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Prevalence and Predictors of Elevated Aspartate Aminotransferase-to-Platelet Ratio Index in Latin American Perinatally HIV-infected Children

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Abstract

Background—Chronic liver disease has emerged as an important problem in adults with longstanding HIV infection, but data are lacking for children. We characterized elevated aspartate aminotransferase (AST)-to-platelet ratio index (APRI), a marker of possible liver fibrosis, in perinatally HIV-infected children.

Methods—NISDI [NICHD (National Institute of Child Health and Human Development) International Site Development Initiative] enrolled HIV-infected children (ages 0.1–20.1 years) from five Latin American countries in an observational cohort from 2002–2009. Twice yearly visits included medical history, physical examination and laboratory evaluations. The prevalence (95% confidence interval [CI]) of APRI>1.5 was calculated and associations with demographic, HIV-related and liver-related variables were investigated in bivariate analyses.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institutes of Health or the Department of Health and Human Services.

Results—APRI was available for 1012 of 1032 children. APRI was >1.5 in 32 (3.2%, 95% CI: 2.2%–4.4%) including 2 of 4 participants with hepatitis B (HBV) infection. Factors significantly associated with APRI >1.5 ($p < 0.01$ compared to APRI ≤ 1.5) included country, younger age, past or current HBV, higher alanine aminotransferase, lower total cholesterol, higher $\log_{10}$ current viral load, lower current CD4 count, lower nadir CD4 count, use of hepatotoxic non-antiretroviral (ARV) medications, and no prior ARV use. Rates of APRI >1.5 varied significantly by current ARV regimen ($p = 0.0002$), from 8.0% for no ARV to 3.2% for non-protease inhibitor (PI) regimens to 1.5% for PI-based regimens.

Conclusions—Elevated APRI occurred in approximately 3% of perinatally HIV-infected children. PI-based ARVs appeared protective while inadequate HIV control appeared to increase risk of elevated APRI. Additional investigations are needed to better assess potential subclinical, chronic liver disease in HIV-infected children.

Keywords

aspartate aminotransferase-to-platelet ratio index (APRI); HIV-1; Perinatal HIV infection; Latin America

Highly active antiretroviral therapy (HAART) has resulted in dramatic decreases in morbidity and improved survival for adults and children with HIV infection [1–3]. However, even as the risk of AIDS-defining illness has decreased, other complications have become more significant causes of morbidity and mortality in long-term survivors. Liver failure and cirrhosis have emerged as leading non-AIDS causes of illness and death in HIV-infected adults, especially in those with hepatitis B (HBV) or C (HCV) co-infection [4]. While co-infections, hepatotoxic antiretroviral medications (ARVs) and other drugs, severe immunosuppression, alcohol use and other traditional (non-HIV-specific) risk factors for hepatic dysfunction have been implicated, hepatic fibrosis and dysfunction also occur in adults with longstanding HIV infection and no other specific risk factors [5–6].

Hepatitis and liver dysfunction are recognized complications of perinatal HIV infection, but the prevalence of clinically recognized disease appears to be much lower than that in adults [7–9]. However, as these children now survive into adulthood and face lifelong HIV infection and treatment, hepatic dysfunction may emerge as an important cause of morbidity and even mortality.

The standard for assessing presence and degree of liver inflammation, fibrosis and cirrhosis is examination of a liver biopsy, but this diagnostic approach is highly invasive and unsuitable for potential hepatic fibrosis screening. The aspartate aminotransferase [AST]-to-platelet ratio index (APRI) is a non-invasive measure of significant hepatic fibrosis that has been used in studies of HIV-mono-infected and HIV/HCV co-infected adults [10–18]. An APRI >1.5 has been validated as evidence of significant liver fibrosis in HIV-HCV co-infected adults [12–14].

In studies of HIV-uninfected children with chronic viral hepatitis and other liver conditions, elevated APRI has been shown to be associated with liver fibrosis - including validation with liver biopsy findings - especially with more advanced stages of liver fibrosis [19–22]. The best APRI cutoff for children has not been established; the adult APRI cutoff of 1.5 appears to be highly specific but relatively insensitive for detection of liver fibrosis in children [19]. APRI has not been previously studied in HIV-infected children. The purpose of this study is to estimate the rate of elevated APRI, as a marker of potential liver fibrosis, in a cohort of perinatally HIV- infected Latin American children.

