INCREASED CANCER RISK WITH LOW CD4 COUNTS PERSISTS DESPITE OVER 2 YEARS OF VIROLOGICAL SUPPRESSION

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BACKGROUND

- Cancer is a leading cause of death amongst people with HIV[1]. While the incidence of AIDS-defining cancers (ADCs) has significantly decreased with antiretroviral therapy (ART), studies have reported inconsistent results on changes in the incidence of non-ADCs (NADCs)[2-3].
- While the risk of ADCs drops with increased time spent with a higher CD4 cell count, the reduction in risk is less clear for NADC, especially once individuals have achieved HIV viral suppression (VS).
- We aimed to assess cancer risk in virologically suppressed people with HIV, but with suboptimal immune reconstitution.

METHODS

- Data was drawn from the D:A:D and RESPOND multi-cohort collaborations, comprising 49,000 people with HIV in D:A:D, and 35,000 people with HIV in RESPOND.
- Individuals with at least 2 years of VS on ART were considered for inclusion; follow-up was from the point of meeting this criteria (baseline) until the earliest of a first cancer event, confirmed virological failure (>200 copies/mL) or cessation of ART for >2 months, final follow-up, or administrative censoring (D:A:D: 1 Feb 2016; RESPOND: 31 Dec 2021).
- Cancers were divided into ADCs and NADCs, and then separately into infection-, smoking-, and BMI-related cancers[1] (the latter were not mutually exclusive).
- Multivariable Poisson regression was used to assess associations between cancer incidence and time updated CD4 count (<350, 350-499, 500-749 and ≥750 cells/μL) stratified by pre-ART nadir CD4 count and adjusted for confounders (footnote figure 1).

RESULTS

- Overall, 51,622 people with VS were included (median [IQR] baseline age 44 years [37, 51], CD4 count 536 cells/μL [376, 729], nadir CD4 count 238 cells/μL [112, 386], 72% male, 36% current smokers).
- 2152 incident cancers occurred during a total of 321,126 person-years of follow-up (PYFU), median 6 years [2.9, 9.5]).

[1] Greenberg L. et al. Cancers 2023; 15(14). [2] Park LS, et al. AIDS. 2016 [3] Worm SW, et al. BMC Infect Dis. 2013.

Despite over 2 years of virological suppression on ART, individuals with poor immune recovery experience a higher incidence of NADC.

This underscores the importance of early diagnosis of HIV with prompt initiation of ART to ensure optimal sustained risk reduction of both ADC and NADC.

- The crude incidence rate of all cancers and cancer subgroups was significantly higher in those with low CD4 counts prior to starting ART (Table 1) and in those with lower recent (time-updated) CD4 counts (Figure 1).
- People who achieved higher CD4 counts on ART had a lower Incidence Rate Ratio of all cancers and cancer subgroups compared with those whose CD4 counts remained below 350 cells/μL after adjustment for potential confounders (Figure 2).

Table 1. Crude incidence rate per 1000 PYFU (and 95%CI) of overall and grouped cancers

	PYFU	All cancers		AIDS-defining cancers		Non-AIDS-defining cancers		Infection-related cancers		Smoking-related cancers		BMI-related cancers	
		No.	Incidence (95% CI)	No.	Incidence (95% CI)	No.	Incidence (95% CI)	No.	Incidence (95% CI)	No.	Incidence (95% CI)	No.	Incidence (95% CI)
Overall	321,126	2152	6.70 (6.42, 6.99)	276	0.86 (0.76, 0.97)	1876	5.84 (5.58, 6.11)	721	2.24 (2.08, 2.41)	927	2.89 (2.70, 3.08)	491	1.53 (1.40, 1.67)
Sex													
Male	242,071	1714	7.08 (6.75, 7.42)	208	0.86 (0.74, 0.98)	1506	6.22 (5.91, 6.54)	597	2.47 (2.27, 2.67)	741	3.06 (2.85, 3.29)	353	1.46 (1.31, 1.62)
Female	79,054	438	5.03 (4.55, 5.54)	68	0.72 (0.55, 0.93)	370	4.31 (3.87, 4.80)	123	1.39 (1.14, 1.68)	186	2.14 (1.83, 2.49)	138	1.66 (1.39, 1.97)
Age at baseline													
≤50 years	235108	1035	4.40 (4.14, 4.68)	170	0.72 (0.62, 0.84)	865	3.68 (3.44, 3.93)	424	1.80 (1.64, 1.98)	417	1.77 (1.61, 1.95)	259	1.10 (0.97, 1.24)
≥50 years	86017	1117	13.0 (12.2, 13.8)	106	1.23 (1.01, 1.49)	1011	11.75 (11.04, 12.5)	296	3.44 (3.06, 3.86)	510	5.93 (5.43, 6.47)	232	2.70 (2.36, 3.07)
Pre-ART nadir CD4 count (cells/μL)													
<200	146204	1150	7.87 (7.42, 8.33)	158	1.08 (0.92, 1.26)	992	6.79 (6.37, 7.22)	416	2.85 (2.58, 3.13)	513	3.51 (3.21, 3.8.)	257	1.76 (1.55, 1.99)
200-350	99070	614	6.20 (5.72, 6.71)	63	0.64 (0.49, 0.81)	551	5.56 (5.11, 6.05)	174	1.76 (1.51, 2.04)	261	2.63 (2.32, 2.97)	154	1.55 (1.32, 1.82)
>350	75851	388	5.15 (4.62, 5.65)	55	0.73 (0.55, 0.94)	333	4.39 (3.93, 4.89)	130	1.71 (1.43, 2.04)	153	2.17 (1.71, 2.36)	80	1.05 (0.84, 1.31)

