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 perimortal condition in addition to HIV disease in the Adult/Adolescent Spectrum of HIV Disease project, 1992–2003.

		Standardized proportionate mortality (%)[a]			Adjusted odds ratio (95% confidence interval)[b]		
Perimortal conditions	Deaths [No. (%)]	Pre-HAART	Early HAART	Contemporary HAART	Early versus pre-HAART	Contemporary versus early HAART	Linear trend
Increasing linear trends							
Septicemia	1096 (11.9)	10.7	12.9	11.6	1.28 (1.11–1.47)	0.94 (0.76–1.16)	1.12 (1.03–1.23)
Kidney disease	808 (8.8)	7.8	9.4	11.7	1.23 (1.04–1.45)	1.17 (0.94–1.47)	1.22 (1.11–1.36)
Liver disease (excluding viral hepatitis)	596 (6.5)	4.9	8.0	10.8	1.69 (1.39–2.05)	1.23 (0.97–1.57)	1.50 (1.34–1.68)
Viral hepatitis	281 (3.1)	1.2	3.4	10.9	2.87 (2.05–4.01)	3.70 (2.77–4.94)	3.27 (2.78–3.84)
Gastrointestinal hemorrhage	164 (1.8)	1.5	2.1	1.8	1.34 (0.94–1.91)	1.09 (0.69–1.73)	1.26 (1.02–1.55)
Ischemic heart disease	80 (0.9)	0.7	0.9	1.9	1.47 (0.86–2.53)	1.66 (0.92–3.00)	1.57 (1.18–2.10)
Alcohol abuse	78 (0.9)	0.5	1.2	1.9	2.54 (1.50–4.32)	1.10 (0.61–1.99)	1.81 (1.35–2.42)
Hypertensive disease	76 (0.8)	0.4	1.3	1.5	3.16 (1.81–5.51)	1.13 (0.64–1.99)	1.88 (1.40–2.52)
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.

Hooshyar et al. *AIDS* 2007, 21:2093-2100.

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.

D.L. Schmucker / Experimental Gerontology 40 (2005) 650–659

Age

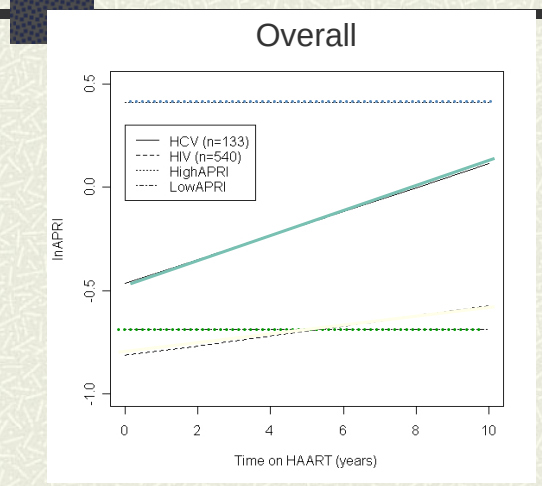
- Other more subtle changes may contribute to reduced hepatic regenerative capacity, shorter post-liver transplant survival and increased susceptibility to liver diseases
  - muted responses to oxidative stress
  - reduced expression of growth regulatory genes
  - diminished rates of DNA repair— particularly 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

D.L. Schmucker / Experimental Gerontology 40 (2005) 650–659

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.

Sterling et al, *Dis Dig Sci*, e-pub 2007



Modeled change in lnAPRI over time (adjusted)

J Acquir Immune Defic Syndr • Volume 44, Number 4, April 1, 2007 *Liver Fibrosis Progression and Antiretroviral Therapy*

