Hepatic fibrosis and factors associated with liver stiffness in HIV mono-infected individuals

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Liver disease has become an important cause of morbidity and mortality even in those HIV-infected individuals who are devoid of hepatitis virus co-infection. The aim of this study was to evaluate the degree of hepatic fibrosis and the role of associated factors using liver stiffness measurement in HIV-mono-infected patients without significant alcohol intake. **Materials and methods**: We performed a cross-sectional study of 101 patients recruited prospectively from March 1, 2014 to October 30, 2014 at the Center for HIV, St István and St László Hospital, Budapest, Hungary. **Results**. LSMs ranged from 3.0-34.0 kPa, with a median value of 5.1 kPa (IQR 1.7). The presence of diabetes ($p<0.0001$), age ($p=0.0435$), CAP value ($p=0.0061$) and a history of taking abacavir ($p=0.063$) were independent covariates that showed a positive correlation with abnormal liver stiffness values. A significant negative association was detected with the history of taking etravirine ($p=0.00469$) and CD4/CD8 ratio ($p=0.04$). **Conclusions**: Our findings underline the possible importance of diabetes, hepatic steatosis and type of antiretroviral treatment in the development of liver fibrosis in HIV mono-infected patients. Further controlled studies are warranted to clarify causal relations.

Hepatic Fibrosis and Factors Associated with Liver Stiffness in HIV Mono-infected Individuals

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Abstract

Liver disease has become an important cause of morbidity and mortality even in those HIV-infected individuals who are devoid of hepatitis virus co-infection. The aim of this study was to evaluate the degree of hepatic fibrosis and the role of associated factors using liver stiffness measurement in HIV-mono-infected patients without significant alcohol intake.

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Conclusions: Our findings underline the possible importance of diabetes, hepatic steatosis and type of antiretroviral treatment in the development of liver fibrosis in HIV mono-infected patients. Further controlled studies are warranted to clarify causal relations.

Introduction

Liver disease has become one of the most important cause of morbidity and mortality in HIV-infected individuals (Weber et al., 2006). While hepatitis B or C co-infections remain the most important cause of liver damage, liver related mortality also affects those infected only with HIV (Collaboration, 2010). Long term antiretroviral and non-antiretroviral medications, HIV induced long term inflammation, metabolic complications and direct cytopathic effects may also contribute to the pathogenesis of liver fibrosis (Rockstroh et al., 2014). An increasing number of papers have been published on HIV/hepatitis virus co-infected patients but only a few studies have appeared on the analysis of data obtained from HIV-mono-infected individuals.

With the availability of noninvasive fibrosis determinations, such as liver stiffness measurements (LSM) with transient elastography, aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and the FIB-4 score, cross-sectional and prospective studies to evaluate prevalence and incidence of liver fibrosis in HIV-infected individuals have become easier. These tests were demonstrated to be acceptable in predicting the absence of fibrosis or mild fibrosis (liver fibrosis < 2 METAVIR score) and the presence of advanced fibrosis (liver fibrosis > 3 METAVIR score) (González Guilabert et al., 2010). Cross-sectional studies in HIV-mono-infected patients reported high rates (8.3-41.9%) of significant liver fibrosis suggesting that HIV itself may contribute independently to liver damage (Rockstroh et al., 2014). Ongoing liver fibrosis is not always accompanied by elevated liver enzymes and the diagnosis of liver fibrosis and the prevention of progression to liver cirrhosis are important challenges. As a result, adequate monitoring strategies of liver disease are clearly needed to optimize care of HIV-infected individuals (Rockstroh et al., 2014).

To date, only a few studies using LS measurements have examined the prevalence and potential risk factors for hepatic fibrosis among HIV-mono-infected patients. Using different cutoff values resulted in a wide range in prevalence estimates (Merchante et al., 2010; Han et al., 2013). Pre-defined cutoffs adopted from the HIV/HCV-co-infected population may lead to an underestimation of the number of HIV-mono-infected patients with clinically significant fibrosis as these cutoffs were determined for a population in which ongoing fibrosis is triggered by HCV co-infection (Han et al., 2013). To overcome this limitation, our aim was to use a continuous scale of LS values in the analysis to identify significant predictors of LS in a cross-sectional study.