Figure 1. Association of time-updated CD4 cell count with incidence of any cancer and cancer subgroup

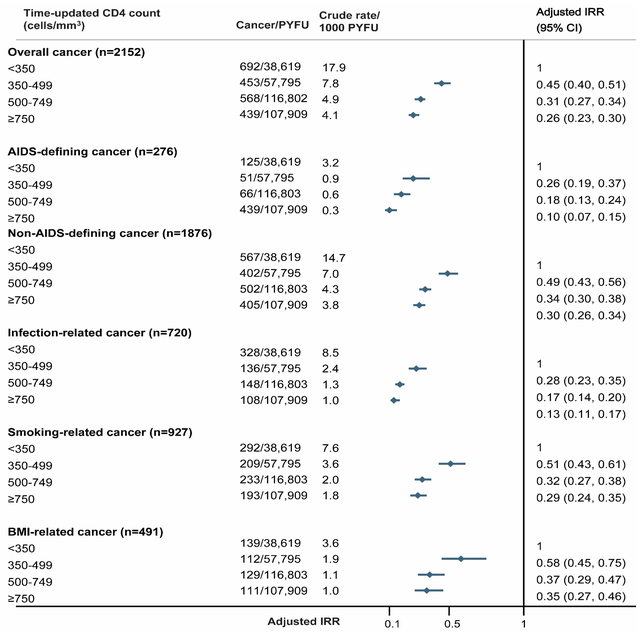
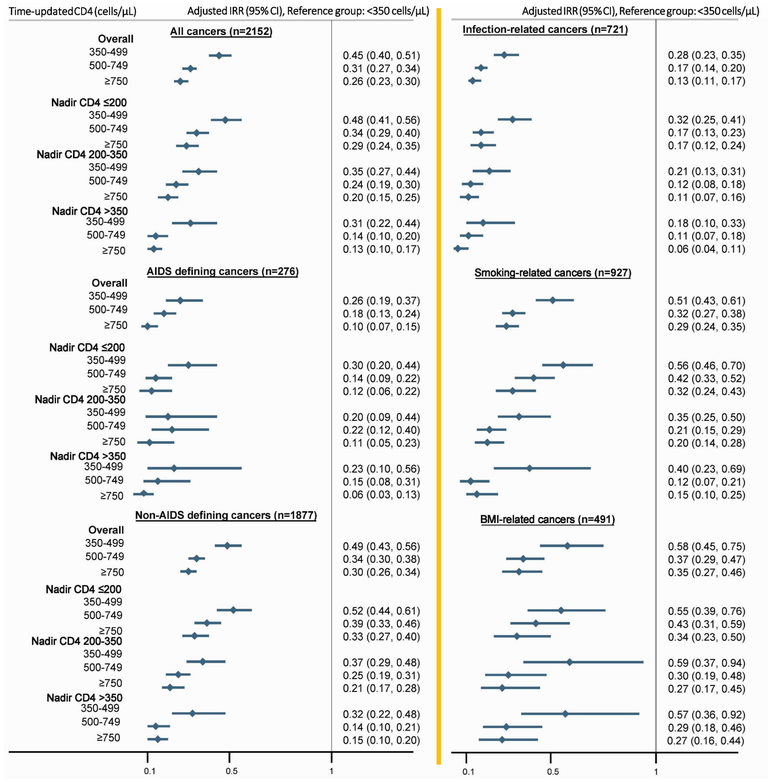


Figure 2. Association of time-updated CD4 with overall cancer incidence and cancer subgroups by nadir CD4 cell count



Footnote Figure 1
Poisson regression models were adjusted for a priori determined factors: gender, ethnicity, geographical region, HIV transmission risk group, duration since HIV diagnosis, prior AIDS non-cancer event, prior ADC, prior NADC, HCV, HBV, BMI, hypertension, diabetes ,cardiovascular disease, chronic kidney disease, and dyslipidaemia all fixed at baseline. Time updated covariates included age, smoking status, as well as any exposure to INSTIs, PIs, nucleoside reverse transcriptase inhibitors (NRTIs), and non-NRTIs (NNRTIs) (as cumulative exposure).

LIMITATIONS

- A median follow-up time of 6 years may be too short for the development of cancer; data on cancer screening and prevention, family history, alcohol consumption and other unmeasured confounders were not collected. Our classification of BMI-, smoking- and infection-related cancers may not be 100% sensitive or specific.

CONCLUSIONS

- A significant reduction in the incidence of all cancers was seen in those who achieved greater CD4 recovery when virologically suppressed on ART for at least 2 years.
- This study provides more support for the importance of strategies to diagnose and treat HIV as soon as possible after acquisition of HIV to ensure optimal sustained risk reduction of both ADC and NADC.

The RESPOND Study Group:
https://www.chip.dk/Studies/RESPOND/Study-Group

The D:A:D Study Group:
https://www.chip.dk/Studies/DAD/Study-Group

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