**BACKGROUND**

Concern exists as to whether extended exposure to combination antiretroviral therapy (cART) is associated with impaired liver function and liver-related deaths (LRD), particularly in those co-infected with hepatitis B (HBV) or hepatitis C (HCV). We assessed whether an association exists between exposure to cART and the risk of LRD.

**METHODS**

23,444 persons were prospectively followed in the DAD collaboration over 76,893 person-years (PPY). By 1st February 2004, 88.7% had received cART for a median of 4.5 (3.6-5.3) years. LRD rates (per 100 PY) were calculated according to years of cART exposure. Relative rates (RR) for factors associated with LRD were estimated using multivariable Poisson regression (age and hepatitis status adjusted as time-updated; information on alcohol use not available).

**RESULTS**

**Mortality**

1238 (5.5%) persons died (n=1300 PPY, 10,832/100 PY) from liver-related causes.

Death rates in relation to latest CD4 cell counts

The latest CD4 count before death was 150 and 1200 cells/µL in 24.5% and 54.2% of patients, respectively. The latest CD4 cell count was measured a median of 40.7 (IQR 15.3-18.4) weeks prior to death, 10.1 (5.3-18.3) and 11.2 (5.3-18.6) weeks before death in those with a latest CD4 cell count ≥100 and ≥1200 cells/µL, respectively. We found a strong relationship between the degree of cellular immunodeficiency and AIDS-related, liver-related and all other deaths (Table 1).

Clinical presentation of liver-related deaths

Among those with LRD, 66.6% had HCV infection (Ab+ or RNA+), and 16.6% had active HBV infection (s/eAg+, or DNA+); 7.1% had both. The most frequently reported immediate causes of LRD were hepatic failure (n=124), bleeding (n=38), infection in patients with end-stage liver disease (n=26), and hepatocellular carcinoma (n=7) (Table 2).

Risk factors for liver-related deaths

There was a strong relationship between immunodeficiency and LRD even after adjusting for other potential confounding variables in multivariable analyses (adjusted RR [95% confidence interval] of 16.66 [8.9-31.2], 15.54 [8.6-29.1], 7.14 [4.1-12.3], 5.9 [3.6-9.6] and 1.67 [0.9-3.0] for those with latest CD4 cell counts of ≥50, 50-99, 100-199, 200-499, and ≥500 cells/µL, respectively, compared with CD4 cell counts ≤499 cells/µL (Table 3).

Other independent predictors of LRD were: older age (adjusted RR per 5 years older 1.73 [1.21-2.4]), HIV acquisition via intravenous drug use (2.01 [1.19-3.37]), HCV infection (6.66 [3.95-11.20]), and active HBV infection (3.72 [2.37-5.88]).

**CONCLUSIONS**

No strong association was found between exposure to cART and the rate of LRD. When controlling for the beneficial effect that cART has on the CD4 count, there was some evidence of an association suggesting the possibility of an increased risk of LRD with extended cART use, but further data are required before a firm conclusion can be drawn.

However, the main risk factors for LRD were low CD4 counts, chronic co-infection with HBV/HCV and age. Additional follow-up will further inform whether cART (or components thereof) affects the risk of LRD.

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Liver-related deaths and duration of exposure to antiretroviral therapy

Liver-related mortality during the study period among those with baseline LRD is shown in Figure 1. LRD rates according to duration of exposure to cART and stratified by the latest CD4 cell counts and HCV status are shown in Figure 2. Death rates remained stable over the first 7 years of exposure to cART. Univariable analyses confirmed that there was no relationship between cumulative exposure to cART or between rate of LRD and cART exposure, as well as other clinical and demographic variables (as shown in Figure 3), modified the relationship with cART slightly (1.00 [0.95-1.05], p=0.50) although the nadir CD4 cell count was less strongly related to LRD (RR per 100 PY: 1.05 [1.01-1.09], p<0.05) than the latest CD4 cell count. Adjustment for the latency of cART use which allows study of the effect of cumulative cART use over and above any positive effects of cumulative cART use on CD4 cell counts - resulted in a somewhat increased risk of liver-related mortality with longer exposure to cART (1.10 [1.01-1.20] per year, p=0.03) (Figure 3)