Antiretroviral Drugs Associated with Chronic ALT Elevations in Persons without HCV or HBV Infection

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BACKGROUND

- HIV-positive persons frequently have chronic elevated liver enzymes, even without HCV- or HBV-co-infection [1].
- Most studies have focused on severe liver enzyme elevations (LEE), defined as ≥3 times the upper limit of normal or more [2], but only limited data are available on elevations just above normal limits. The underlying cause of chronic LEE is often unclear.

Study Aim

- To identify risk factors associated with chronic alanine aminotransferase (ALT) elevation above normal limits, including demographic, clinical and HIV-specific variables, focusing on antiretroviral therapy (ART).

METHODS

- The D:A:D Study is a prospective cohort collaboration of ≈49,000 HIV-positive persons from 11 cohorts in Europe, Australia, and the United States.
- Chronic LEE for males/females was defined as ALT >50>35 U/L at ≥2 visits spanning at least 6 months within 2 years.
- ART exposure was categorized as follows: no exposure; ongoing exposure for < or ≥2 years after initiation; and discontinuation for < or ≥2 years.
- D:A:D participants without HCV/HBV infection, with ≥3 ALT measurements, ≥6 months of follow-up and normal ALT at baseline were followed from study entry to the earliest of chronic LEE, death, 1st February 2013, or last follow-up. Cohort specific baseline dates were chosen according to the introduction of routine ALT monitoring.
- Poisson regression was used to assess chronic LEE and its association with ART and traditional risk factors.

RESULTS

- A total of 18,060 persons without HCV/HBV and with normal ALT at baseline were included in the analyses (Figure 1).
- Over 92,059 person-years (PY): 5412 participants developed chronic LEE (incidence 5.88/100 PY [95% CI 5.72-6.04]).
- Baseline characteristics are displayed in Table 1. Median number of ALT measurements per person was 14 (IQR 8-23). APRI score was >1.5 in 5% and FIB-4 Score was >3.25 in 6% of 10,470 persons with available scores (58%).

- In the multivariable analysis, earlier (1999-2001 vs 2010-2013), younger age, increased body mass index, dyslipidemia, use of lipid-lowering drugs, arterial hypertension and high HIV RNA levels were associated with chronic LEE. Black ethnicity and male gender were inversely correlated (Table 2).
- Chronic LEE was associated with ongoing exposure to regimens containing ddI, d4T, TDF, FTC, Efavirenz and NVP. No evidence for an association with increased risk was found for 3TC, ABC, AZT, and all tested PIs (Table 3). EFV exposure for ≥2 years was inversely correlated.
- Because the association with TDF was unexpected, we further analysed commonly used TDF-containing regimens (Figure 2). The association was found to be more pronounced when TDF was used in combination with FTC and/or EFV.

Sensitivity analyses

- Using a LEE definition of a single ALT value >100 U/L, the observed association with TDF remained unchanged.
- There was no evidence that the TDF effect was modified by analyzing exclusively ART-naive persons initiating ART.
- When using a common definition of chronic ALT elevation (>50 U/L) for both men and women, the gender effect reversed.

CONCLUSION

- Whilst ddI, d4T, NVP and EFV have been described to be hepatotoxic [3, 4], we observed an additional association between TDF and chronic LEE emerging within first 2 years after drug initiation.
- The TDF signal seems to be enhanced when TDF is used in the combination with FTC and/or EFV.
- The results are consistent with other small case studies [5-8].
- The reasons for and clinical implications of this novel TDF-LEE signal calls for further investigations.

References