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D:A:D

Impact of Specific Antiretroviral Drugs on Non-AIDS Mortality; the D:A:D Study

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On behalf of the D:A:D Study Group

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BACKGROUND

- In some previous studies, use of protease inhibitors (PIs) has been associated with an increased risk of death and non-AIDS events, such as some non-AIDS cancers and cardiovascular events (1, 2, 3).
- Further, previous studies have shown that there is no significant difference between specific antiretroviral (ARV) drugs in the incidence of AIDS- and non-AIDS events for a given CD4 count and HIV RNA viral load (VL) (4).

STUDY AIM

- To investigate whether specific PIs and non-nucleoside transcriptase inhibitors (NNRTIs) are associated with increased non-AIDS mortality in the D:A:D Study, and whether there are significant differences in ARV specific non-AIDS mortality rates within different CD4 count- and VL strata.

METHODS

- The D:A:D Study is an observational study of >49,000 HIV+ persons from 11 cohorts across Europe, Australia and the USA. The primary aim of the study is to investigate potential associations between the use of ARV drugs and cardiovascular disease (CVD), AIDS- and non-AIDS cancers, end stage renal disease, end stage liver disease and deaths.
- All clinical events are collected in real-time and then centrally validated. Underlying causes of deaths are classified using the Coding Causes of Death in HIV (Code) methodology (5).
- In this study, D:A:D study participants were followed from study enrolment until the earliest of death, 1/2/2013 or 6 months after last clinic visit.
- Exposure to specific PIs/NNRTIs was classified as recent (current use or use in last 6 months) or cumulative (per 1 year (/year)). As most treated patients in the D:A:D Study will have been exposed to ARV drugs for many years, we additionally expressed the same results for cumulative exposure as per 5 years (/5 years), so that the association would relate to a more clinically relevant duration of exposure.
- Total- and drug specific non-AIDS mortality rates were calculated within different CD4 count- and VL strata for both recent and cumulative exposure. Follow-up among individuals dying from AIDS-related causes was censored on the date of death.
- Poisson regression models were used to compare non-AIDS mortality rates for both recent and cumulative exposure in three separate models, each of which was adjusted for baseline factors (gender, mode of HIV acquisition, ethnicity) and time-updated factors (age, CD4 count, VL, HBV/HCV status, smoking, hypertension, diabetes and calendar year).

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1. C Chao et al., AIDS 2012;26(17):2223-31, 2. S Worm et al., JID 2010;201(3):318-30, 3. S Worm et.al., JID 2012;205(4):535-9,
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Table 1

Baseline characteristics of 49,717 persons at D:A:D Study entry

		N	%
Gender	Male	36,678	74
Mode of HIV-acquisition	MSM*	21,922	44
	IDU**	7,619	15
	Heterosexual	16,202	33
	Other/Unknown	3,974	8
Ethnicity	White	25,171	51
	Black	4,872	10
	Other/Unknown	19,666	40
Age at recruitment (years)	Median (IQR)	38	(32.5, 45.0)
AIDS at baseline	Yes	11,060	22
Viral load (log_{10} copies/ml)	Median (IQR)	3.0	(1.7, 4.5)
CD4 (cells/mm³)	Median (IQR)	400	(243, 590)
Ever received ART	N	30,383	61
Total years ART exposure	Median (IQR)	2.9	(1.2, 4.8)
Smoking status	Current smoker	17,552	35
	Ex-smoker	8,386	17
	Never smoked/Unknown	23,779	48
Hypertension	Yes	7,857	16
Diabetes	Yes	1,377	3

*MSM: Men who have sex with men, **IDU: Intravenous drug use

Table 2

Rates of non-AIDS deaths, stratified by current a) CD4 count and b) Viral load

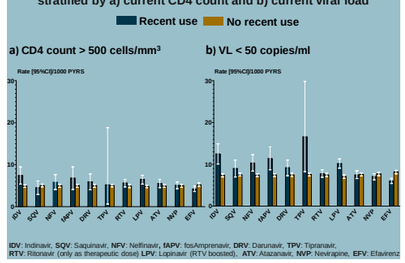
a) CD4 count, cells/mm³	N deaths	PYRS	Rate per 1,000 PYRS	95% CI
<50	198	4,629	**42.77**	36.81, 48.73
≥50≤200	671	26,846	**24.99**	23.10, 26.89
>200≤350	820	65,759	**12.47**	11.62, 13.32
>350≤500	601	88,596	**6.78**	6.24, 7.33
>500	878	175,475	**5.00**	4.67, 5.33

b) Viral load, copies/ml	N deaths	PYRS	Rate per 1,000 PYRS	95% CI
<50	1,675	221,013	**7.58**	7.22, 7.94
≥50≤10,000	845	85,820	**9.85**	9.18, 10.51
>10,000≤100,000	353	39,036	**9.04**	8.10, 9.99
>100,000	265	12,711	**20.85**	18.34, 23.36

Table does not include persons with missing information on CD4 count (N=108) and VL (N=138).

