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Cancer Risk and Use of PI or NNRTI-based Combination Antiretroviral Therapy (cART): The D:A:D Study

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BACKGROUND

The potential effects of cART on cancer risk, especially regimens including protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), are unclear [1-4]. The aim of this study was to assess the relationship between cancer risk and cART, PI and NNRTI use.

METHODS

D:A:D participants were followed from the latest of D:A:D Study entry or 1/1/2004 (start of prospective cancer data collection) until the earliest of a first incident cancer diagnosis (any type, excluding pre-cancer stages), 1/2/2012, death, or 6 months after last visit.

Poisson regression models assessed associations between the incidence of cancer and cumulative (per year) use of either cART or PI and NNRTI.

Each outcome was considered in a separate analysis: any cancer, grouped non-AIDS-defining cancers (NADC), grouped AIDS-defining cancers (ADC) and most frequent individual ADC: invasive cervical cancer, Kaposi's sarcoma and Non-Hodgkin's lymphoma, and NADC: lung cancer, invasive anal cancer, Hodgkin's lymphoma and head/neck cancer.

Analyses were adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AID cancer, hepatitis B/C status and smoking status.

Sensitivity analyses included adjustment for baseline CD4 count.

RESULTS

41,762 persons were included in the analysis, contributing 239,832 person-years (PY) of follow-up. Baseline characteristics are displayed in **Table 1**.

During a median follow-up of 6.4 years (interquartile range [IQR] 3.7-8.1), a total of 2,242 cancers were diagnosed (incidence rate [IR]: 0.93/100PY [95% confidence interval (CI): 0.90-0.97]), 1,151 ADC (IR: 0.48/100PY; 95%CI: 0.45-0.51) and 1,091 NADC (IR: 0.45/100PY; 95%CI: 0.43-0.48).

The most frequent AIDS-defining and non-AIDS-defining cancers were cervical cancer (496 cases, IR: 0.21/100PY; 95%CI: 0.19-0.22) and lung cancer (194 cases, IR: 0.081/100PY; 95%CI: 0.070-0.092), respectively.

Table 1

Baseline characteristics

		n	%
Number of patients		41,762	100%
Gender	Male	30,564	73.2
	Female	11,186	26.8
Mode of acquisition	MSM	18,307	43.8
	IDU	6,047	14.5
	Heterosexual	14,715	35.2
	Other/unknown	2,693	6.5
Ethnic group	White	20,828	49.9
	Black African	2,919	7.0
	Other	836	2.0
Smoking status	Current smoker	16,607	39.8
	Ex-smoker	7,370	17.7
	Never smoker	10,382	24.9
HCV status	Negative	26,305	63.0
	Positive	4,392	10.5
HBV status	Negative	27,561	66.0
	Positive	1,767	4.2
Prior cancer		2,953	7.1
		Median	(IQR)
Age (years)		39	(33, 46)
CD4 count (cells/mm^3)		433	(281, 620)
HIV RNA (log$_{10}$ copies/ml)		2.3	(1.7, 4.3)

Some percentages do not add to 100 due to unknown categories (not shown)

Figure 1

Incidence of any non-AIDS-defining cancer (with 95% CI) stratified by years of exposure to cART

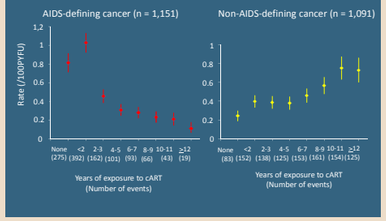
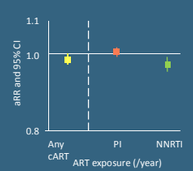


Figure 2

Adjusted rate ratios (aRR) for associations between cART, PI and NNRTI use (per year) and any cancer (n = 2,242)



Adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AIDS cancer, smoking status, HCV and HBV status

According to the duration of cART exposure, NADC IR increased from 0.24/100PY (95%CI: 0.19-0.30) among unexposed patients to 0.73/100PY (95%CI: 0.60-0.86) after >12 years of cART exposure, **Figure 1**. ADC IR decreased from 0.81/100PY (95%CI: 0.72-0.91) among unexposed patients to 0.11/100PY (95%CI: 0.07-0.17) after >12 years of cART exposure, **Figure 1**.

