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Original Article

Assessment of Liver Dysfunction Using Combination Biomarkers in Children Living with HIV Infection

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ABSTRACT

Aim: Overall, around 14-18% of non-acquired immunodeficiency syndrome-related deaths are due to liver disease in human immunodeficiency virus (HIV) patients. With a prevalence of 15%, cirrhosis appears to be a more serious consequence. There are many non-invasive markers for assessing liver fibrosis but their utility in pediatric HIV patients has not been explored.

Materials and Methods: To assess the occurrence of liver dysfunction and the levels of combination biomarkers of liver dysfunction [aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) index] in HIV positive children. A total of 44 HIV positive children aged <15 years attending the antiretroviral therapy (ART) clinic were enrolled and evaluated for liver dysfunction using non-invasive biomarkers and ultrasonography (USG) scoring.

Results: Deranged biomarkers-AST/ALT ratios, APRI scores, and FIB-4 index were found in 95%, 6.8%, and 4.5% children respectively. 7% of children showed moderate to severe liver fibrosis on USG scoring. Also, anemia, nevirapine in ART regimen, longer ART duration, immunosuppression, and lower body mass index values were found as risk factors associated with deranged biomarkers.

Conclusion: Hepatic dysfunction is reflected by deranged AST/ALT ratios among HIV-positive children in this study. Further, the elevated APRI scores and FIB-4 index in some cases signal evolving liver fibrosis.

Keywords: HIV, hepatic dysfunction, liver fibrosis, biomarkers, APRI score, FIB-4 index

Introduction

Liver disease has emerged as the most common non-acquiredimmunodeficiency syndrome-related cause of death among human immunodeficiency virus (HIV)-positive patients, accounting for 14-18% of all deaths (1). Nearly half of deaths among hospitalized HIV-positive patients in the highly active antiretroviral therapy (ART) era have been attributed to liver diseases, which range from asymptomatic mild elevations of liver enzymes to cirrhosis and end-stage liver disease with all its complications (1). Liver cirrhosis is a more serious consequence and the prevalence of significant liver fibrosis in those with HIV approaches 15% (2). Patients with HIV have a proclivity to develop liver cirrhosis (2,3).

Liver biopsy is currently considered the gold standard for fibrosis assessment but carries many shortcomings (cost, invasiveness, and complications) (4). Recently, many non-invasive markers for assessing liver fibrosis have been developed for the assessment of liver fibrosis (studied in hepatitis B patients) (4). When liver disease is suspected, non-invasive screening methods such as the FibroScan may

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be beneficial but in many circumstances are prohibitively expensive and/or not accessible for children (5). Combination biomarkers, such as the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST-to-platelet ratio index (APRI), and the fibrosis-4 (FIB-4) index have been reported as potentially useful for predicting hepatic fibrosis in children with non-alcoholic fatty liver disease (6), chronic viral hepatitis (7), or chronic liver disease from various etiologies.

There is a paucity of literature from India on liver dysfunction in children living with HIV. Also, the role of combination biomarkers in identifying liver disease in children with HIV is still not clear. In this paper, we have assessed the existence of liver dysfunction in Indian children living with HIV and also evaluated them for the presence of liver fibrosis using non-invasive markers of liver dysfunction.

Materials and Methods

This cross-sectional study was conducted at the ART clinic of the Department of Pediatrics at an institute located in New Delhi, India, after taking permission from the Institutional Ethics Committee. This study was conducted from March, 2018 to March, 2019 and a total of 44 HIV-positive children were enrolled and evaluated for liver dysfunction. The objective of this study was to assess the occurrence of liver dysfunction in children living with HIVand to assess the levels of combination biomarkers of liver dysfunction in these children. Children more than 18 months of age were confirmed to have HIV using three ELISA tests as per National AIDS Control Organization guidelines and those less than 18 months of age were diagnosed by virological tests [DNA Polymerase chain reaction (PCR)] from dried blood spots. All children less than 15 years of age with HIV were invited to be a part of this study. After taking written informed consent and assent (for children >7 years of age) from the parents or caregivers of the children, basic patient information such as their name, age, sex, demographic details, clinical history and examination, anthropometric measurements, immunological data, and details of antiretroviral treatment were recorded as per pre-structured pro-forma. All opportunistic infections were investigated and actively treated before ART commencement.

