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Association Between Dideoxynucleoside Analogues (d-drugs) and End-Stage Liver Disease (ESLD)

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BACKGROUND

- Whilst some antiretroviral (ARV) drugs, including d-drugs (stavudine [d4T], didanosine [ddI], zalcitabine [ddC]), may cause biomarker-defined hepatotoxicity [1-8], their association with clinically-defined end-stage liver disease (ESLD) remains unknown
- Whilst rarely used anymore in resource-rich settings, d4T remains widely used in resource-limited settings. DdI and ddC are also still occasionally used

METHODS

- The D:A:D Study is a prospective cohort-collaboration study of >49,000 HIV-positive persons from 11 cohorts in Europe, Australia, and the US
- ESLD in D:A:D is a centrally validated endpoint collected real-time and includes variceal bleeding, grade III/IV hepatic encephalopathy, hepatorenal syndrome and liver transplantation
- Information on ESLD is derived from a designated ESLD event form or from a Cause of Death (CoDe) form, details at www.chip.dk
- Study participants were followed from 1/2/2004 to the earliest of ESLD, death, 6 months after last visit or 1/2/2012
- Poisson regression models were used to explore associations between ESLD and cumulative use of d-drugs, other nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), non-NRTIs (NNRTIs), and possible confounders (including demographics, HIV-related factors and viral hepatitis status), and considered whether any drug effects were reversed upon cessation
- The incidence rate ratios (IRR) for drug expose and ESLD were fitted per year of additional drug exposure as in previous D:A:D analyses of cardiovascular disease

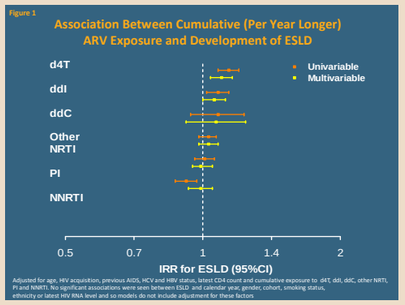
RESULTS

- A total of 45,498 persons were included in analysis
- Over 252,660 person-years (PY), 204 persons experienced ESLD (incidence 0.81/1000 PY [95%CI 0.70-0.92])
- Included persons were predominantly Caucasian (50%) males (74%) having acquired HIV by MSM and with a median age of 40 (IQR 34-46) years and median CD4 count of 433 (IQR 280-621) cells/mm^3. Characteristics of those developing ELSD in **Table 1**
- The most common clinical manifestations of ESLD were encephalopathy (43%) and variceal bleeding (30%)

Table 1 Characteristics Of Those Developing ESLD

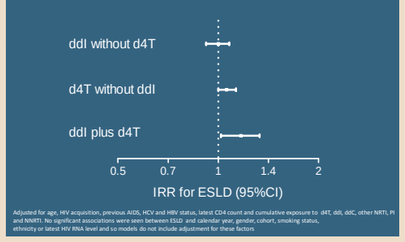
Number (%) of persons with ESLD		204	(100.0)
Event form	ESLD	145	(71.1)
	CoDe	59	(28.9)
Gender	Male	156	(76.5)
Age at ESLD (years)	Median (range)	46	(41-51)
Mode of acquisition	MSM	36	(17.7)
	IDU	117	(57.4)
Ethnic group	White	120	(58.8)
	Unknown	77	(37.8)
CD4 count (cells/mm^3) (n=201)	Median (IQR)	230	(101, 380)
HIV RNA (log_{10}copies/mL) (n=199)	Median (IQR)	1.70	(1.70, 3.64)
HCV status	Positive	47	(23.0)

Figure 1 Association Between Cumulative (Per Year Longer) ARV Exposure and Development of ESLD



Adjusted for age, HIV acquisition, previous AIDS, HCV and HBV status, latest CD4 count and cumulative exposure to d4T, ddI, ddC, other NRTI, PI and NNRTI. No significant associations were seen between ESLD and calendar year, gender, cohort, smoking status, ethnicity or latest HIV RNA level and so models do not include adjustment for these factors

Figure 2 Associations Between ESLD and Cumulative Use of ddI and d4T In Combination With or Without Each Other



Adjusted for age, HIV acquisition, previous AIDS, HCV and HBV status, latest CD4 count and cumulative exposure to d4T, ddI, ddC, other NRTI, PI and NNRTI. No significant associations were seen between ESLD and calendar year, gender, cohort, smoking status, ethnicity or latest HIV RNA level and so models do not include adjustment for these factors

