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The relationship between smoking, current CD4, viral load and cancer in persons living with HIV

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Abstract

Background It is unknown if the carcinogenic effect of smoking is influenced by CD4 count and viral load (VL) in persons living with HIV.

Material and Methods RESPOND participants with known smoking status were included. Poisson regression adjusting for baseline confounders investigated the interaction between current CD4/VL strata (good [CD4>500/mm^3 and VL<200 copies/mL], poor [CD4<350/mm^3 and VL>200 copies/ml] and intermediate [all other combinations]), smoking status and all cancers, non-AIDS defining cancers (NADC), smoking-related cancers (SRC), and infection-related cancers (IRC).

Results Of 19602 persons, 41.3% were never smokers 44.4% current and 14.4% previous smokers at baseline. CD4/VL strata were poor in 3.4%, intermediate in 44.8% and good in 51.8%. There were 513 incident cancers; incidence rate 6.9/1000 PYFU (95% CI 6.3–7.5). Current smokers had higher incidence of all cancer (adjusted incidence rate ratio 1.45; 1.17-1.79), NADC (1.65; 1.31-2.09), SRC (2.21; 1.53-3.20), and IRC (1.38; 0.97-1.96) vs never smokers. Those with poor CD4/VL had increased incidence of all cancer (5.36; 95% CI 3.71-7.75), NADC (3.14; 1.92-5.14), SRC (1.82; 0.76-4.41) and IRC (10.21; 6.06-17.20) versus those with good CD4/VL. There was no evidence that the association between smoking and cancer subtypes differed depending on the CD4/VL strata (p>0.1, test for interaction).

Conclusions In the large RESPOND consortium, the impact of smoking on cancer was clear and reducing smoking rates should remain a priority. The association between current immune deficiency, virological control and cancer was similar for never smokers, current smokers and previous smokers suggesting similar carcinogenic effects of smoking regardless of CD4 count and VL.

Introduction

The prevalence of smoking is 2-3 times higher in people living with HIV (PLWH) compared to HIV-negative persons, and likely associated with a wide range of factors including higher rates of alcohol consumption, and illicit drug use. [1-4] Smoking cessation in PLWH may [5] include barriers of competing priorities and lack of confidence in the ability to stop smoking and in nicotine replacement therapy.[6] Smoking not only increases the risk of lung cancer but also certain cancers of the urinary and gastro-intestinal tract, some gynaecological cancers and specific types of leukaemia. [7] The consequences of smoking in PLWH have been reported to be worse than in HIV-negative persons[8-10] and are likely to be far-reaching, as rates of common tobacco-related comorbidities are higher in PLWH compared to HIV-negative individuals.[11, 12] In PLWH, it is possible that smoking may enhance viral replication, increasing the formation of free radicals leading to oxidative stress and mitochondrial dysfunction and increase levels of inflammation.[9, 13-19] Smoking also increases the risks of several AIDS events,[20-22] and PLWH are also known to have higher risks of several cancers, for which smoking further increases the risk.[22-24]In PLWH, the association between CD4 count and increased risk of cancer is well established, while uncontrolled viremia is also prognostic. [25-28] Non-HIV-specific risk factors for cancer are well described and include obesity as well as coinfections i.e. oncogenic viruses such as human papilloma virus (HPV) and viral hepatitis,[29] while chronic inflammation may also play a role.[30, 31] Taken together these findings could suggest that the association between smoking and cancer varies based on HIV-related immune impairment and inflammation, which potentially increases the carcinogenic effects of smoking on PLWH.[22, 32-35] To date there is no evidence to support this hypothesis.

The aims of this study were to investigate whether the impact of smoking on development of cancer is similar for those with different combinations of CD4 and VL, reflecting both viral suppression and immune dysfunction.

