RESPOND International Cohort Consortium of Infectious Diseases

D:A:D

Risk of cancer in people with HIV with poor immune recovery despite sustained virological suppression for >2 years on effective ART

Working group: Win Min Han, Lene Ryom, Caroline Sabin, Lauren Greenberg, Kathy Petoumenos, Jennifer Hoy
on behalf of RESPOND and D:A:D cohort collaborations

Australian HIV & AIDS Conference 2024, 16-18 September, ICC, Sydney

Acknowledgements

- Acknowledge country

- All people with HIV who have generously participated in this research

Disclosure of interests

- No conflicts of interests to declare

Background

- Landscape in HIV care – shift from opportunistic infections and AIDS-related cancers to aging-related conditions, including non-AIDS cancers
- Better immune recovery reduces AIDS-defining cancer risk
- Impact on non-AIDS cancers remains unclear, especially with sustained viral suppression
- **RESPOND and D:A:D –** prospective, multi-cohort collaborations from across Europe, Australia and North America, comprising ~49,000 people with HIV from 11 cohorts in D:A:D (2004-2016), and 35,000 people from 17 cohorts in RESPOND (2017-ongoing)

Anna Maria Cattelan et al. Cancers 2024; Lauren Greenberge et al. Cancers 2024; Hernández-Ramírez RU et al. Lancet HIV 2017; Tanwei Yuan et al. eClin Med 2022; Frédérique Chammartin et al. Ann Int Med 2021; Malmström S et al. AIDS 2022.

Objective

- Using larger cohort and longer-term follow-up from the combined RESPOND and D:A:D studies, we assessed whether poor immune recover despite viral suppression is associated with an increased risk of cancer
- And whether these trends vary by pre-ART nadir CD4 counts

Methods

- People with HIV ≥18 years in RESPOND and D:A:D cohorts who achieved **at least 2 years of viral suppression (VS) on ART** were included
- Follow-up was from ***baseline (date of VS for 2 years)*** 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 date
- Participants were required to have:

❑ >1 CD4 count available in addition to baseline measurement,

❑ >1 CD4 count in the year prior to the cancer diagnosis,

❑ an average of 1 CD4 count each 2 years of follow-up to the cancer event or last visit date

Methods

- **Multivariable Poisson regression** was used to assess associations between time updated CD4 count (<350, 350-499, 500-749 and >750 cells/µL) and cancer incidence:

❑ Cancer overall (excluding pre-cancer dysplasia, non-melanoma skin cancers and cancer relapse)

❑ AIDS-defining cancer (ADC) (NHL, KS and cervical cancer)

❑ Non-AIDS defining cancers (NADC) (infection-related, smoking-related, and obesity-related cancer)

- **Adjusted incidence rates and 95% CIs** were calculated for any cancer overall and each cancer group separately

Methods

- **Analyses were stratified by pre-ART nadir CD4 count** and adjusted for **confounders** determined a priori:

Fixed at baseline covariates:

- sex, ethnicity, geographical region, HIV mode of acquisition, HBV, HCV, BMI, smoking, hypertension, diabetes, dyslipidemia, a prior non-cancer AIDS event, end stage liver and kidney disease, cardiovascular disease, or chronic kidney disease and a prior ADC or NADC

Time-updated covariates:

- Age and any exposure to antiretroviral drugs (NRTI, NNRT, PI, and INSTI)

- Associations between **change in CD4 count**, **pre-ART nadir CD4 count**, and cancer risks were also investigated

❑Change in CD4 count from baseline = Time-updated CD4 – baseline CD4

Results

- 51,622 (*75% male; 56% White and 7% Black*) participants with ≥2 years of viral suppression included from 37 countries in Europe and Australia
- At baseline, median age was 44 (IQR 37, 51) years, median time since HIV diagnosis was 7·7 (3·4, 13·8) years
- Median pre-ART nadir CD4 count was 238 (112, 386) cells/µL
- 37·1% were current smokers, 5·8% and 22% were overweight and obese

