APRI and FIB4: Associated With D-drug Exposure, Low CD4 Count and Monocyte Activation

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Background

Liver disease is common in HIV-1 infected populations. Aside from hepatitis B and C (HBV and HCV) viral coinfection, hepatotoxicity of antiretroviral therapy (ART) and excessive alcohol intake likely are involved in the pathogenesis. Additionally, HIV infection may also affect the liver, possibly mediated through microbial translocation[1,2].

Fibrosis 4 (FIB-4) score and aspartate aminotransferase (AST) to platelet ratio (APRI) index are non-invasive scores that predict clinically significant and advanced liver biopsy confirmed fibrosis[3] and have prognostic value for liver-related and all-cause mortality in HIV/HCV coinfected and in HIV mono-infected patients[4].

[1]Rockstroh et al, Curr Op HIV AIDS 2014; [2]Joshi et al, Lancet 2011; [3]Sterling, Hepatol Baltim Md 2006; [4]Lo Re et al, Ann Int Med 2014

Objectives

- compare the severity of liver fibrosis, using APRI and FIB-4, between HIV-1-infected (all with HIV-1 viral load <200 c/mL in prior year) and HIV-uninfected AGE$_h$IV Cohort Study participants aged ≥45 years;
- investigate whether treated HIV infection, HIV- and ART-related parameters are independently associated with FIB-4;
- explore the role of microbial translocation and immune activation, assessed by levels of soluble (s)CD14 and sCD163.

Methods

598 HIV-1-infected and 550 HIV-uninfected participants, aged ≥ 45 years Enrolled between 2010 and 2012 at the Academic Medical Center and STD clinic of the Municipal Health Service, Amsterdam, the Netherlands

→ Exclusion of participants with HIV-viral load >200c/mL (n=70), detectable HCV-RNA (n=24) or HBsAg (n=37)

475 HIV-1-infected and 499 HIV-uninfected participants

Calculation of Fibrosis-4 (FIB-4) score and APRI index , using aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in U/L

$$FIB\text{-}4 = \frac{age \times AST}{(platelets * \sqrt{ALT})} \qquad APRI = \frac{AST}{40} * \frac{100}{platelets}$$

→ Exclusion of 42 HIV-infected and 25 HIV-uninfected participants with missing data

Physical examination (BMI); Questionnaire (demographics, smoking, alcohol use); Measurement of soluble (s)CD14 and sCD163, anti-HBs and anti-HCV

HIV-positive participants: historical laboratory measurements and treatment data (ATHENA cohort)

433 HIV-1-infected and 474 HIV-uninfected participants

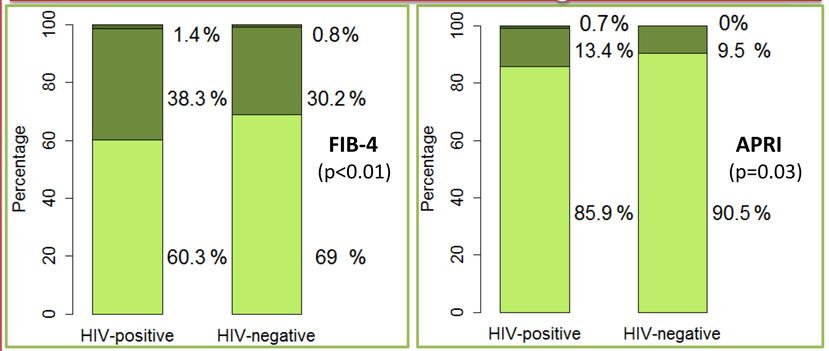
FIB-4 and APRI are categorized as advanced fibrosis (≥3.25/≥1.5), significant fibrosis (1.45-3.25/0.5-1.5) and no significant fibrosis (<1.45/<0.5). Prevalence is compared using non-parametric test for trend. Multivariable linear regression analysis with log-transformed FIB-4 as outcome to investigate any independent associations with HIV and covariates of interest. P-value <0.05 considered statistically significant.