Methods

Study Design and Participants

The International Cohort Consortium of Infectious Diseases (RESPOND) is a collaboration of 17 cohort studies, including 29,432 PLWH from across Europe and Australia.[36] Standardised data including information on demographics, HIV-related factors, antiretroviral therapy (ART), coinfections, comorbidities and various biomarkers were collected at enrolment and updated annually (details at https://www.chip.dk/Studies/RESPOND). [37] All cohorts used the HIV Cohorts Data Exchange Protocol (HICDEP) for data collection (details at https://hicdep.org/) and deaths are centrally validated using the CoDe methodology.[38] RESPOND collects information on cancer events (excluding pre-cancers and non-melanoma skin cancers) both as part of the annual data collection and by designated Case Report Forms (CRF). In brief, all cancer events occurring during the qualifying period (12 months prior to the last cohort visit before RESPOND enrolment and all events occurring during follow-up) are reported via a CRF, which are centrally validated by clinicians at the RESPOND coordinating centre using prespecified algorithms available at https://chip.dk/Portals/0/files/RESPOND/RESPOND%20Manual%20of%20Operations%20

MOOP__Version%201.6.pdf?ver=2019-11-05-124535-643).[37] A selection of events are also annually reviewed by an external senior oncologist. Due to potential reporting delays for more recent events this analysis contains both centrally validated (almost 90% of cases) and electronically reported events. There is an extensive quality assurance system in place in RESPOND checking for completeness and accuracy of data. (https://www.chip.dk/Portals/0/files/Eurosida/EuroSIDA/RESPOND_EuroSIDA_D47_Electronic_Submission_Tool_User_guide_Version3.pdf?ver=2019-10-02-143730-970).

Baseline was defined as enrolment to RESPOND or the first date where smoking status was known if this occurred after enrolment. All persons had prospective follow-up and a CD4 count and VL measured in the 12 months prior to baseline, or where none was available, in the 6 months following baseline. Information on smoking status (current smoker or not) is available at baseline and during study follow-up. Information on duration of smoking, use of cigarettes or tobacco and/or quantity of smoking is not collected. Cohorts in RESPOND with >70% completeness on smoking status at baseline and during follow-up were included. Persons were followed to their first new cancer diagnosis (AIDS [Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer] or non-AIDS defining [all other cancers, apart from non-melanoma skin cancers and pre-cancers]), last visit or 31/12/2018, whichever occurred first. Persons with a prior cancer diagnosis were included and followed to a new cancer diagnosis.

In addition, all cancers diagnosed during prospective follow-up were grouped (Table 1) into smoking related cancers (SRC), infection related cancers (IRC), BMI related cancers (BMIRC) and AIDS-defining cancers (ADC) based on recommendations from the RESPOND cancer working group. These classifications were not mutually exclusive.

Statistical methods

Baseline was defined as the first date smoking information was available at or after enrolment into RESPOND. Individuals were followed to their first cancer event, last visit or 31 December 2018, whichever occurred first. Eleven different measures of immune deficiency and viremia (all time updated) and relationship with cancer and smoking were investigated, including nadir CD4, peak viral load, current CD4 and VL, the proportion of time with a low or high CD4 ($<350/mm^3$ or $> 500/mm^3$), viremic (>200 copies/mL), lagging CD4 or VL by 6 or 12 months, and combinations of these (such as proportion of follow-up time with a CD4$<350/mm^3$ and VL > limit of detection [LOD]). A series of bivariable Poisson regression models investigated which of the markers, together with smoking status, best predicted cancer, as measured by the Akaike Information Criteria (AIC). Interactions between each of the markers, smoking status and cancer was also investigated. Based on these preliminary analyses, there were only small differences in the statistical fit of the markers investigated, and no differences in the results of the statistical interaction tests. More complex measures, such as proportion of follow-up time with CD4$<350/mm^3$ and VL > LOD, had a marginally poorer statistical fit as well as being more complex to calculate. In the interests of having clear and simple categories, the combination of markers incorporating both current CD4 and VL defined as 'good' (CD4 $>500/mm^3$ and VL < 200 copies/mL),

'poor' (CD4 < 350/mm^3 and VL >200 copies/mL) and 'intermediate' (all other combinations of CD4 and VL) was chosen to investigate the interactions of interest.

Current CD4/VL strata (good, intermediate and poor) and current smoking status (defined as never smokers, current smokers or previous smokers) were included in multivariable Poisson regression models adjusted for baseline factors, gender, ethnicity, HIV risk group, hepatitis B (HBV) and C (HCV) status, ART status (naïve, experienced with VL < 200 copies/mL, VL > 200 copies/mL), body mass index, hypertension, diabetes. Models were additionally adjusted for prior AIDS (as cancer or non-cancer AIDS defining event), cardiovascular disease (CVD), non-AIDS defining cancer (NADC), end stage liver disease (ESLD), chronic kidney disease (CKD, defined as a confirmed estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m2 using the CKD-EPI formula[39] over >3 months) , use of protease inhibitors (PIs) given prior research suggesting an association with some cancers[25, 40, 41], time since HIV diagnosis, nadir CD4, baseline date and age. A priori we were interested in the interaction between CD4/VL strata, smoking and cancer, and this interaction was assessed for cancers overall, for NADC, SRC and IRC, where the number of events were greatest. Analyses were repeated excluding persons with pre-existing cancers at baseline, adjusting for cohort rather than comorbidities in multivariable models, taking into account cohort variability in data completeness in comorbidities and finally including only centrally validated events.
All analyses were performed using Statistical Analysis Software (version 9.4, Cary, NC, USA) and all tests of significance were 2-sided.