Baseline participants characteristics

- 2152 (4·2%) participants developed cancer during follow-up
- At baseline, participants with cancer were older (51 vs. 44 years), while the median CD4 count at baseline (510 vs. 537 [cells/µL), and the median pre-ART nadir CD4 (181 vs. 240 cells/µL) were each lower in the cancer group
- Higher proportions of current smokers (44·3% vs. 36·7%), prior cancer diagnosis (10·2% vs 6·2%), and HBV (5·6% vs. 4·0%) or HCV (25% vs. 20%) at baseline in participants w/ cancers
- Slightly higher proportion of people reported injecting drug use as transmission risk in the cancer group (17.4% vs. 12.8%)

Cancer incidence

During 321,126 person-years of follow-up (PYFU) (median follow-up: 6·0 [IQR 2·9, 9·5] years):

	All cancers		AIDS-defining cancers		Non-AIDS-defining cancers	
	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	2152	6·7 (6·2, 7.0)	276	0·9 (0·8, 1.0)	1876	5·8 (5·6, 6·1)
Sex						
Male	1714	7·1 (6·7, 7·4)	208	0·9 (0·7, 1.0)	1506	6·2 (5·9, 6·5)
Female	438	5·0 (4·5, 5·5)	68	0·7 (0·6, 0·9)	370	4·3 (3·9, 4·8)

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Age at baseline, years						
≤50	1035	4·4 (4·1, 4·7)	170	0·7 (0·6, 0·8)	865	3· (3·4, 3·9)
>50	1117	13·0 (12·2, 13·8)	106	1·2 (1·0, 1·5)	1011	11·8 (11·0, 12·5)
Pre-ART nadir CD4, cells/µL						
<200	1150	7·9 (7·4, 8·3)	158	1·1 (0·9, 1·3)	992	6·8 (6·37, 7·22)
200-350	614	6·2 (5·7, 6·7)	63	0·6 (0·5, 0·8)	551	5·6 (5·11, 6·05)
>350	388	5·2 (4·6, 5·6)	55	0·7 (0·5, 0·9)	333	4·4 (3·93, 4·89)

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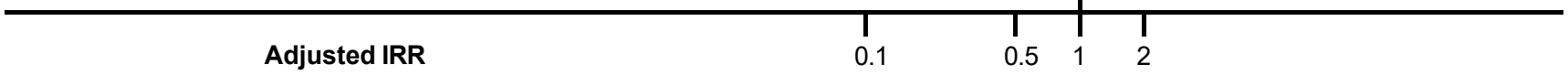
Most common cancers in D:A:D and RESPOND

AIDS-defining cancers (n=276)		Non-AIDS-defining cancers (n=1877)		Infection-related cancers (n=721)		Smoking-related cancers (n=927)		Obesity-related cancers (N=491)	
Cancer	Number (%)	Cancer	Number (%)	Cancer	Number (%)	Cancer	Number (%)	Cancer	Number (%)
Non-Hodgkin's Lymphoma	161 (58.3)	Lung cancer	263 (14.0)	Anal cancer	189 (26.2)	Lung cancer	263 (28.4)	Liver cancer	129 (26.3)
Kaposi's Sarcoma	73 (26.4)	Anal cancer	189 (10.1)	Non-Hodgkin's Lymphoma	161 (22.3)	Liver cancer	129 (13.9)	Breast cancer	83 (16.9)
Cervical cancer	42 (15.2)	Prostate cancer	178 (9.5)	Liver cancer	129 (17.9)	Unspecified head and neck cancer	87 (9.4)	Colon cancer	76 (15.5)

