

Exposure to Antiretroviral Therapy and the Risk of Liver-Related Death (LRD): Is there an Association? Results from the D:A:D Study

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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

23,441 persons were prospectively followed in the DAD collaboration over 76,893 person-years (PY).

By 1st February 2004, 88.7% had received cART for a median of 4.5 (2.3-6.3) 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 fitted as time-updated; information on alcohol use not available).

RESULTS

Mortality

1248 (5.3%) persons died (1.6/100 PY), 183 (15%) from liver-related causes.

Death rates in relation to latest CD4 cell counts

The latest CD4 count before death was <50 and <200 cells/ μ L in 24.5% and 54.2% of patients, respectively. The latest CD4 cell count was measured a median of 10.7 (IQR 5.3-18.4) weeks prior to death, 10.1 (5.3-18.3) and 11.1 (5.1-18.6) weeks before death in those with a latest CD4 cell count <200 and \geq 200 cells/ μ L.

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, 66.1% had HCV infection (Ab+ or RNA+) and 16.9% 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=21), and hepatocellular carcinoma (n=17) [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 intervals] of 16.06 [8.13-31.74], 11.54 [6.06-21.99], 7.14 [4.13-12.37], 3.95 [2.34-6.68] and 1.67 [0.91-3.10] for those with latest CD4 cell counts of <50, 50-99, 100-199, 200-349, and 350-499, respectively, compared with CD4 cell counts \geq 500 cells/ μ L [Figure 1]).

Other independent predictors of LRD were: older age (adjusted RR per 5 years older 1.32 [1.21-1.44]), HIV acquisition via intravenous drug use (2.01 [1.19-3.37]), HCV infection (6.66 [3.95-11.24]), and active HBV infection (3.73 [2.37-5.88]).

Table 1 Death rates (95% CI) / 100 Person Years of follow-up, stratified by the latest CD4 count*						
CD4 / mL	AIDS		Liver-related		All other	
	No.	Rate	No.	Rate	No.	Rate
<50	202	12.19 (10.51 -13.87)	22	1.33 (0.77 -1.88)	79	4.77 (3.72 -5.82)
50-99	50	2.92 (2.11 -3.73)	21	1.23 (0.70 -1.75)	52	3.04 (2.21 -3.87)
100-199	69	1.14 (0.87 -1.41)	44	0.73 (0.51 -0.94)	132	2.18 (1.81 -2.56)
200-349	32	0.21 (0.14 -0.28)	52	0.34 (0.25 -0.43)	152	0.99 (0.83 -1.14)
350-499	20	0.11 (0.07 -0.18)	21	0.12 (0.07 -0.17)	104	0.59 (0.48 -0.71)
\geq 500	11	0.03 (0.02 -0.06)	21	0.06 (0.04 -0.09)	155	0.45 (0.38 -0.52)

* Results from univariable Poisson regression analyses confirmed that the relationship between each cause of death and the latest CD4 cell count were all highly significant (p<0.0001)

