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Liver aminotransferases in under-five HIV-positive children on HAART

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Abstract

Background: Higher mortality rates were reported in developing countries during early months of HAART initiation than in developed countries. The study aimed at assessing the effect of Highly Active Antiretroviral Therapy (HAART) on liver function of under-fives.

Method: Two hundred and thirty-eight under-fives children were enrolled from five hospitals in Southern Nigeria. Ethical permission and written consent were obtained. Group A involved 91 seropositive-children on HAART regimen while Group B1 involved 24 seronegative-infants who received nevirapine from birth till age 6-week. Group B2 (18) and B3 (48) involved seronegative-children who received co-trimoxazole and were 6-month and 18-month old respectively. Group C involved 11 seropositive-children who received co-trimoxazole only. Group D involved 46 seronegative-children who served as the control group. A 2ml blood sample was obtained from each participant during first phase of the study and was analysed for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using kits manufactured by Randox®. Group A children returned for second and third phases of the study after 3-month and 6-month respectively. Data were analysed by using ANOVA.

Results: The results showed that ALT was highest in group A (12.8±11.0IU/L) suggesting hepatotoxicity while AST was highest in group B2 (35.4±53.1IU/L). Second phase, ALT and AST of group A were significantly reduced by 39.3% ($p<0.05$), 29.9% ($p<0.05$) respectively suggesting resolved hepatotoxicity. Third phase, ALT and AST were significantly reduced by 50.6% ($p<0.05$) and 32.2%($p<0.05$) respectively suggesting resolved hepatotoxicity.

Conclusion: Hepatotoxicity observed among HIV-infected children on HAART was resolved after 6-month of monitoring.

Keywords: *Under-five HIV children, ALT, AST, resolved hepatotoxicity, HAART*

Résumé

Contexte: Des taux plus élevés de mortalité ont été signalés dans les pays en voie de développement au cours des premiers mois d'initiation à l'HAART que dans les pays développés. L'étude visait à évaluer l'effet de la thérapie antirétrovirale hautement active (HAART) sur la fonction hépatique des enfants moins de cinq ans.

Méthode: Deux cent trente-huit enfants, moins de cinq ans, étaient enrôlés provenant de cinq hôpitaux dans le sud du Nigeria. Permission éthique et consentement écrits ont été obtenus. Groupe A compris 91 enfants séropositifs sur-traitement HAART tandis que le groupe B1 compris 24 enfants séronégatifs qui ont reçu la névirapine dès la naissance jusqu'à l'âge de 6 semaines. Le groupe B2 (18) et B3 (48) compris d'enfants séronégatifs qui ont reçu le co-trimoxazole et étaient de 6 mois et de 18 mois respectivement. Groupe C compris 11 enfants séropositifs qui ont reçu le co-trimoxazole seulement. Groupe D compris 46 enfants séronégatifs qui ont servi de groupe témoin. Un échantillon de 2 ml de sang a été obtenu provenant de chaque participant lors de la première phase de l'étude et a été analysé pour l'alanine amino-transférase (ALT) et aspartate amino-transférase (AST) en utilisant des kits fabriqués par Randox®. Les enfants du groupe A se sont retournés pour la deuxième et la troisième phase de l'étude, après 3 mois et 6 mois respectivement. Les données ont été analysées en utilisant ANOVA.

Résultats: Les résultats ont montré que ALT était le plus élevé dans le groupe A (12,8 ± 11.0IU / L) suggérant l'hépato-toxicité tandis que AST était le plus élevé dans le groupe B2 (35,4 ± 53.1IU / L). Deuxième phase, ALT et AST du groupe A ont été significativement réduites de 39,3% ($p<0,05$), 29,9% ($p<0,05$) suggérant respectivement hépato-toxicité résolu. Troisième phase, ALT et AST ont été

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significativement réduites de 50,6% (p <0,05) et 32,2% (p <0,05) suggérant respectivement hépato-toxicité résolu.
Conclusion: Hépato-toxicité observé chez les enfants infectés par le VIH sous l'HAART a été résolu après 6 mois de suivi.