Time-updated CD4 counts and cancer association

Time-updated CD4 count (cells/μL)	Cancer/ PYFU	Crude rate/ 1000 PYFU	Adjusted IRR (95% CI)	P-value
Overall cancer (n=2152)				<0·0001
<350	692/38,619	17·9	1	
350-499	453/57,795	7·8	0·45 (0·40, 0·51)	
500-749	568/116,802	4·9	0·31 (0·27, 0·34)	
≥750	439/107,909	4·1	0·26 (0·23, 0·30)	

	Cancer/PYFU	Incidence rate/1000 PYFU	aIRR (95% CI)	
AIDS-defining cancer (n=276)				<0·0001
<350	125/38,619	3·2	1	
350-499	51/57,795	0·9	0·26 (0·19, 0·37)	
500-749	66/116,803	0·6	0·18 (0·13, 0·24)	
≥750	439/107,909	0·3	0·10 (0·07, 0·15)	
Non-AIDS-defining cancer (n=1876)				<0·0001
<350	567/38,619	14·7	1	
350-499	402/57,795	7	0·49 (0·43, 0·56)	
500-749	502/116,803	4·3	0·34 (0·30, 0·38)	
≥750	405/107,909	3·8	0·30 (0·26, 0·34)	
Infection-related cancer (n=720)				<0·0001
<350	328/38,619	8·5	1	
350-499	136/57,795	2·4	0·28 (0·23, 0·35)	
500-749	148/116,803	1·3	0·17 (0·14, 0·20)	
≥750	108/107,909	1·0	0·13 (0·11, 0·17)	
Smoking-related cancer (n=927)				<0·0001
<350	292/38,619	7·6	1	
350-499	209/57,795	3·6	0·51 (0·43, 0·61)	
500-749	233/116,803	2·0	0·32 (0·27, 0·38)	
≥750	193/107,909	1·8	0·29 (0·24, 0·35)	
Obesity-related cancer (n=491)				<0·0001
<350	139/38,619	3·6	1	
350-499	112/57,795	1·9	0·58 (0·45, 0·75)	
500-749	129/116,803	1·1	0·37 (0·29, 0·47)	
≥750	111/107,909	1·0	0·35 (0·27, 0·46)	