METHODS

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) enrolled HIV-infected children up to age 19 years from five Latin American and Caribbean countries (Argentina, Brazil, Jamaica, Mexico, and Peru) into an observational cohort from 2002–2009. A description of the earlier NISDI Pediatric study (2002–2007) has been published [23]. The later NISDI PLACES (Pediatric Latin American Countries Epidemiologic Study) study enrolled HIV-infected children younger than age 6 years from 2008–2009. NISDI Pediatric study subjects were eligible to continue in PLACES if they were younger than age 6 years at the time of enrollment in the Pediatric study. The protocol was approved by ethical review boards at each clinical site, the sponsoring institution (NICHD), the data management and statistical center (Westat), and the Brazilian National Ethics Committee (CONEP). Informed consent was obtained from adult participants, or from parents or guardians of minor participants.

Evaluations at twice yearly study visits included medical history, physical examination, flow cytometer, HIV RNA concentration (viral load) and standard biochemical and hematologic assays. Aspartate aminotransferase (AST) and platelet levels were measured by routine methods at each site's local laboratory. HBV and HCV infection status was based on available data in the medical and laboratory records. Medication history (ARV and non-ARV) was assessed at the enrollment visit and ongoing medication use was assessed at each study visit. HAART was defined as at least 3 drugs from at least 2 ARV classes. All reported medications underwent clinician review and classification for potential hepatotoxicity by two independent physicians, one using the Pediatric Dosage Handbook, Lexis-Comp, 14th edition as the reference to determine whether a medication was potentially hepatotoxic and the other using the 19th edition Harriet Lane Handbook, as well as the Micromedex for medications not listed in the Harriet Lane Handbook [24–26]. A third physician reviewed assessments that were discrepant and made the tie-breaking determination, usually based on US FDA labeling information (See Appendix, Supplemental Digital Content 1, <http://links.lww.com/INF/B621> for classification of potentially hepatotoxic medications). Body mass index (BMI)-for-age z-score was calculated according to WHO standards (WHO Child Growth Standards, Department of Nutrition for Health and Development, WHO SAS Anthro module, WHO software package, 2007 version).

Participants were eligible for this analysis at the first study visit for which an AST level and a platelet count were available, and the first on-study AST-to-platelet ratio index (APRI) for each subject was calculated as:

$$\text{APRI} = 100 * (\text{AST} / \text{AST upper limit of normal} [\text{ULN}_{\text{AST}}]) \div \text{platelet count} (10^9/\text{L})$$

Prevalence of elevated APRI ($\text{APRI} > 1.5$) was computed as the percentage with elevated APRI and the exact (Clopper-Pearson) 95% confidence interval (CI) of the binomial proportion was calculated. Associations of elevated APRI with demographic, HIV-related and liver-related variables were investigated in univariate analyses using Fisher's exact test (categorical measures) or Student's t-test (continuous). Multivariable logistic regression modeling was used to explore adjusted associations of select covariates with elevated APRI. Analyses were conducted using SAS version 9.2 statistical software (SAS Institute Inc., Cary, NC).

RESULTS

As of December 31, 2010, 1032 perinatally HIV-infected children were enrolled. Twenty did not have on-study laboratory results available for calculation of APRI, resulting in 1012 children included for analysis (age range: 0.1–20.1 years).

The median of the first available APRI for all subjects was 0.29 (range: 0.05–29.67). The APRI was elevated (> 1.5) in 32 children (3.2%, 95% CI: 2.2%–4.4%). Two of the four participants with past or current HBV infection and none of the six participants with past or current HCV infection had an elevated APRI. When those with HBV or HCV infection were excluded, the overall rate of elevated APRI was essentially unchanged at 30/1002 (3.0%, 95% CI: 2.0–4.3%). Elevated APRI occurred in only 7 out of 693 subjects (1.0%, 95% CI: 0.4%–2.1%) after 6 months of HAART. None of the subjects with 6 months of virologic suppression and 6 months of HAART had an elevated APRI (0/167; 0.0%, CI: 0.0%–2.2%).

