



The relationship between smoking, current CD4, viral load and cancer in PLWH

A Mocroft, K Petoumenos, F Wit, JJ Vehreschild, G Guaraldi, JM Miro, L Greenberg, R Zangerle, A Rieger, HF Günthard, H Bucher, S De Wit, C Necsoi, A Castagna, V Spagnuolo, A D'Arminio Monforte, P Reiss, N Chkhartishvili, N Bolokadze, J Hoy, A Sonnerborg, V Svedhem, M Bower, A Volny-Anne, H Garges, F Rogatto, B Neesgaard, L Peters, JD Lundgren, L Ryom

Background

- High prevalence of smoking and comorbidities in PLWH¹⁻²
- Smoking increases risk of many cancers and cancer rates higher in PLWH³⁻⁴
- Smoking may enhance viral replication and increase inflammation, potentially increasing carcinogenic effects of smoking in PLWH⁵⁻⁶

- Investigate whether the impact of smoking on cancer incidence is similar for those with different levels of viral suppression and immune dysfunction
- *Is there an interaction between smoking and immune function/viremia and subsequent development of different cancers?*

Methods (1)

- RESPOND: collaboration of 17 cohort studies, including 29,432 PLWH from across Europe and Australia
- Standardised computerized annual data collection* prospectively from 2017 and retrospectively back to 2012
- Wide range of clinical and laboratory data collected
- Information on all cancers collected on designated forms and centrally validated against pre-defined algorithms
- Cancers grouped into ADC, NADC, smoking related, infection related and BMI-related using published literature and cancer working group

*https://chip.dk/Portals/0/files/Eurosida/EuroSIDA/RESPOND_EuroSIDA_CARE_SOP_Electronic_Version3%200_2019_final.pdf?ver=2019-10-02-141500-817

Methods (2)

- Baseline: later of RESPOND enrolment/known smoking status
- Excluded
 - No CD4/VL in 12 months prior to/6 months after baseline
 - Cohorts with <70% completeness on smoking status
- Persons followed to earliest of first new cancer diagnosis, last visit or 31/12/2018
- Current CD4/VL categorised as
 - **GOOD** → **CD4 $\geq$ 500 and VL < 200**
 - **POOR** → **CD4 $\leq$ 350 and VL > 200**
 - **INTERMEDIATE** → **all other combinations**
- Poisson regression for assessing relationship between current smoking status, current CD4/VL (good, intermediate, poor)

Results: Demographics

		All		Never smoked		Current smokers		Previous smokers	
		N	%	N	%	N	%	N	%
All		19602	100.0	8088	41.3	8699	44.4	2815	14.4
Gender	Male	14544	74.2	5613	69.4	6855	78.8	2076	73.7
	Female	5058	25.8	2475	30.6	1844	21.2	739	26.3
Ethnic origin	White	15150	77.3	5736	70.9	7318	84.1	2096	74.5
	Other	2696	13.8	1673	20.7	527	6.1	496	17.6
	Unknown	1756	9.0	679	8.4	854	9.8	223	7.9
HIV risk	MSM	8411	42.9	3579	44.3	3587	41.2	1245	44.2
	IDU	3116	15.9	477	5.9	2293	26.4	346	12.3
	Het	6691	34.1	3414	42.2	2215	25.5	1062	37.7
	Other/Unknown	1384	7.1	618	7.6	604	6.9	162	5.8
Prior ARVs	Naïve	1568	8.0	690	8.5	772	8.9	106	3.8
	Experienced, VL < 200	13534	69.0	5561	68.8	5745	66.0	2228	79.1
	Experienced, VL >200	4500	23.0	1837	22.7	2182	25.1	481	17.1
CD4/VL	Poor	675	3.4	323	4.0	300	3.4	52	1.8
	Intermediate	8772	44.8	3814	47.2	3876	44.6	1082	38.4
	Good	10155	51.8	3951	48.9	4523	52.0	1681	59.7
		Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age		46	38–54	46	37–54	45	37–52	51	44–57
Nadir CD4		206	93–321	210	100–324	209	93–334	180	78–279
Years HIV+		11	4–19	9	3–16	11	4–19	17	10–22
Years since started ART		9	3–15	7	2–14	8	3–15	14	8–18

