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D:A:D

Is Nelfinavir Exposure Associated with Cancer Incidence in HIV-positive individuals?

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BACKGROUND

Nelfinavir exhibits potent anti-cancer properties against a range of tumour types.[1] However, in 2006/07, nelfinavir supplies were accidently contaminated with ethyl mesilate, a known carcinogen.[2] This analysis investigated the association between nelfinavir and cancer risk in a large cohort of HIV-positive persons.

METHODS

D:A:D participants were followed from the latest of 1/Jan/2004 or D:A:D study entry (baseline), until the earliest of a first incident cancer diagnosis, 1/Feb/2014, death, or 6 months after the last visit. We performed analyses on all cancer types, AIDS-defining, non-AIDS-defining, and non-infection-related cancer types. Poisson regression models were used to assess associations between cancer incidence and cumulative nelfinavir exposure, current nelfinavir exposure, and exposure to nelfinavir between 1/Jul/2006 and 30/Jun/2007 (the period in which nelfinavir was most heavily contaminated).

RESULTS

- Baseline characteristics of included persons are shown in **Table 1**.
- 42,006 participants contributed 303,005 person-years of follow-up.
- 8,305 participants had a median of 1.7 (IQR 0.7-3.4) years of prior nelfinavir exposure. During follow-up, 8,781 individuals contributed 4,376 person-years of nelfinavir use; 1,063 of whom were potentially exposed to contaminated nelfinavir.
- Overall, 2,279 cancers were diagnosed at a rate of 0.75 (95%CI 0.72-0.78) per 100 person-years; 810 were AIDS-defining (0.27 [0.25-0.29]), 1,469 were non-AIDS-defining (0.48 [0.46-0.51]), and 763 were non-infection-related (0.25 [0.23-0.27]).
- Greater cumulative exposure to nelfinavir and current use of nelfinavir were not associated with a reduced cancer risk compared with use of other protease inhibitors (**Table 2A and 2B, respectively**).
- Incidences of the cancer types evaluated were similar amongst individuals exposed to potentially contaminated nelfinavir and other nelfinavir users (**Figure 1**).
- These comparisons remained similar when adjusted for important demographic variables and hepatitis status (**Table 3**).

CONCLUSIONS

Nelfinavir use was not associated with reduced cancer incidence compared to other protease inhibitor regimens. It appears the 2006/07 carcinogenic contamination of nelfinavir did not increase cancer incidence in those exposed.

Table 1

Baseline characteristics of eligible D:A:D participants

		42006	(100.0%)
Gender	Male	30716	**(73.1%)**
Age (years)	Median (range)	40	**(33, 46)**
Mode of HIV acquisition	MSM	18404	**(43.8%)**
	IDU	6007	**(14.3%)**
	Heterosexual	14948	**(35.6%)**
	Other/unknown	2647	**(6.3%)**
Smoking status	Current smoker	17020	**(40.9%)**
	Ex-smoker	7359	**(17.7%)**
	Never smoker	11530	**(27.7%)**
	Unknown	5727	**(13.8%)**
CD4 count (cells/mm^3) (n=39956)	Median (IQR)	434	**(282, 620)**
HIV RNA (log_{10} copies/ml) (n=39001)	Median (IQR)	2.3	**(1.7, 4.3)**
Hepatitis C antibody	Negative	27705	**(66.0%)**
	Positive	7899	**(18.8%)**
	Unknown	6402	**(15.2%)**
Hepatitis B surface antigen	Negative	28950	**(68.9%)**
	Positive – active	1956	**(4.7%)**
	Positive – inactive	5905	**(14.1%)**
	Unknown	5195	**(12.4%)**
Previous cancer		2384	**(5.7%)**
Previous AIDS diagnosis		9901	**(23.6%)**

MSM=men who have sex with men; IDU=intravenous drug user; IQR=interquartile range

Table 2

Association between cancer and A) cumulative exposure (per additional 5 years), and B) current exposure to different antiretroviral therapy regimens