Results

A total of 19602 persons were included in this analysis. After excluding cohorts with incomplete data on smoking status, an additional 1611 were excluded due to missing data. Compared to the 19602 included, the 1611 excluded were more likely to be treatment experienced, have a later study baseline, be of non-white ethnicity, been diagnosed with HIV for longer, and more likely to be HCV-positive.

The demographics of the included persons are shown in Table 2. At baseline, 8088 (41.3%) were never smokers, 8699 (44.4%) were current smokers and 2815 (14.4%) were previous smokers. CD4/VL strata at baseline were defined as poor for 675 (3.4%), intermediate for 8772 (44.8%) and good for 10155 (51.8%). There was a high prevalence of comorbidities, including previous AIDS, hypertension and diabetes and the median age was 46 (interquartile range [IQR] 38–54 years). The population had a high median CD4 count of 556 (IQR 385–754/mm^3) and low CD4 nadir of 206 (IQR 93–321/mm^3). Persons had been diagnosed with HIV for a median of 11 years (IQR 4–19) with a median baseline date of 02/14 (IQR 01/12–10/15). The population across the smoking strata was heterogeneous; current smokers were more likely to be male, HCV coinfected, less likely to be overweight, were younger, and with a higher baseline CD4 count. Previous smokers had a higher prevalence of most comorbidities, including hypertension, diabetes, cardiovascular disease and AIDS.

Incidence of cancer and relationship with current smoking status and current CD4/VL strata

There were 513 cancer diagnoses in 507 persons (6 persons had 2 different primary cancer diagnoses on the same date) during 73868 person-years of follow-up (PYFU); incidence rate

(IR) 6.9/1000 PYFU (95% confidence interval [CI] CI 6.3–7.5), a median follow-up of 3.5 [IQR 2.0-6.2] years per person. There were 437 NADC (IR 5.9; 5.4-6.5), 204 SRC (IR 2.7; 2.4-3.1), and 184 IRC (IR 2.5; 2.1-2.9) although these groups were not mutually exclusive as shown in Table 1. The most common diagnoses were lung cancer (n=65), anal (n=46) and prostate cancer (n=42; Table 1).

Figure 1a shows the crude incidence rates of the cancer subtypes, stratified by type of cancer and current smoking status. Current smokers have the highest rates of cancer, followed by previous smokers; the lowest rates were in never smokers. This varied across types of cancer, with the most marked differences in smoking status for SRC and the smallest differences for BMIRC. The crude rates of NADC and SRC were higher in current smokers compared to never smokers while both ADC and BMIRC had the lowest rates in previous smokers, albeit with wide CIs. There was a strong increase in the crude incidence rates of all cancers moving from those in a good CD4/VL strata to those in a poor CD4/VL strata (Figure 1b), with incidence rates increasing from 5.9/1000 PYFU (95% CI 5.3–6.6) to 15.5/1000 PYFU (95% CI 9.9–21.0). The difference between those in the good and poor CD4/VL strata was most marked for ADC and for IRC.

Table 3 shows the univariable and multivariable association for current (latest; time-updated) CD4/VL strata and smoking, both for cancer overall and the different groups of cancers. Compared to persons in the good CD4/VL strata, those in the poor strata had a significantly increased incidence of all cancer (adjusted incidence rate ratio [aIRR] 5.36; 95% CI 3.71-7.75). The largest association was seen for ADC (aIRR 16.56; 95% CI 7.84–35.00), followed by IRC (aIRR 10.21; 65% CI 6.06-17.2) and NADC (aIRR 3.14; 95% CI 1.92–5.14). A non-significant increased risk in those in the poor CD4/VL strata was seen for SRC and BMIRC. Compared to never smokers, current smokers had a significantly increased incidence of all cancer (aIRR 1.45; 1.17-1.79), which was greatest for SRC (2.21; 1.53-3.20), NADC (1.65; 1.31-2.09), and a marginally increased incidence for IRC (1.38; 0.97-1.96). Current smoking status was not significantly associated with ADC or BMIRC. There was a trend towards an increased incidence rates of cancers among previous smokers compared to never smokers, but this was not statistically significant for any cancer subgroup. There were relatively few events among past smokers and the power for this comparison was limited.