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Results: Cancer events

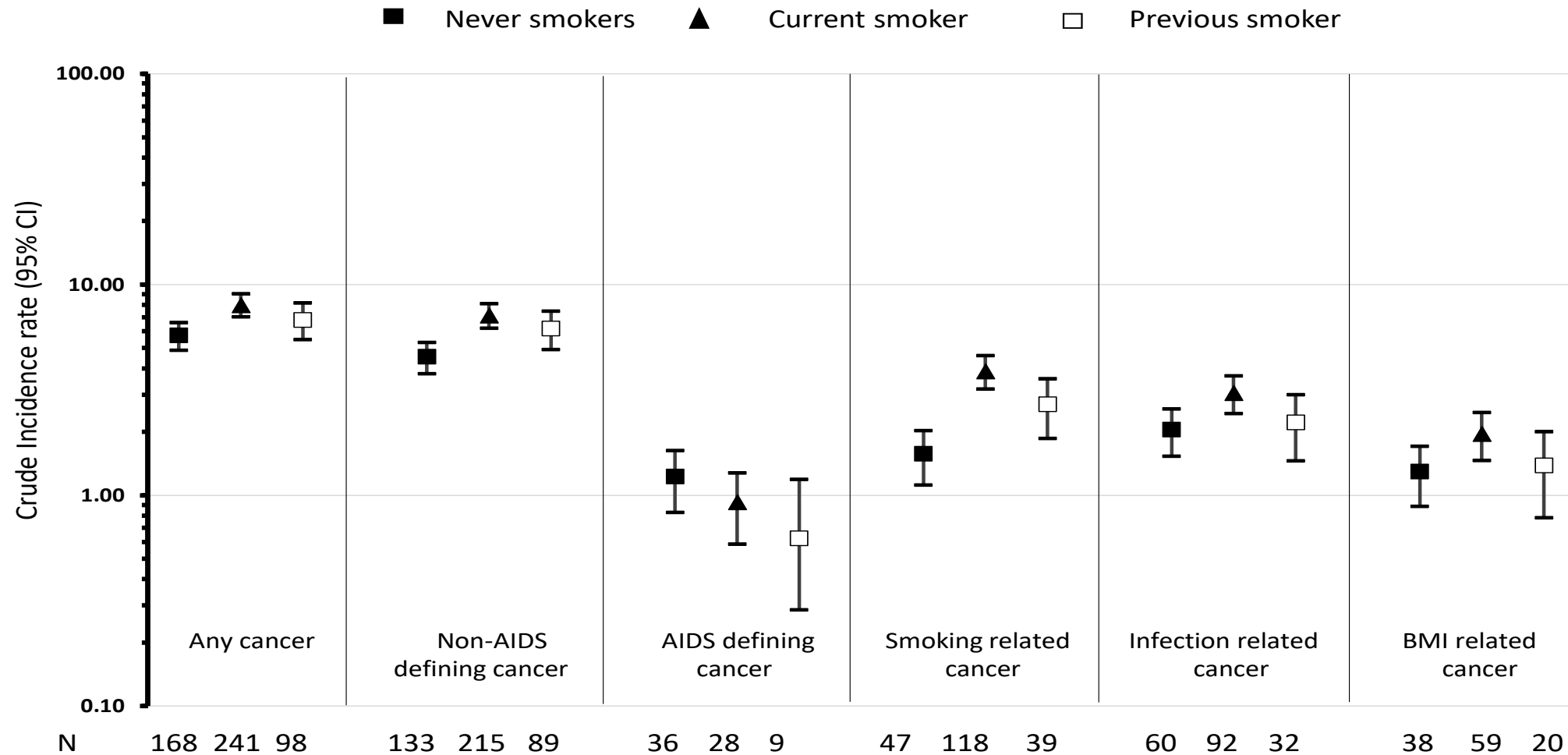
- 513 cancer events in 507 individuals in 73868 PYFU
- Incidence 6.9/1000 PYFU (95% CI 6.3–7.5)
- 437 persons with NADC**, 73 ADC
- 204 SRC, 184 IRC, 119 BMIRC

Smoking related cancer (SRC)			Infection related cancer (IRC)			BMI related cancer (BMIRC)		
	N	%		N	%		N	%
All	204	39.8		184	35.9		119	23.2
Lung	65	31.9	Anal	46	25.0	Liver	38	31.9
Liver	38	18.6	Liver	38	20.7	Colon	21	17.7
Bladder	26	12.8	NHL	33	17.9	Breast	15	12.6
Colon	21	10.3	KS	31	16.9	Pancreatic	13	10.9
Pancreatic	13	6.4	HDL	14	7.6	Kidney	8	6.7
Cervical ²	9	4.4	Cervical ²	9	4.9	Gall bladder	8	6.7
Kidney	8	3.9	Stomach	7	3.8	Rectum	7	5.9
Stomach	7	3.4	Oropharyngeal	3	1.6	Oesophagus	6	5.0
Rectum	7	3.4	Penile	3	1.6	Thyroid	3	2.5
Oesophageal	6	2.9						
Oropharyngeal	3	1.5						
AML	1	0.5						

*2 persons had different SRC on the same date (204 diagnoses in 202 persons); and different BMIRC on the same date (119 diagnoses in 117 persons).

