AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000004579

# 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

Alisa TIMIRYASOVA [1], Lauren GREENBERG [1], Pere DOMINGO [2], Philip E. TARR [3], Alexander EGLE [4], Charlotte MARTIN [5], Cristina MUSSINI [6], Ferdinand WIT [7], Antonella CINGOLANI [8], Clara LEHMANN [9,10], Antonella CASTAGNA [11], Kathy PETOUMENOS [12], Caroline A. SABIN [13], Alvaro BORGES [1,14], Wafaa EL-SADR [15], Jens LUNDGREN [1], Sean HOSEIN [16], Christina CARLANDER [17], Alain AMSTUTZ [18,19,20], Katharina GRABMEIER-PFISTERSHAMMER [21], Harmony GARGES [22], Andrea MARONGUI [23], Lital A. YOUNG [24], Lars PETERS [1], Lene RYOM [1,25,26] for the D:A:D and RESPOND Study Groups

[1] CHIP, Centre of Excellence for Health, Immunity and Infections; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark

[2] HIV Infeciton Unit. Hospital de la Santa Creu I Sant Pau. Sant Quintí, 89. 08025 Barcelona. Spain Reial Acadèmia de Medicina de Catalunya

[3] Swiss HIV Cohort Study (SHCS), University of Basel, Kantonsspital Baselland, 4101 Bruderholz, Switzerland

[4] 3rd Medical University Department, Paracelsus Medical University, Salzburg 5020, Austria

[5] Université Libre de Bruxelles, CHU Saint-Pierre, Infectious Diseases Dept, (322 rue Haute, 1000) Brussels, Belgium

[6] Modena HIV Cohort, Università Degli Studi Di Modena and Reggio Emilia, 41125 Modena, Italy

[7] AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, HIV Monitoring Foundation, 1105 BD Amsterdam, The Netherlands

[8] Italian Cohort Naive Antiretrovirals (ICONA), Fondazione Policlinico A. Gemelli, IRCCS, Roma, L.go A. Gemelli 8, 00168 Roma, Italy

[9] Department I of Internal Medicine, Medical Faculty and University Hospital Cologne, University of Cologne, 50937 Cologne, Germany

[10] German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, 50937 Cologne, Germany

[11] San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, Milano 20132, Italy

[12] The Australian HIV Observational Database (AHOD), Kirby Institute, UNSW, Sydney 2052, Australia

[13] Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, London NW3 2PF, UK

[14] Department of Infectious Disease Immunology, Center for Vaccine Research, Statens Serum Institut, Copenhagen, DK-2300, Denmark

[15] CPCRA (USA), CAP-Columbia University and Harlem Hospital, New York, NY, 10032, USA

[16] European AIDS Treatment Group, 1000 Brussels, Belgium

[17] Department of Infectious Diseases, Karolinska University Hospital, 141 86, Stockholm, Sweden

[18] Division of Clinical Epidemiology, University Hospital Basel, 4051 Basel, Switzerland

[19] Electronic Health Records Group, Population Health Sciences, Bristol Medical School,University of Bristol, Bristol BS8 1QU , UK

[20] Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, University of Oslo, 0372 Oslo, Norway

[21] Department of Dermatology, Medical University of Vienna, 1090 Vienna, Austria

[22]ViiV Healthcare, Global Medical, Durham, NC 277709, USA

[23]Gilead Sciences, Real World Evidence Virology department, London, WC1V 7EE, UK;

[24]Merck Sharp & Dohme, Global Medical Affair, Rahway, New Jersey 07065, USA

[25] Department of clinical medicine, University of Copenhagen, DK-1165 Copenhagen, Denmark

[26]Department of Infectious Diseases 144, Hvidovre University Hospital, DK-2650 Copenhagen, Denmark



**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

**Corresponding author:**

Alisa Timiryasova, CHIP, Centre of Excellence for Health, Immunity, and Infections. Section 2100,

Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

E-mail: alisa.timiryasova@regionh.dk

**Alternative corresponding author:**

Lene Ryom, CHIP, Centre of Excellence for Health, Immunity, and Infections. Section 2100,

Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark and Department of Infectious Diseases, 144, Hvidovre University Hospital, Copenhagen, Denmark

E-mail: lene.ryom@regionh.dk

This work has in part been presented in part at the International Workshop on HIV and Hepatitis Observational Databases (IWHOD) in Toledo, Spain 27-29th March 2025 and at the Nordic HIV & Virology conference at Stockholm, Sweden, 24-26th September 2025.

This work is not under consideration elsewhere.

* A complete list of authors and institutional affiliations is provided in the acknowledgments.

**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



## 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.

**Acknowledgements**

**Financial support**

The International Cohort Consortium of Infectious Disease (RESPOND) is supported by The CHU St Pierre Brussels HIV Cohort, The Austrian HIV Cohort Study, The Australian HIV Observational Database, The AIDS Therapy Evaluation in the Netherlands National Observational HIV cohort, The EuroSIDA cohort, The Frankfurt HIV Cohort Study, The Georgian National AIDS Health Information System, The Nice HIV Cohort, The ICONA Foundation, The Modena HIV Cohort, The PISCIS Cohort Study, The Swiss HIV Cohort Study, The Swedish InfCare HIV Cohort, The Royal Free HIV Cohort Study, The San Raffaele Scientific Institute, The University Hospital Bonn HIV Cohort, The University of Cologne HIV Cohort, The Brighton HIV Cohort and The National Croatian HIV cohort. RESPOND is further financially supported by ViiV Healthcare, Merck Life Sciences, Gilead Sciences,

Centre of Excellence for Health, Immunity and Infections (CHIP) and the AHOD cohort by grant No. GNT1050874 of the National Health and Medical Research Council, Australia.

**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.

**D:A:D study group**

**D:A:D study group**

D:A:D Participating Cohorts

Aquitaine, France; CPCRA, USA; NICE Cohort, France; ATHENA, The Netherlands; EuroSIDA, Europe; SHCS, Switzerland, AHOD, Australia; HIV-BIVUS, Sweden; St.Pierre Brussels Cohort, Belgium; BASS, Spain, The ICONA Foundation, Italy

**D:A:D Steering Committee**: Names marked with *, Chair with ¢

**Cohort PIs**: W El-Sadr* (CPCRA), G Calvo* (BASS), F Bonnet and F Dabis* (Aquitaine), O Kirk* and A Mocroft* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (Brussels)

**Cohort coordinators and data managers**: A Lind-Thomsen (coordinator), R Salbøl Brandt, M Hillebreght, S Zaheri, FWNM Wit (ATHENA), A Scherrer, F Schöni-Affolter, M Rickenbach (SHCS), A Tavelli, I Fanti (ICONA), O Leleux, J Mourali, F Le Marec, E Boerg (Aquitaine), E Thulin, A Sundström (HIVBIVUS), G Bartsch, G Thompsen (CPCRA), C Necsoi, M Delforge (Brussels), E

Fontas, C Caissotti, K Dollet (Nice), S Mateu, F Torres (BASS), K Petoumenos, A Blance, R Huang, R Puhr (AHOD), K Grønborg Laut, D Kristensen (EuroSIDA)

**Statisticians**: CA Sabin*¢, AN Phillips*, DA Kamara, CJ Smith, A Mocroft*

**D:A:D coordinating office**: CI Hatleberg, A Lind-Thomsen, RS Brandt, D Raben, C Matthews, A Bojesen, AL Grevsen, JD Lundgren*, L Ryom ¢

**Members of the D:A:D Oversight Committee**: B Powderly*, N Shortman*, C Moecklinghoff*, G Reilly*, X Franquet*

**D:A:D working group experts**:

Kidney: L Ryom ¢, A Mocroft*, O Kirk *, P Reiss*, C Smit, M Ross, CA Fux, P Morlat, E Fontas, DA Kamara, CJ Smith, JD Lundgren *