Materials and Methods

The investigation was performed in accordance with the Helsinki Declaration and was approved by the Institutional Review Board of St. István and St. László Hospital, Budapest, Hungary. Written informed consent was taken from all study participants. The present cross-sectional study is an analysis of the data collected for a previous study, with methodology already described in (Sulyok et al., 2015). Individuals older than 18 years of age were enrolled after providing their written informed consent. Pregnant women and patients with unreliable transient elastography measurement were excluded. Patients with known HCV or HBV infection or anti-HBc positivity, known other causes of liver diseases, and significant daily alcohol intake (>50g/day) were excluded from the analysis.

Clinical parameters and blood samples were collected as previously described (Sulyok et al., 2015). Transient elastography examination was performed at the Hepatology Center of Buda, Budapest, Hungary, using a FibroScan 502 equipment (Echosens, Paris, France). Examinations with 10 successful shots and an interquartile range (IQR) for liver stiffness less than 30% of the median value were considered as reliable.

The primary outcome variable was liver stiffness. The univariate association with categorical variables was assessed by a two independent sample Mann-Whitney *U* test (i.e. Wilcoxon rank-sum test). The univariate correlation with continuous variables was assessed using the Pearson and Kendall-τ rank-correlation coefficient, visualization was performed with scattergrams indicating best fitting linear curve and LOWESS-smoother.. For multivariate analysis, each candidate covariate was added to a linear regression model, with the response variable being LS. No interaction was added. The necessity of non-linearity was investigated by extending the model using restricted cubic splines for the continuous variables, and using Wald-*F* test to check their (joint) significance. The obtained model was checked to pass routine residual diagnostics. To internally validate the model, calibration curve and optimism-corrected R^2 was calculated using bootstrap with 1000 replications (E., 2009). *p*-values below 0.05 were considered significant. Calculations were performed under R software package version 3.1.2 (Team, 2014) and library rms, with a custom script developed for this purpose which is available from the corresponding author on request.

From March 1, 2014 to October 30, 2014 all HIV-infected patients who attended the outpatient clinic at the HIV Center, St. István and St. László Hospital (Budapest, Hungary) were invited to participate in the study (*n=756*). Liver stiffness measurements were performed on 139

patients. Out of this cohort 101 individuals were eligible for the final analysis (Fig. 1). In all patients the mode of transmission of HIV was reported to be sexual intercourse. The baseline study population characteristics are summarized in Table 1.

Results

LSM ranged from 3.0 kPa to 34 kPa with a median value of 5.1 kPa (IQR 1.7). According to the HIV/HCV co-infection LS cutoffs (Vergara et al., 2007), significant liver fibrosis defined as LS<7.2 kPa was detectable in 10/101 individuals. Presence of cirrhosis (LS >14.6 kPa) was observed in 2 participants. Applying the cutoff (5.3 kPa) from a healthy population as described in the study by Han et al (Han et al., 2013), significant fibrosis was detected in 56/101 patients. Significant Pearson and Kendall correlation was found between LS and controlled attenuation parameter (CAP) value ($p=0.022$; $p<0.001$), age ($p=0.003$; $p=0.006$), body mass index ($p=0.01$; $p=0.0001$) and the cumulative length of antiretroviral therapy (ART) exposure ($p=0.049$, $p=0.008$). With regard to categorical variables, the only significant association was found with the presence of arterial hypertension ($p=0.045$). Associations of liver stiffness and different continuous and categorical variables are presented in Tables 2-3 and Fig. 2. Non-linearity was deemed unnecessary ($p=0.1787$) in the multivariate model. The linear regression identified CAP value ($p=0.0061$), age ($p=0.04356$) and the presence of diabetes ($p<0.0001$) as independent positive covariates. History of taking etravirine ever over the course of ART ($p=0.0046$) and CD4/CD8 ratio ($p=0.04$) were independent negative covariates. Nevertheless, the model exhibited weak fit ($R^2=0.5472$, optimism-corrected $R^2=0.2116$). Regression coefficients and confidence intervals are summarized in Table 4 and presented graphically in Fig. 3.

136

137 Discussion

138

139 To our knowledge, so far only a few published studies assessed liver stiffness in HIV-
140 infected patients without HBV or HCV infection. In these publications, by using different cutoff
141 values the prevalence of liver fibrosis ranged from 10% to 47% (Merchante et al., 2010; Han et
142 al., 2013).