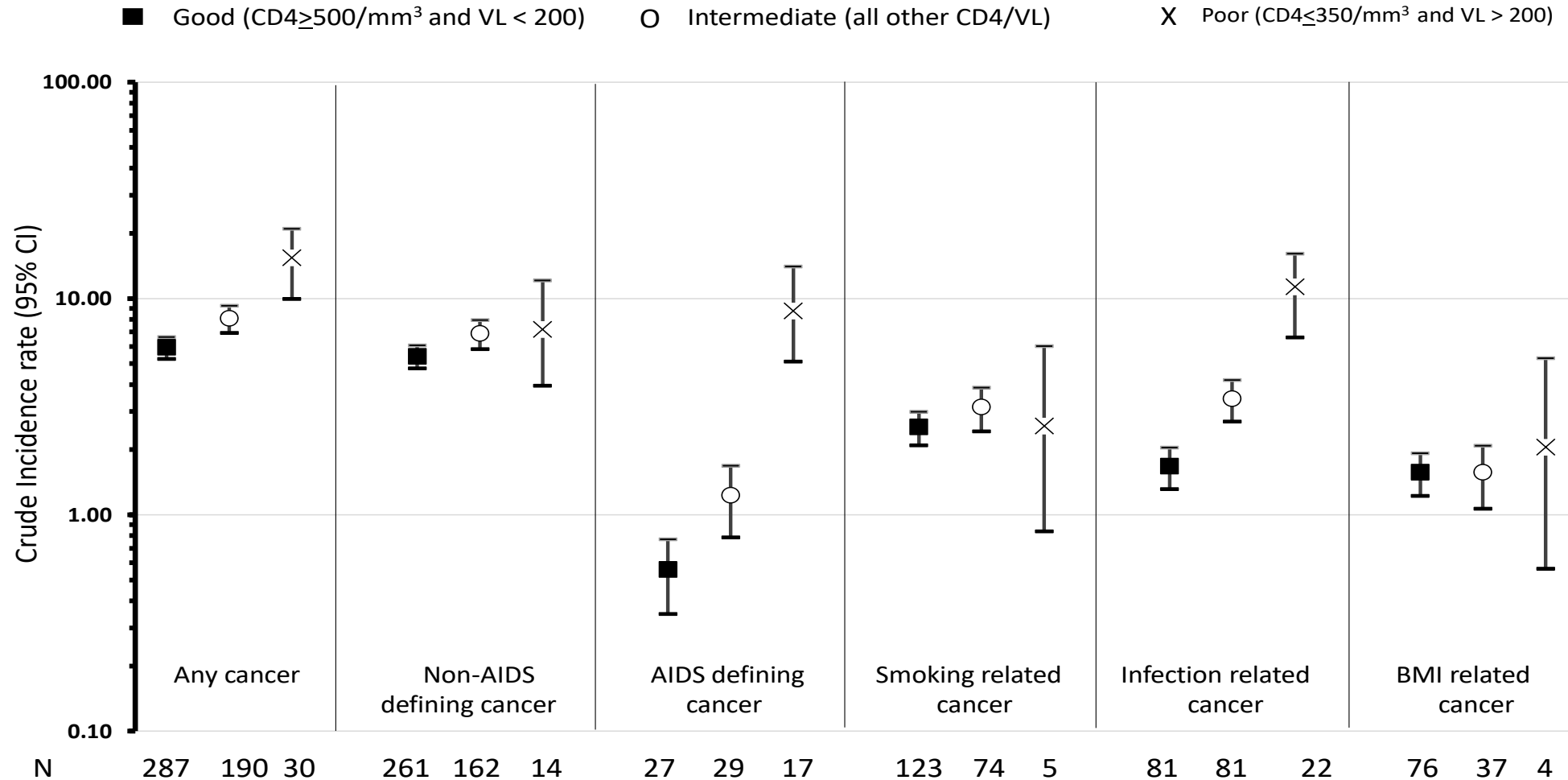
**Classification is not mutually exclusive

Crude incidence of cancer stratified by current smoking status



Crude incidence of cancer is generally highest in current smokers and lowest in never smokers with the biggest differences seen for smoking related cancers

Crude incidence of cancer stratified by current CD4/VL group



Crude incidence of cancer is generally highest with poor CD4/VL and lowest in those with good CD4/VL with the biggest differences seen for AIDS and infection related cancers