Mortality: CJ Smith, L Ryom ¢, CI Hatleberg, AN Phillips*, R Weber*, P Morlat, C Pradier*, P Reiss*, FWNM Wit, N Friis-Møller, J Kowalska, JD Lundgren*

Cancer: CA Sabin*¢, L Ryom ¢, CI Hatleberg, M Law*, A d'Arminio Monforte*, F Dabis*, F Bonnet*, P Reiss*, FWNM Wit, CJ Smith, DA Kamara, J Bohlius, M Bower, G Fätkenheuer, A Grulich, JD Lundgren*

**External endpoint reviewers**: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology)

**RESPOND Study Group**

**AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA):** F Wit, M van der Valk, M Hillebregt, Stichting HIV Monitoring (SHM), Amsterdam, Netherlands

**The Australian HIV Observational Database (AHOD):** K Petoumenos, M Law, J Hutchinson, D Rupasinghe, W Min Han, UNSW, Sydney, Australia

**Austrian HIV Cohort Study (AHIVCOS):** R Zangerle, H Appoyer, Medizinische Universität Innsbruck, Innsbruck, Austria

**Brighton HIV cohort:** J Vera, A Clarke, B Broster, L Barbour, D Carney, L Greenland, R Coughlan, Lawson Unit, Royal Sussex County Hospital, University Hospitals Sussex NHS Foundation Trust, Brighton, United Kingdom

**CHU Saint-Pierre**: C Martin, S De Wit, M Delforge, Centre de Recherche en Maladies Infectieuses a.s.b.l., Brussels, Belgium

**Croatian HIV cohort:** J Begovac, University Hospital of Infectious Diseases, Zagreb, Croatia

**EuroSIDA Cohort**: G Wandeler, CHIP, Rigshospitalet, RegionH, Copenhagen, Denmark

**Frankfurt HIV Cohort Study:** C Stephan, M Bucht, Johann Wolfgang Goethe-University Hospital, Frankfurt, Germany

**Infectious Diseases, AIDS and Clinical Immunology Research Center (IDACIRC):** A Abutidze, O Chokoshvili, Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia

**Italian Cohort Naive Antiretrovirals (ICONA):** A d'Arminio Monforte, A Rodano, A Tavelli, ASST Santi Paolo e Carlo, Milan, Italy; I Fanti, Icona Foundation, Milan, Italy

**Modena HIV Cohort**: C Mussini, V Borghi, M Menozzi, A Cervo, Università degli Studi di Modena, Modena, Italy

**Nice HIV Cohort**: C Pradier, E Fontas, K Dollet, C Caissotti, Université Côte d'Azur et Centre Hospitalier Universitaire, Department of Public Health, Nice, France

**PISCIS Cohort Study:** J Casabona, JM Miro, JM Llibre, A Riera, J Reyes- Urueña, Centre Estudis Epidemiologics de ITS i VIH de Catalunya (CEEISCAT), Badalona, Spain

**Royal Free Hospital Cohort:** F Burns, C Smith, F Lampe, C Chaloner, Royal Free Hospital, University College London, London, United Kingdom

**San Raffaele Scientific Institute:** A Castagna, A Lazzarin, A Poli, R Lolatto, Università Vita-Salute San Raffaele, Milano, Italy

**Swedish InfCare HIV Cohort:** C Carlander, A Sönnerborg, P Nowak, J Vesterbacka, L Mattsson, D Carrick, K Stigsäter, Department of Infectious Diseases, Karolinska University Hospital, and Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet, Sweden

**Swiss HIV Cohort Study (SHCS):** H Günthard, B Ledergerber, H Bucher, K Kusejko, University of Zurich, Zurich, Switzerland

