Poster # 691

Factors associated with hepatotoxicity in an international HIV/HBV co-infected cohort on long-term HAART

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Abstract:

Background: Co-infection with HIV and HBV increases the risk for hepatotoxicity in patients receiving highly-active anti-retroviral therapy (HAART). Most studies of hepatotoxicity in HIV-HBV co-infected patients have primarily concentrated on the first year of HAART. HAART can lead to hepatotoxicity from multiple causes including direct drug toxicity, immune reconstitution disease and development of HBV drug-resistance. In order to understand clinical factors associated with hepatotoxicity in HIV-HBV co-infected individuals receiving >1 year HAART, we studied an international cohort of subjects on long-term HAART.

Methods: We enrolled 170 HIV-HBV co-infected participants on HAART from the US, Australia, and Thailand in a prospective longitudinal cohort study. Subjects were followed every 6 months with a clinical assessment and laboratory assessments including HBV DNA, hepatitis B e antigen (HBeAg), CD4 count, HIV RNA, and ALT. Hepatotoxicity was defined using ALT (ACTG criteria: Grade 0-4). Upper limit of normal of ALT was 30 for men and 19 for women. Longitudinal analyses were performed using a person-visit approach with the outcome of significant hepatotoxicity (SH) defined as grade 2 or higher. Factors associated with SH were identified using multiple logistic regression with robust variance estimates to account for within subject correlation across study visits.

Results: Median follow-up time was 3.5 (range 0 to 4.4) years and the median time on HAART was 4.9 (range 0-15.3) years. Of those on HAART at enrolment (85%), 70% were receiving HBV-active HAART (including lamivudine (LMV)/emtricitabine (FTC) or tenofovir or both). Median ALT for the entire period was 35, with 10.8% of person-visits classified as SH. At baseline the prevalence of SH was 13% and this did not significantly change during follow-up. Factors associated (p<0.05) with SH in univariate analysis included a history of AIDS, HBV DNA>2000 IU/ml, HBeAg positive, LMV/FTC therapy, HAART <12 months, CD4 <200 cells/ml, and nadir CD4 cells <200 cells/ml. In the multivariate analysis, CD4 <200 (OR 1.88, p=0.03) and HBV DNA >2,000 IU/ml (OR 2.5, p=0.02) were independently associated with SH.

Conclusions: CD4 count <200 and HBV DNA >2,000 IU/ml were significantly associated with an increased risk of SH among HIV-HBV co-infected people on long-term HAART. This finding provides further support for current guidelines recommending earlier initiation of HAART in HIV-HBV co-infected patients.

Hypothesis:

The mechanisms by which chronic HBV infection leads to increased hepatotoxicity are likely to be multi-factorial. For HIV/HBV co-infected individuals, it is not known how HBV viral load, HBV eAg status, prolonged therapy or drug resistance influences the risk of hepatotoxicity. We hypothesised that long-term HAART would be associated with a decrease in the risk of hepatotoxicity.

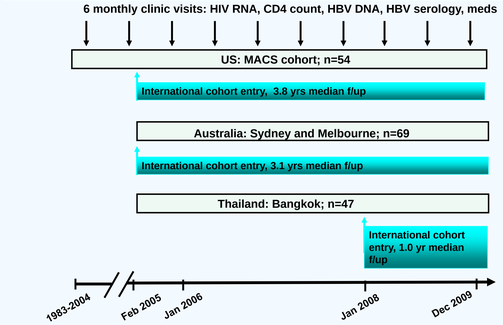
Aim:

To examine the prevalence of hepatotoxicity and to define factors associated with hepatotoxicity in HIV-HBV co-infected individuals on long-term HAART (> 12 months).

Methods:

- Hepatotoxicity was defined using ALT (ACTG criteria: Grade 0-4). Upper limit of normal of ALT was 30 for men and 19 for women.
- Longitudinal analyses were performed using a person-visit approach with the outcome of significant hepatotoxicity (SH) defined as grade 2 or higher. Factors associated with SH were identified using multiple logistic regression with robust variance estimates to account for within subject correlation across study visits.