Figure 1

Drug specific non-AIDS death rates for recent exposure, stratified by a) current CD4 count and b) current viral load



IDV: Indinavir, SQV: Saquinavir, NFV: Nelfinavir, fAPV: fosAmprenavir, DRV: Darunavir, TPV: Tipranavir, RTV: Ritonavir (only as therapeutic dose) LPV: Lopinavir (RTV boosted), ATV: Atazanavir, NVP: Nevirapine, EFV: Efavirenz

RESULTS

- 3,276 non-AIDS deaths occurred in 371,333 person years (PYRS) (incidence: 8.8/1000 PYRS; 95% CI; 8.5-9.1).
- Baseline characteristics of study participants at D:A:D Study entry are displayed in **Table 1**.
- Unadjusted death rates stratified by current CD4 count and VL are shown in **Table 2.** The drug specific unadjusted death rates for recent and cumulative exposure to each ARV drug (here considering follow-up only during periods when the current CD4 count was >500 cells/mm³ or VL <50 copies/ml), are displayed in **Figure 1 and Figure 2.** Relative differences were similar across time-updated CD4 count- and VL strata.
- After adjustment for baseline factors and time-updated factors, including adjustment for continuous CD4 count and VL, there was no significant association between recent exposure to commonly used PIs/NNRTIs and increased death rates. In contrast, recent exposure to efavirenz (EFV) (adjusted relative rate: 0.86) was significantly associated with a decreased death rate. The results for recent exposure in uni- and multivariable models for individual ARV drugs are shown in **Figure 3.**
- For cumulative exposure, the commonly used PIs/NNRTIs lopinavir/ritonavir (LPV/r), atazanavir (ATV), saquinavir (SQV) and nevirapine (NVP) were significantly associated with small increases in death rates. The results for cumulative exposure in uni- and multivariable models are expressed as /year and /5 years for individual ARV drugs in **Figure 4.**
- Results were consistent across time-updated CD4 count- and VL strata; when restricting analyses to those currently on ARV drugs; excluding unknown causes of deaths and excluding intravenous drug users.

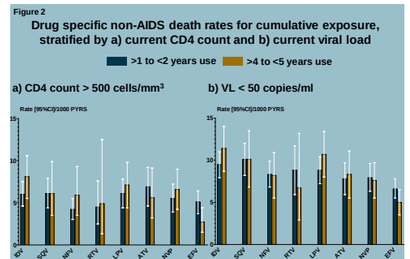
CONCLUSION

- Our findings suggest that cumulative exposure to some PI/NNRTIs is associated with a small but increased risk of non-AIDS mortality. Conversely, recent exposure to EFV was associated with a reduced risk of non-AIDS mortality. There were no significant differences in ARV-specific death rates within different CD4 count- and VL strata.
- The effects were consistent among various types of PIs and of an extent comparable to earlier findings for non-AIDS events in the D:A:D Study.
- The choice of PIs/NNRTIs may affect long-term HIV prognosis and although potential confounding cannot be ruled out, our results argue for continued pharmacovigilance.

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Figure 2

Drug specific non-AIDS death rates for cumulative exposure, stratified by a) current CD4 count and b) current viral load



fAPV, DRV, TPV: Not enough PYRS to stratify by > 1year

IDV: Indinavir, SQV: Saquinavir, NFV: Nelfinavir, fAPV: fosAmprenavir, DRV: Darunavir, TPV: Tipranavir, RTV: Ritonavir (only as therapeutic dose) LPV: Lopinavir (RTV boosted), ATV: Atazanavir, NVP: Nevirapine, EFV: Efavirenz

Figure 3

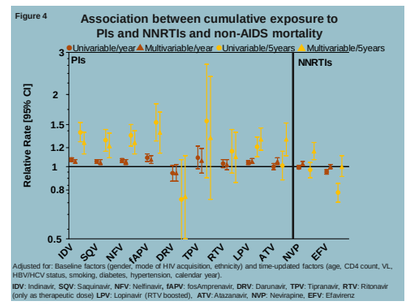
Association between recent exposure to PIs and NNRTIs and non-AIDS mortality

Adjusted for: Baseline factors (gender, mode of HIV acquisition, ethnicity) and time-updated factors (age, CD4 count, VL, HBV/HCV status, smoking, diabetes, hypertension, calendar year).

IDV: Indinavir, SQV: Saquinavir, NFV: Nelfinavir, fAPV: fosAmprenavir, DRV: Darunavir, TPV: Tipranavir, RTV: Ritonavir (only as therapeutic dose) LPV: Lopinavir (RTV boosted), ATV: Atazanavir, NVP: Nevirapine, EFV: Efavirenz

Figure 4

Association between cumulative exposure to PIs and NNRTIs and non-AIDS mortality



Adjusted for: Baseline factors (gender, mode of HIV acquisition, ethnicity) and time-updated factors (age, CD4 count, VL, HBV/HCV status, smoking, diabetes, hypertension, calendar year).

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