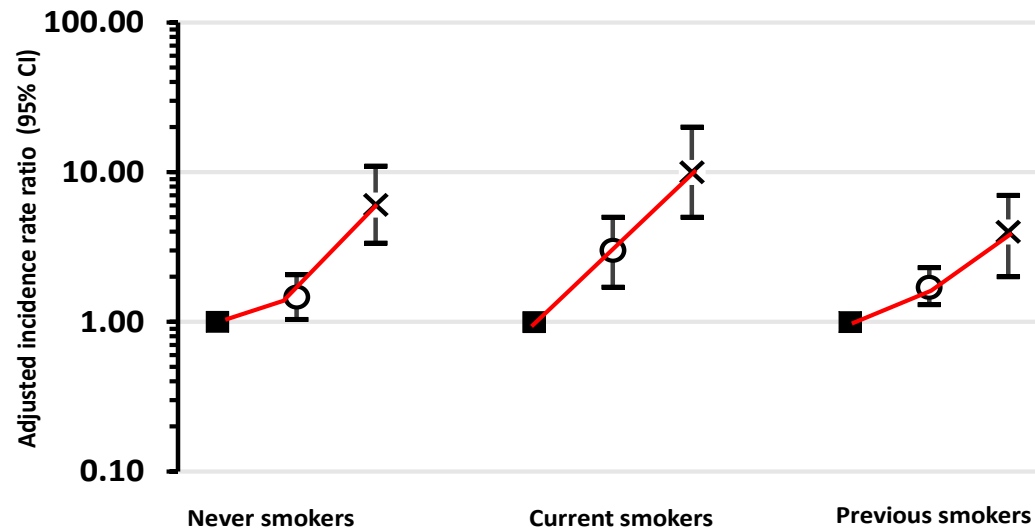
Is there an interaction between smoking and immune function/viremia and subsequent development of different cancers?

■ Good ($CD4 \geq 500/mm^3$ and $VL < 200$)

○ Intermediate (all other $CD4/VL$)

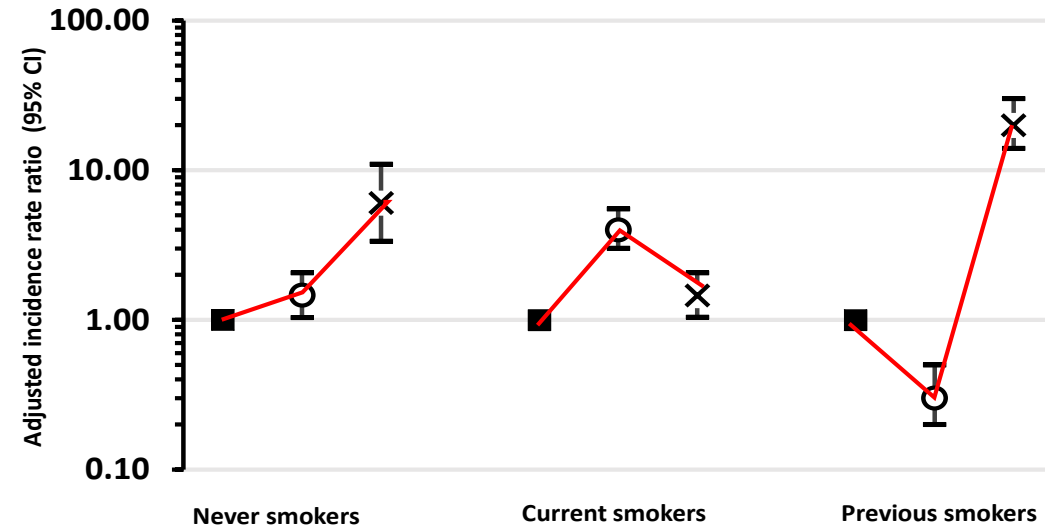
X Poor ($CD4 \leq 350/mm^3$ and $VL > 200$)