**University Hospital Bonn:** JC Wasmuth, J Rockstroh, Bonn, Germany

**University Hospital Cologne:** C Lehmann, G Fätkenheuer, M Scherer, G Sauer, Cologne, Germany

**RESPOND Executive Committee**

L Ryom∗, K Petoumenos∗, J Rooney, M Dunbar, R Campo, C Mussini, C Martin, J van Wyk, H Günthard, J Lundgren, V Vannappagari, L Young, R Zangerle (*Chairs)

**RESPOND Scientific Steering Committee**

J Lundgren∗, H Günthard∗, J Begovac, C Martin, F Burns, A Castagna, R Campo, D Thorpe, J van Wyk, J Kowalska, C Mussini, L Peters, O Kirk, H Butcher, J Vera, K Petoumenos, C Pradier, D Raben, J Rooney, L Ryom, C Carlander, V Vannappagari, C Lehmann, N Dedes, J Rockstroh, A Volny-Anne, F Wit, L Young, R Zangerle (*Chairs)

**RESPOND Cancer Working Group Members**

L Greenberg, A Timiryasova, L Ryom, B Neesgaard, F Wit, A Castagna, C Duvivier, JJ Vehrechild, C Hatleberg, E Fontas, P Gabunia, H Bucher, A Borges, JM Miro, J Hoy, M Law, PM Peterson, V Vannappagari, A Marongiu, I McNicholl, F Rogatto, N Jaschinski, L Young, G Clifford, M Bower, L Peters, K Petoumenos, F Chammartin, C Muccini, J Brännström, C Carlander, M Bottanelli, S Malnström

**External Clinical Reviewers**

Kirstine Lærum Sibilitz (Clinical Cardiology), P Meidal Petersen (Clinical Oncology)

**Community Representatives**

A Volny-Anne, N Dedes, L Mendão (European AIDS Treatment Group), E Dixon Williams (UK)

**RESPOND Staff**

Coordinating Centre and Data Management: N Jaschinski, A Timiryasova, B Neesgaard, O Valdenmaier, M Gardizi, TW Elsing, L Ramesh Kumar, S Shahi, JF Larsen, D Raben, L Peters, L Ryom

Statistical Staff: L Greenberg, L Bansi-Matharu, K Petoumenos, W Min Han, W Bannister

**References:**


1. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. **Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): A multicohort collaboration.** *The Lancet.* 2014 Jul 19;384(9939):241–8. doi:10.1016/S0140-6736(14)60604-8

2. Tusch E, Ryom L, Pelchen-Matthews A, Mocroft A, Elbirt D, Oprea C, et al. **Trends in Mortality in People With HIV From 1999 through 2020: A Multicohort Collaboration.** *Clin Infect Dis.* 2024 Nov 22;79(5):1242–57.

3. Trickey A, McGinnis K, Gill MJ, Abgrall S, Berenguer J, Wyen C, et al. **Longitudinal trends in causes of death among adults with HIV on antiretroviral therapy in Europe and North America from 1996 to 2020: a collaboration of cohort studies.** *Lancet HIV*.

2024 Mar 1;11(3):e176–85. doi:10.1016/S2352-3018(23)00272-2 PubMed PMID: 38280393.

4. Kesselring A, Gras L, Smit C, Van Twillert G, Verbon A, De Wolf F, et al. **Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy.** *Clin Infect Dis*. 2011 Jun 15;52(12):1458–65. doi:10.1093/cid/cir207

5. Riedel DJ, Stafford KA, Vadlamani A, Redfield RR. **Virologic and immunologic outcomes in HIV-infected patients with cancer.** *AIDS Res Hum Retroviruses.* 2017 May 1;33(5):482–9. doi:10.1089/aid.2016.0181

6. Calkins KL, Chander G, Joshu CE, Visvanathan K, Fojo AT, Lesko CR, et al. **Immune Status and Associated Mortality after Cancer Treatment among Individuals with HIV in the Antiretroviral Therapy Era**. *JAMA Oncol*. 2020 Feb 1;6(2):227–35. doi:10.1001/jamaoncol.2019.4648 PubMed PMID: 31804663.