Mots-clés: *Enfants VIH moins de cinq ans, ALT, AST, hépato-toxicité résolu, HAART*

Introduction

There were 570,000 AIDS-related deaths among children aged less than 15 years in sub-Saharan Africa in 2005. HIV disease progressed rapidly in children and AIDS-related mortality among infants was exceptionally high. Approximately more than 33% of untreated HIV- infected infants in the developing world died during the first year of life and greater than 50% died by the age of 2 years [1]. Sub-Saharan Africa was the worst-affected region, with an estimated 22.5 million people living with HIV-infection which was 67% of the global estimate. In sub-Saharan Africa, 1.3 million deaths occurred which was 72% of the global death. New HIV-infection was estimated at 1.8 million in sub-Saharan Africa [2]. Success of HAART in treatment of HIV infection resulted in prolonged lifespan and reduced mortality associated with HIV infection thereby requiring continuous use of HAART [3].

WHO commissioned systematic reviews on antiretroviral drug toxicities and laboratory monitoring strategies. The reviews highlighted some evidence gaps in the potential increased risk of toxicity associated with long-term use of antiretroviral drugs. The use of antiretroviral drugs in pregnant women, breastfeeding mothers, children and adolescents should be monitored for toxicity. Hence, it was important to monitor the use of antiretroviral drugs in developing countries where toxicities might present a different pattern in association with environmental or behavioural factors. Surveillance of antiretroviral drug toxicity would help to understand the long-term risk of antiretroviral drug toxicity. Increased risk of toxicity associated with long term use of antiretroviral drugs, renal and bone toxicity should necessitate further research most especially in developing countries [4].

Lack of clinical trials in children due to specific challenges in conducting clinical trials in children resulted in inadequate data on paediatric safety and efficacy of many pharmaceutical products leading to risks of adverse events [5, 6]. It was reported in a study conducted among 20 HIV-infected mothers on HAART and their seronegative breastfeeding infants on prophylactic zidovudine in Botswana, that the maternal median breast-milk concentration of nevirapine, lamivudine and zidovudine were 0.67, 3.34 and 3.21 times, respectively, those in maternal serum. The median seronegative breastfeeding infant serum concentration of nevirapine was 40 times the 50% inhibitory concentration of nevirapine which might expose infants to the risk of drug-related toxicity. There were 3 serious episodes of neutropenia reported in the study [7]. Another study was done in France on HIV-infected women on combination of zidovudine and lamivudine and their children were followed up from birth to 2years. As a result of drug toxicity, 65 children had premature treatment discontinuation and six of them had liver biochemical abnormalities [8].

HAART-induced hepatotoxicity was a frequent cause of morbidity, mortality and treatment discontinuation in HIV-infected persons [9]. Approved antiretroviral drugs were associated with elevation of liver enzymes, ALT and AST. Major mechanisms of HAART-induced hepatotoxicity were metabolic host-mediated toxicity, hypersensitivity reactions, mitochondrial toxicity and immune reconstitution phenomenon [10].

The severity of HAART-induced hepatotoxicity could start from the absence of symptoms to liver decompensation while their outcomes could range from spontaneous resolution to liver failure and death [11]. Most episodes of HAART-induced hepatotoxicity were asymptomatic and most ALT and AST elevation resolved spontaneously probably due to adaptation [12]. However, a few drug-induced hepatotoxicities could be overt and would have fatal consequences [10].

HAART-induced hepatotoxicity was either predictable indicating high incidence or unpredictable indicating low incidence. Hepatotoxicity would occur through direct toxicity of the drug, its metabolites and idiosyncratic response in persons with a specific genetic predisposition. Predictable hepatotoxicity was dose dependent and host independent. Early-onset toxicity was strong evidence for direct drug toxicity especially where there was no earlier exposure. Unpredictable hepatotoxicity was host dependent and non-dose dependent [13]. Most drug reactions were unpredictable and occurred when the drug was transformed into an intermediate metabolite which was either toxic (host-mediated metabolism) or provoked an immunological response (hypersensitivity reaction) [10]

WHO recommended replacement of NVP + AZT + 3TC, which was the preferred first line

regimen, in Nigeria and other African countries with ABC + 3TC + Efv (or LPv/r) as the preferred first line regimen in under-fives. The reason indicated was due to potential clinical disadvantages of NVP and AZT. This recommendation was yet to be implemented in Nigeria. Hence, there was need for laboratory monitoring for hepatotoxicity in under-five seropositive children on HAART who were born to HIV-infected mothers on HAART. In order to assess hepatotoxicity of HAART on under-five HIV-infected children, it was important that a quantitative (observational) study should be conducted [4].

This study aimed to assess the effects of highly active antiretroviral drugs on liver of under-five HIV-infected children in Southern Nigeria.