All HIV confirmed children attending the ART clinic, irrespective of their ART status, were enrolled and screened for liver dysfunction using non-invasive biomarkers of liver dysfunction. The liver function tests were evaluated using serum bilirubin, ALT, AST, and serum proteins levels. Abnormal liver enzymes aredefined as ALT or AST enzyme levels >1.25 times the upper limit of normal (ULN). The liver enzyme abnormalities were graded as follows; grade 1 hepatotoxicity: ALT or AST level 1.25 to 2.5 times ULN, grade 2 hepatotoxicity: ALT or AST level 2.6 to 5 times ULN, grade 3 hepatotoxicity: ALT or AST level 5.1 to 10 times ULN, grade 4 hepatotoxicity: ALT or AST level >10 times ULN (8,9). A routine hemogram including platelet counts and CD4 counts was obtained.

Also, any history of jaundice was recorded, and viral markers were taken in order to assess for the presence of any co-infection with hepatitis B or C.

Computation of biomarkers of liver dysfunction was carried out. These included the AST/ALT ratios; a value of >0.7 was considered abnormal, the APRI score was calculated via the formula [(AST/ULN)/platelet count (10^9/L)]×100; a value of >1.5 suggested liver fibrosis, and also the FIB-4 index was calculated via the formula age (yrs)×AST level/platelet count×√ALT; a value of ≤1.3 has been reported to have a 90% negative predictive value for cirrhosis. These cut-off values were based on previous studies by Siberry et al. (10), Kapogiannis et al. (11), Pokorska-Śpiewaket al. (12), Aurpibul et al. (13), Iacobellis et al. (14), and Shah et al. (15).

The relationships between abnormal AST/ALT ratios, abnormal APRI scores, and abnormal FIB-4 index values with the individual risk factors of liver dysfunction [mode of acquisition of HIV, the type of ART, duration of ART, level of immunosuppression, presence of anemia, and body mass index (BMI)] were assessed.

In cases of abnormal biomarkers of liver dysfunction, a routine ultrasound scan was performed. An ultrasound score was allotted based on the presence of 6 abnormal ultrasound variables (presence of liver enlargement, irregular liver surface, abnormal liver echotexture, blunted liver edge, the presence of splenomegaly, and dilated portal veins). Each variable was assigned a score of 1 and a total resultant score was calculated for all these patients. The presence of liver fibrosis was assessed using the allotted score.

Statistical Analysis

Data entry was performed using a Microsoft Excel sheet and analyzed statistically using SPSS software 17. Appropriate tests with a 90% confidence interval were applied. Qualitative variables were expressed as frequency and percentage. Quantitative variables were expressed as mean, median, and inter-quartile ranges. Covariates considered as potential predictors of elevated APRI were

identified using appropriate statistical tests and significance was set at a p-value of <0.05.

Results

During the study period, a total of 44 HIV-positive children were recruited into this study. Out of these 44 children, 40 (91%) had acquired HIV from their mother, 2 (5%) acquired it from a blood transfusion and 1 (2%) from an infected needle. In the one other case, the status of the parents was not known as the child was adopted by an non-governmental organizations. On clinical examination, pallor was found in 13 (30%), hepatomegaly in 12 (27%), and lymphadenopathy in 6 (14%), while the commonly seen clinical symptoms were recurrent cough (16%), recurrentdiarrhea (14%), and abdominal pain (8%). Clinically visible jaundice was found in 2 (4.5%) patients only. Out of the 44 children, 25 (56.8%) were on zidovudine, 23 (52,3%) were on efavirenz, 14 (31.8%) on abacavir, 13 (29.5%) were on nevirapine, 5 (11.4%) were on tenofovir, and 8 (18.2%) were on protease inhibitor-based regimen. Out of the 44 children, 2 (4%) were in stage IV, 6 (14%) were in stage III, 7 (16%) were in stage II, and 29 (66%) were in Stage I of the HIV illness [as per World Health Organization (WHO) classifications].

