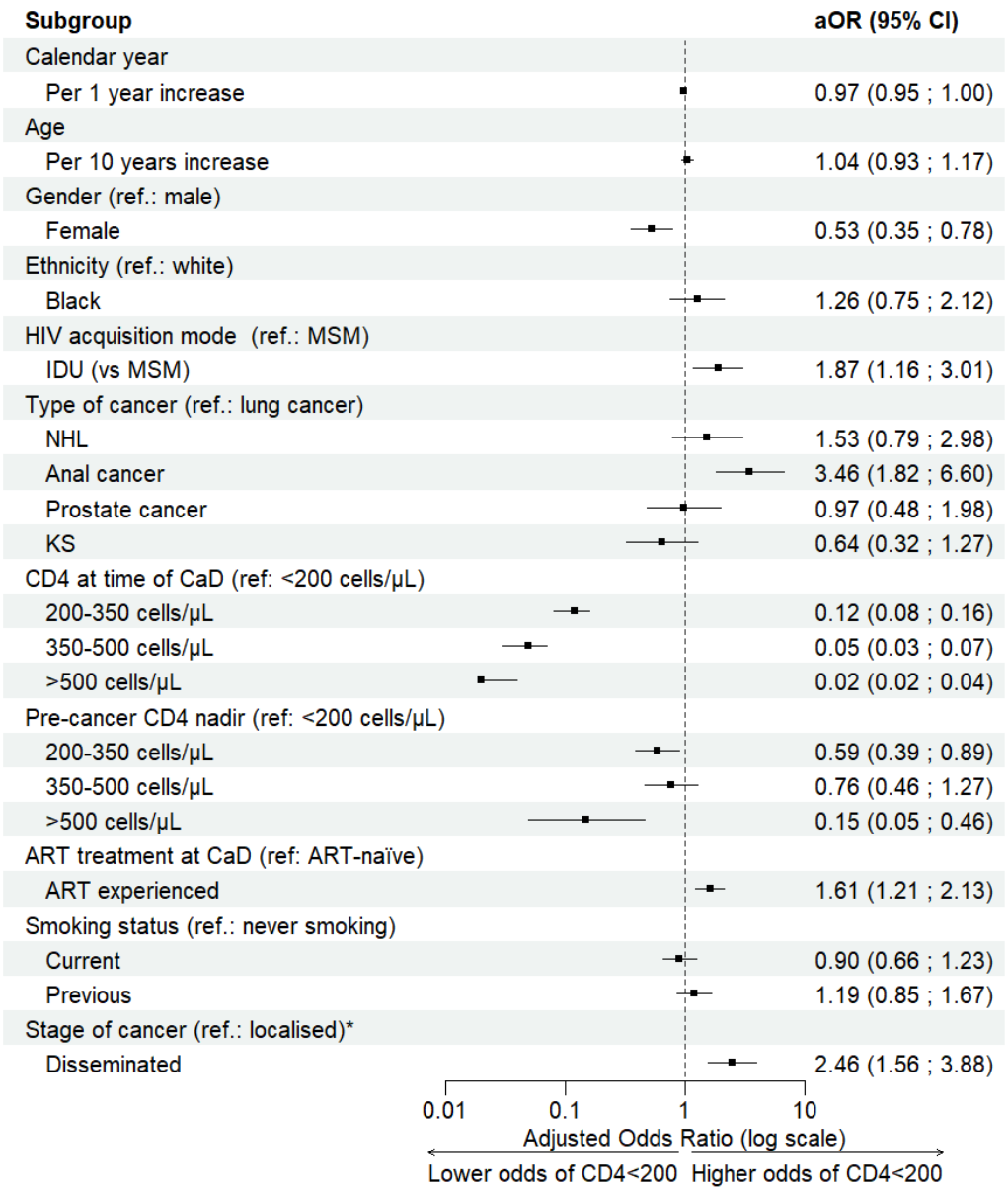
Number of participants with available CD4 measurements

KS	234	279	482	475	436	415	397	370	338
NHL	262	280	361	363	311	286	267	249	221
Lung cancer	172	173	188	193	132	88	71	60	49
Anal cancer	282	281	297	310	278	242	231	211	178
Prostate cancer	207	213	209	220	201	180	170	154	144

Abbreviations: KS – Kaposi's sarcoma, NHL – Non-Hodgkin's Lymphoma

*Proportions are calculated among the participants with known CD4 count. Participants with unknown CD4 count were excluded.

Figure 2. Adjusted Odds Ratios (aOR, (95% Confidence Interval) for CD4 <200 cells/µL after cancer diagnosis



Abbreviations: CaD – cancer diagnosis, IDU - injection drug user, MSM – men who have sex with men, NHL – non-Hodgkin lymphoma, KS – Kaposi's sarcoma, ART – antiretroviral treatment; ref. – reference group,

*Cancer stage data was available only for lung, anal and prostate cancer, therefore it was fit in a separate multivariable model assessing risk factors of CD4<200 in after these 3 cancers only