7. World Health Organization (WHO) Guidelines. **Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery And Monitoring.** *Optics InfoBase Conference Papers.* 2021. 249 p. Available from: ISBN: 978-92-4-003159-3

8. **European AIDS Clinical Society (EACS) Guidelines v.13.0.** 2025. Available from: https://eacs.sanfordguide.com/eacs-part2/cancer/cancer-treatment-monitoring

9. Kaplan J, Benson C, Holmes K, Brooks J, Pau A, Masur H, et al. **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America**. *MMWR Recomm Rep.* 2009. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm

10. Gandhi R, Landovitz R, Sax P, Smith DM, Springer SA, Günthard HF, et al. **Antiretroviral Drugs for Treatment and Prevention of HIV in Adults: 2024 Recommendations of the International Antiviral Society–USA Panel**. *JAMA*. 2024 Dec 1;333(7):609–28.

11. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, D'Arminio Monforte A, et al. **Cardiovascular disease risk factors in HIV patients - Association with antiretroviral therapy. Results from the DAD study.** *AIDS.* 2003 May 23;17(8):1179–93. doi:10.1097/00002030-200305230-00010

12. The RESPOND Study Group. **How to RESPOND to modern challenges for people living with HIV: A profile for a new cohort consortium**. *Microorganisms.* 2020 Jul 27;1164(8). doi:10.3390/microorganisms8081164

13. D:A:D study group. **Manual of Operations MOOP Data Collection on Adverse Events of Anti-HIV Drugs.** *D:A:D study website,* 2013. Available from: https://chip.dk/Research/Studies/DAD/Study-Documents

14. RESPOND study group. **Manual of Operations (MOOP) for clinical events**. *RESPOND study website,* 2025. Available from: https://chip.dk/Research/Studies/RESPOND/Study-documents

15. Greenberg L, Ryom L, Bakowska E, Wit F, Bucher HC, Braun DL, et al. **Trends in Cancer Incidence in Different Antiretroviral Treatment-Eras amongst People with HIV.** *Cancers* (Basel). 2023 Jul 1;15(3640). doi:10.3390/cancers15143640

16. Fine JP, Gray RJ. A Proportional Hazards **Model for the Subdistribution of a Competing Risk.** *J Am Stat Assoc.* 1999 Jul 1;94(446):496–509. doi:10.1080/01621459.1999.10474144

17. Mayer KH, Torres HA, Mulanovich V**. Management of HIV infection in patients with cancer receiving chemotherapy.** *Clin. Infect. Dis.* 2014 Mar 18;59(1):106–14. doi:10.1093/cid/ciu174

18. Pfister NT, Cao Y, Schlafstein AJ, Switchenko J, Patel PR, McDonald MW, et al. **Factors Affecting Clinical Outcomes Among Patients Infected With HIV and Anal Cancer Treated With Modern Definitive Chemotherapy and Radiation Therapy**. *Adv Radiat Oncol*. 2023 Dec;8(2). doi:10.1016/j.adro.2022.101155

19. Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen SE, et al. **Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**. *Annals of Oncology*. 2021;32(9):1087–100. doi:10.1016/j.annonc.2021.06.015

20. Coghill AE, Han X, Suneja G, Lin CC, Jemal A, Shiels MS. **Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base.** *Cancer.* 2019 Aug 15;125(16):2868–76. doi:10.1002/cncr.32158 PubMed PMID: 31050361.