Does the association between smoking and cancer differ according to CD4/VL strata?

Figure 2 presents the stratified analysis for all cancers, NADC, IRC and SRC. Results are not shown for ADC and BMIRC as the number of events was comparatively small. The association between current CD4/VL strata and each of these diagnoses is consistent for never smokers, current smokers and previous smokers and all tests of interaction were not significant ($p>0.1$). For example, among never smokers, those in the poor CD4/VL stratum had over a 6-fold increased incidence of all cancers compared to those in the good CD4/VL stratum (aIRR 6.06; 95% CI 3.35 -10.97). A similar relationship was seen in current smokers in the poor versus good CD4/VL strata (aIRR 5.54; 95% CI 3.32–9.26) and in previous smokers (aIRR 3.24; 95% CI 0.74–14.21), with wide confidence intervals in the previous smoker's group. For NADC and IRC the same pattern was seen with the highest adjusted incidence rates seen in those in the poor CD4/VL strata in never smokers, current smokers and previous smokers. The smallest differences between CD4/VL strata and SRC were seen

for never smokers, although the confidence intervals were wide due to limited data in the previous smokers, and the multivariable estimates were unstable (data not shown).

Sensitivity and validated cancer event analyses

Various sensitivity analyses were performed as noted in the Methods. Persons with pre-existing cancers at baseline were excluded; this reduced the number of persons included to 18113 (92.4%), with 465 cancer diagnoses and 68370 PYFU (incidence 6.8/1000 PYFU; 95% CI 6.2–7.4). Results were consistent with our findings above and there were no interactions between CD4/VL strata and smoking status either for all cancers or for SRC, BMIRC, or IRC considered separately. Given the heterogeneity in the completeness of data on comorbidities, we repeated analyses adjusting for participating cohort in place of comorbidities with similar findings.

The final sensitivity analysis included only centrally validated cancer events. There were 311 validated events (of 335 qualifying events, 92.8%) during 34020 PYFU, incidence 9.2 (95% CI 8.2-10.2/1000 PYFU). There were 274 NADC, 154 SRC, and 111 IRC. There were 22 events in those with poor CD4/VL, 119 events in those with intermediate CD4/VL and 171 events in those with good CD4/VL. There were 87 events among never smokers, 165 among current smokers and 60 events among previous smokers. The most common diagnoses were lung (n=59), liver (n=28) and prostate cancer (n=24). Given the more limited number of validated events, this sensitivity analysis focused on all cancer and found similar results throughout. There was no interaction between CD4/VL and smoking status (p=0.43) for all cancers, indicating that the relationship between smoking status and all centrally validated cancer events was similar regardless of current CD4/VL.

Discussion

This large study including over 19,000 persons and more than 500 incident cancer events found no evidence that the relationship between current CD4/VL strata and cancer was different depending on smoking status. This finding was consistent across all cancers, NADC, IRC and SRC. To our knowledge, this is the first study to investigate this relationship in PLWH and suggests similar carcinogenic effects of smoking regardless of current CD4 count and VL.

Smoking is an established risk factor for cancer and one of the leading preventable causes of cancer in the general population and the relationship between smoking and the development of a wide range of cancers is well established in PLWH.[7] Our results showing an increased cancer incidence in current smokers, particularly for SRC, confirm that finding. We did not find a significantly increased incidence of cancers for previous smokers, although there was a non-significant trend towards an increased incidence for SRC. A decreased incidence of cancer was noted one year after smoking cessation for smoking related (non-lung) cancers among HIV-positive persons in the D:A:D study in 2019.[42] While the median follow-up in the present study was 3.5 years, development of incident cancer may take several years. There were less than 20 cancers of any type diagnosed in those with smoking cessation during follow-up and we were unable to investigate the association between CD4/VL strata and duration since smoking cessation due to limited power. .