143

144 Han et al reported abnormal LS values in 39/93 (41.9%) patients on ART for at least 12
145 months without hepatitis virus co-infection (Han et al., 2013). By using the same cutoff value,
146 the proportion of individuals with abnormal LS was slightly higher in our study population
147 (56/101; 55.44 %). In contrast, Merchante et al (Merchante et al., 2010) identified 29/258
148 (11.2%) of their study population to have significant liver fibrosis. In the prospective study of
149 Rivero-Juarez et al the incidence of significant LF was 10.6% with the same cutoff (Rivero-
150 Juárez et al., 2013). Applying their cutoff values (>7.2 kPa), we had similar results: abnormal LS
151 values were detected in 10/101 (9.9%) individuals.

152

153 These diverse results underline the importance of identifying better cutoff values in HIV
154 mono-infected patients. The most reliable method for this would be to perform liver biopsy and
155 to compare its results with those of transient elastography. Nevertheless, to our knowledge, no
156 such study has been carried out yet. The discrepancies in cutoff values might lead to unreliable
157 estimation of the rate and grade of liver fibrosis. Therefore, similar to Han et al (Han et al.,
158 2013), instead of dichotomizing our study population to patients with abnormal and normal LS

159 values we used a continuous scale of LS for our correlation and regression analyses to avoid
160 uncertainty arising from using a pre-defined „abnormal" value as cutpoint.

161

162 Using multivariate regression analysis, significant positive correlations were found with
163 CAP, age and the presence of diabetes. However, if we also take the confidence intervals of
164 regression coefficients into account, diabetes remains the most important independent positive
165 covariate. Previous studies in HIV mono-infected patients also identified diabetes (Bailony et al.,
166 2013) and elevated homeostasis model assessment-estimated insulin resistance levels (Rivero-
167 Juárez et al., 2013) to be associated with LS. A study using the non-invasive APRI score in 432
168 HIV-mono-infected patients enrolled in the Center For AIDS Research Database also identified
169 diabetes (adjusted OR, 3.15; 95% CI, 1.12–10.10) and detectable HIV viremia (adjusted OR,
170 2.56; 95% CI, 1.02–8.87) as independent covariates for significant fibrosis after controlling for
171 active alcohol use and site (DallaPiazza et al., 2010). These results shed light on the importance
172 of diabetes in the development of LF which can be triggered by ongoing HIV replication.
173 However, the relationship between insulin resistance, increasingly seen in persons infected with
174 HIV, and viral replication is unclear and must be established (Rockstroh et al., 2014).

175

176 Data suggesting direct HIV-induced effects on the pathogenesis of fibrosis generation has
177 been described mainly in patients with HIV/HCV co-infection (Rockstroh et al., 2014) but the
178 mechanism has still not been exactly determined. An accepted marker of immune dysregulation,
179 the abnormal CD4/CD8 ratio (Serrano-Villar et al., 2014) as a negative independent significant
180 covariate supports this theory. In HCV infected patients the CD4/CD8 ratio as a contributing
181 factor to liver fibrosis has also been considered (Feuth et al., 2014). CD4 cells can stimulate anti-

182 fibrotic natural killer (NK) cell activity, therefore, loss and impaired activity of CD4 cells may
183 contribute to the progression of liver fibrosis (Rockstroh et al., 2014). Age was also previously
184 identified as a predictor of fibrosis (Merchante et al., 2010) (adjusted OR 1.05, 95% confidence
185 interval [CI] 1.002-1.1; P=0.004). CAP value also showed significant linear and monotone
186 correlation (and it was also identified as an independent covariate in multivariate analysis) as it
187 was previously described in an unselected HIV infected population (Sulyok et al., 2015),
188 however, in another study by Macías et al. (Macías et al., 2014) no association was found with
189 LS and abnormal CAP values (>238 dB/m). The presence of steatosis assessed with CAP is not
190 unexpected in HIV-mono-infected patients with liver fibrosis (Rivero-Juárez et al., 2013).
191
192 With regard to ART, the history of taking etravirine (ever in the course of treatment) was
193 found to be independently and negatively associated with LS. This antiretroviral (ARV) is
194 considered not to be hepatotoxic and showed a favorable profile in patients with advanced liver
195 fibrosis (Casado et al., 2014). Interestingly, no significant association was found with other
196 ARVs. Han et al found that the cumulative exposure to boosted protease inhibitors (PI) was a
197 significant independent negative predictor [OR, 0.941; 95% confidence interval (CI), 0.889–
198 0.997; P=0.039] (Han et al., 2013). The authors conclude that ritonavir boosting may have a
199 protective effect. Considering the metabolic changes associated with boosted protease inhibitors
200 this result is surprising (Rockstroh et al., 2014). Associations with didanosine and stavudin with
201 liver fibrosis were previously described (Akhtar et al., 2008; Merchante et al., 2010; Blanco et
202 al., 2011). In our investigated population the number of dideoxynucleoside exposed patients was
203 negligible (*n=2*), therefore, we did not include these ARVs in our analysis. An unexpected
204 finding, namely, significant association of LS and previous abacavir exposure (AOR 3.01, 95%