21. Yuan T, Hu Y, Zhou X, Yang L, Wang H, Li L, et al. **Incidence and mortality of non-AIDS-defining cancers among people living with HIV: A systematic review and meta-analysis**. *EClinicalMedicine*. 2022 Oct;52. doi:10.1016/j.eclinm.2022.101613

22. Trickey A, May MT, Gill M, Grabar S, Vehreschild J, Wit FWNM, et al. **Cause-specific mortality after diagnosis of cancer among HIV-positive patients: A collaborative analysis of cohort studies.** *Int J Cancer.* 2020;146(11):3134–46. doi:10.1002/ijc.32895

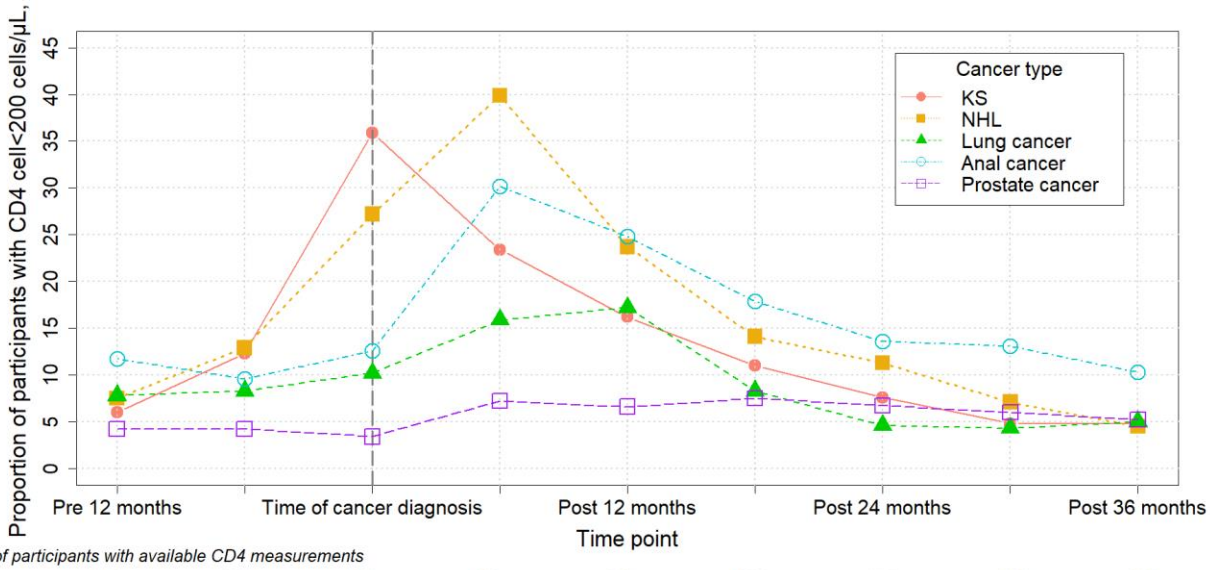
23. Timiryasova A, Greenberg L, Domingo P, Tarr PE, Egle A, Martin C, et al. **Mortality and Non-Fatal Clinical Outcomes After the Most Common Cancers in People with HIV: A Multicohort Collaboration.** *Cancers (Basel).* 2025 Dec 16;17(24):4000. doi:10.3390/cancers17244000

24. Lyman GH. **Impact of chemotherapy dose intensity on cancer patient outcomes**. *J Natl Compr Canc Netw.* 2009 Jan 7;7(1):99–108. doi:10.6004/jnccn.2009.0009

25. Nash D, Katyal M, Brinkhof M, Keiser O, May M, Hughes R, et al. **Long-term immunologic response to antiretroviral therapy in low-income countries: A collaborative analysis of prospective studies.** *AIDS.* 2008 Nov 12;22(17):2291–302. doi:10.1097/QAD.0b013e3283121ca9

26. Maskew M, Brennan AT, Westreich D, McNamara L, MacPhail AP, Fox MP. **Gender differences in mortality and CD4 count response among virally suppressed HIV-positive patients.** *J Womens Health.* 2013 Feb;22(2):113–20. doi:10.1089/jwh.2012.3585