Participant characteristics by APRI status are shown in Table 1. The average age of subjects with elevated APRI was significantly lower than that of subjects with APRI ≤ 1.5 (3.3 vs. 6.4 years, $p<.0001$). Participants with elevated APRI differed by country when compared to those with APRI ≤ 1.5 ($p=.0004$), with the prevalence of elevated APRI ranging from 0.7% (1/147) in Mexico to 12.8% (10/78) in Peru. Those with elevated APRI were more likely to have past or current HBV infection (6.3%) compared to those with APRI ≤ 1.5 (0.2%; $p=.0056$). The two groups did not differ significantly in terms of sex, BMI-for-age z-score, or past/current HCV infection.

Comparisons of laboratory evaluations among those with and without elevated APRI are shown in Table 2. The mean ALT level among subjects with elevated APRI was 227.7 mU/mL, significantly higher than the mean of 31.7 mU/mL among those with APRI ≤ 1.5 ($p=.0003$). Although the elevated APRI group had a significantly lower mean total cholesterol than the non-elevated group (121.5 vs. 154.6 mg/dL, $p=.0002$), there was no significant difference in mean triglyceride levels between the two groups (129.7 vs. 123.1 mg/dL, $p=.68$). The median of the platelet level used to calculate the APRI for those with elevated APRI was $79.5 \times 10^3/\text{mm}^3$ [25th percentile (Q1), 75th percentile (Q3): 58.0, 230.5]. The median of the AST and the (AST/ULN_{AST}) for those with elevated APRI was 114.5 [Q1, Q3: 44.0, 372.5] and 2.5 [Q1, Q3: 1.2, 8.1], respectively.

Subjects with elevated APRI had less well-controlled HIV than subjects with APRI ≤ 1.5 (Table 3). Compared to those with APRI ≤ 1.5 , the mean $\log_{10}$ viral load was significantly higher among those with elevated APRI (5.2 vs. 3.4, $p<.0001$); the percentage with viral load <400 copies/ml was 0% vs. 36.4%, respectively ($p<.0001$). The mean $\log_{10}$ peak viral load was also significantly higher among those with elevated APRI (5.8 vs. 5.3; $p=.0039$). Those with elevated APRI had a lower mean CD4 count (743.3 vs. 1052.9 cells/ mm^3 ; $p=.0087$) and CD4% (19.1% vs. 28.1%; $p<.0001$). The mean nadir CD4 count (600.6 vs. 876.9 cells/ mm^3 ; $p=.0006$) and mean nadir CD4% (17.9% vs. 25.6%; $p<.0001$) were also significantly lower among the elevated APRI group.

Comparisons of medication use by APRI group show that a lower proportion of subjects with elevated APRI had prior ARV use compared to those with APRI ≤ 1.5 (65.6% vs. 85.3%; $p=.0053$) (Table 4). The prevalence of elevated APRI varied significantly by current ARV regimen ($p=.0002$): 8.0% among children on no ARV, 3.2% among children on non-protease inhibitor (PI) regimens, and 1.5% among children on PI-based regimens. Additionally, those with elevated APRI had a shorter mean duration of PI use (498.4 vs. 1114.0 days; $p=.0008$). Among the 542 subjects receiving a PI-containing regimen at APRI measurement, the most commonly received PIs were lopinavir/ritonavir (47.6%), nelfinavir (36.0%) and full-dose ritonavir (11.6%); only 1.3% received regimens with more than one PI. A higher proportion of those with APRI > 1.5 used potentially hepatotoxic non-ARV medications (75.0% vs. 48.8%; odds ratio [OR] = 3.2; $p=.0037$). The two groups did not differ significantly in terms of use of potentially hepatotoxic ARV medications overall, though didanosine use was less common among those with elevated APRI.

