PREVALENCE AND PATIENT CHARACTERISTICS OF **NONINVASIVELY MEASURED LIVER FIBROSIS** IN PERINATALLY HIV-1-INFECTED CHILDREN

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KEY POINTS

The prevalence of noninvasively measured liver fibrosis is low in perinatally HIV-1-infected children stable on cART.

Hypercoagulability (low protein C and S activity) may put HIV-infected children at increased risk of liver fibrosis.

OBJECTIVE

In the era of combination antiretroviral treatment (cART), biochemical findings suggestive of significant liver fibrosis have been reported in up to 8% of HIV-infected children[1-4]. Recently, several cases of non-cirrhotic portal hypertension in didanosine (ddI)-exposed adolescents without viral hepatitis or drug/alcohol abuse[5] prompted us to investigate the prevalence and clinical characteristics of liver fibrosis in cART-treated HIV-infected children.

METHODS

We included perinatally HIV-infected children from the Emma Children's Hospital in Amsterdam and Sophia Children's Hospital in Rotterdam, excluding patients with viral hepatitis and other pre-existing liver diseases. Liver fibrosis was defined as an aspartate-aminotransaminase-to-platelet ratio index (APRI) >1.5, fibrosis-4 (FIB-4) score >1.3, enhanced liver fibrosis (ELF) score, >10.18 and transient elastography (TE)-measured liver stiffness >7.4 kPa. We explored associations between liver fibrosis and patient characteristics using multivariable linear regression analysis.

RESULTS

Clinical characteristics

We included 88 participants (Table 1). The most prevalent biochemical and radiological abnormalities were elevated ALT (23%), and low protein S activity (53%), and liver size >2SD above the age- and sex-appropriate mean (27%) (Table 2). There were no signs of splenomegaly, widening of bile ducts, abnormal aspect of the liver or gallbladder, or collateral vessel formation.

Low prevalence of liver fibrosis

APRI and FIB-4 scores were not suggestive of clinically significant fibrosis in any participants. TE and ELF indicated clinically significant fibrosis in 3%-4% of participants, respectively (Table 2).

TABLE 1 STUDY PARTICIPANTS

88 HIV-infected children
median age 11.2 years
53% male

history: 26% CDC-C diagnosis; nadir CD4⁺ T-cells 720 *10⁶/L (Z-score -0.7)

cART: 93% on cART since median age 2.1 years; 28% ddI-exposed for median of 18 months

currently: 88% HIV viral load <400 copies/ml; CD4⁺ T-cells 900 *10⁶/L (Z-score -0.0)

TABLE 2 BIOCHEMICAL/RADIOLOGICAL FINDINGS

Haematological	*n*	median (IQR)	<LLN
Hemoglobin (mmol/L)	86	7.7 (7.2-8.1)	7 (8%)
Platelets (10^9 cells/mm^3)	86	289 (232-335)	3 (3%)
Protein C activity (%)	80	101 (85-109)	4 (5%)
Protein S activity (%)	79	65 (54-81)	42 (53%)

Biochemical	*n*	median (IQR)	>ULN
ALT (U/L)	87	19 (14-24)	20 (23%)
AST (U/L)	86	31 (24-35)	10 (12%)
GGT (U/L)	86	25 (17-33)	16 (19%)
Bilirubin (µmol/L)	87	5 (3-12)	11 (13%)

Radiological markers	*n*	median (IQR)	>2
Liver size (Z-score)	88	1.5 (0.8-2.1)	24 (27%)

Liver fibrosis tests	*n*	median (IQR)	**Fibrosis**
APRI	85	0.27 (0.21-0.33)	**0 (0%)**
FIB-4	85	0.25 (0.16-0.38)	**0 (0%)**
ELF	72	9.04 (8.35-9.59)	**3 (4%)**
TE (kPa)	73	4.3 (3.6-5.1)	**2 (3%)**

Values exceeding limits of normal were calculated using the age- and sex-specfic referenge ranges from each center's laboratory. For abnormal ALT values, we used alternative, more sensitive sex-adjusted reference values proposed by Schwimmer et al.[6]

Abbreviations: LLN=lower limit of normal; ULN=upper limit of normal; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase; APRI=AST-to-platelet-ratio index; FIB-4=fibrosis-4 score; ELF=Enhanced liver fibrosis test; TE=transient elastography.