CI 1.18-7.67; p=0.02) was previously shown (Merchante et al., 2010). Our study can support this observation: a remarkable, but slightly not significant association was detected (*p=0.063)*. The proinflammatory effect of abacavir was previously described but the exact mechanisms of inducing liver damage is unclear (Therapy/INSIGHT and Groups, 2008) These observations raise the question as to certain types of ARVs are in causal relationship with LF. Clearly, further prospective, controlled trials will be needed to clarify the role of these side effects in the pathogenesis of LF in HIV-infected individuals.

Our study has considerable limitations, the low patient number being probably the most important one. Other causes of liver disease were also not explored in details, but no patients with previously diagnosed liver diseases were included. The low number of excluded patients with significant alcohol intake has also to be dealt with caution. Since alcohol consumption was assessed by self-reporting, there is a possibility that not all affected individuals were identified.

Moreover, the distance between the HIV center, where screening occurred and the hepatology center where transient elastography measurement took place was the main reason to reject participation in the study. This could lead to selection bias, since low-compliance patients, such as drug users could be underrepresented in the study population.

In conclusion, using previously described cutoff values we identified a high prevalence of liver fibrosis. The association between liver stiffness and diabetes reflects on the possible role of metabolic changes in HIV. An unexpected negative association was found with etravirine, whereas the positive association with abacavir supports previously published data. These results

raise the question whether development liver fibrosis may be influenced by certain types of antiretrovirals and warrant further research in this area. Data from controlled trials would be necessary to clarify causal relations and identify liver-friendly medications and treatment strategies.

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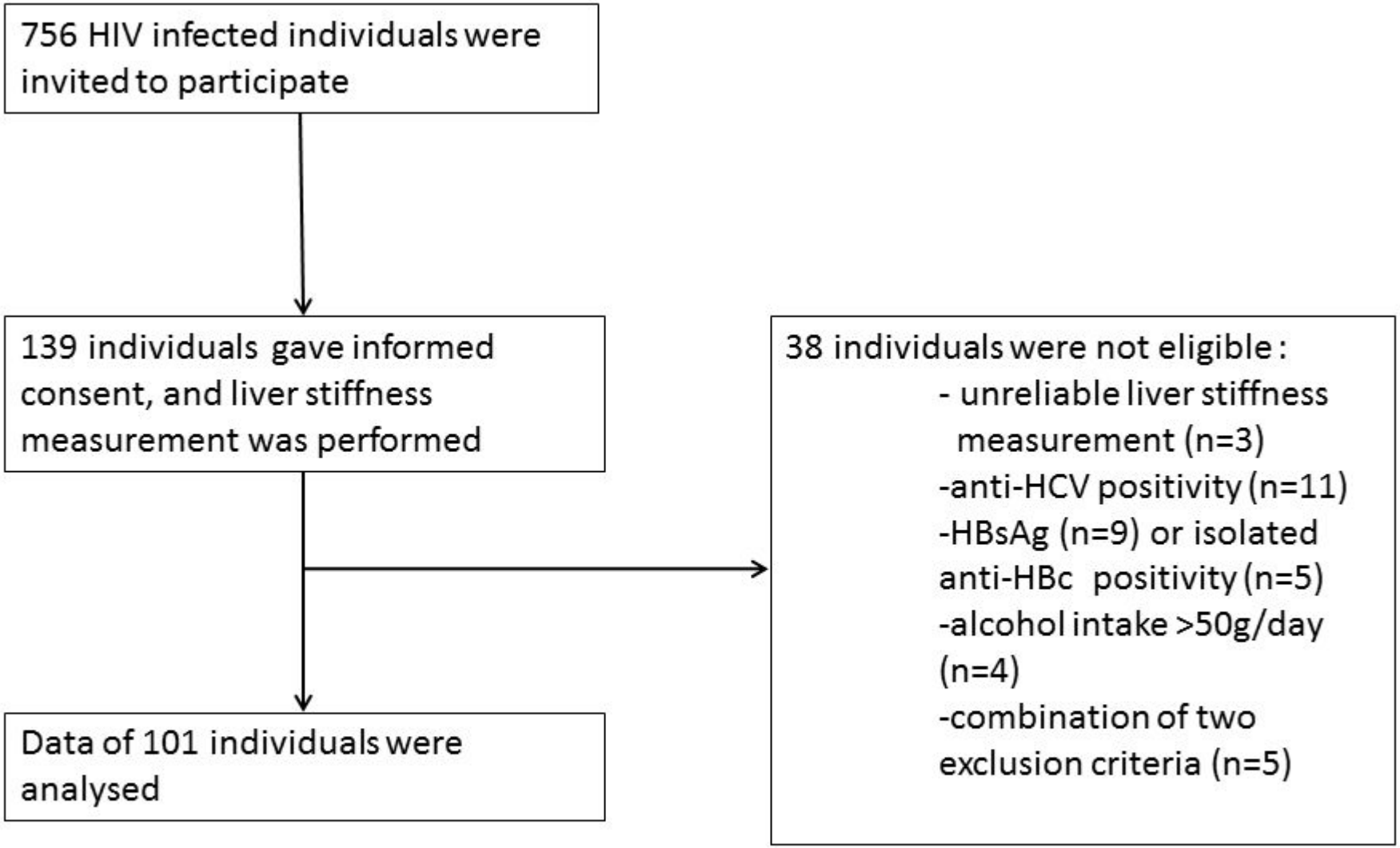
Figure 1(on next page)