Mitochondrial dysfunction

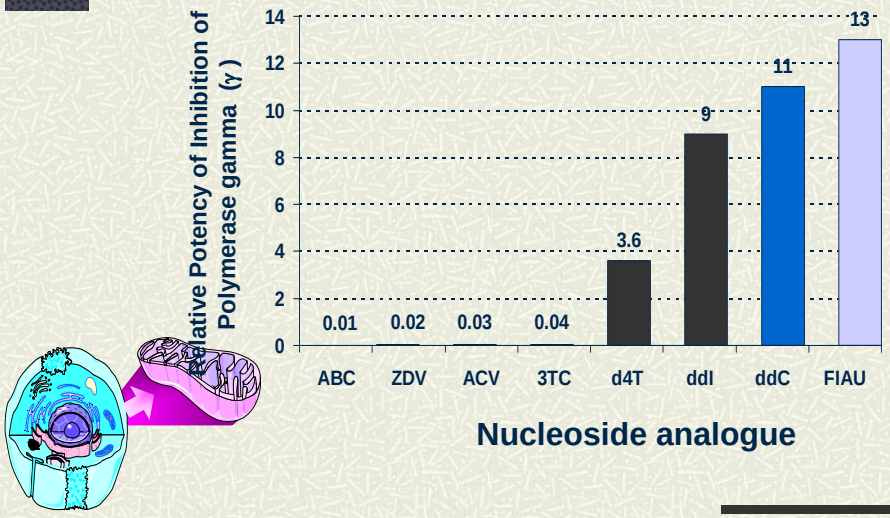
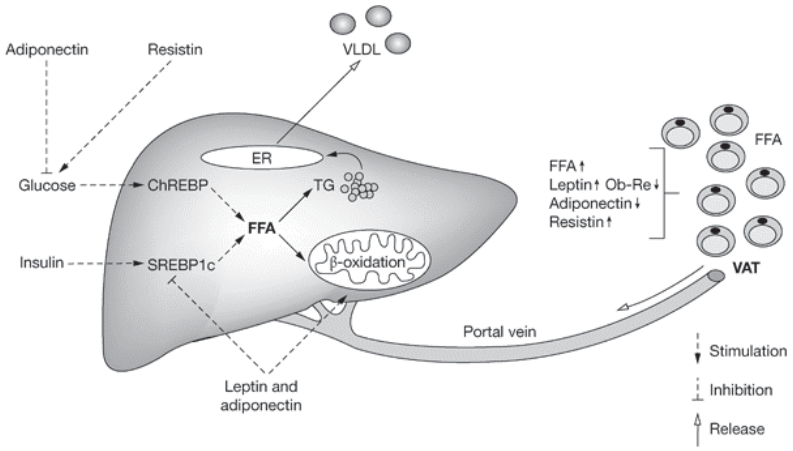


Figure 2 Visceral adipose tissue and fatty liver disease



Schäffler A *et al.* (2005) Mechanisms of Disease: adipocytokines and visceral adipose tissue—emerging role in nonalcoholic fatty liver disease *Nat Clin Pract Gastroenterol Hepatol* **2:** 273–280 doi:10.1038/ncpgasthep0186

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Steatosis

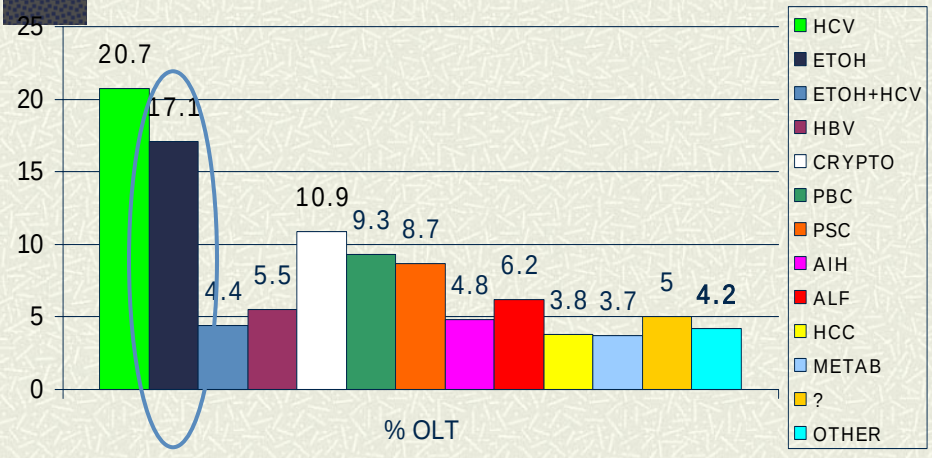
- Non-alcoholic fatty liver disease (NAFLD), which can evolve into non-alcoholic steato-hepatitis (NASH), cirrhosis and ultimately hepatic failure is inc. observed
- Hepatic steatosis (liver fat content 5%) identified in 42% of 33 unselected HIV+ without ESLD using magnetic resonance spectroscopy
- Hepatic 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 sig 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

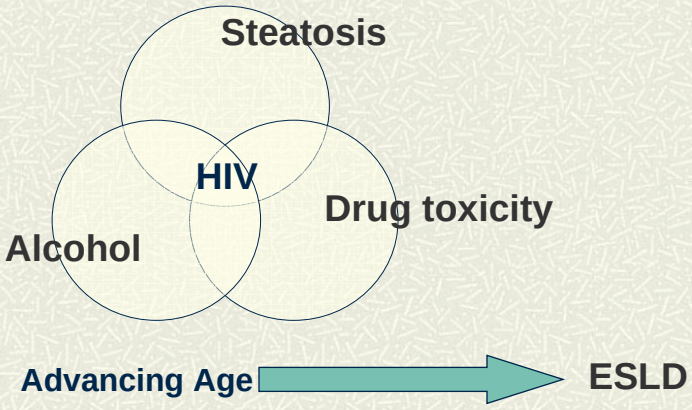
- Alcohol use extremely common in HIV infected populations (50% + moderate drinkers and >10% classifiable as hazardous drinkers in a variety of different cohorts)
- Heavy alcohol use has been linked to a number of adverse outcomes (non-adherence, disease progression, mortality)

HCV and Alcohol are Top Transplant Indications in the USA



Seaberg EC et al. Clin Transpl. 1998, UNOS 1987-1998; N=24,900

Complex Interplay



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