Materials and method

In order to assess effect of HAART on liver of under-fives, a quantitative observational approach was used. Two hundred and thirty-eight (238) under-fives children were enrolled from five hospitals such as University College Hospital, Ibadan, University of Uyo Teaching Hospital, Federal Medical Centre, Umuahia, Emmanuel Hospital, Eket and St Luke Hospital Anua. After ethical permission to commence the study in the centres, written consent was obtained from the care-givers of the participants. This study was done in compliance with the standard requirements of Ethics Committee of the five centres.

The study participants were grouped into six such as:

i. *Group A* involved 91 seropositive infants and children who were receiving Highly Active Anti-retroviral Therapy (HAART).

ii. *Group B1* involved 24 seronegative infants born to breastfeeding HIV-mothers on HAART. The children were receiving single daily dose prophylactic nevirapine for first six weeks of life. They were six week old at blood collection time.

iii. *Group B2* involved 18 seronegative infants born to breastfeeding HIV-mothers on HAART. The children were receiving prophylactic co-trimoxazole and were six months old at blood collection time.

iv. *Group B3* involved 48 seronegative infants born to breastfeeding HIV-mothers on HAART. The children were receiving prophylactic co-trimoxazole and were eighteen months old at blood collection time. They had stopped breastfeeding at least six months before blood collection.

v. *Group C* involved 11 seropositive children born to HIV- mothers on HAART. These children were receiving prophylactic co-trimoxazole because of their uncompromised immunity.

vi. *Group D* involved 46 drug-free seronegative children born to seronegative parents. They served as the control group.

This study was focused on under-fives hence details of HAART regimen received by mothers of participants in group B1 could not be obtained. The study protocol did not involve mother's HAART regimen, thus, there was no access to mothers' folders. Mothers of HIV-infected under-fives were attending adult HIV clinic which was separated from the paediatric HIV clinic. All HIV-infected participants were diagnosed either with HIV-1 or HIV-2 infection.

A 2ml blood sample was obtained from each study participant during first phase of the study and was analysed for alanine aminotransferase (ALT) and aspartate amino transferase (AST) using kits manufactured by Randox®. AST/ALT ratio was calculated from the obtained AST and ALT values. HIV-infected children who were receiving HAART were followed up for second and third phase of the study after three and six months respectively. Other participants such as group B1, B2, B3, C and D were not followed up for the second and third phases of the study because they were not registered in the HIV clinic and the management at the clinics did not allow them to participate in second and third phases.

Determination of alanine aminotransferase (ALT) was done by using pipette to add 0.5 mL of buffer into a test tube without serum which was known as the sample blank tube. Pipette was used to add 0.5 mL of buffer and 0.1 mL of serum into another test tube which was known as the sample. Each of the test tubes was mixed and incubated for exactly 30 minutes at 37°C. Pipette was used to add 0.5 mL of 2, 4-dinitrophenylhydrazine and 0.1 mL of sample into the sample blank tube. A 0.5 mL of 2, 4-dinitrophenylhydrazine was added into the sample tube with the use of pipette. Each of the tubes was mixed and allowed to stand for exactly 20 minutes at 25°C. Then, 5.0 mL of Sodium Hydroxide (0.4 mol/L) was added both into the sample blank tube and the sample tube. Each tube was mixed and put in the Unispec 23D Spectrophotometer (UNISCOPE) made by Surgifriend Medicals, England. The absorbance of the sample was read against the sample blank after 5 minutes. The absorbance was compared with established values on the manufacturer's leaflets.

The same procedure was used for determination of AST. ALT buffer kit contained phosphate buffer (100 mmol/L), pH 7.4, L-alanine (200 mmol/L) and α-oxoglutarate (2 mmol/L). AST buffer kit contained phosphate buffer (100 mmol/

L), pH 7.4, L-aspartate (100 mmol/L) and α-oxoglutarate (2 mmol/L).

Data obtained were stored using Microsoft Office 2008. Data were analyzed using descriptive statistics such as frequency tables, percentages and charts to describe the distribution of the participants with respect to the measured characteristics. Inter-group comparison of data was done in the first phase of blood collection while intra-group comparison was done for the second and third phases. Further analysis was performed on the data by using analysis of variances at 5% level of significance. Post hoc test such as Dunnett t-test was done to compare group A with control groups. Statistical Package for Social Sciences (SPSS) software version 20.0 (SPSS Inc. Chicago, III, USA) was used

The result of liver function test showed that liver enzyme ALT was highest in group A (12.8±11.01U/L). Liver enzyme AST was highest in group B2 (35.4±53.11U/L). AST/ALT ratio was highest in group B2 (4.9±4.3). Details were shown in table 3. The statistical analysis of variance was used to compare the means among the groups, the results showed that ALT ($p<0.05$), AST ($p<0.05$) were significant while AST/ALT ratio ($p>0.05$) was not significant. Effect of HAART was also shown by comparing biochemical parameters of under-five HIV-infected participants on HAART with those of control groups. Details are shown in table 4.