No interaction



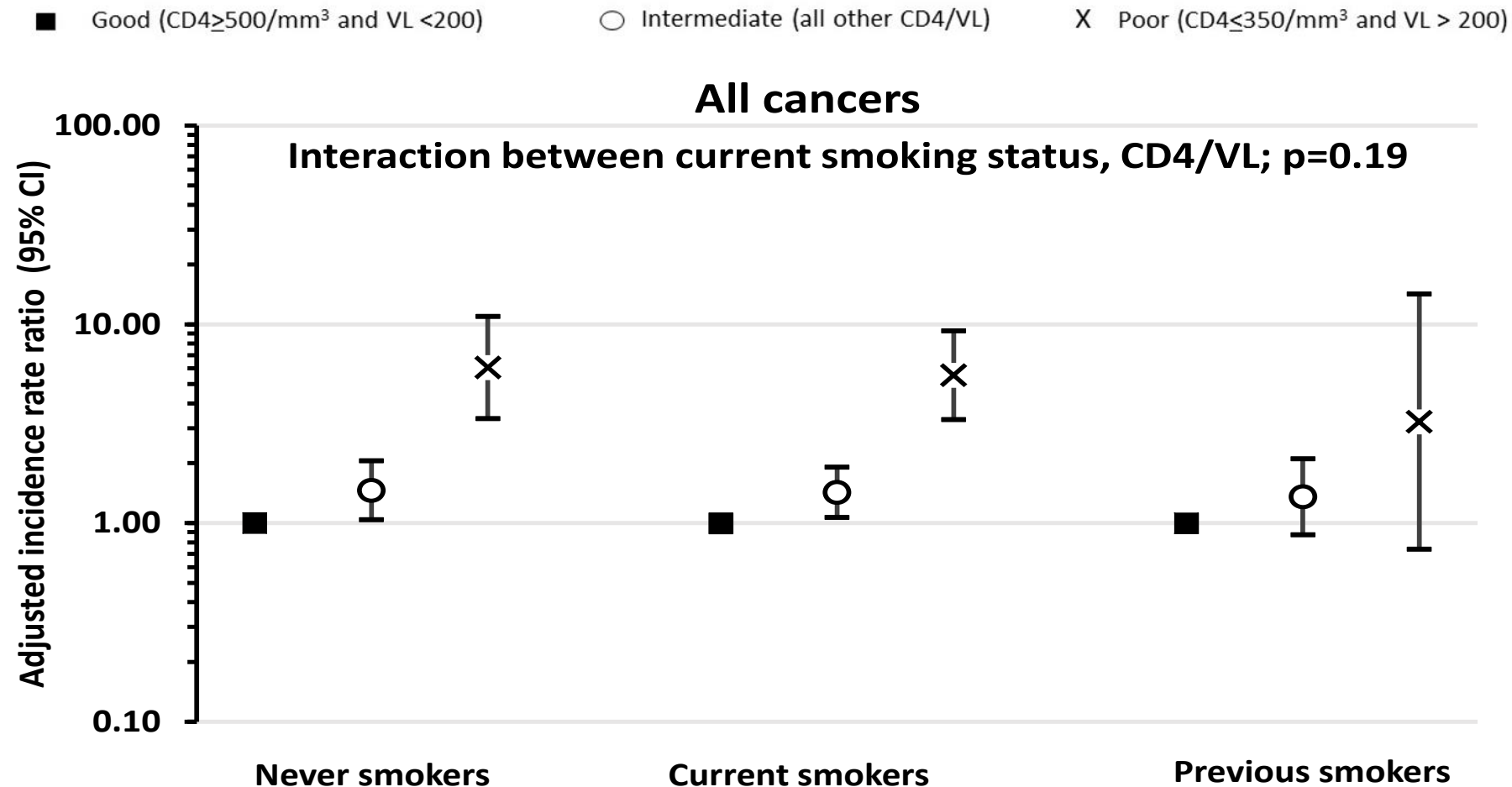
The pattern is the same for never smokers, current smokers and past smokers irrespective of whether the response is 'good', 'intermediate' or 'poor'

Interaction



The pattern is different for never smokers, current smokers and past smokers

The association between CD4/VL and cancer is the same regardless of current smoking status