Our results also confirm the results of many previous studies showing an association between CD4 count, VL and increased cancer incidence,[28, 43-45] which was not surprisingly most marked for ADC and IRC. We investigated a range of different ways of incorporating

information about immune deficiency and viremia, including the proportion of follow-up time spent with immune deficiency or viremia. However, as with most observational studies, we do not know when HIV-infection occurred for the majority of individuals, which limits the use of any cumulative measure of immune suppression or exposure to viremia, which will be underestimated. We chose to focus on a combination of current CD4 and viral load, a measure previously used in EuroSIDA,[47] and that is easier to understand and apply in a clinical setting rather than calculating proportions of follow-up. Current CD4/VL strata was not significantly associated with BMIRC, although with a very wide CI reflecting the comparatively small size of this group. Obesity has been linked to immune activation and inflammation in PLWH[48], and may itself be associated with immune suppression[49]. The heterogeneity of the cancers included in this group, or the small number of events, may in part explain our lack of an association.

We found no evidence to support our hypothesis that the impact of current smoking on cancer incidence differed for those in the poor or good CD4/VL strata. This suggests that the relationship between smoking and CD4/VL markers of immune suppression and virologic control are additive rather than multiplicative, as suggested previously and specifically for lung cancer.[50] While the strata we chose (CD4/VL categorised as good, poor and intermediate) provided the best statistical fit to our data, none of the measures we investigated showed a consistent interaction, and we interpreted our data cautiously given the repeated statistical testing when investigating the different markers. Studies have suggested that HIV replication is enhanced by nicotine [51] and also that cigarette smoke contains immune modifying agents with both immunosuppressive and proinflammatory effects[52], which would suggest that the effect of smoking on cancer risk might differ depending on immune suppression or viremia, especially for IRC, where the prevalence of prooncogenic infections in PLWH, such as hepatitis, human papillomavirus and Epstein-Barr virus, is high[7]. The lack of interaction between immune suppression and/or viral replication in our study, and individually for IRC, provides preliminary evidence that smoking does not enhance viral replication, although further large studies are required given the limited power when testing for statistical interactions.

Despite the substantial size and follow-up in RESPOND the lack of adequate power is one potential explanation for our findings, although the results in Figure 2 were consistent across smoking strata for cancer overall and for IRC, SRC and NADC, suggesting that the differences were small regardless of statistical power. The lack of a strong interaction between current smoking status and immune function or virologic control is consistent with a direct effect of smoking on cancer risk, as demonstrated by many previous studies[23, 24] and the stronger association of smoking with SRC versus other cancer types would support this hypothesis. Tobacco smoke contains multiple carcinogenic substances, and cancer development may be mediated through various pathways simultaneously.[53] Even without an interaction, our data showed that HIV-associated immune dysfunction and/or virologic replication was strongly associated with all cancers in PLWH. The strongest impact is seen for ADC , and other carcinogenic risk factors such as smoking are more pronounced for NADC.[54, 55] It is also possible there are pharmacokinetic or pharmacodynamic interactions between antiretrovirals and smoking related carcinogens independent of CD4 and VL which

drive the higher incidence of cancers, or that there is a biological effect of smoking on effectiveness of ART through cytochrome P-450 polymorphisms [56].

The strengths of our study were the large size and heterogeneity, a rigorous quality assurance program using centrally validated events, and that we addressed a question that, to our knowledge, has not previously been considered. Limitations include missing data on smoking status, as well as the absence of information on duration, type of smoking (cigarette versus pipe smoking) and/or intensity of smoking. Our intermediate CD4/VL category was heterogeneous and we also combined groups of cancers, which assumes that the interaction between current CD4/VL strata and smoking is similar across all cancers included in our subgroups. Further, using a CD4 count cut off of 350/mm^3, rather than a lower limit such as 200/mm^3, may limit our ability to detect the effect of more serious immune suppression on cancer development. Other important confounders, such as alcohol use, family history and infection with viruses such as human papillomavirus or Epstein-Barr virus, are not collected in RESPOND. RESPOND is a cohort of predominantly persons of White ethnicity, and results may differ in other ethnic groups. We lacked the power to study individual malignancies, which may show different associations between CD4/VL and smoking than those shown here.

In conclusion, both smoking and current CD4/VL strata were strongly associated with incidence of cancer, and smoking cessation should remain a priority. The association between current immune deficiency or virological control was similar for never smokers, current smokers and previous smokers suggesting similar carcinogenic effects of smoking regardless of CD4 count and VL. Reducing the burden of cancer from smoking and uncontrolled HIV infection should remain a priority for all HIV-positive individuals.