On assessing the liver function tests, the mean value of serum bilirubin was 0.55 [standard deviation (SD) 0.3], the mean serum ALT level was 31.93 (SD 21), and the mean serum AST level was 37 (SD 16). The mean value of total serum protein was 7.5 (SD 0.75) and serum albumin was 4.1 (SD 0.49). Theserum bilirubin level was elevated in only 2 patients (4.5%), serum ALT level was elevatedin 7 (16%) patients, and serum AST level was elevated in 8 patients (18%) (Table I). Out of the 7 patients who had elevated ALT, 5 patients had grade 1 hepatotoxicity and 2 patients had grade 2 hepatotoxicity, whereas all 8 patients with elevated AST had grade 1 hepatotoxicity.

Out of the 44 children, 42 (95%) had abnormal AST/ALT ratios. Out of these 42 children, 29 (69%) were males and 13 (31%) were females. There was no statistical difference between males and females in terms of abnormal ALT/AST ratios (p-value 0.57) (Table II). Fifteen out of the 16 (94%) children with anemia had an abnormal AST/ALT ratios. All 13 children who were on the nevirapine-based ART regimen had an abnormal AST/ALT ratio. The duration of ART for more than 1 year was significantly associated with abnormal AST/ALT ratios. We found that ART initiation was significantly associated with abnormal AST/ALT ratios. Seventeen out of the 18 (94.4%) children with CD4 counts of less than 500 and 25 out of the 26 (96%) children with CD4 counts of more than 500 had an abnormal AST/ALT ratio. All 9 children with BMI less than the 5th percentile had an abnormal AST/ALT ratio (Table III).

Table I. Liver function test estimates

Lab. parameters	Elevated (n) (%)	Normal (n) (%)	Mean (SD)
Serum bilirubin			
<5 years	1	3	
5-10 years	0	16	
>10 years	1	23	
Total	2 (4.5)	42 (95.5)	0.55 (0.3)
***Serum AST levels**			
<5 years	1	3	
5-10 years	4	12	
>10 years	3	21	
Total	8 (18)	36 (82)	37.52 (16)
***Serum ALT levels**			
<5 years	0	4	
5-10 years	4	12	
>10 years	3	21	
Total	7 (16)	37 (84)	31.93 (21)

*Cut-offs as per the Harriet Lane handbook 20th edition and Abnormal liver enzymes (ALT/AST) of >1.25 times the ULN (upper limit of normal).
SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Out of the 44 children, 3 (7%) had abnormal APRI scores, all of these were males and 2 (5%) had a FIB-4 index of >1.3, with both of these being males. Out of the 3 children with APRI >1.5, two were more than 5 years of age. This was significant (p-value<0.001). Also, 2 out of the 3 with elevated APRI had anemia with hemoglobin less than 11 gm/dL.This was significant (p-value=0.004). Out of the 13 children on the nevirapine-based ART regimen, none had an abnormal APRI score. There were significantly more children with APRI >1.5 among those on ART for more than 1 year. Also, age at ART initiation was not significant in APRI elevation. Two out of the 18 (11%) children with CD4 counts of less than 500 and only 1 child with CD4 count of more than 500 had an abnormal APRI score. Those with CD4 counts of more than 350 cells/cumm had lower APRI scores. Low BMI (below the 5th percentile) was not significantly different in the two APRI groups (Table IV).

Only 2 (5%) children out of the 40 aged more than 5 years old had an abnormal FIB-4 index. None of the children less than 5 years had an abnormal FIB-4 index. Only 1 child out of the 16 (6.3%) children with anemia had an abnormal FIB-4 index. Out of the 13 children on the nevirapine-based ART regimen, none had an abnormal FIB-4 index. This was statistically significant. Only 1 child out of the 34 (2.9%) with an ART duration of more than 1 year had an abnormal FIB-4 index. No child with age at ART initiation of less than 5 years had an abnormal FIB-4 index. Two out of the 22 (9%) children with age at ART initiation of more than 5 years had an abnormal FIB-4 index. No child with CD4 counts of more than 350 had an abnormal FIB-4 index. Only 1 child out of the 9 (11%) children with BMI less than the 5th percentile had an abnormal FIB-4 index. This was statistically significant (Table V).