Out of ninety-one (91) HIV-infected children aged 0-5 years on HAART that were enrolled for the study during the first phase of blood collection

Table 1: Characteristics of study participants during first phase in Southern Nigeria

Characteristics		Groups	AGE** (months)			BMI (kg/m²)
Total number	238		Mean±SD	Mode	Median	Mean±SD
Male	118 (49.5%)	A	44.8±20.5	36	44	18.9±10.9
Female	120 (50.4%)	B1	1.45±0.5	1	1	19.4±9.7
Mean age (months)	27.5	B2	3.7±0.8	3	3.5	20.2±8.9
Average Weight (Kg)	13.3±7.5	B3	15.3±6.4	18	15	24.1±9.3
Mean CD4 (cells/mm³)	945±548.2	C	35.7±24.2	60	25	21.7±7.7
Stage	1	D	27.7±24.5	18	18	17.1±2.8

***Age of participants declared by care-givers was subjective. BMI=Body mass index.*

Results

Two hundred and thirty-eight (238) study participants comprising one hundred and eighteen (49.6%) boys and one hundred and twenty (50.4%) girls were enrolled for the study in Southern Nigeria during the first phase of blood collection. The study participants were enrolled at a mean age of 27.5month with mean weight of 13.3kg. Details were shown in table 1.

Table 2: Characteristics of HIV-infected children on HAART during second and third phase in Southern Nigeria

Characteristics	Second Phase	Third Phase
Number of participants	59	56
Male	33 (55.9%)	32 (57.1%)
Female	26 (44.0%)	24 (42.8%)
Mean age (months)	50.5±18.6	52.9±20.6
Average weight (kg)	17.1±4.8	16.8±4.0
BMI (kg/m²)	18.3±3.7	17.1±2.5
Mean CD4 (cells/mm³)	897.1±503.0	999.2± 551.6
Stage	1	1

in Southern Nigeria, fifty-nine (64.8%) children were followed up after three months of monitoring. Thirty-three boys and twenty-six girls receiving HAART were followed up. Their mean age was 50.5months and mean weight of 17.1kg. Details were shown in table 2. The results of biochemical analysis of HIV-infected children on HAART after 3 months of follow up were ALT (7.9±6.01U/L), AST (17.0±8.81U/L) and AST/ALT ratio (3.4±3.1). Comparing with the first phase, ALT and AST were significantly reduced by 39.3% ($p<0.05$), 29.9% ($p<0.05$), respectively. Details were shown in table 5.

Fifty-six (61.5%) study participants were followed up after 6 months of monitoring. Thirty-two (57.1%) boys and twenty-four (42.8%) girls were followed up. The study participants that were followed up had a mean age of 52.9 months and mean weight of 16.8kg. Details were shown in table 3. The results of biochemical analysis showed that children on HAART after 6 months of follow up were ALT (6.3±4.01U/L), AST (16.2±8.71U/L) and AST/ALT ratio (3.7±3.9). Details were shown in table 5.

Table 3: Impacts of HAART on liver of study participants in Southern Nigeria during first phase

Groups		Liver Function Test			Death
Number of participants		ALT (IU/L)	AST (IU/L)	AST/ALT Ratio	No. of participants
Upper limit of normal		12.0	12.0	1.0	
A	91	12.8±11.0	23.9±27.3	3.1±6.1	5
B1	24	10.9±7.8	22.8±12.8	2.4±1.3	0
B2	18	11.7±20.7	35.4±53.1	4.9±4.3	0
B3	48	11.2±6.9	24.9±15.9	3.0±2.4	0
C	11	6.5±2.6	16.7±7.6	2.7±1.3	0
D	46	5.8±3.4	12.4±6.8	2.9±2.6	0
P-VAUE(ANOVA)		P<0.05	P<0.05	p>0.05	

Table 4: Comparison of HIV-infected under-fives on HAART with control groups in first phase

	ALT	AST	AST/ALT ratio
Group A vs Group C	NS	NS	NS
Group A vs Group D	p=0.001	p=0.043	NS