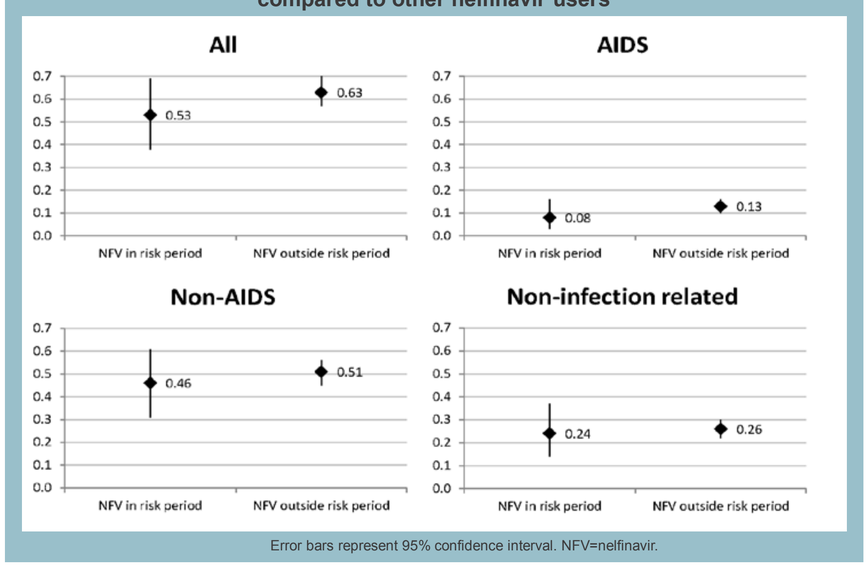
A) Cumulative	All		AIDS-defining		Non-AIDS-defining		Non-infection-related	
	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p
NFV-ART	0.93 (0.82, 1.06)	0.26	0.59 (0.45, 0.77)	0.01	1.19 (1.03, 1.37)	0.02	1.17 (0.96, 1.43)	0.12
Non-NFV, PI-ART	0.82 (0.78, 0.87)	0.01	0.47 (0.41, 0.54)	0.01	1.05 (0.99, 1.13)	0.12	0.98 (0.89, 1.07)	0.63
NNRTI-ART	0.68 (0.63, 0.73)	0.01	0.27 (0.23, 0.33)	0.01	0.97 (0.89, 1.05)	0.43	0.97 (0.86, 1.08)	0.54
Other ART	0.92 (0.85, 1.00)	0.05	0.65 (0.55, 0.77)	0.01	1.09 (0.99, 1.19)	0.08	1.03 (0.90, 1.17)	0.68

B) Current	All		AIDS-defining		Non-AIDS-defining		Non-infection-related	
	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p
NFV-ART	0.98 (0.68, 1.41)	0.92	1.28 (0.72, 2.28)	0.40	0.86 (0.54, 1.37)	0.52	0.73 (0.35, 1.55)	0.41
Non-NFV, PI-ART	1	-	1	-	1	-	1	-
NNRTI-ART	0.81 (0.73, 0.89)	0.01	0.73 (0.61, 0.88)	0.01	0.85 (0.76, 0.95)	0.01	0.93 (0.79, 1.09)	0.38
Other ART	0.85 (0.71, 1.02)	0.07	0.78 (0.56, 1.10)	0.16	0.88 (0.71, 1.08)	0.21	0.97 (0.73, 1.29)	0.84
No ART	1.39 (1.23, 1.56)	0.01	2.35 (1.97, 2.80)	0.01	0.78 (0.65, 0.93)	0.01	1.01 (0.80, 1.28)	0.92

All models adjusted for age, gender, mode of infection, hepatitis B surface antigen/hepatitis C antibody status and history of a previous cancer. As in previous D:A:D analyses, CD4 and HIV viral load are not included in the models as they are on the causal pathway between ART use and cancer occurrence. NFV=nelfinavir; ART= antiretroviral therapy; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; aRR=adjusted rate ratio; CI=confidence interval.

Figure 1

Incidence (per 100 person-years) of cancers amongst participants that used nelfinavir between 1 July 2006 and 30 June 2007 compared to other nelfinavir users



Error bars represent 95% confidence interval. NFV=nelfinavir.

Table 3

Association between cancer and nelfinavir exposure between 1 July 2006 and 30 June 2007

	All		AIDS-defining		Non-AIDS-defining		Non-infection-related	
	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p	aRR (95%CI)	p
Exposed to NFV in risk period	1.07 (0.78, 1.46)	0.68	0.58 (0.25, 1.31)	0.19	1.23 (0.88, 1.72)	0.23	1.25 (0.78, 2.00)	0.35
Exposed to NFV outside risk period	1.07 (0.74, 1.21)	0.31	1.02 (0.77, 1.36)	0.87	1.08 (0.94, 1.25)	0.27	1.07 (0.87, 1.30)	0.53

Reference group for each treatment category is all other ART exposure. All models adjusted for age, gender, mode of infection, hepatitis B surface antigen/hepatitis C antibody status and history of previous cancer. As in previous D:A:D analyses, CD4 and HIV viral load are not included in the models as they are on the causal pathway between ART use and cancer occurrence. NFV=nelfinavir; aRR=adjusted rate ratio; CI=confidence interval.

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1) Gantt S *et al*. *Curr Opin Oncol* 2013,**25**:495-502; 2) European Medicines Agency. Questions and answers on the follow-up to the contamination of Viracept (nelfinavir) with ethyl mesilate. London; 24 July 2008.

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