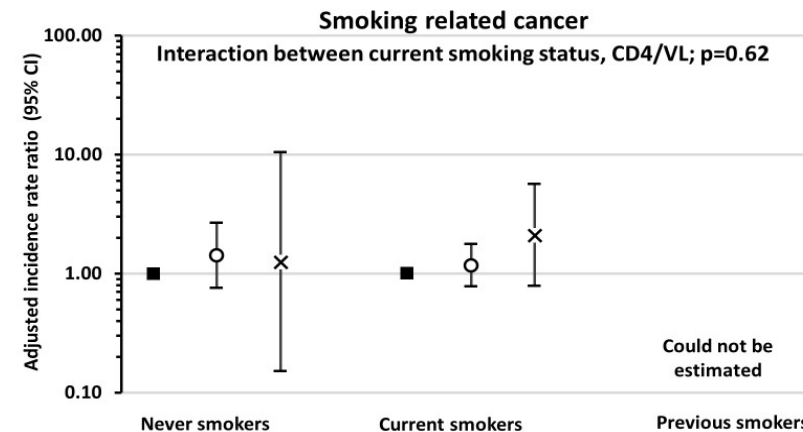
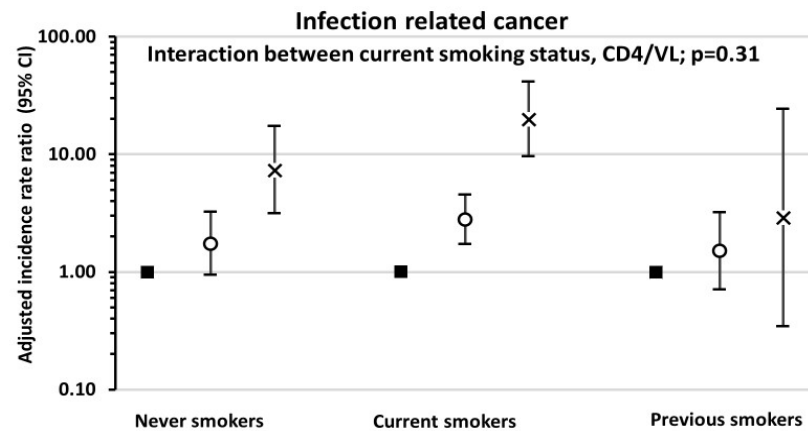
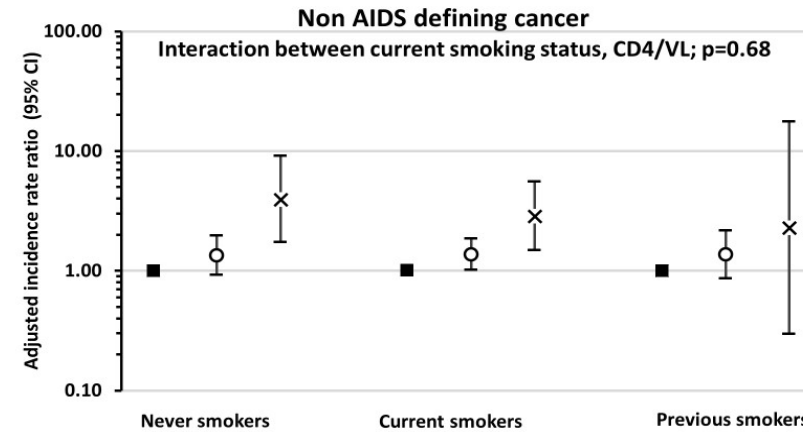
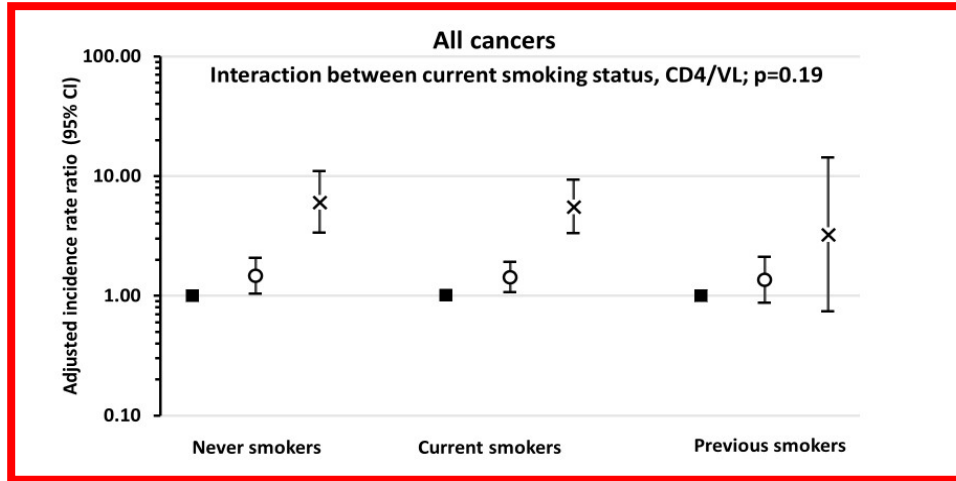
Adjusted for (baseline) gender, ethnicity, HIV risk group, hepatitis B/C status, antiretroviral status (naïve, experienced with $VL < LOD$, experienced, $VL > LOD$), BMI, hypertension, diabetes, AIDS, CVD, NADM, ESLD, prior exposure to PIs, CKD, time HIV+, nadir CD4, baseline, age

The association between CD4/VL and cancer is the same regardless of current smoking status

■ Good ($CD4 \geq 500/mm^3$ and $VL < 200$)

○ Intermediate (all other $CD4/VL$)

X Poor ($CD4 \leq 350/mm^3$ and $VL > 200$)



*Adjusted for (all at baseline) gender, ethnicity, HIV risk group, hepatitis B and C status, antiretroviral status (naïve, experienced with $VL < LOD$ and experienced, $VL > LOD$), BMI, hypertension, diabetes, AIDS, CVD, NADM, ESLD, prior exposure to PIs, CKD, time HIV positive, nadir $CD4$, baseline date and age

Strengths and limitations

- **Strengths**

- Large size and heterogeneity
- Rigorous quality assurance program
- Centrally validated events

- **Limitations**

- Missing data on smoking status and duration, type or intensity of smoking
- Heterogeneous CD4/VL categories
- Important confounders, such as alcohol use, family history and coinfection with HPV/EBV are not collected in RESPOND
- Lacked the power to study individual malignancies, which may show different associations between CD4/VL and smoking than those shown here

Conclusions

- Current smokers and those with poor HIV control were at highest risk of developing cancer
- Reducing smoking and good HIV control remains important for reducing cancer incidence
- No evidence that the relationship between current CD4/VL strata and cancer was different depending on smoking status (*non significant interactions*)
- Provides evidence that current immune deficiency or lack of virological control does not worsen the impact of smoking on the development of cancer
- Consistent findings across all cancers, NADC, IRC and SRC

Acknowledgements

Cohort principal investigators:

De Wit (St. Pierre, Brussels), R. Zangerle (AHICOS), M. Law (AHOD), F. Wit (ATHENA), G. Wandeler (EuroSIDA), C. Stephan (Frankfurt), N. Chkhartishvili (IDACIRC), C. Pradier (Nice HIV cohort), A. d'Arminio Monforte (ICoNA), C. Mussini (Modena), J. Casabona & J.M. Miro (PISCIS), H. Günthard (SHCS), A. Sönnernborg (Swedish InfCare), C. Smith (Royal Free HIV cohort), A. Castagna (St. Rafael, Milano), J.C. Wasmuth (Bonn, HIV Cohort) and J.J. Vehreschild (Cologne, HIV cohort).