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D:A:D

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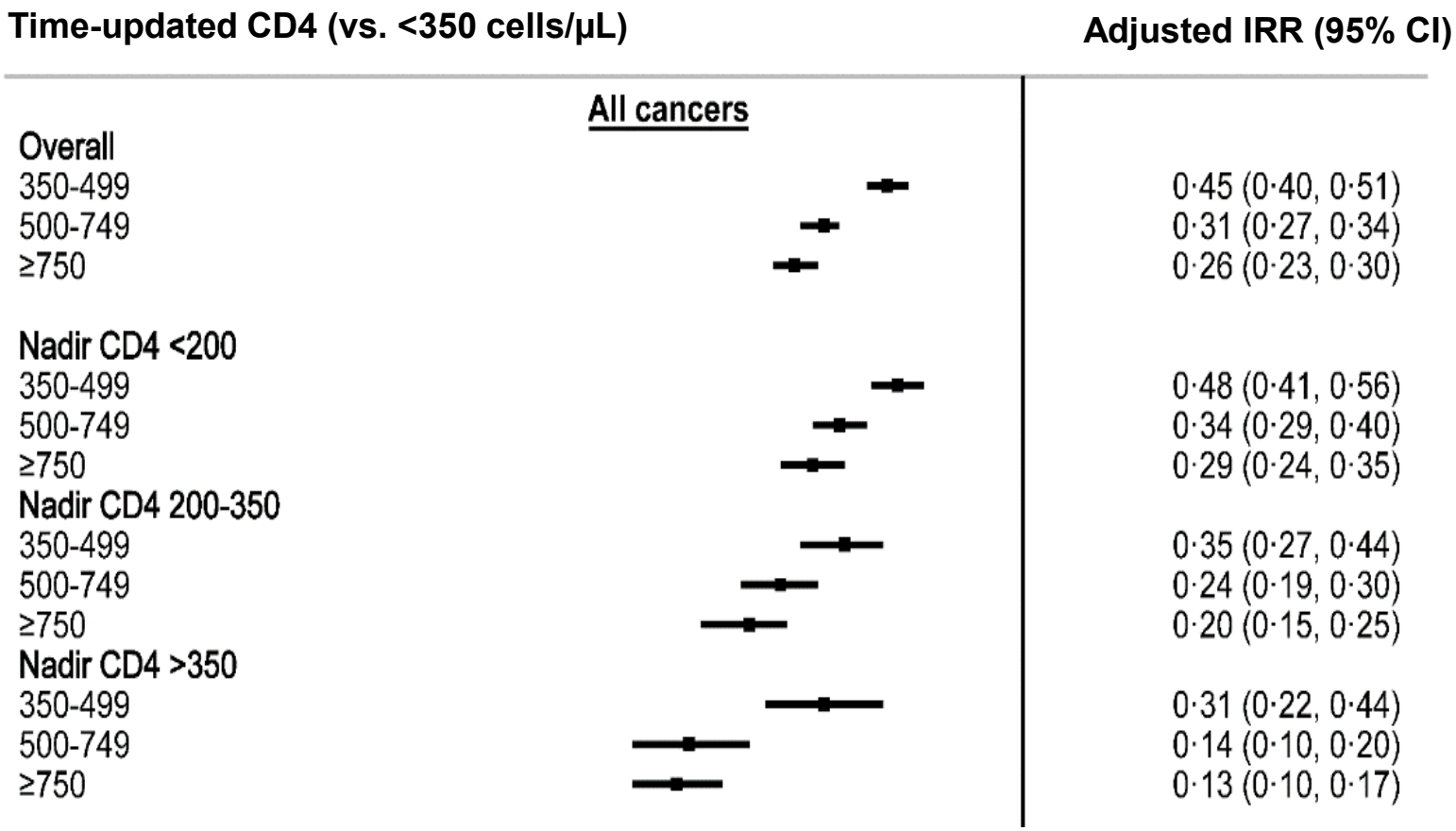
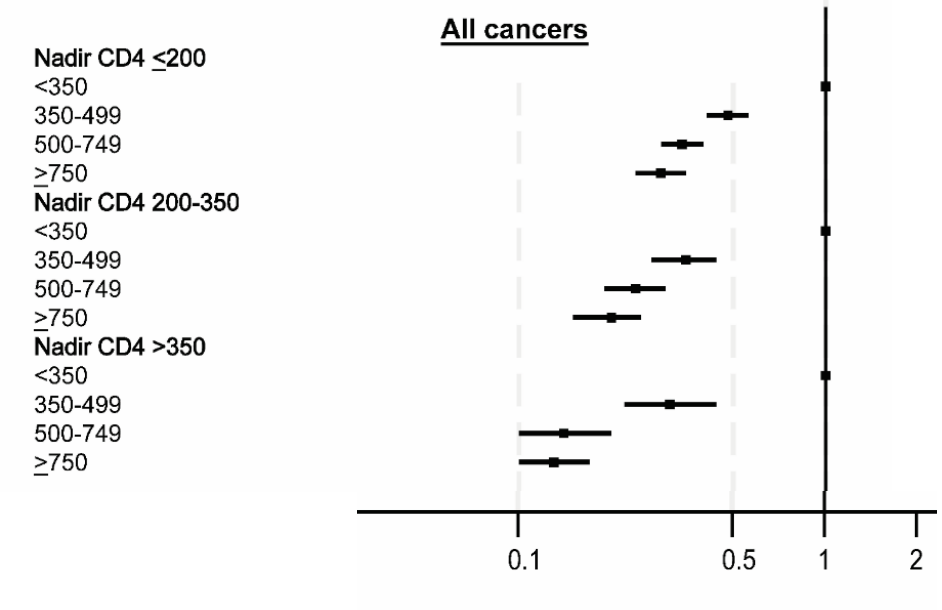
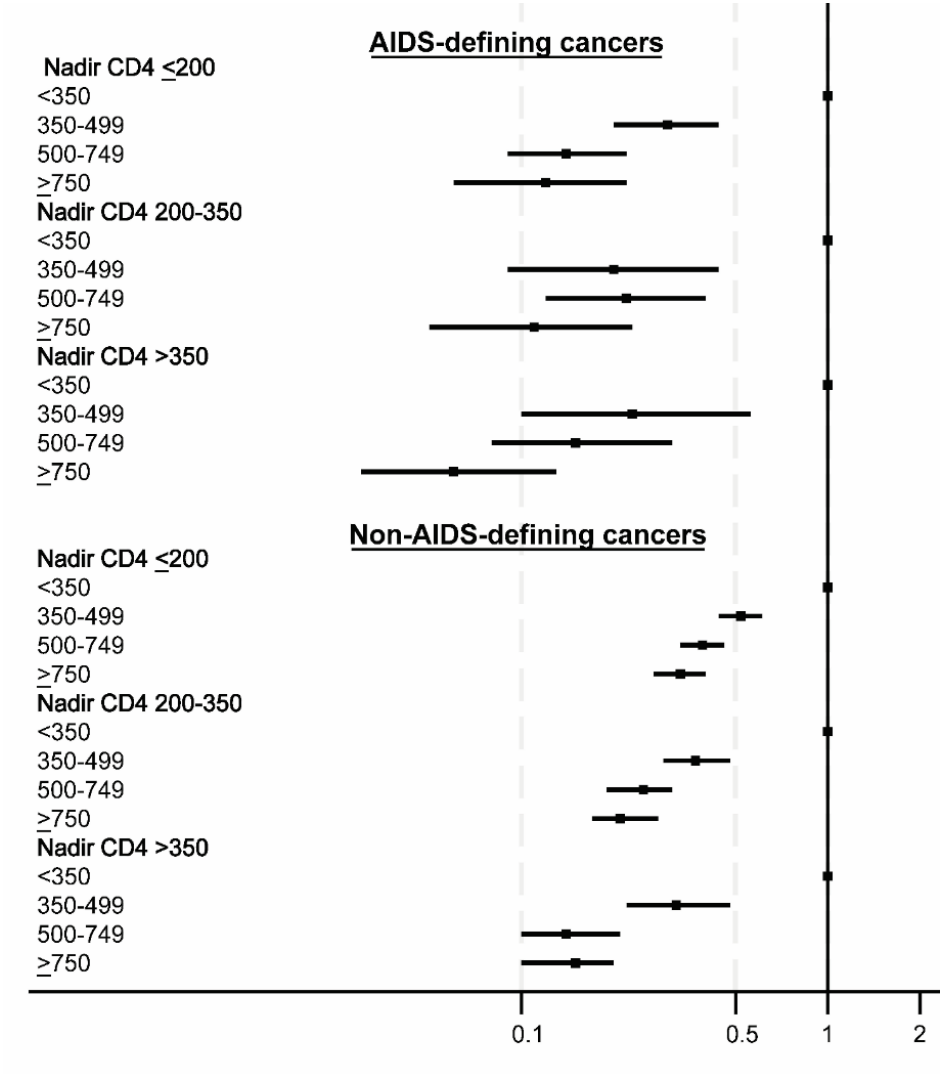
D:A:D