The relatively small number of events precluded full multivariable analysis but limited logistic regression modeling was undertaken to explore the association of younger age with elevated APRI. When elevated APRI was regressed on age, the odds ratio (OR) of 0.98 per one year increase in age was significant ($p < 0.0001$), and this association was unchanged when any ARV use, any toxic ARV use or any toxic medication use was added individually to the model. However, when log HIV viral load and age were in the model together, age was no longer significant (adjusted OR 0.99, $p = 0.12$) but log viral load had a large and significant effect (adjusted OR 3.55 per one log increase, $p < 0.0001$).

DISCUSSION

We report the first study of APRI elevation, a non-invasive marker of liver fibrosis, in a perinatally HIV-infected pediatric cohort. In this cohort of Latin American children, 3.2% had an APRI above 1.5, a threshold that has been associated with advanced liver fibrosis in adults with HIV-HCV co-infection and in children with viral hepatitis and other liver disorders [12–14, 19–22]. The risk of elevated APRI was increased in HBV co-infected, but not HCV co-infected children; however, the burden of known viral hepatitis in this cohort was very low overall, and excluding children with known viral hepatitis did not affect the estimated prevalence of elevated APRI. The rate of elevated APRI in this pediatric cohort appears consistent with rates of 3.0–3.9% reported in several studies of HIV-infected adults [10, 15, 18] but lower than the 8% rate observed in one adult study [11].

The factors associated with elevated APRI were largely indicators of poor HIV disease control, including high VL, low CD4, and lack of ART. The findings of a lower rate of elevated APRI among children who have been on HAART for 6 months (1%) and no cases of elevated APRI among those who achieve virologic suppression after 6 months of HAART add further strength to this interpretation. The association of younger age with elevated APRI that was observed in bivariate analyses did not persist in logistic regression modeling that adjusted for HIV viral load, strongly suggesting that the age effect was due to confounding by VL. These findings are also consistent with findings from studies of HIV mono-infected adults in which higher viral load, as well as lower CD4 counts (in some of the studies), were associated with elevated APRI [10–11, 18].

Reduction in elevated APRI rates with effective HIV treatment may mean that liver fibrosis will become less of a problem for perinatally infected children who face a lifetime of infection and ART. However, the need for treatment of comorbidities may entail use of potentially hepatotoxic medications, which appear to increase the risk of elevated APRI in the present study by three-fold. In adults, HAART use was associated with a reduction in mean APRI over time in those with HIV mono-infection, but with increased mean APRI over time in those with HIV-HCV co-infection [15]. Furthermore, complications may only emerge after prolonged use of individual ARV drugs or combinations, as exemplified by non-cirrhotic portal hypertension after prolonged didanosine use in adults and at least one perinatally infected child [27–28]. It is noteworthy that didanosine use in the current analysis was less common in those with APRI elevation. While the dominant effect of HAART appears to be beneficial for liver outcomes (as measured by APRI), the potential for toxicity related to specific agents and comorbidities merits evaluation in long-term studies.

This study has the limitations of an observational cohort in which treatments are not assigned, but it has the advantage of prospective, protocol-driven collection of data and evaluations. It is possible that some children had undetected HCV or HBV infection, since the protocol did not require viral hepatitis testing, but this number is expected to be small. APRI is one among many measures proposed for non-invasive assessment of liver fibrosis.

Other studies in HIV-infected adults, for instance, have found that FIB-4 has been a useful predictor of liver status and even mortality [17, 29]. However, FIB-4, which uses age in its calculation, has never been used or validated in any population under 18 years of age, making it a less appropriate choice for assessing for evidence of liver fibrosis in children.

While the finding of elevated APRI does not prove the presence of liver fibrosis in these HIV mono-infected children, APRI has been validated against liver biopsy findings for identifying liver fibrosis in adults with HCV infection and HIV-HCV co-infection and in children with other conditions. In children with viral hepatitis, elevated APRI has high specificity but low sensitivity when compared to liver biopsy findings: specificity of 90% and 100% and sensitivity of 47% and 18% for APRI > 0.5 and APRI > 1.5, respectively [19]. The performance characteristics for APRI as a fibrosis indicator in that pediatric study raise concerns about possible liver fibrosis in HIV-infected children with APRI > 1.5 in the current study and suggest that the true prevalence of liver fibrosis in HIV-infected children could be significantly greater than the 3% estimate we report. Studies that use elastography or even liver biopsy in HIV-monoinfected children with persistently elevated APRI will be important for evaluating the risk and outcome of liver fibrosis and for validating the use of APRI in children for this purpose.

