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


On behalf of the D:A:D Study Group

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Table 1: LRD rates according to duration of exposure to cART and stratified by the latest CD4 count

<table>
<thead>
<tr>
<th>Latest CD4 count</th>
<th>Total no. (%)</th>
<th>LRD rate (per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>202</td>
<td>12.19</td>
</tr>
<tr>
<td>50-99</td>
<td>22</td>
<td>1.33</td>
</tr>
<tr>
<td>100-199</td>
<td>96</td>
<td>4.40</td>
</tr>
<tr>
<td>200-349</td>
<td>112</td>
<td>2.18</td>
</tr>
<tr>
<td>350-499</td>
<td>22</td>
<td>0.73</td>
</tr>
<tr>
<td>≥500</td>
<td>35</td>
<td>0.34</td>
</tr>
</tbody>
</table>

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

23,543 persons were prospectively followed in the D:A:D collaboration over 76,895 person-years (PY).

By 1st February 2004, 88.7% had received cART for a median of 4.5 (3.6-5.0) 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

Immediately:

12.8 (5.5%) persons died (6.6/100 PY) at risk 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 100.7 (IQR 5.1-18.4) weeks prior to death; 20.1 (3.5-18.6) and 11.6 (9.8-18.6) weeks before death in those with a latest CD4 cell count ≥ 200 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 (p<0.01).

Clinical presentation of liver-related deaths

Among those with LRD, 66.6% had HIV infection (Ab+ or RNA+), 16.0% had active HBV infection (sAg+, or DNA+); 13% had co-infection with hepatitis C (HCV; HCV RNA+ and/or HCV Ab+). 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 hepatic 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 interval] for latest CD4 cell counts of 6.66 [3.95-11.43], 10.12 [5.37-22.18], 11.24 [5.55-22.89], 16.67 [10.12-29.45], and 16.67 [10.12-29.45] for those with latest CD4 cell counts of 0, ≥ 50, 100-199, 200-349, and ≥ 350-499, respectively, compared with CD4 cells ≥ 500 cells/µl (Figure 1).

Other independent predictors of LRD were: older age (adjusted RR per 5 years older 1.32 [1.21-1.44]), CD4 cell acquisition via intravenous drug use (1.20 [1.04-1.37]), HIV infection (6.66 [3.95-11.43]), and active HBV infection (3.73 [2.37-5.88]).

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 in patients with lower CD4 counts 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 1].

Association between time of death 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 cART exposure.

Univariable analyses confirmed that there was no relationship between cumulative exposure to cART and latest CD4 cell count and HCV status are shown in Figure 2. Death rates remained stable over the first 7 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).

Factors associated with mortality

Univariable and multivariable coefficients for factors associated with LRD are shown in Table 2. Significant predictors of LRD included lower CD4 cell counts, chronic hepatitis C infection, older age, and previous CVD.

Liver-related deaths and duration of exposure to antiretroviral therapy

LARD rates according to duration of exposure to cART and stratified by the latest CD4 cell counts and HCV status are shown in Figure 2. 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 in patients with lower CD4 counts 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 1].

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