Appendix, http://links.lww.com/QAD/B957

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Figure 1a
Crude incidence of cancer types stratified by current smoking status

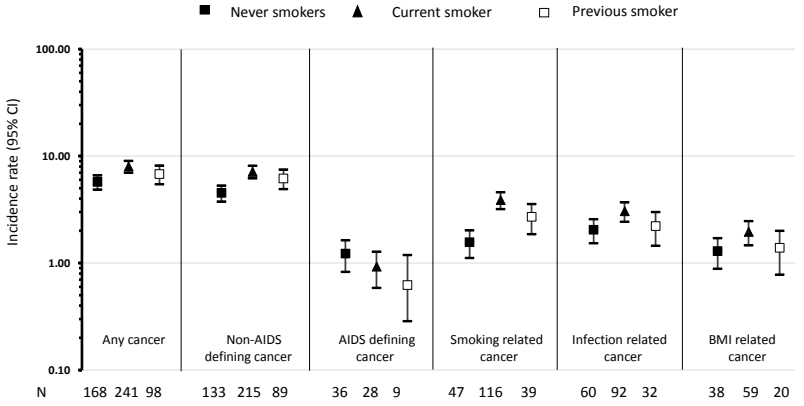


Figure 1b
Crude incidence of cancer types stratified by current HIV markers

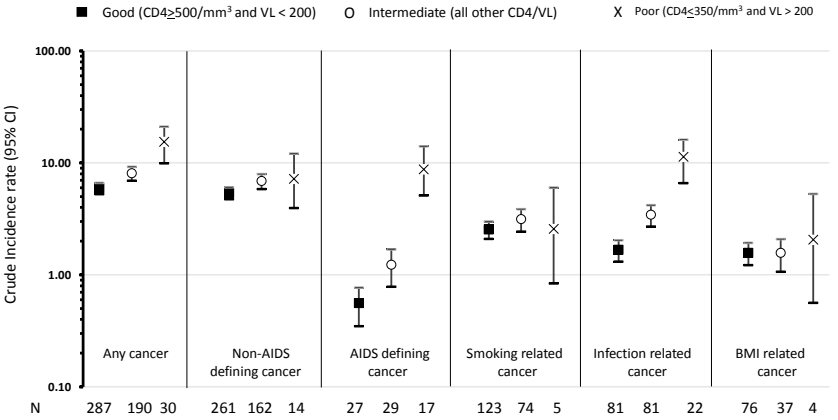
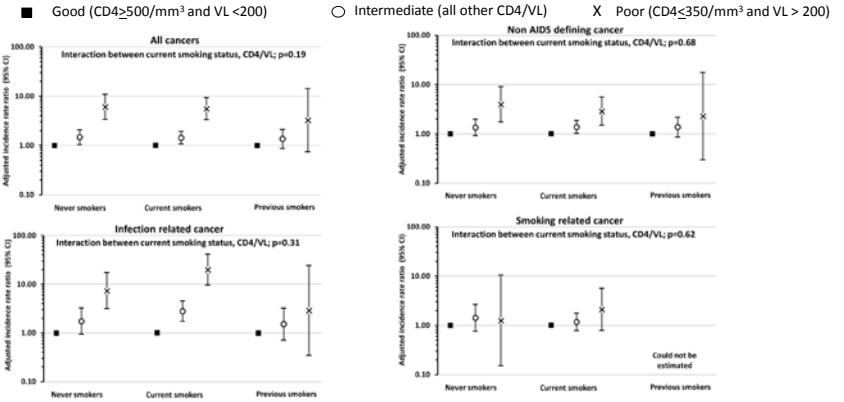


Figure 2
Adjusted* incidence rate ratio of cancer : Relationship with current HIV markers and smoking status



*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, prior cardiovascular disease, non-AIDS defining cancer, end stage liver disease, chronic kidney disease, prior exposure to PIs, time HIV positive, nadir CD4, baseline date and age