Table II. Showing abnormal biomarkers of liver dysfunction in the enrolled children (n=44)

	Males	Females	Total
AST/ALT ratios >0.7	29	13	42
APRI score >1.5	3	0	3
FIB-4 index >1.3	2	0	2

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, APRI: AST-to-platelet ratio index, FIB-4: Fibrosis-4

Table III. Showing the relation between abnormal AST/ALT ratio (>0.7) with the risk factors of liver dysfunction in the enrolled children (n=42)

Risk factors of liver dysfunction	AST/ALT ratio >0.7 n	AST/ALT ratio <0.7 n	p-values
Age <5 yrs (n=4)	4	0	0.13
Age >5 yrs (n=40)	38	2	<0.001
Anemia Hb<11 (n=16)	15	1	0.001
Nevirapine based ART (n=13)	13	0	0.001
Duration of ART (yrs)			
<1 (n=10)	9	1	0.02
1-5 (n=18)	18	0	0.001
>5 (n=16)	15	1	0.001
Age at ART initiation (yrs)			
<5 (n=22)	21	1	0.001
>5 (n=22)	21	1	0.001
Immunosuppression			
CD4 counts <350 (n=9)	8	1	0.039
CD4 counts 350-500 (n=9)	9	0	0.004
CD4 counts >500 (n=26)	25	1	<0.001
BMI <5th percentile (n=9)	9	0	0.004

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ART: Antiretroviral therapy, BMI: Body mass index, Hb: Hemoglobin

Table IV. Showing the relation between abnormal APRI (>1.5) with the risk factors of liver dysfunction in recruited children (n=3)

Risk factors of liver dysfunction	APRI >1.5 n	APRI <1.5 n	p-values
Age <5 yrs (n=4)	1	3	0.625
Age >5 yrs (n=40)	2	38	<0.001
Anemia Hb<11 (n=16)	2	14	0.004
Nevirapine based ART (n=13)	0	13	0.001
Duration of ART (yrs)			
<1 (n=10)	2	8	0.109
1-5 (n=18)	0	18	0.001
>5 (n=16)	1	15	0.001
Age at ART initiation (yrs)			
<5 (n=22)	1	21	0.001
>5 (n=22)	2	20	0.001
Immunosuppression			
CD4 counts <350 (n=9)	2	7	0.18
CD4 counts 350-500 (n=9)	0	9	0.004
CD4 counts >500 (n=26)	1	25	<0.001
BMI <5th percentile (n=9)	2	7	0.18

APRI: AST-to-platelet ratio index, ART: Antiretroviral therapy, BMI: Body mass index

Table V. Showing relation between abnormal FIB-4 index (>1.3) with the risk factors of liver dysfunction in the enrolled children (n=2)

Risk factors of liver dysfunction	FIB-4 index (>1.3) (%)	FIB-4 index (<1.3) (%)	p-values
Age <5 yrs (n=4)	0	4	0.125
Age >5 yrs (n=40)	2	38	<0.001
Anemia Hb<11 (n=16)	1	15	0.001
Nevirapine based ART (n=13)	0	13	0.001
Duration of ART (yrs)			
<1 (n=10)	1	9	0.021
1-5 (n=19)	0	18	0.001
>5 (n=15)	1	15	0.001
Age at ART initiation (yrs)			
<5 (n=22)	0	22	0.001
>5 (n=22)	2	20	0.001
Immunosuppression			
CD4 counts <350 (n=9)	2	7	0.18
CD4 counts 350-500 (n=9)	0	9	0.004
CD4 counts >500 (n=26)	0	26	<0.001
BMI <5th percentile (n=9)	1	8	0.039

ART: Antiretroviral therapy, FIB-4: Fibrosis-4, BMI: Body mass index, Hb: Hemoglobin

Forty-one out of the 44 (93%) children had an ultrasound score of 0-1 indicating mild or no fibrosis, which was significantly more than the 3 (7%) children with an ultrasound score of 2-3.

Co-infection with hepatitis B and/or hepatitis C-only 1 child was found to be positive for hepatitis B. No child was positive for hepatitis C.

Discussion

This cross-sectional study enrolled 44 children with HIV and evaluated them for liver dysfunction using non-invasive biomarkers of liver dysfunction and an ultrasound scoring system.