Time-updated CD4 counts and cancer association, stratified by pre-ART nadir CD4 counts

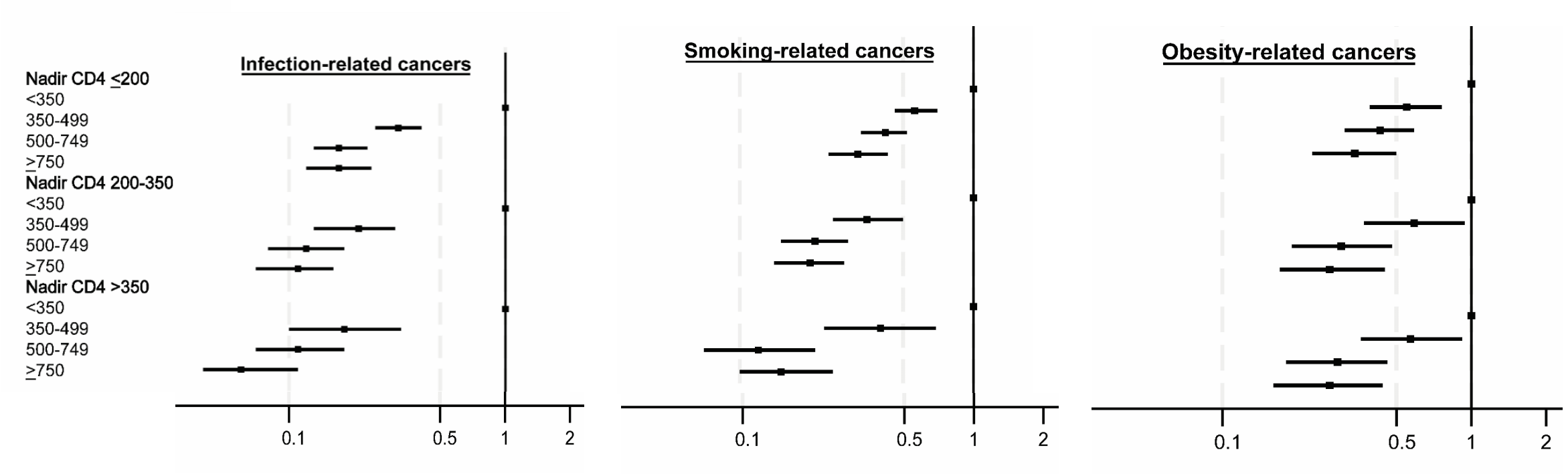


Time-updated CD4 counts and cancer association, stratified by pre-ART nadir CD4 counts for all cancers, ADC and NADC





Time-updated CD4 counts and cancer association, stratified by pre-ART nadir CD4 counts for infection-related, Smoking-related and Obesity-related cancers



Associations between change in CD4 or pre-ART nadir CD4 count and cancer risk

Change in CD4 count*, (per 50 cells/µL increase)	Univariable			Multivariable		
	IRR	95% CI	P-value	aIRR	95% CI	P-value
All cancers (N=2152)						
Overall	0.90	(0.89, 0.91)	<0.0001	0.91	(0.90, 0.92)	<0.0001
Pre-ART nadir CD4, cells/µL						
<200	0.89	(0.88, 0.91)	<0.0001	0.90	(0.89, 0.91)	<0.0001
200-350	0.88	(0.86, 0.89)	<0.0001	0.89	(0.87, 0.90)	<0.0001
>350	0.92	(0.90, 0.94)	<0.0001	0.93	(0.91, 0.95)	<0.0001

*Change in CD4 count was calculated as the change from time-updated CD4 count to baseline CD4 count.

- Higher CD4 count change or increased CD4 from baseline was consistently associated with reduced cancer risk in overall cancers and all cancer types.

Pre-ART nadir CD4 count (cells/µL	Univariable			Multivariable		
	IRR	95% CI	P-value	aIRR	95% CI	P-value
All cancers (N=2152)						
Pre-ART nadir CD4 count			<0.001			0.31
<200	1			1		
200-350	0.78	(0.70, 0.86)		0.96	(0.87, 1.07)	
>350	0.64	(0.57, 0.72)		0.90	(0.80, 1.02)	

- Pre-ART nadir CD4 was associated with reduced cancer risk of AIDS-defining cancers and infection-related cancers but not other cancer types.

