Liver Fibrosis in HIV-Infected Patients without Chronic Viral Hepatitis – Prevalence, Clinical Characteristics and Potential Causes

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Background: Chronic liver disease in HIV+ patients is usually related to hepatotropic viral infections. The availability of non-invasive tools to assess liver fibrosis has allowed the identification of a group of HIV+ patients in whom advanced liver fibrosis has developed in the absence of any recognisable etiology.

Methods: **All HIV+ patients on follow-up at our institution have been regularly examined by transient elastometry (FibroScan) since September 2004. Advanced liver fibrosis (ALF) was defined as liver elasticity >9.5 Kpa, and liver cirrhosis as >14 Kpa; patients with <7 Kpa were considered as having no liver fibrosis. Only HIV+ patients with negative serum HCV-RNA and HBsAg/HBV-DNA were included in this study. Current or past alcohol consumption was recorded by patient's interview; iron or copper overload, α1-antitrypsin deficiency and auto-immune diseases were discarded in all instances. Exposure to antiretroviral (ARV) drugs was assessed using the pharmacy-computerized database**

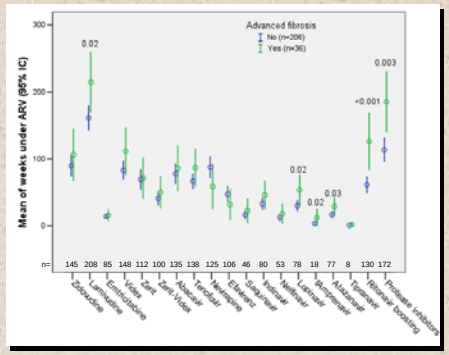
Table 1. Characteristics of patients

	Advanced liver fibrosis	Not advanced liver fibrosis	p
No. (%)	36 (2.7)	1,271 (97.3)	
Mean age (years)	47	44	0.006
Alcohol abuse (%)	37	15	0.009
Mean CD4 count (cells/μL)	481	573	0.14
Mean ALT (IU/L)	58	39	0.002
Mean glucose (mg/dL)	110	102	0.09
Mean triglycerides (mg/dL)	253	185	0.08
Mean cholesterol (mg/dL)	204	208	0.2

Results

A total of 1,307 HIV+ patients without known underlying viral liver disease were identified. Overall, 83% had no liver fibrosis, and 36 (2.7%) showed ALF (Table 1). Half of the latest had cirrhosis, and 10 (0.8%) had developed episodes of hepatic decompensation.

Figure 2. Length of exposure to antiretrovirals

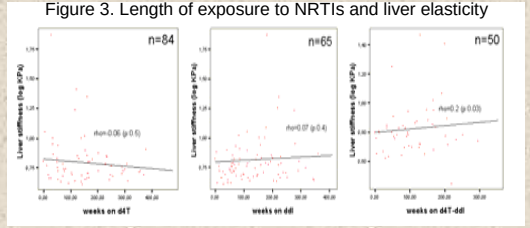


The distribution of risks groups was: IDUs 45%, MSM 35% and Heterosex 17%. In a univariate analysis, patients with and without ALF had older age (47 vs 44 years, p=0.006), elevated alcohol consumption (37 vs 15%, p=0.009), lower mean CD4 counts (481 vs 573 cells/μL, p=0.14), greater ALT (58 vs 39 IU/L, p=0.002), glucose (110 vs 102 mg/dL, p=0.09), triglycerides (253 vs 185, p=0.08), and similar cholesterol (204 vs 208 mg/dL, p=0.23).

A total of 1,601 patients-years of ARV exposure were further examined in 233 randomly selected HIV+ patients. Only 5% were HAART-naive, while 54%, 45% and 74% had received NVP, EFV or PI in the past. Mean duration of ARV exposure was 7.8 vs 6.6 years in patients with ALF vs non-ALF (p=0.03) (Figure 1). Mean length of exposure to atazanavir, lopinavir, fosamprenavir, boosted-PI and PI in general was longer in patients with ALF as compared with non-ALF (Figure 2).

No association between d4T or ddI length of exposure and liver fibrosis was found; a direct correlation was observed between time on ddI-d4T and liver fibrosis (Figure 3).

Figure 3. Length of exposure to NRTIs and liver elasticity



In a multivariate logistic regression analysis (OR [95% CI], p), only older age (1.71 [0.93-3.13], 0.08), alcohol abuse (3.15 [1.12-8.87, 0.03) and longer exposure to ritonavir-boosted PI regimens (1.2 [0.97-1.53], 0.08) were independently associated with ALF (Table 2).

Table 2. Multivariate analysis

	OR	95% CI, p
Older age (per year)	1.71	0.93-3.13, 0.08
Alcohol abuse	3.15	1.12-8.87, 0.03
RTV-boosted PI regimen (per year)	1.2	0.97-1.53, 0.08

Figure 4. Metabolic alterations under antiretrovirals

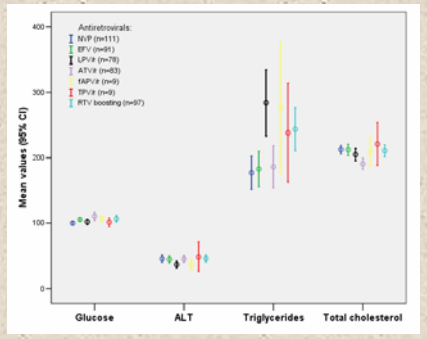
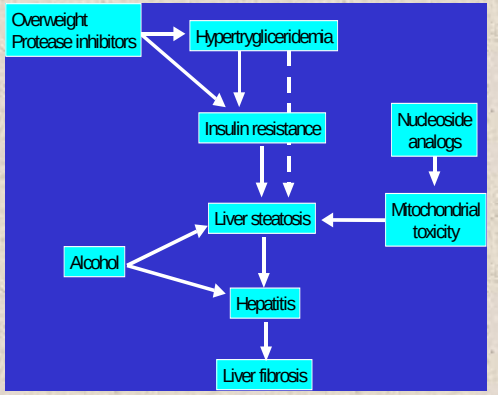


Figure 4 shows different metabolic alterations under NNRTI or PI containing regimens, which may be responsible for the induction of liver damage through different pathways described in Figure 5.

Figure 5. Pathways to liver fibrosis



Conclusions

•Liver fibrosis may be detected in HIV infected patients without underlying chronic viral hepatitis:

•Alcohol abuse may be the cause in most patients

•There is a remaining of patients with liver fibrosis of unknown origin. Possible causes are:
- -Idiopathic portal fibrosis
- -Nodular regenerative hyperplasia
- -Autoimmune phenomena
- -Recurrent intestinal infections (pylephlebitis)
- -The role of antiretrovirals remains uncertain

•Non-invasive tools to assess liver fibrosis may be particularly useful for screening in the HIV infected population

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