Table 1 Classification of 513 cancers occurring in 507 individuals*

All cancers			Smoking related cancer (SRC)			Infection related cancer (IRC)			BMI related cancer (BMIRC)		
	N	%		N	%		N	%		N	%
All	**513**	**100**	**All**	**204**	**39.8**		**184**	**35.9**		**119**	**23.2**
Lung	65	12.7	Lung	65	31.9	Anal	46	25.0	Liver	38	31.9
Unclassified[1]	62	12.1	Liver	38	18.6	Liver	38	20.7	Colon	21	17.7
Anal	46	9.0	Bladder	26	12.8	NHL	33	17.9	Breast	15	12.6
Prostate	42	8.2	Colon	21	10.3	KS	31	16.9	Pancreas	13	10.9
Liver	38	7.4	Pancreas	13	6.4	HL	14	7.6	Kidney	8	6.7
NHL	33	6.4	Cervical[2]	9	4.4	Cervical[2]	9	4.9	Gall bladder	8	6.7
KS	31	6.0	Kidney	8	3.9	Stomach	7	3.8	Rectum	7	5.9
Bladder	26	5.1	Stomach	7	3.4	Oropharyngeal	3	1.6	Oesophagus	6	5.0
Colon	21	4.1	Rectum	7	3.4	Penile	3	1.6	Thyroid	3	2.5
Head/Neck[1]	16	3.1	Oesophagus	6	2.9						
Breast	15	2.9	Oropharyngeal	3	1.5						
HL	14	2.7	AML	1	0.5						
Melanoma	14	2.7									
Pancreas	13	2.5									
Cervical[2]	9	1.8									
Gall bladder	8	1.6									
Kidney	8	1.6									
Stomach	7	1.4									
Gynaecological[1]	7	1.4									
Rectum	7	1.4									
Brain	6	1.2									
Oesophagus	6	1.2									
Oropharyngeal	3	0.6									
Thyroid	3	0.6									
MM	3	0.6									
Penile	3	0.6									
Salivary gland	2	0.4									
AML	1	0.2									
Bone	1	0.2									
Connective tissue	1	0.2									
Lip	1	0.2									
Testicular	1	0.2									

AIDS defining cancers: Kaposi sarcoma, cervical cancer and non-Hodgkin lymphoma. Non-AIDS defining cancers included all cancers except those which were AIDS defining, non-malignant melanoma skin cancers and pre-cancers.

[1] Further classification not available. [2] Cancer of the cervix. AML; acute myeloid leukaemia. KS; Kaposi sarcoma. NHL; non-Hodgkin lymphoma. HL; Hodgkin lymphoma. MM; multiple myeloma.

*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).

Table 2 Baseline characteristics of included population stratified by baseline smoking status

		All		Never smoked		Current smokers		Previous smokers		p
		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	<0.0001
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	<0.0001
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	
	Heterosxeual	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	<0.0001
Hepatitis	Negative	16993	86.7	7014	86.7	7457	85.7	2522	89.6	
B status	Positive	1062	5.4	418	5.2	494	5.7	150	5.3	
	Unknown	1547	7.9	656	8.1	748	8.6	143	5.1	<0.0001
Hepatitis C	Negative	13625	69.5	6440	79.6	5018	57.7	2167	77.0	
Status	Positive	5063	25.8	1206	14.9	3283	37.7	574	20.4	
	Unknown	914	4.7	442	5.5	398	4.6	74	2.6	<0.0001
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	<0.0001
Body Mass	<=18	516	2.6	120	1.5	320	3.7	76	2.7	
Index	18-25	10104	51.5	3773	46.6	4925	56.6	1406	49.9	
	25-30	4690	23.9	2118	26.2	1696	19.5	876	31.1	
	>30	1498	7.6	767	9.5	458	5.3	273	9.7	
	Unknown	2794	14.3	1310	16.2	1300	14.9	184	6.5	<0.0001
Hypertension	No	14023	71.5	5748	71.1	6544	75.2	1731	61.5	
	Yes	5579	28.5	2340	28.9	2155	24.8	1084	38.5	<0.0001
Diabetes	No	18365	93.7	7521	93.0	8310	95.5	2534	90.0	
	Yes	1237	6.3	567	7.0	389	4.5	281	10.0	<0.0001
Prior AIDS	No	15280	78.0	6413	79.3	6802	78.2	2065	73.4	
(any)	Yes	4322	22.0	1675	20.7	1897	21.8	750	26.6	<0.0001
Prior AIDS	No	18883	96.3	7823	96.7	8388	96.4	2672	94.9	
(cancer)	Yes	719	3.7	265	3.3	311	3.6	143	5.1	<0.0001