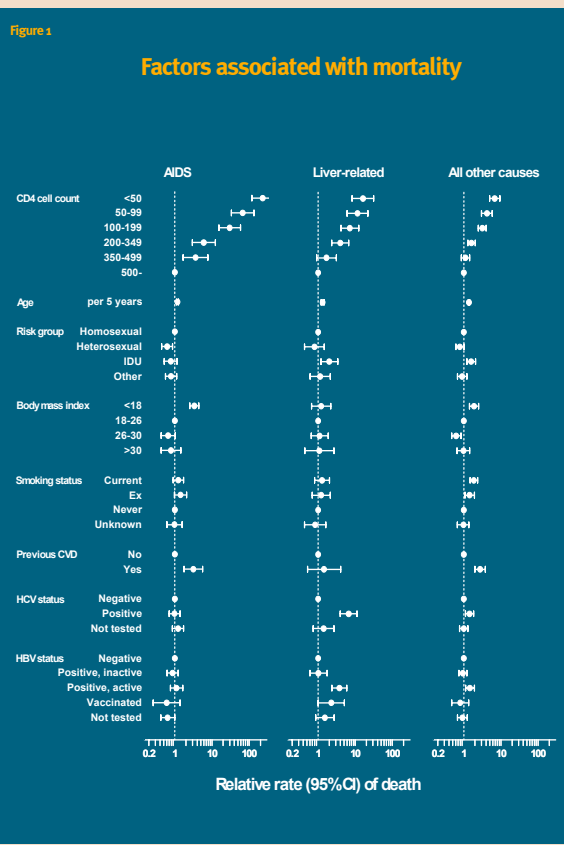
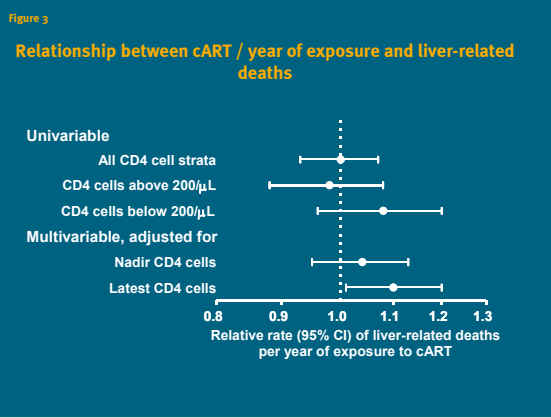
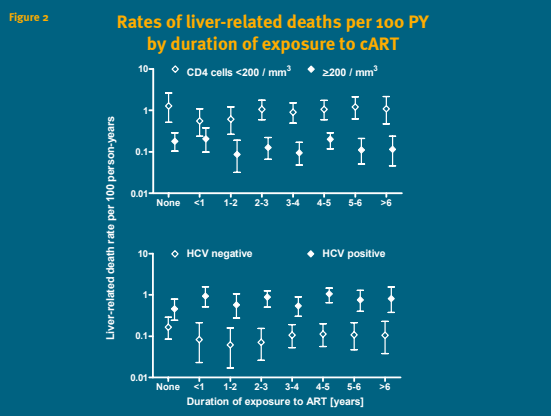


Table 2 Reported events at time of liver-related death, stratified by last measured CD4 count			
Events*	Total	<200/mL	\geq 200/mL
Total no. (%)	183 (100.0)	87 (47.5)	96 (52.5)
Hepatic failure	124 (67.8)	60 (69.0)	64 (66.7)
Hepatocellular carcinoma	17 (9.3)	9 (10.3)	8 (8.3)
Bleeding	21 (11.5)	9 (10.3)	12 (12.5)
Other bleeding	17 (9.3)	12 (13.8)	5 (5.2)
Assumed toxicity of medication	5 (2.7)	1 (1.1)	4 (4.2)
Concomitant event in end-stage liver disease			
Bacterial peritonitis	2 (1.1)	0 (-)	2 (2.1)
Pneumonia	9 (4.9)	5 (5.7)	4 (4.2)
Other bacterial infection	10 (5.5)	5 (5.7)	5 (5.2)
AIDS-defining illness	8 (4.4)	4 (4.6)	4 (4.2)
Pulmonary embolism	2 (1.1)	0 (-)	2 (2.1)
Rejection of liver transplant	1 (0.5)	1 (1.1)	0 (-)

* One patient can be coded with more than one event, i.e. the total no. of events is \geq 100%



Liver-related deaths and duration of exposure to antiretroviral therapy

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 either overall (1.00 [0.93-1.07] per year of exposure, p=0.93) or in either CD4 cell count strata (<200 cells/ μ L: 1.08 [0.96-1.20], p=0.20; \geq 200 cells/ μ L: 0.98 [0.88-1.08], p=0.66) or HCV strata (negative: 0.99 [0.87-1.12], p=0.85; positive: 1.01 [0.92-1.10], p=0.82).

Adjustment for the *nadir* CD4 cell count (as a continuous log₂ transformed variable), as well as other clinical and demographic variables (as shown in figure 1), modified the relationship with cART slightly (1.04 [0.95-1.13], p=0.37) although the nadir CD4 cell count was less strongly related to LRD (RR per halving: 1.05 [1.01-1.09], p=0.02) than the latest CD4 cell count.

Adjustment for the *latest* CD4 cell count - 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].

CONCLUSIONS

No strong association was found between exposure to cART for up to 7 years 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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