Cohort Coordinator, operational team members and data management:

C. Necsoi, M. Delforge (St. Pierre, Brussels), H. Appoyer, U. Dadogan, G. Leierer (AHIVCOS), J. Hutchinson, N. Rose. (AHOD), P. Reiss, M. Hillebregt, T. Rutkens, D. Bergsma (ATHENA), F. Ebeling, M. Bucht, (Frankfurt), O. Chokoshvili, E. Karkashadze (IDACIRC), E. Fontas, K. Dollet, C. Caissotti (NICE, HIV cohort), J. Fanti, A. Tavelli, A. Rodanò (ICoNA), V. Borghi (Modena), A. Bruguera, J. Reyes-Urueña, A. Montoliu (PISCIS), H. Bucher, A. Scherrer, J. Schuhmacher, A. Traytel (SHCS), V. Svedhem-Johansson, L. Mattsson, K. Alenadaf, (Swedish InfCare), F. Lampe, C. Chaloner (Royal Free, HIV cohort), A. Lazzarin, A. Poli, S. Nozza (St. Rafael, Milano), K. Mohrmann, J. Rockstroh (Bonn, HIV cohort), G. Fätkenheuer, N. Schulze, B. Frank, M. Stecher and H. Weiler (Cologne HIV cohort).

RESPOND Scientific Steering Committee:

J. Lundgren (co-chair), H. Günthard (Co-Chair), C. Mussini, R. Zangerle, A. Sönnernborg, V. Vannappagari, J.C. Wasmuth, M. Law, F. Wit, R. Haubrich, H. Bucher, C. Pradier, H. Garges, C. Necsoi, G. Wandeler, C. Smith, J.J. Vehreschild, F. Rogatto, C. Stephan, N. Chkhartishvili, A. d'Arminio Monforte, A. Bruguera and A. Castagna.

Community representatives:

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

RESPOND Executive committee:

Mocroft (Chair), J. Lundgren, R. Zangerle, H. Günthard, G. Wandeler, M. Law, F. Rogatto, C. Smith, V. Vannappagari, S. De Wit, J. Rooney, H. Garges

RESPOND coordination office, data management and quality assurance:

D Raben, L Peters, JF Larsen, L Ryom, B Neesgaard, ML Jakobsen, T Bruun, A Bojesen, EV Hansen, TW Elsing, D Kristensen, S Thomsen, T Weide

Scientific interest group moderators:

L. Ryom, A. Mocroft (Outcomes with antiretroviral treatment), L. Peters, J. Rockstroh (Hepatitis), D. Raben and J. Kowalska (Public Health), O. Kirk, A. Philips, V. Cambiano and J. Lundgren (PrEP)

Members of the scientific interest group:

Hepatitis, Public Health, Outcomes with antiretroviral treatment, PrEP, Resistance

Statisticians:

A Mocroft, L Greenberg, L Bansi-Matharu, A Pelchen-Matthews, K Petoumenos, N Rose

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Association between current smoking status, CD4/VL and cancer

			Univariable			Multivariable		
			IRR	95% CI	p	aIRR	95% CI	p
All	HIV markers CD4/VL	Good	1.00			1.00		
		Int	1.39	1.15-1.67	0.0005	1.39	1.14-1070	0.0010
		Poor	4.17	3.05-5.69	<0.0001	5.36	3.71-7.75	<0.0001
	Smoking	Never	1.00			1.00		
		Current	1.40	1.15-1.70	0.0008	1.45	1.17-1.79	0.0007
		Previous	1.19	0.93-1.53	0.17	1.06	0.82-1.37	0.65
Non-AIDS Defining Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	1.31	1.08-1.60	0.0071	1.35	1.09-1.66	0.0050
		Poor	2.06	1.32-3.21	0.0015	3.14	1.92-5.14	<0.0001
	Smoking	Never	1.00			1.00		
		Current	1.58	1.27-1.96	<0.0001	1.65	1.31-2.09	<0.0001
		Previous	1.36	1.04-1.78	0.024	1.14	0.87-1.50	0.35
AIDS Defining Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	2.34	1.32-4.14	0.0037	2.02	1.10-3.69	0.023
		Poor	29.44	16.69-51.95	<0.0001	16.56	7.84-35.00	<0.0001
	Smoking	Never	1.00			1.00		
		Current	0.76	0.46-1.24	0.27	0.81	0.48-1.37	0.43
		Previous	0.51	0.25-1.06	0.070	0.76	0.36-1.62	0.48