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Table 1

Participant characteristics overall and according to initial APRI

Characteristic ¹	Overall N=1012	Elevated Initial APRI (>1.5)		p-value ²
		Yes N=32	No N=980	
Age (years)				
Mean (SD)	6.3 (4.1)	3.3 (2.9)	6.4 (4.1)	<0.0001
Median	5.4	2.2	5.5	
Country, N (%)				
Argentina	70 (6.9)	1 (3.1)	69 (7.0)	0.0004
Brazil	695 (68.7)	19 (59.4)	676 (69.0)	
Jamaica	22 (2.2)	1 (3.1)	21 (2.1)	
Mexico	147 (14.5)	1 (3.1)	146 (14.9)	
Peru	78 (7.7)	10 (31.3)	68 (6.9)	
Sex, N (%)				
Female	537 (53.1)	15 (46.9)	522 (53.3)	0.48
Male	475 (46.9)	17 (53.1)	458 (46.7)	
BMI-for-age z-score				
Mean (SD)	0.1 (1.2)	0.3 (1.3)	0.1 (1.2)	0.24
Median	0.1	0.2	0.1	
Past or current Hepatitis B diagnosis, N (%)	4 (0.4)	2 (6.3)	2 (0.2)	0.0056
Past or current Hepatitis C diagnosis, N (%)	6 (0.6)	0 (0.0)	6 (0.6)	1.0
CDC HIV disease classification, N (%)				
N	133 (13.2)	6 (18.8)	127 (13.0)	0.26
A	222 (22.0)	3 (9.4)	219 (22.4)	
B	312 (31.0)	10 (31.3)	302 (30.9)	
C	341 (33.8)	13 (40.6)	328 (33.6)	

APRI = aspartate aminotransferase-to-platelet ratio index; N = number; SD = standard deviation; BMI = body mass index.

¹ BMI missing for 2 subjects with elevated APRI and 6 subjects with APRI that were not elevated; CDC classification missing for 4 subjects with APRI that were not elevated and 0 subjects with elevated APRI; missing were excluded from p-value calculations.² P-values for continuous variables are from Student's t-test; p-values for categorical variables are from Fisher's exact test.

Table 2

Laboratory evaluations overall and according to initial APRI

Characteristic ¹	Overall N=1012	Elevated Initial APRI (>1.5)		p-value ²
		Yes N=32	No N=980	
APRI:				
Mean (SD)	0.5 (1.3)	4.8 (6.1)	0.3 (0.2)	---
Median	0.3	2.9	0.3	
Q1, Q3	0.2, 0.4	1.9, 4.8	0.2, 0.4	
AST (mU/mL):				
Mean (SD)	46.9 (86.6)	278.2 (421.3)	39.4 (18.0)	0.0031
Median	36.0	114.5	36.0	
Q1, Q3	30.0, 44.0	44.0, 372.5	30.0, 43.0	
AST/ULN _{AST} :				
Mean (SD)	1.1 (1.7)	6.1 (7.8)	0.9 (0.4)	0.0006
Median	0.8	2.5	0.8	
Q1, Q3	0.7, 1.1	1.2, 8.1	0.7, 1.1	
Platelet (10 ³ /mm ³):				
Mean (SD)	306.1 (111.3)	148.1 (135.8)	311.3 (106.6)	<0.0001
Median	295.0	79.5	298.0	
Q1, Q3	238.5, 363.0	58.0, 230.5	243.0, 364.5	
ALT (mU/mL):				
Mean (SD)	37.9 (63.6)	227.7 (269.4)	31.7 (25.5)	0.0003
Median	28.0	105.5	27.0	
Q1, Q3	18.0, 39.0	35.0, 294.0	18.0, 38.0	
Cholesterol (mg/dL):				
Mean (SD)	153.6 (45.4)	121.5 (39.7)	154.6 (45.2)	0.0002
Median	151.0	133.0	152.0	
Q1, Q3	127, 181	95.0, 151.0	127.0, 182.0	
Triglycerides (mg/dL):				
Mean (SD)	123.2 (81.2)	129.7 (85.7)	123.1 (81.1)	0.68
Median	109.0	115.0	109.0	
Q1, Q3	74.0, 152.0	68.0, 144.0	74.0, 152.0	