Limitations and strengths

Limitations

- Generalizability – relatively young cohort and few non-white people with HIV; mainly from Europe and Australia
- Median follow-up time: 6 years

Strengths

- Large combined RESPOND and D:A:D cohorts
- Rigorous analysis with the inclusion of various measures of CD4 counts

Summary

- People with suboptimal immune recovery experienced an increased risk of incident cancers, including ADC and NADC despite achieving durable viral suppression
- Findings highlight importance of HIV diagnosis at the earliest opportunity and promptly initiating ART to ensure:
  - ➢ Optimal immune recovery and sustained risk reduction for both ADC and NADC and
  - ➢ People with poor immune recovery despite effective ART undergo appropriate cancer screening strategies

Acknowledgements

- Lene Ryom
- Caroline A Sabin
- Lauren Greenberg
- Kathy Petoumenos
- Jennifer Hoy
- D:A:D and RESPOND study teams

ACKNOWLEDGEMENTS

Cohort principal investigators:
S De Wit (St. Pierre), R Zangerle (AHICOS), K Petoumenos (AHOD), F Wit (ATHENA) J Kowalska (EuroSIDA), N Chkhartishvili (IDACIRC), C Pradier (Nice HIV cohort), A d'Arminio Monforte (ICoNA), C Mussini (Modena), H Günthard (SHCS), A Sönnerborg (Swedish InfCare), F Burns (Royal Free HIV cohort), J Begovac (Croatia, HIV cohort), A Castagna (San Raffaele, Milano), JC Wasmuth (Bonn, HIV cohort), JJ Vehreschild (Cologne, HIV cohort), J Vera (Brighton HIV cohort).

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Members of the Scientific Interest Groups:
Hepatitis/Viral Coinfection, Public Health, Outcomes with Antiretroviral Treatment, Tuberculosis, Gender specific outcomes

Members of the Working Groups:
Cancer, Weight Gain on INSTI, Two-drug vs three-drug, Heavy treatment experience, Cardiovascular Disease, Causes of death, Ageing/multimorbidity, Methodology, Long-acting ART, Liver disease and NASH, Resistance

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Funding:
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. U01-AI069907 from the U.S. National Institutes of Health, and GNT2023845 of the National Health and Medical Research Council, Australia.

ACKNOWLEDGMENTS

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

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Additional slides

Sensitivity analyses

- Several sensitivity analyses were conducted:
  - ❑ Lagging time-updated CD4 count by 6 months for the main exposure of interest
  - ❑ Including only centrally validated cancer events,
  - ❑ Excluding participants with cancers diagnosed prior to baseline,
  - ❑ Censoring follow-up time when VL increased to over 1000 copies/mL,
  - ❑ Using time-weighted average of area under time-updated CD4 count measurements curve using the trapezoidal rule [1],
  - ❑ Using complete case series analysis excluding any participants with missing data on any variables

1. Cole SR et. al. Am J Epidemiol. 2010

Sensitivity analyses

- **Summary – findings** are largely consistent with the primary analyses
- The associations between lagged time-updated CD4 count and all cancer risk become slightly attenuated despite strong evidence persists

Association between 6-months lagged time-updated CD4 and cancers

		All cancer			AIDS-defining cancer			Non-AIDS-defining cancer		
Multivariable Poisson regression*	Time-updated CD4	aIRR	(95% CI)	P-value	aIRR	(95% CI)	P-value	aIRR	(95% CI)	P-value
Time-updated CD4 lagged by 6 months (N=51,516)	<350	1		<0.0001	1		<0.0001	1		<0.0001
	350-499	0.68	(0.59, 0.79)		0.42	(0.29, 0.61)		0.75	(0.64, 0.87)	
	500-749	0.63	(0.56, 0.72)		0.35	(0.25, 0.50)		0.70	(0.61, 0.81)	
	≥750	0.63	(0.55, 0.72)		0.25	(0.17, 0.36)		0.73	(0.63, 0.85)	

Similar trends were found for other cancer groups such as infection-related, obesity-related and smoking-related cancers.