Group A= HIV-infected participants on HAART.
Group C= HIV-infected participants on co-trimoxazole.
Group D= seronegative children, ALT= alanine aminotransferase.
AST= aspartate aminotransferase, NS= non significance

Table 5: Impacts of HAART on liver of HIV-infected children on HAART after follow-up in Southern Nigeria

Phase	Group	Number of participants	Liver Function Test ALT (IU/L)	AST (IU/L)	RATIO
First phase	A	91	12.8±11.0	23.9±27.3	3.1±6.1
Second phase	A	59	7.8±6.1	16.7±8.6	3.4±3.2
% increase of Group A in phase II (Dunnett t-test)			-39.3% (p<0.05)	-29.9% (p<0.05)	12.2% (p>0.05)
Third Phase	A	56	6.3±3.9	16.2±8.7	3.7±3.9
% increase of Group A in phase III (Dunnett t-test)			-50.6% (p<0.05)	-32.2 (p<0.05)	20.3% (p>0.05)

Death casualty

Five (5.4%) of the HIV-infected children who received HAART from the centres died. Death was not associated with progression of HIV- infection and they were known to be adherent to therapy. Accesses to folders of deceased were denied by authorities at the hospitals after their death.

Discussion

Yet, to date, there were limited reports on evaluation of effects of HAART on liver of under-fives. Under-five HIV-infected children on HAART had elevated ALT suggesting hepatotoxicity. Previous studies indicated that HAART was responsible for hepatotoxicity in adults [14, 15]. Puoti *et al.*, reported in their study that liver damage in patients treated with HAART was an emerging problem because of its increasing frequency and severe adverse clinical outcome. Their study focused on incidence of severe hepatotoxicity and liver failure. Immune reconstitution against hepatitis virus antigens in liver cells seemed to have a major role in the pathogenesis of severe hepatotoxicity of HAART as evidenced by the association of the occurrence of severe hepatotoxicity [15]. HAART-induced hepatotoxicity was either predictable indicating high incidence or unpredictable indicating low incidence. Hepatotoxicity would occur through direct toxicity of the drug, its metabolites and idiosyncratic response in persons with a specific genetic predisposition. Predictable hepatotoxicity were dose dependent and host independent. Early-onset toxicity was strong evidence for direct drug toxicity especially where there was no previous exposure. Unpredictable hepatotoxicity were host dependent and non-dose dependent [13]. Most drug reactions were

unpredictable and occurred when the drug was transformed into an intermediate metabolite which was either toxic such as host-mediated metabolism or provoked an immunological response such as hypersensitivity reaction.

Elevated liver enzyme AST was more pronounced among HIV-exposed children on co-trimoxazole at six months. The pronounced elevation of AST among HIV-exposed children at six months was suggested to be due to drug interaction between co-trimoxazole ingested by the children and HAART that were secreted in the breast milk of HIV-mothers on HAART. Previous study had shown that sulphonamide and trimetoprim form additive toxicity with lamivudine and zidovudine causing elevated transaminases [16]. Lamivudine was excreted mainly unchanged in the urine by renal clearance and active tubular secretion. Dose reductions were recommended in pre-existing renal impairment due to concurrent administration of nephrotoxic drugs such as intravenous cidofovir. In addition other drugs which are actively secreted by the organic cationic transport system such as trimethoprim, might inhibit the excretion of lamivudine. Administration of co-trimoxazole at doses used for prophylaxis of *Pneumocystis carinii pneumonia* resulted in a 40% increase in lamivudine levels which was caused by trimethoprim. However, unless the patient had renal impairment, no dosage adjustment of lamivudine was necessary. Co-administration of lamivudine with high-dose trimethoprim such as when co-trimoxazole, or dapsone and trimethoprim, were used to treat *P. carinii pneumonia* should be avoided. Care should be taken when lamivudine would be used with other myelosuppressive drugs because thrombocytopenia, transient elevations in liver enzymes, and increases in serum amylase were reported [16].