APRI = aspartate aminotransferase-to-platelet ratio index; N = number; SD = standard deviation; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

¹ Q1 and Q3 correspond to 25th and 75th percentile of distribution. Missing values for cholesterol (67), triglycerides (73), and ALT (4).

² P-values are from Student's t-test.

Table 3

HIV-related laboratory evaluations measured at time of initial APRI

Characteristic ¹	Overall ¹ N=1012	Elevated Initial APRI (>1.5)		p-value ²
		Yes N=32	No N=980	
Log ₁₀ HIV RNA (copies/mL)				
Mean (SD)	3.5 (1.4)	5.2 (0.8)	3.4 (1.4)	<0.0001
Median	3.6	5.2	3.5	
HIV RNA <400 copies/mL, N (%)	354 (35.3)	0 (0.0)	354 (36.4)	<0.0001
Log ₁₀ peak HIV RNA (copies/mL)				
Mean (SD)	5.3 (1.0)	5.8 (0.8)	5.3 (1.0)	0.0039
Median	5.4	5.8	5.4	
CD4 count (cells/mm ³)				
Mean (SD)	1043.0 (657.1)	743.3 (528.5)	1052.9 (658.8)	0.0087
Median	893.0	581.5	898.0	
CD4 %				
Mean (SD)	27.8 (9.8)	19.1 (11.1)	28.1 (9.6)	<0.0001
Median	27.5	17.5	28.0	
Nadir CD4 count (cells/mm ³)				
Mean (SD)	868.0 (571.8)	600.6 (403.5)	876.9 (574.5)	0.0006
Median	764.0	560.5	767.0	
Nadir CD4 %				
Mean (SD)	25.3 (10.1)	17.9 (10.2)	25.6 (10.0)	<0.0001
Median	25.0	16.0	26.0	

APRI = aspartate aminotransferase-to-platelet ratio index; N = number; SD = standard deviation.

¹ Missing values for HIV RNA (9), Log₁₀ peak HIV RNA (3), CD4 count (11), nadir CD4% (112) and nadir CD4 % (11)² P-values are from Student's t-test.

Table 4

Medication use overall and according to initial APRI

Characteristic*	Overall N=1012	Elevated initial APRI (>1.5)		P value ¹
		Yes N=32	No N=980	
ARV at any time, N (%)	857 (84.7)	21 (65.6)	836 (85.3)	0.0053
ARV Regimen at APRI measurement: N (%)				
PI-containing	542 (53.6)	8 (25.0)	534 (54.5)	0.0002
Non-PI-containing	283 (28.0)	9 (28.1)	274 (28.0)	
No ARVs	187 (18.5)	15 (46.9)	172 (17.6)	
Cumulative Duration of PI- containing ART (days):				
Mean (SD)	1098.1 (726.7)	498.4 (558.7)	1114.0 (724.3)	0.0008
Median	1048.0	412.5	1071.5	
Past or current use of potentially hepatotoxic ARV, N (%)	925 (91.4)	27 (84.4)	898 (91.6)	0.19
Ever used didanosine?, N (%)	530 (52.4)	8 (25.0)	522 (53.3)	0.0019
Past or current use of potentially hepatotoxic non-ARV medications, N (%)	502 (49.6)	24 (75.0)	478 (48.8)	0.0037

APRI = aspartate aminotransferase-to-platelet ratio index; N = number; ARV = antiretroviral (drug); PI = protease inhibitor; SD = standard deviation.

¹ P-values for continuous variables are from t-test; p-values for categorical variables are from Fisher's Exact Test.