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


**BACKGROUND**

- Whilst some antiretroviral (ARV) drugs, including d-drugs ( stavudine [d4T], didanosine [ddI], zalcitabine [ddC]), may cause biomarker-defined hepatotoxicity (1-3), 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, hepatosplenomegaly, 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

**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/mm³. Characteristics of those developing ESLD in Table 1
- The most common clinical manifestations of ESLD were encephalopathy (43%) and variceal bleeding (30%)

**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

**REFERENCES**