Forty out of the 44 (91%) children had perinatally acquired HIV highlighting the mother-to-child transmission of HIV. It is well known that more than 95% of pediatric HIV cases are acquired via vertical transmission. Many studies have shown the same. A study by Kapogiannis et al. (11) showed that 65% of HIV-positive children had perinatally acquired HIV infections. The study by Aurpibulet al. (13) showed 98% were perinatally infected. Studies by Siberry et al. (10) in Latin America and by Siberry et al. (16) in the United States were performed only in perinatally acquired HIV children. In two children in our study, the mother was negative and these children had acquired their infection via blood transfusion. In one case, the child was an intravenous drug user and had acquired the infection by a parenteral route.

On analyzing liver functions, we found that serum bilirubin level was elevated in only 2 (4.5%) cases, whereas ALT was elevated in 7 (16%) cases and AST was elevated in 8 (18%) cases. The levels of ALT were seen to be higher in this study compared to the study carried out on south-east Asian children (13), the possible explanation could be the variable stage of HIV and the poor nutritional status of the patients enrolled in this study. The increase in ALT levels was found to be more (32%) in South African children as 74% of those patients were in WHO stage 3 or 4 of the HIV in that study (17).

Out of the 44 children, 42 (95.5%) showed abnormal AST/ALT ratios, only 3 (7%) showed abnormal APRI scores and only 2 (4.5%) showed abnormal FIB-4 index. This was seen because most of the children had been on ART for more than 1 year at the time of recruitment. It is well known that combination ART is protective against liver enzyme elevations. This was also seen because most children were diagnosed early and started on ART early in the course of their HIV disease. The findings in our study are similar to the study by Aurpibul et al. (13) in Asian children, where after ART initiation, AST/ALT ratios >0.7 were seen in 845 out of 852 (99%) children, APRI scores >1.5 were seen in 27 out of 852 (3.2%) children, and an FIB-4 index >1.3 was seen in 6 out of 852 (0.7%) children.

We found that 15 out of the 16 (94%) children with anemia had an abnormal AST/ALT ratio, which shows the presence of anemia is related to liver dysfunction. This is because children with anemia have more advanced HIV disease, malnutrition, and concomitant infection, thus forming a vicious cycle in them and thus making them unable to compensate for the physiological stress caused by the inflammatory response to the initial treatment. This finding is similar to the study by Aurpibul et al. (13) on Asian children.

It is wellknown that liver enzyme elevations are common in HIV infections. In many HIV-positive patients with elevated liver enzymes, the elevation is not explained

by an identified underlying liver disease or toxin and thus may directly occur either due to antiretroviral drug toxicity or the HIV infection itself. Studies from developed countries have reported correlations between HIV viral load and serum aminotransferase levels in HIV-positive antiretroviral (ART)-naive patients (18). There are no similar studies from India for comparison.

However, one study conducted in Uganda found that the risk of clinically significant hepatotoxicity was low, even in HIV-positive patients on ART and among HIV/hepatitis B virus (HBV) co-infected persons. Nevertheless, there is emerging evidence that HIV infection, even in the absence of ART toxicity and other cofactors, may have a direct impact on liver fibrosis pathogenesis, and on further progression to liver disease (19,20).

Thus, it appears that children with perinatally acquired HIV develop overt liver fibrosis due to early exposure to HIV and this manifests in their adult life. During childhood, these subtle hepatic enzymes indicate an ongoing necro-inflammatory process in the liver.

In this study, we tried to explore any significant associations with elevated AST/ALT ratios. Thirty-eight children out of the 40 (95%) aged more than 5 years old had an abnormal AST/ALT ratio (p-value<0.001). Fifteen out of the 16 (94%) children with anemia had an abnormal AST/ALT ratio. All 13 children on the nevirapine-based ART regimen had an abnormal AST/ALT ratio. ART initiation was significantly associated with an abnormal AST/ALT ratio. Seventeen out of the 18 (94.4%) children with CD4 counts of less than 500 and 25 out of the 26 (96%) children with CD4 counts of more than 500 had an abnormal AST/ALT ratio. Children with better CD4 counts because of ART had significantly elevated ALT/AST ratios. All 9 children with BMI less than the 5th percentile had an abnormal AST/ALT ratio. Thus, it appears that older age, ART (especially nevirapine), and low BMI are associated with abnormal AST/ALT ratios.