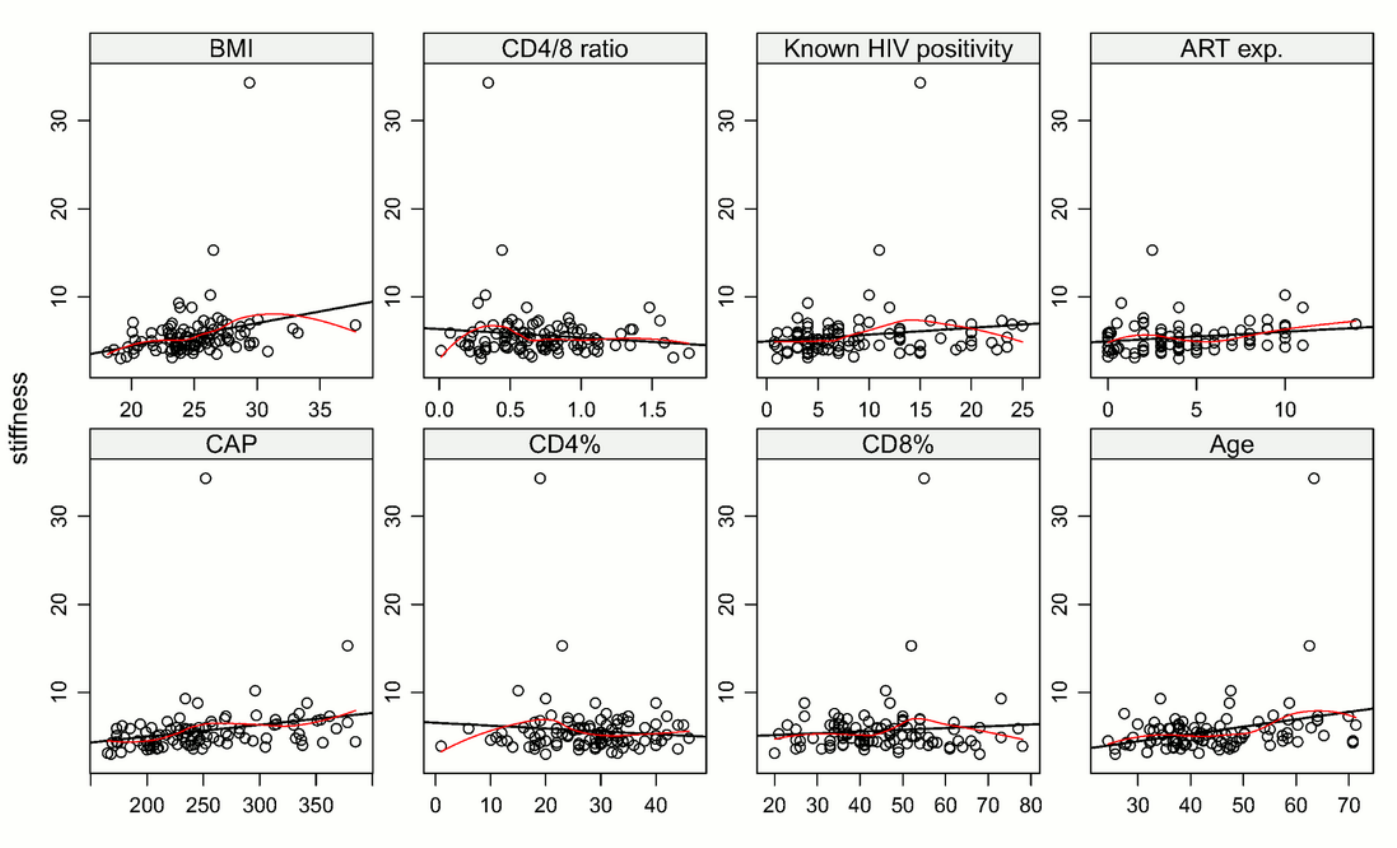
Recruitment Flow of Study Participants.