Longer exposure to cART was associated with a lower risk of cancer overall (adjusted rate ratio [aRR]: 0.98/year; 95%CI: 0.97-1.00; p=0.009). No association was seen between PI use and risk of cancer overall (aRR: 1.01/year; 95%CI: 0.99-1.02), whereas longer NNRTI use was associated with a lower risk (aRR: 0.97/year; 95%CI: 0.95-0.99; p=0.0009), **Figure 2**.

Both longer PI (aRR: 0.93/year; 95%CI: 0.90-0.97; p=0.0001) and longer NNRTI (aRR: 0.84/year; 95%CI: 0.80-0.88; p=0.0001) use were associated with a lower ADC risk, **Figure 3**; this trend was consistent when cervical cancer and Kaposi's sarcoma were considered individually, however PI exposure was not associated with Non-Hodgkin's lymphoma occurrence, **Table 2**.

Longer PI use (aRR: 1.03/year; 95%CI: 1.01-1.05; p=0.0003), but not NNRTI (aRR: 1.00/year; 95%CI: 0.98-1.02), use was associated with a higher NADC risk, **Figure 3**. Specifically, PI use was associated with a higher risk of anal cancer, but not with other frequently observed NADCs (Hodgkin's lymphoma, lung and head and neck cancers), **Table 3**.

Additional analyses investigated the association between PI exposure and anal cancer stratified by gender (with adjustment for mode of acquisition) with similar findings (data not shown).

These results were robust to further adjustment for CD4 count.

LIMITATIONS

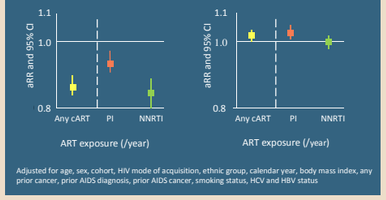
Residual confounding cannot be ruled out in this observational study.

CONCLUSION

Cumulative use of any cART was associated with reduced ADC, but increased NADC risk. Both PI and NNRTI use appeared to be protective for the development of ADC, while the increased risk of NADC associated with cART appeared to be restricted to PI use (3% higher risk per year). Biological mechanisms for the latter association possibly indicative of an adverse effect of PI merit further investigation.

Figure 3

Further investigation of cancer associations; adjusted rate ratios (aRR) for associations between cART, PI and NNRTI use (per year) and AIDS- and non-AIDS-defining cancer



Adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AIDS cancer, smoking status, HCV and HBV status

Table 2

Adjusted rate ratios (aRR) for associations between cART use (per year longer exposure, whether PI or NNRTI-based) and specific AIDS defining cancers

	Cervical cancer			Kaposi's sarcoma			Non Hodgkin's lymphoma		
	aRR	95% CI	p	aRR	95% CI	p	aRR	95% CI	p
PIs	0.89	0.84-0.95	0.0002	0.93	0.87-1.00	0.05	0.97	0.92-1.03	0.34
NNRTIs	0.82	0.76-0.89	0.0001	0.82	0.74-0.91	0.0002	0.87	0.80-0.94	0.0009

Table 3

Adjusted rate ratios (aRR) for associations between cART use (per year longer exposure, whether PI or NNRTI-based) and specific non-AIDS defining cancers

	Lung cancer			Anal cancer			Hodgkin's lymphoma			Head and neck cancer		
	aRR	95% CI	p	aRR	95% CI	p	aRR	95% CI	p	aRR	95% CI	p
PIs	1.01	0.97-1.05	0.58	1.09	1.04-1.14	0.0003	0.97	0.90-1.04	0.44	1.02	0.96-1.07	0.56
NNRTIs	0.97	0.93-1.02	0.25	1.03	0.97-1.09	0.32	0.88	0.80-0.97	0.01	1.03	0.97-1.10	0.30

Adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AIDS cancer, smoking status, HCV and HBV status

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