Characteristics of Study Participants

		HIV-infected, n= 433 % or median (IQR)	HIV-uninfected, n= 474 % or median (IQR)
Demographics	age, years	53.2 (48.3 – 59.8)	52.4 (48.1 – 58.1)
	gender (male)	89.4%	85.4%
	men who have sex with men	74.9%	70.1%
	ethnicity (black)	12.9%	7.8%
	excessive alcohol intake*	5.1%	6.6%
Viral hepatitis	detectable anti-HCV◊	5.5%	0.4%
	detectable anti-HBc◊	54.5%	24.9%
Metabolic	BMI, kg/m^2	24.2 (22.3 – 26.4)	24.5 (22.9 – 27.0)
	diabetes mellitus (DM)·	6.2%	3.4%
Monocyte activation	sCD163, ng/mL	283 (204 – 404)	242 (177 – 331)
	sCD14, ng/mL	1479 (1293 – 2012)	1338 (1071 – 1711)
HIV	time since HIV diagnosis, years	12.8 (7.5 – 17.4)	
	nadir CD4, cells/mm^3	170 (60 – 250)	
	CD4 at enrollment, cells/mm^3	590 (455 – 780)	
	history of AIDS	33.0%	
ART	ever exposed to d-drugs^	48.6%	
	cumulative exposure, years	4.4 (1.8 – 8.1)	

**daily or almost daily intake ≥5 units (males) or ≥3 units (females) ◊confirmed HCV RNA resp. HBsAg negative ·HbA1c (IFCC) ≥48 mmol/mol and/or blood glucose (non-fasting) ≥11.1 mmol/L and/or blood glucose (fasting) ≥7.0 mmol/L, and/or in those taking antidiabetic medication ^dideoxynucleoside analogues: stavudine (d4T), didanosine (ddi), zalcitabine (ddC)*

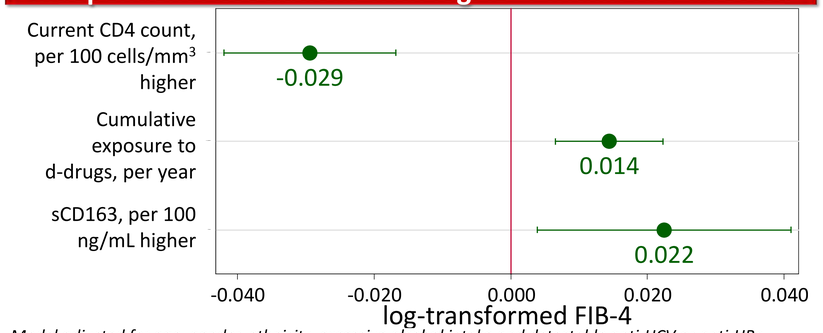
FIB-4 and APRI Fibrosis Categories



No fibrosis FIB-4 <1.45 / APRI <0.5 | **Significant fibrosis** FIB-4 1.45–3.25 / APRI 0.5–1 | **Advanced fibrosis** FIB-4 ≥3.25 / APRI ≥1.5

After adjustment for age, gender, ethnicity, excessive alcohol intake (defined as daily or almost daily intake ≥5/≥3 units (males/females), detectable anti-HCV/anti-HBc, BMI and DM, HIV remained independently associated with logAPRI (+0.06, 95% CI 0.01 – 0.12, p=0.02), but not with logFIB-4.

Independent Associations with logFIB-4 within HIV-infected



Model adjusted for age, gender, ethnicity, excessive alcohol intake and detectable anti-HCV or anti-HBc. Similar associations were observed with log-transformed APRI.

Conclusions and Future Plans

Conclusions

This cross-sectional comparative analysis shows **higher values of FIB-4 and APRI** in virologically suppressed HIV-1-infected individuals compared to HIV-uninfected controls of similar age and background, in the absence of chronic hepatitis B or C infection.

The observed differences were small and most values were within the **significant rather than advanced fibrosis** range. Virologically suppressed HIV **was not independently associated** with higher FIB-4 values.

The association between increased **sCD163 levels and higher FIB-4** scores in HIV-infected study participants may indicate a role for activated hepatic macrophages (Kupffer cells) in the pathogenesis of liver fibrosis in the context of HIV infection, possibly resulting from microbial translocation.

Past exposure to **dideoxynucleoside analogues** as well as **lower current CD4 cell count** were identified as additional contributors to liver fibrosis.

Future plans

Further analyses will focus on FIB-4, considering its superior predictive value for liver fibrosis[1] and demonstrated predictive value towards liver decompensation and mortality[2].

More extensive exploration of the association between immune activation and liver fibrosis is planned as well as longitudinal follow-up of FIB-4 within the AGE$_h$IV Cohort

[1]Holmberg, CID 2013; [2] Berenguer, CID 2014

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