The Aging Liver and HIV

Contribution of Factors other than Hepatitis to Endstage Liver Disease in HIV
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US Multicenter observational clinical cohort
Adult/Adolescent spectrum of HIV Disease project

Table 2. Proportions of deaths, standardized proportionate mortality by calendar period, and estimated changes in proportionate mortality among decedents with at least one reported perinatal condition in addition to HIV disease in the Adult/Adolescent Spectrum of HIV Disease project, 1992–2003.

<table>
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<tr>
<th>Perinatal Condition</th>
<th>Standardized proportionate mortality (%)</th>
<th>Adjusted odds ratio 95% confidence interval</th>
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<tbody>
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<td>Pre-HAART Early HAART Contemporary HAART</td>
<td>Pre-HAART Early HAART Contemporary versus early HAART</td>
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- Septicemia: 1096 (11.9) 10.7 12.9 11.6 1.28 (1.11–1.47) 0.94 (0.76–1.18) 1.12 (1.03–1.23)
- Cholestasis: 408 (8.5) 7.8 9.4 11.7 1.25 (1.06–1.48) 1.17 (1.06–1.31) 1.23 (1.14–1.34)
- Liver disease (excluding viral hepatitis): 596 (6.5) 4.9 8.0 10.8 1.09 (1.39–2.05) 1.23 (1.07–1.53) 1.30 (1.14–1.50)
- Severe congenital anomaly: 369 (4.5) 3.7 5.2 3.9 1.15 (1.00–1.32) 1.08 (0.95–1.22) 1.26 (1.06–1.50)
- Intrauterine growth retardation: 628 (7.3) 5.8 8.4 7.1 1.23 (1.08–1.40) 1.19 (1.06–1.34) 1.33 (1.17–1.50)
- Premature birth: 1488 (17.6) 15.6 19.6 17.2 1.09 (1.04–1.15) 1.06 (1.02–1.12) 1.14 (1.10–1.19)
- Intrauterine death: 374 (4.4) 3.3 4.5 3.7 1.10 (0.98–1.23) 1.10 (0.97–1.23) 1.14 (1.05–1.23)

- Alcohol abuse: 78 (0.9) 0.5 1.2 1.9 1.54 (1.50–1.62) 1.10 (0.63–1.99) 1.41 (0.35–2.42)
- Hypertensive disease: 76 (0.8) 0.4 1.3 1.5 1.36 (1.18–1.55) 1.13 (0.64–1.99) 1.48 (1.00–2.25)
- Diabetes mellitus: 68 (0.7) 0.6 0.7 1.7 1.13 (0.62–2.06) 2.62 (1.37–5.01) 1.58 (1.16–2.17)

*: standardized by sex, race/ethnicity, age at death, HIV transmission category, and lowest CD4 cell count for all decedents.

Challenges

- ESLD is a growing concern in HIV infection
- Research into other causes of ESLD overshadowed by the epidemic of HCV co-infection which account in large measure for excess liver related morbidity and mortality
- A number of factors require consideration which could act in concert with the natural aging process and HIV infection
  - alcohol consumption
  - steatosis
  - chronic hepatotoxicity of antiretrovirals

Age

- Several age-related changes in liver have been documented in the elderly, including:
  a. a decline in liver volume and blood flow
  b. an increase in the hepatic dense body compartment
  c. moderate declines in the Phase I metabolism of drugs
  d. shifts in the expression of a variety of proteins
  e. diminished hepatobiliary functions.
- Functional consequences of these changes, if any have not been clearly elucidated.
Age

Other more subtle changes may contribute to reduced hepatic regenerative capacity, shorter post-liver transplant survival and increased susceptibility to liver diseases

- muted responses to oxidative stress
- reduced expression of growth regulatory genes
- diminished rates of DNA repair— particularly in the mitochondrial genome
- telomere shortening

With the exception of diminished bile acid secretion and increased biliary cholesterol, liver function tests have failed to identify significant age-related deficits

Whether HIV itself impacts the aging process is not known

LFTs in HIV without HCV or HBV

- Retrospective cross-sectional analysis (n=679)
- increased AST (19%), ALT (15%), and ALP (42%)
- majority were grade 1–2 with only 1–2% having elevations > 5XULN (grade 3–4).
- Independent predictors of increased AST and ALT were: HTN, absence of PI use, CD4<200 and presence of the metabolic syndrome (ALT)
- Features typical of hepatic steatosis (DM and BMI) were only associated with increased ALP.

Overall Modeled change in lnAPRI over time (adjusted)

Mitochondrial dysfunction

Nucleoside analogue

Relative Potency of Inhibition of Polymerase gamma (γ)
Figure 2 Visceral adipose tissue and fatty liver disease

Steatosis

- Non-alcoholic fatty liver disease (NAFLD), which can evolve into non-alcoholic steato-hepatitis (NASH), cirrhosis and ultimately hepatic failure is increasingly observed.
- Hepatic steatosis (liver fat content 5%) identified in 42% of 33 unselected HIV+ without ESLD using magnetic resonance spectroscopy.
- Hepatic fat content was significantly correlated with HOMA-IR ($r = 0.68$, $P < 0.0001$) and increased visceral adiposity ($r = 0.60$, $P < 0.001$).
- Subjects with steatosis had significantly increased BMI and ALT and TG levels, and increased intramuscular fat compared to subjects without steatosis.
- Steatosis was not related to duration of HIV, ARV exposure, or HCV co-infection.

Hadigan et al, JAIDS e-pub 2007
Alcohol

- Alcohol use extremely common in HIV infected populations (50% + moderate drinkers and >10% classifiable as hazardous drinkers in a variety of different cohorts)
- Heavy alcohol use has been linked to a number of adverse outcomes (non-adherence, disease progression, mortality)

HCV and Alcohol are Top Transplant Indications in the USA

Complex Interplay

Steatosis
HIV
Drug toxicity
Alcohol
Advancing Age
ESLD

Conclusions: Research Needs

Define contribution of various non-hepatitis related factors to liver disease in HIV and role of aging in this process

To accomplish this:
- Focus on non-hepatitis related liver disease
- Better monitoring and diagnostic tools
- Methods for dealing with complex interactions of various factors and co-morbidities
- Understand underlying mechanisms
- Evaluation of interventions to alter liver disease progression