Characteristics associated with liver fibrosis

Higher ELF scores were associated with lower activity of protein C (coef=-0.01; *P*=.007) and S (coef=-0.02; *P*<.001), and higher CD4+ T-cell counts (coef=0.61; *P*<.001). Children with a CDC stage B diagnosis had lower ELF scores (coef=-0.70; *P*=.003) (Figure 1).

No associations were found between any of the clinical characteristics and TE-measured liver stiffness. APRI and FIB-4 were not analyzed, as these did not indicate significant liver fibrosis.

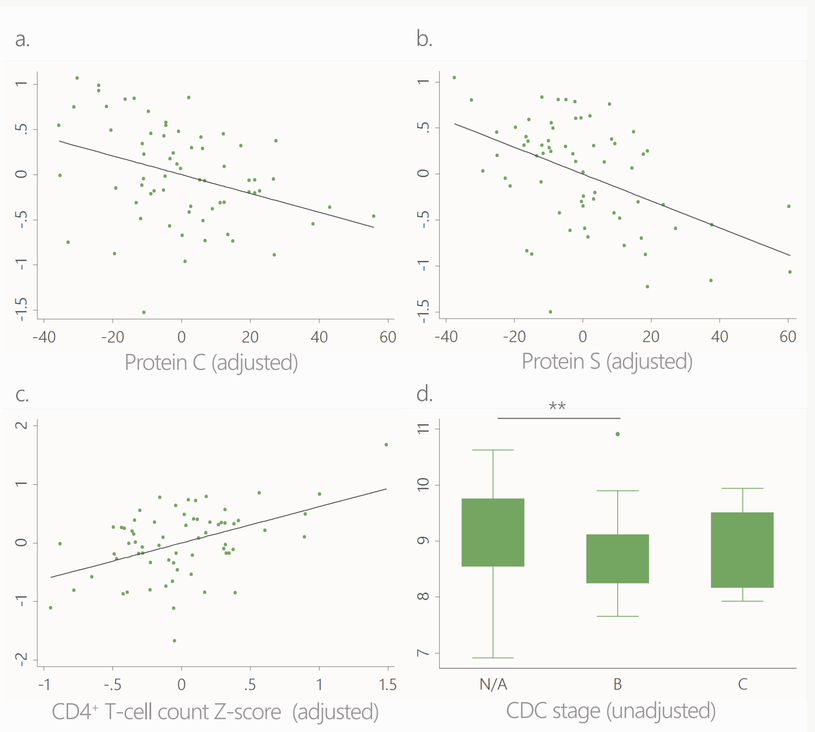

Figure 1. Associations with ELF score.

a-c:) added variable-plots for the partial correlations between ELF score (y-axis) and protein C, protein S and CD4⁺ T-cell Z-score; d) unadjusted box plot illustrating the association between ELF score (y-axis) and a CDC stage B diagnosis. The final age- and sex-adjusted model included CD4 T-cells count (Z-score), CDC stage, protein C activity, protein S activity, hemoglobin level, platelet count, and liver size (Z-score). No associations were found with body mass index, ethnicity, zenith viral load, current HIV viral load, age at cART initiation, being treatment naive, duration of ddI exposure, and ALT.

CONCLUSIONS

» We found a very low prevalence of significant fibrosis in this cohort of perinatally HIV-1-infected children, of which the large majority was virologically surpressed on cART.

» Lower protein C and S activity – but not poor virological control or low CD4+ T-cell counts – were associated with higher ELF scores, suggesting careful monitoring of this subgroup of patients.

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