The HAART-naïve HIV-infected children and the HIV-exposed children aged about eighteen months did not have adversely elevated liver enzymes probably because they did not have exposure to HAART. They were only receiving co-trimoxazole and had cessation of breast-feeding at least six months earlier. It was a common practice in West Africa that HIV-infected mothers would breastfeed their children exclusively for six months before introduction of meals while some mothers would breastfeed children till one year of age. Parker et al., indicated that among low-income HIV-infected mothers who were living in developing countries, exclusive breastfeeding was accepted and feasible as demonstrated by the high adherence rate. Early breastfeeding cessation was challenging due to maternal fears, household food insecurity and social stigma. Mothers learned to accept early weaning as an HIV prevention strategy with consistent counselling and support. Exclusive breastfeeding to 6 months was widely promoted for optimal feeding within the general population of Malawi, regardless of HIV status, and thus carried no stigma. Southern Africa had also reported success using counselling sessions to promote exclusive breastfeeding. Early breastfeeding cessation at 4 months significantly increased the risk of growth faltering, severe morbidity and death [17].

Less than half of the participants on HAART were lost to follow up. Berheto *et al.* indicated 26.7% loss to follow up among patients on HAART in Makonde district, Zimbabwe. He also indicated 38.8% loss to follow up among patients on HAART in United Kingdom. In their study, it was observed that attrition from care was directly associated with length of stay with antiretroviral care. They reported high rate of attrition from care in first 6 months of HAART initiation. The risk of attrition increased with longer period of stay on HAART. The high risk factors responsible for attrition were poor counselling service, refilling and assessment of antiretroviral by medical officer [18].

Both liver enzymes ALT and AST of the HIV-infected children on HAART were reduced after monitoring at third and sixth month which probably indicated resolution of hepatotoxicity. This was consistent with reports of previous studies in adults [10,19]. Nunez and Soriano concluded that the contribution of each particular drug to the development of hepatotoxicity in a HAART regimen is difficult to evaluate. The incidence of liver toxicity was not well known for most of the antiretrovirals. Although it was most often mild, fatal cases of acute hepatitis linked to the use of HAART have been reported across all classes of antiretrovirals. Acute hepatitis was related to hypersensitivity reactions in the case of non-nucleosides and to mitochondrial toxicity in the case of nucleoside analogues. Nunez and Soriano indicated that the management of liver toxicity was based mainly on its clinical impact, severity and pathogenic mechanism. Although mild HAART-related hepatotoxicity most often would spontaneously resolve, severe hepatotoxicity require discontinuation of the antiretrovirals, for example when there was liver decompensation, hypersensitivity reaction or lactic acidosis [19]. Nunez reported that antiretrovirals were metabolized in the liver through the cytocrome pathways, hence, idiosyncratic polymorphisms of the enzymatic complexes might lead to significant heterogeneity in drug metabolism, predisposing to the development

of hepatotoxicity in certain individuals. Some drugs might potentiate the activation of death receptors or intracellular stress pathways. Liver cells promoted mechanisms of cytoprotection against the oxidative stress caused by drug metabolism. Heat-shock proteins were induced by various forms of stress such as drugs might exert cytoprotective functions to prevent potentially damaging toxicants. An increase in heat-shock proteins in individuals with polymorphisms might help the liver adapt to and minimize drug toxicity. Anti-oxidation stress mechanisms might explain the spontaneous normalization in the levels of transaminases despite continuity of HAART regimen [9]. The observation was that effect of HAART on liver enzymes ALT and AST were resolved after three and six months of follow up respectively. The increasing AST/ALT ratio after third and sixth month of follow up was of non- significance to the liver function.

Though the causes of death of five (5.4%) HIV-infected children who received HAART regimen from the centres could not be ascertained, one of the deceased had confirmed severely enlarged liver (hepatomegaly) which probably indicated that her death could be due to HAART regimen. This study showed presence of death casualty after HAART initiation in children which was in conformity with report in a previous study led by Puthanakit. It was reported that the higher mortality rates in poor economy countries during the first few months of HAART initiation, compared with those in developed countries, could be explained by the low CD4 cell counts, advanced clinical stage, prevalence of coexisting infection at the time of HAART initiation, occurrence of IRS in these patients with late-stage HIV infection and adverse events caused by antiretroviral drugs were responsible for morbidity and mortality [20]. In this study all the participants on HAART were asymptomatic and the cause of death of asymptomatic HIV-infected under-fives on HAART was unknown.

The limitations of the study were lack of screening of participants for HCV/ HBV which could be confounding factor and access to folders of participants that died before the completion of study.

Conclusion

This study was able to establish that there was a significant association of HAART with decreasing alanine aminotransferase and aspartate aminotransferase after initial increase which implied resolution of impaired liver function among 0-5 year old participants.

Recommendations

Regular monitoring of liver for elevated alanine aminotransferase and aspartate aminotransferase among HIV-infected under-fives on HAART was hereby recommended.

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