- For 91% the underlying ESLD cause was viral hepatitis and/or alcohol use
- After adjustment, longer d-drug use was associated with increased ESLD rates (overall adjusted rate ratio 1.07 [95% CI 1.02-1.12]/year; d4T 1.10 [1.04-1.16]; ddI 1.06 [1.00-1.12]; ddC 1.07 [0.92-1.24]), **Figure 1**
- In contrast, no associations were seen with longer use of other NRTIs (1.03 [0.98-1.08]), PIs (0.99 [0.95-1.05]) nor NNRTIs (0.99 [0.93-1.05])
- Of the 19,033 persons on d-drugs, 90% stopped use at least once, with only 22% of the PY in those exposed to d-drugs being in current users
- When analyses were repeated after excluding any follow-up time during which an individual also received d4T, the ddI association became non-significant (RR 1.00 [95%CI 0.92-1.08] per year). In contrast, when analyses were repeated after excluding any follow-up time during which an individual also received ddI, the association with d4T remained unchanged (RR 1.06 [95%CI 1.00-1.13] per year). Combined ddI and d4T use showed evidence of synergism for developing ESLD (1.17 [95%CI 1.02-1.33] per year of exposure to the two drugs concurrently), **Figure 2**
- There was no evidence that the d-drug effect was modified by viral hepatitis B or C status (p>0.1 for interaction)
- Those stopping d-drugs had higher ESLD rates than those currently on d-drugs; this effect did not wane in the first 8 years after cessation, **Table 2**
- Other ESLD risk factors were older age (2.20 [1.20-4.03] >35 vs <35 years), latest CD4 (0.77 [0.74-0.80] per 50 cells/mm^3 higher), hepatitis C (1.66 [1.08-2.55]) and hepatitis B (2.63 [1.63- 4.25]) coinfection and injection drug use as the mode of HIV acquisition (4.45 [3.22-6.14] compared to those infected through MSM), **Figure 3**

CONCLUSION

- Cumulative use of d-drugs, but not other ARV drugs, was associated with increased ESLD rates, without evidence for reversibility upon cessation
- The higher rates in those stopping d-drugs may suggest selective discontinuation in those at highest risk of ESLD
- Our results suggest that d-drugs should be avoided if possible, particularly in those with the highest underlying risks of ESLD

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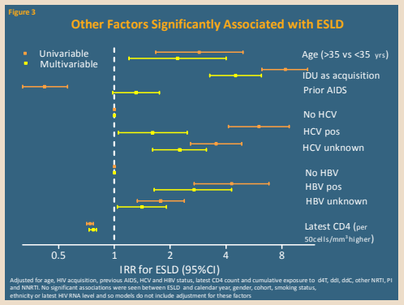
Table 2 Associations Between Current and Cumulative Exposure to d-drugs and Development of ESLD

			Adjusted for:	
			Exposure to other NRTIs, PIs and NNRTIs	Exposure to other NRTIs, PIs and NNRTIs and potential confounders*
	Rate /1000 PY# (95% CI#)	Relative rate[b] (95% CI)	Relative rate (95% CI)	Relative rate (95% CI)
Never received d-drugs	0.042 (0.031-0.052)	0.75 (0.41-1.38)	0.74 (0.40-1.36)	1.35 (0.73-2.49)
Currently on d-drugs	0.086 (0.050-0.122)	Ref.	Ref.	Ref.
Stopped d-drugs and off for:				
≥0, <2 years	0.167 (0.111-0.222)	2.28 (1.32-3.94)	2.31 (1.33-4.02)	2.01 (1.17-3.48)
≥2, <4 years	0.144 (0.093-0.196)	1.90 (1.09-3.32)	1.97 (1.12-3.47)	1.91 (1.09-3.36)
≥4, <6 years	0.172 (0.113-0.230)	2.23 (1.29-3.85)	2.38 (1.36-4.16)	2.45 (1.40-4.28)
≥6, <8 years	0.114 (0.066-0.183)	1.51 (0.79-2.86)	1.66 (0.86-3.20)	1.75 (0.91-3.38)
≥8 years	0.067 (0.033-0.119)	0.91 (0.44-1.91)	1.01 (0.47-2.18)	1.09 (0.51-2.36)
Cumulative exposure (/year) to d-drugs	n/a	1.07 (1.01-1.12)	1.07 (1.01-1.14)	1.07 (1.01-1.13)

#PY: person years; CI: confidence interval; [a]adjusted for time since stopping d-drug and cumulative exposure to d-drug; [b]age, injection drug use as mode of HIV acquisition, previous AIDS diagnosis, viral hepatitis C/B coinfection, latest CD4 count, time since stopping d-drug and cumulative exposure to d-drug; no significant associations were seen between ESLD and calendar year, gender, cohort, smoking status, ethnicity or latest HIV RNA level and so models do not include adjustment for these factors

Figure 3 Other Factors Significantly Associated with ESLD



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