756 HIV infected individuals were invited to participate
139 individuals gave informed consent, and liver stiffness measurement was performed
38 individuals were not eligible :
- unreliable liver stiffness measurement (n=3)
-anti-HCV positivity (n=11)
-HBsAg (n=9) or isolated anti-HBc positivity (n=5)
-alcohol intake >50g/day (n=4)
-combination of two exclusion criteria (n=5)
Data of 101 individuals were analysed

2

Correlations between Continuous Variables and the Liver Stiffness Value.

The black line shows the best-fitting linear curve, the red line shows the LOWESS smoother for nonparametric regression. Liver stiffness is expressed in kPa, BMI is kg/m2, age, the length of known HIV positivity and cumulative ART duration in years, CAP, controlled attenuation parameter in dB/m



3

Multivariate analysis: covariates with regression coefficients and confidence intervals.

The Figure shows the regression coefficients of the covariates. For categorical variables, the change is understood as the change to the modal category, for continuous variables, it is 1 IQR change. In each case, this is explicitly indicated with two values separated with colon after the variable. BMI is expressed in kg/m2, age, cumulative ART duration and the length of known HIV positivity in years, and liver stiffness in kPa. ART, antiretroviral therapy; CAP, controlled attenuation parameter (dB/m); lipodystrophy, facial lipodystrophy. Thick dark blue lines represents 90% CIs, thick light blue lines 95% CIs, and narrow light blue lines 99% CIs.