Abnormal AST/ALT ratios were seen in almost all patients in this study. An AST/ALT ratio of >1 is considered significant in predicting advanced liver disease in adult patients, whereas in this study, the cut-off ratio of 0.7 was taken to be significant after being derived from similar pediatric studies. Although this test is cost-effective and easily available, it has less specificity according to various studies (21,22) carried out in the past on adult patients. However, the higher ratioused in adult studies could be considered to identify liver diseases in pediatric patients living with HIV.In a meta-analysis of 40 studies, investigators concluded that APRI scores greater than 0.7 had a sensitivity of 77% and a specificity of 72% in predicting significant hepatic fibrosis (23). The higher the value of the APRI (>1.5), the greater its positive predictive value (and its ability to rule in cirrhosis). In our study out of the 44 children, 3 had APRI of more than 1.5. Also, as thrombocytopenia is common among HIV-positive patients and platelet count is used in APRI calculation, higher APRI values in HIV-positive individuals may be due to their HIV infection rather than the underlying liver disease. Multiple factors like chronic HIV infection and thrombocytopenia contribute to negatively affect APRI scores.

There were significantly more children with APRI less than 1.5 among those who had been on ART for more than 1 year. However, age at ART initiation was not significant on APRI elevation. Those with CD4 counts of more than 350 cells/cumm had lower APRI scores. Lower BMI than the 5th percentile was not significantly different in those with elevated APRI.Thus, it appears that the initiation of ART is protective and is associated with lower APRI scores. ART was protective against liver dysfunction with studies by Kapogiannis et al. (11) in the United States, Aurpibul et al. (13) in Asia, Siberry et al. (10) in Latin America, Siberry et al. (16) in the United States, and Pokorska-Śpiewaket al. (12) in Poland showing that longer and better ART led to lower APRI scores.

Next in this study, the FIB-4 index was estimated. Only 2 children out of the 40 (5%) aged more than 5 years had an abnormal FIB-4 index. None of the children less than 5 years had an abnormal FIB-4 index. Out of the 13 children on the Nevirapine-based ART regimen, none had an abnormal FIB-4 index. This was statistically significant. No child with age at ART initiation of less than 5 years had an abnormal FIB-4 index. Two out of the 22 (9%) children with age at ART initiation of more than 5 years had an abnormal FIB-4 index. No child with CD4 counts more than 500 had an abnormal FIB-4 index showing that the immunocompetent state is associated with better control of HIV infection and thus reduces the risk of liver fibrosis. The study by Kapogiannis et al. (11) highlighted the same.

Thus, it appears that older children (more than 5 years old) with delayed ART initiation have abnormal FIB-4 index.

Hepatic echotexture was assessed in these children and a USG scoring as per Afzalet al. (24) was carried out to assess the extent of liver fibrosis. Forty-one out of the 44 (93%) children had an ultrasound score of 0-1 indicating mild to no fibrosis.

In our study, only 1 child was positive for hepatitis B and had acquired this infection through intravenous drug

use. All the biomarkers including the AST/ALT ratio, APRI, and FIB-4 were abnormal in this child. It is well known that HIV/HBV co-infection is associated with liver dysfunction. This has been highlighted in various studies by Shiferaw et al. (25) in Ethiopia, Siberry et al. (10) in Latin America, and Pokorska-Śpiewak et al. (12) in Poland.

Study Limitations

The small number of children in this study was a limiting factor.

Conclusion

It appears that chronic HIV infection is associated with hepatic dysfunction. This was reflected by abnormal AST/ALT ratios in a large number of children in this study. However, the high cut-off value for the AST/ALT ratio has to be reconsidered in children. Furthermore, elevated APRI scores and FIB-4 index in some of them signal evolving liver fibrosis. None of these were hepatitis C virus infected. Thus, HIV infection caused abnormalities in liver function through multiple pathogenetic mechanisms. A longer follow-up with a large number of children may reveal many more children with HIV-associated liver diseases.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted at the ART clinic of the Department of Pediatrics at an institute located in New Delhi, India, after taking permission from the Institutional Ethics Committee (protocol no: 19/9/17, dated: 27.10.2017).

Informed Consent: Informed consent was obtainedfrom all patients included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.K., Design: R.K., Data Collection and/or Processing: S.Y., Analysis and/or S.Y., Interpretation: S.Y., R.K., Literature Search: D.K., Writing: D.K.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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