Table 2 continued…. Baseline characteristics of included population stratified by baseline smoking status

		All		Never smoked		Current smokers		Previous smokers		p
		N	%	N	%	N	%	N	%	
All		19602	100.0	8088	41.3	8699	44.4	2815	14.4	
Prior CVD	No	18912	96.5	7871	97.3	8410	96.7	2631	93.5	
	Yes	690	3.5	217	2.7	289	3.3	184	6.5	<0.0001
Prior CKD	No	16492	84.1	6604	81.7	7341	84.4	2547	90.5	
	Yes	666	3.4	278	3.4	229	2.6	159	5.6	
	Unknown	2444	12.5	1206	14.9	1129	13.0	109	3.9	<0.0001
Prior NADC	No	18883	96.3	7823	96.7	8388	96.4	2672	94.9	
	Yes	719	3.7	265	3.3	311	3.6	143	5.1	<0.0001
Prior ESLD	No	19456	99.3	8038	99.4	8627	99.2	2791	99.1	
	Yes	146	0.7	50	0.6	72	0.8	24	0.9	0.22
Prior fracture	No	18729	95.5	7841	96.9	8225	94.6	2663	94.6	
	Yes	873	4.5	247	3.1	474	5.4	152	5.4	<0.0001
HIV markers	Poor	675	3.4	323	4.0	300	3.4	52	1.8	
CD4 / VL^{+}	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	<0.0001
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Age	Years	46	38–54	46	37–54	45	37–52	51	44–57	<0.0001
CD4	/mm^3	556	385–754	536	377-716	570	380-782	590	428–796	<0.0001
Nadir CD4	/mm^3	206	93–321	210	100–324	209	93–334	180	78–279	<0.0001
Time HIV+*	Years	11	4–19	9	3–16	11	4–19	17	10–22	<0.0001
Baseline	Month/year	2/14	1/12–10/15	10/13	1/12–10/15	7/14	1/12–11/15	12/12	1/12–9/15	<0.0001
Years since started ART		9	3- 15	7	2–14	8	3–15	14	8–18	<0.0001

Baseline was defined as enrolment to RESPOND or the first date where smoking status was known if this occurred after enrolment. $^{+}$Poor; CD4 < 350/mm^3 and HIV VL > 200 copies/mL. Good; CD4> 500/mm^3 and VL < 200 copies/mL. Intermediate; all other combinations of CD4 and VL. *missing for n=707 (3.6%), 266 (3.3%) from non-smokers, 299 (3.4%) from current smokers and 142 (5.0%) from past smokers.

MSM: men having sex with men. IDU; intravenous drug user. CVD; cardiovascular disease. CKD; chronic kidney disease. NADC; non-AIDS defining cancer. ESLD; end stage liver disease.

Table 3. Association between current smoking status, HIV markers and cancer

			univariable			Multivariable		
			IRR	95% CI	p	aIRR	95% CI	p
All	HIV markers	Good	1.00			1.00		
	CD4/VL	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	HIV markers	Good	1.00			1.00		
Defining	CD4/VL	Int	1.31	1.08-1.60	0.0071	1.35	1.09-1.66	0.0050
Cancer		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	HIV markers	Good	1.00			1.00		
Defining	CD4/VL	Int	2.34	1.32-4.14	0.0037	2.02	1.10-3.69	0.023
Cancer		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
Infection	HIV markers	Good	1.00			1.00		
Related	CD4/VL	Int	2.11	1.54-2.90	<0.0001	2.02	1.44-2.83	<0.0001
Cancer		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	HIV markers	Good	1.00			1.00		
Related	CD4/VL	Int	1.30	0.98-1.73	0.072	1.35	0.99-1.83	0.054
Cancer		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	HIV markers	Good	1.00			1.00		
Related	CD4/VL	Int	1.00	0.68-1.48	0.99	1.01	0.67-1.53	0.97
Cancer		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 >500/mm^3 and VL < 200 copies/mL. Poor; CD4 <350/mm^3 and VL > 200 copies/mL. Intermediate; all other CD4 / VL combinations. All models shown include HIV markers CD4/VL, smoking status and are additionally 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, chronic kidney disease, cardiovascular disease , NADC, end-stage liver disease, CKD, exposure to PIs, time HIV positive, nadir CD4 count, baseline date and age.

IRR incidence rate ratio. aIRR adjusted incidence rate ratio. CI; confidence interval.