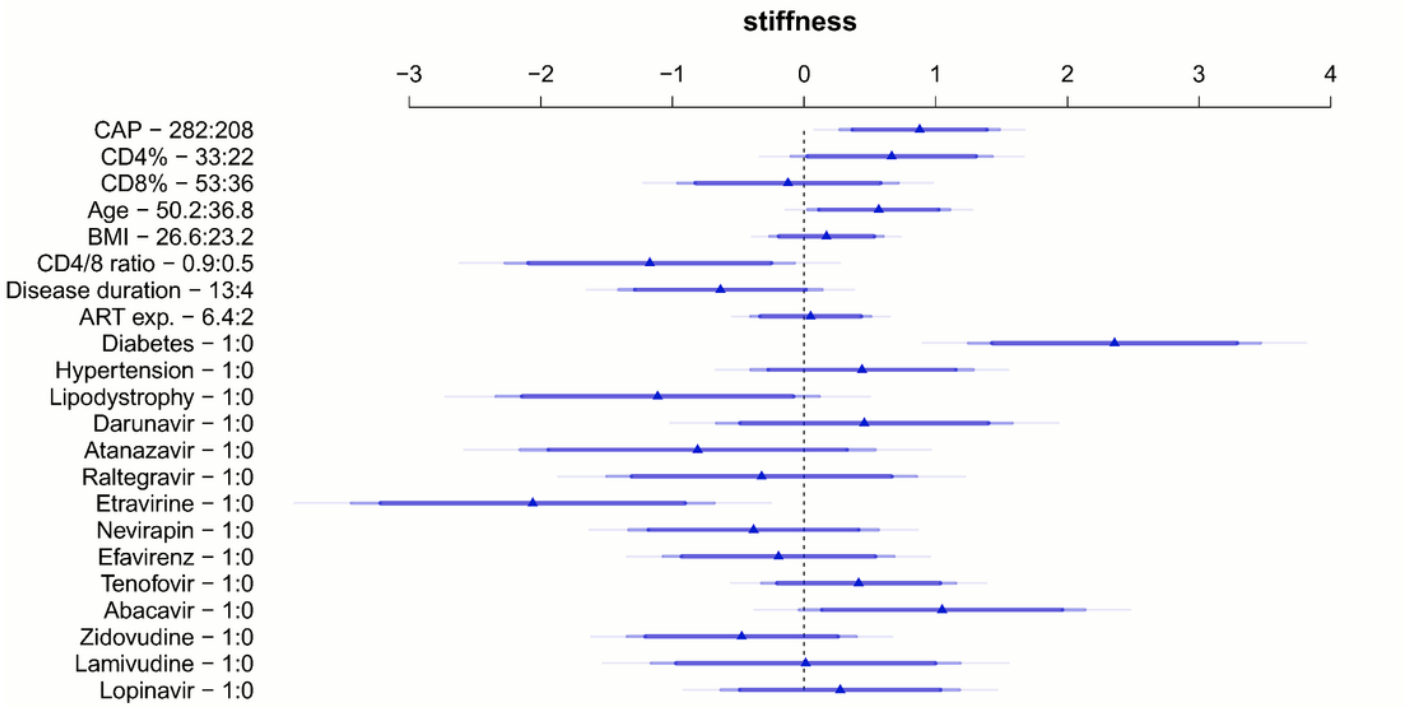


Table 1(on next page)

Baseline Study Population Characteristics.

[a]Controlled attenuation parameter; [b]Antiretroviral therapy

1

Parameter	**Mean (Median) ± SD (IQR) [Min-Max]**
CD4 %	27.64 (29) ± 8.99 (11) [1-46]
CD8%	45.06 (44) ± 12.68 (17) [20-78]
CD4/8 ratio	0.69 (0.63) ± 0.36 (0.45) [0.012-1.76]
Age (years)	44.62 (42.36) ± 11.39 (13.42) [24.35-71.33]
BMI (kg/m2)	24.97 (24.75) ± 3.23 (3.32) [18.11-38.73]
Serum trigliceride (mmol/L)	2.83 (1.95) ± 2.51 (2.42) [0-13.1]
Serum cholesterol (mmol/L)	5.44 (5.4) ± 1.51 (1.85) [0-10.9]
Known HIV positivity (years)	9.19 (7) ± 6.43 (9) [0.75-25]
Liver Stiffness (kPa)	5.66 (5.1) ± 3.33 (1.7) [3-34.3]
CAP[a] (dB/m)	250.6 (239) ± 56.38 (74) [165-385]
ART exposition (years)	4.33 (4) ± 3.32 (4.37) [0-14]
	N (%)
ART[b] ever taken 125	8 (7.92)
Gender (male)	99 (98)
Diabetes	11 (10.89)
Hypertension	21 (21.21)
Lipodystrophy	12 (11.88)

2

Table 2(on next page)

Univariate Analysis: Associations of Liver Stiffness Value with Continuous Variables.

Results are presented in mean (median) ±SD (IQR) [minimum–maximum] format. *p*-value pertains to the null hypothesis of no correlation. [a] Controlled attenuation parameter; [b]Antiretroviral therapy

1

	Pearson		Kendall	
Variable	***r***	***p***	**τ**	***p***
CAP[a]	0.226	0.0229	0.295	<0.0001
CD4%	-0.087	0.3869	0.008	0.9017
CD8%	0,075	0.4533	-0.018	0.7891
CD4/8 ratio	-0.106	0.2912	-0.003	0.9601
Trigliceride	0.026	0.7897	0.079	0.2508
Cholesterol	0,028	0.7819	0.059	0.3915
Age	0.285	0.0037	0.185	0.0065
BMI	0.255	0.0103	0.261	0.0001
ART exposition	0.208	0.0490	0.196	0.0082

2

Table 3(on next page)

Univariate Analysis: Associations of Liver Stiffness Value with Categorical Variables.