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



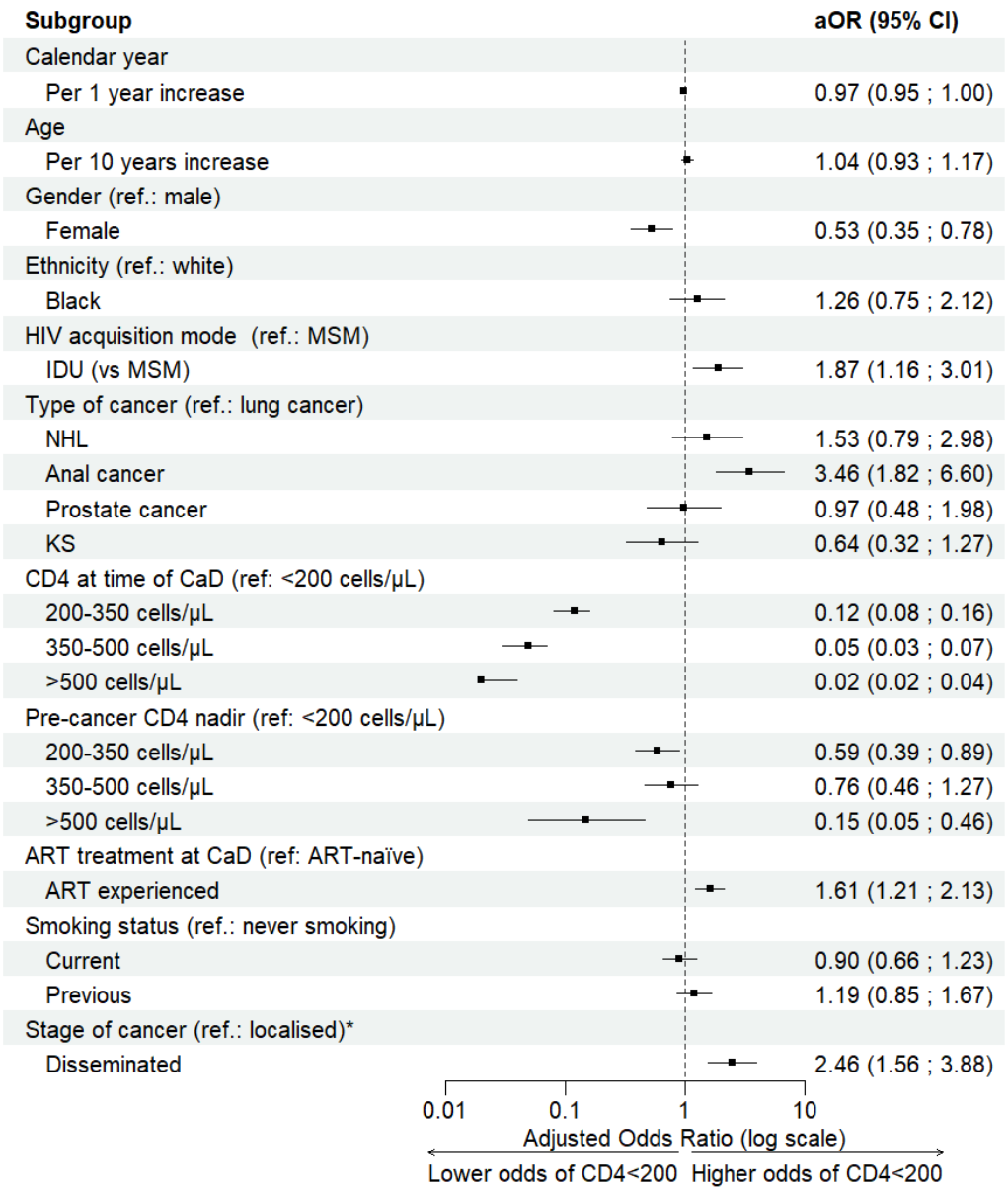

*Number of participants with available CD4 measurements*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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