Methods (cont.):



Results 1: Cohort characteristics

Table 1: Cohort characteristics on study entry

Characteristic	Number (%)
Gender (m/f) (n=170)	154 (91) / 16 (9)
Aged >40 years	109 (64)
HIV risk factor: ever IDU (Y)	17 (10)
HIV risk factor: MSM contact (Y)	125 (74)
HBeAg status, positive/negative (n=161)	80 (50) / 81 (50)
HBV DNA ≥ 2,000 IU/ml (n=154)	33 (21)
Detectable HIV RNA (≥400 copies/ml), n=161	33 (21)
CD4<200 cells/ml (n=161)	28 (17)
Nadir CD4 <200 cells/ml (n=168)	104 (62)
Alcohol intake (mean drinks/week) n=167:	
None	55 (33)
<14	97 (58)
≥14	5 (9)
More than 1 year since HAART initiation	157 (92)
Current ARVs:	
NRTI	149 (88)
PI	61 (36)
NNRTI	95 (56)
HBV-active regimen:	
None	51 (30)
LMV+FTC only	15 (9)
TDF only	14 (8)
TDF+LMV+FTC	90 (53)

Results 2: Changes in ALT over time

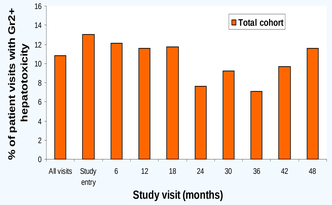


Figure 1a: Percentage of patient visits with ≥grade 2 hepatotoxicity for total cohort by study visit

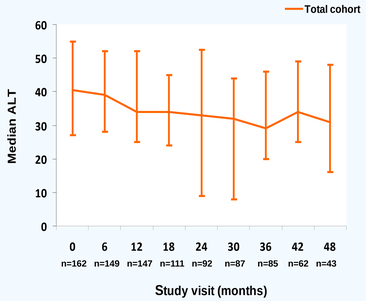


Figure 1b: Change in median ALT over time. Error bars represent the IQR

Results 3: Univariate associations with hepatotoxicity

Table 2: Variables associated with significant (Grade 2 or higher) hepatotoxicity in a univariate analysis

Variable	*p* value
Age >40 years	0.07
History of AIDS	0.002
HBV DNA >2,000 IU	0.008
HBeAg positive	0.001
Receiving LMV/FTC only	0.045
<1 year on HAART	<0.001
CD4 count <200 cells/ml	0.004
Nadir CD4 count <200 cells/ml	0.001
Child-Pugh score >5	0.02

- Variables not statistically significant included :recruitment site location, sex, study visit, HIV risk factor anti-HBe positive/negative, current HAART, current NRTI, current PI, current nNRTI, detectable HIV RNA (>400 copies/ml) and mean weekly alcohol intake.

Results 4: Multivariate associations with hepatotoxicity

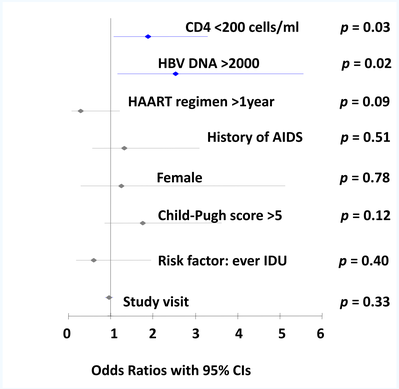


Figure 2: Multiple regression analysis: variables independently associated with hepatotoxicity. An initial series of models examined demographic and behavioural characteristics; HBV-related characteristics and HIV-related characteristics. The final model (shown above) incorporated variables that were identified as statistically significant (or close) in the initial models.

Conclusions

- CD4 count <200 cells/ml and HBV DNA >2,000 IU/ml were significantly associated with an increased risk of SH among HIV-HBV co-infected people on long-term HAART
- This finding provides further support for current guidelines recommending earlier initiation of HAART in HIV-HBV co-infected patients.

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