Results are presented in mean (median) ± SD (IQR) [minimum–maximum] format. *p*-value pertains to the null hypothesis of stochastic equivalence of the two populations (presence/absence). [a] Controlled attenuation parameter; [b]Antiretroviral therapy

1

Variable	Presence of variable	Absence of variable	*p*
Diabetes	6.96 (6.3) ± 3.31 (2.65) [3.9-15.3]	5.5 (5) ± 3.32 (1.6) [3-34.3]	0.063
Sex	4.66 (4.9) ± 0.58 (0.55) [4-5.1]	5.69 (5.15) ± 3.38 (1.85) [3-34,3]	0.446
Hypertension	6.11 (5.4) ± 2.44 (1.5) [4-15.3]	5.51 (4,9) ± 3.57 (1.77) [3-34.3]	0.045
Lipodystrophy	5.28 (5.05) ± 0.98 (1.55) [4-6.9]	5.71 (5.1) ± 3.53 (1.7) [3-34.3]	0.821
Darunavir	5.64 (5.3) ± 1.71 (1.97) [3.5-10.2]	5.66 (5) ± 3.63 (1.7) [3-34.3]	0.410
Atanazavir	5.32 (5.2) ± 1.26 (1.6) [3.6-7.3]	5.68 (5.05) ± 3.44 (1.7) [3-34.3]	0.840
Lopinavir	6.73 (5) ± 6.08 (1.8) [3.6-34.3]	5.29 (5.1) ± 1.41 (1.7) [3-10.2]	0.652
Raltegravir	6.15 (5) ± 3.74 (0.65) [3.9-15.3]	5.62 (5.2) ± 3.31 (1.9) [3-34.3]	0.914
Lamivudine	5.74 (5.1) ± 3.49 (1.8) [3.1-34.3]	5.06 (4.4) ± 1.77 (1.85) [3-9.3]	0.221
Tenofovir	6.33 (5.3) ± 5.13 (2.12) [3.1-34.3]	5.26 (5) ± 1.34 (1.65) [3-10.2]	0.548
Abacavir	5.59 (5.8) ± 1.83 (2) [3.6-10.2]	5.67 (5) ± 3.51 (1.75) [3-34.3]	0.819
Zidovudine	5.51 (4.9) ± 2.01 (1.65) [3.7-15.3]	5.76 (5.15) ± 3.96 (1.85) [3-34.3]	0.941
Etravirine	4.93 (4.8) ± 1.04 (1.9) [3.6-6.3]	5.73 (5.1) ± 3.47 (1.75) [3-34.3]	0.424
Nevirapine	5.28 (5.3) ± 1.14 (1.8) [3.6-7.4]	5.76 (5) ± 3.72 (1.7) [3-34.3]	0.853
Efavirenz	5.42 (5.3) ± 1.44 (2.35) [3.1-8.8]	5.75 (5.05) ± 3.80 (1.67) [3-34.3]	0.590
ART[b] ever taken	5.27 (5.1) ± 1.92 (1.62) [3-9.3]	5.69 (5.1) ± 3.43 (1.9) [3.1-34.3]	0.605

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Table 4(on next page)

Results of Multivariate Analysis with Linear Regression.

[a] Controlled attenuation parameter; [b]Antiretroviral therapy

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	Estimate	Std. Error	*t* value	*p*
(Intercept)	0.247	2.198	0.112	0.911
CAP[a]	0.012	0.004	2.835	0.006
CD4%	0.061	0.035	1.709	0.092
CD8%	-0.007	0.025	-0.286	0.776
Age	0.042	0.021	2.060	0.044
BMI	0.051	0.066	0.774	0.442
CD4/8 ratio	-2.603	1.245	-2.090	0.041
Diabetes	2.358	0.566	4.170	<0.0001
Hypertonia	0.440	0.431	1.020	0.311
Lipodystrophy	-1.112	0.626	-1.775	0.081
Known HIV positivity	-0.071	0.044	-1.610	0.112
Darunavir	0.458	0.573	0.799	0.427
Atanazavir	-0.809	0.688	-1.175	0.245
Raltegravir	-0.322	0.600	-0.537	0.593
Etravirine	-2.061	0.703	-2.932	0.005
Nevirapine	-0.383	0.484	-0.792	0.431
Efavirenz	-0.194	0.447	-0.434	0.666
Tenofovir	0.415	0.376	1.101	0.275
Abacavir	1.049	0.554	1.893	0.063
Zidovudine	-0.474	0.444	-1.067	0.290
Lamivudine	0.012	0.599	0.021	0.984
Lopinavir	0.275	0.463	0.594	0.555
Length of ART[b] exposure	0.011	0.053	0.215	0.830

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