Good; CD4 $\geq 500/\text{mm}^3$ and VL < 200 copies/mL. Poor; CD4 $\leq 350/\text{mm}^3$ and VL > 200 copies/mL. Intermediate; all other CD4 / VL combinations. Adjusted for (all at baseline) gender, ethnicity, HIV risk group, hepatitis B and C status, antiretroviral status (naïve, experienced with VL $< \text{LOD}$ and experienced, VL $> \text{LOD}$), BMI, hypertension, diabetes, AIDS, chronic kidney disease, cardiovascular disease, NADC, end-stage liver disease, CKD, exposure to PIs, time HIV positive, nadir CD4 count, baseline date and age

Association between current smoking status, CD4/VL and cancer

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Association between current smoking status, CD4/VL and cancer

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			IRR	95% CI	p	aIRR	95% CI	p
Infection Related Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	2.11	1.54-2.90	<0.0001	2.02	1.44-2.83	<0.0001
		Poor	10.63	7.03-16.08	<0.0001	10.21	6.06-17.20	<0.0001
	Smoking	Never	1.00			1.00		
		Current	1.50	1.08-2.07	0.015	1.38	0.97-1.96	0.073
		Previous	1.09	0.71-1.67	0.70	1.09	0.70-1.70	0.69
	Smoking Related Cancer	Good	1.00			1.00		
		Int	1.30	0.98-1.73	0.072	1.35	0.99-1.83	0.054
		Poor	1.25	0.55-2.83	0.60	1.82	0.76-4.41	0.18
	Smoking	Never	1.00			1.00		
		Current	2.48	1.76-3.49	<0.0001	2.21	1.53-3.20	<0.0001
		Previous	1.73	1.13-2.65	0.012	1.30	0.84-2.01	0.24
BMI Related Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	1.00	0.68-1.48	0.99	1.01	0.67-1.53	0.97
		Poor	1.31	0.48-3.58	0.60	1.49	0.50-4.44	0.47
	Smoking	Never	1.00			1.00		
		Current	1.51	1.01-2.28	0.046	1.10	0.70-1.73	0.67
		Previous	1.07	0.62-1.84	0.80	0.75	0.43-1.31	0.31

Good; CD4 $\geq 500/\text{mm}^3$ and VL < 200 copies/mL. Poor; CD4 $\leq 350/\text{mm}^3$ and VL > 200 copies/mL. Intermediate; all other CD4 / VL combinations. Adjusted for (all at baseline) gender, ethnicity, HIV risk group, hepatitis B and C status, antiretroviral status (naïve, experienced with VL $< \text{LOD}$ and experienced, VL $> \text{LOD}$), BMI, hypertension, diabetes, AIDS, chronic kidney disease, cardiovascular disease, NADC, end-stage liver disease, CKD, exposure to PIs, time HIV positive, nadir CD4 count, baseline date and age

Association between current smoking status, CD4/VL and cancer

			Univariable			Multivariable		
			IRR	95% CI	p	aIRR	95% CI	p
Infection Related Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	2.11	1.54-2.90	<0.0001	2.02	1.44-2.83	<0.0001
		Poor	10.63	7.03-16.08	<0.0001	10.21	6.06-17.20	<0.0001
	Smoking	Never	1.00			1.00		
		Current	1.50	1.08-2.07	0.015	1.38	0.97-1.96	0.073
		Previous	1.09	0.71-1.67	0.70	1.09	0.70-1.70	0.69
Smoking Related Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	1.30	0.98-1.73	0.072	1.35	0.99-1.83	0.054
		Poor	1.25	0.55-2.83	0.60	1.82	0.76-4.41	0.18
	Smoking	Never	1.00			1.00		
		Current	2.48	1.76-3.49	<0.0001	2.21	1.53-3.20	<0.0001
		Previous	1.73	1.13-2.65	0.012	1.30	0.84-2.01	0.24
BMI Related Cancer	HIV markers CD4/VL	Good	1.00			1.00		
		Int	1.00	0.68-1.48	0.99	1.01	0.67-1.53	0.97
		Poor	1.31	0.48-3.58	0.60	1.49	0.50-4.44	0.47
	Smoking	Never	1.00			1.00		
		Current	1.51	1.01-2.28	0.046	1.10	0.70-1.73	0.67
		Previous	1.07	0.62-1.84	0.80	0.75	0.43-1.31	0.31

Good; CD4 $\geq 500/\text{mm}^3$ and VL < 200 copies/mL. Poor; CD4 $\leq 350/\text{mm}^3$ and VL > 200 copies/mL. Intermediate; all other CD4 / VL combinations. Adjusted for (all at baseline) gender, ethnicity, HIV risk group, hepatitis B and C status, antiretroviral status (naïve, experienced with VL $< \text{LOD}$ and experienced, VL $> \text{LOD}$), BMI, hypertension, diabetes, AIDS, chronic kidney disease, cardiovascular disease, NADC, end-stage liver disease, CKD, exposure to PIs, time HIV positive, nadir CD4 count, baseline date and age