MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Pediatrics & Neonatal Biology Open Access
ISSN: 2640-2726

Hepatic Markers Profile in Cytolysis and Cholestasis during Antiretroviral Treatment at the Charles de Gaulle University Hospital

Soudre FM[1,2]* , Kouraogo GA[3,4], Kiba A[1,5], Sawadogo J[1,2], Ouedraogo SAP[6], Kyetega A[2], Sire D[2], Karfo R[1,7], Kabre E[1,8] and Sakande J[1,7]

[1]Training and Research Unit in Health Sciences, Joseph Ki-Zerbo University, Burkina Faso
[2]Biochemistry Unit of the Charles de Gaulle Pediatric University Hospital, Burkina Faso
[3]Biochemistry Unit of University Hospital Sourou Sanou, Burkina Faso
[4]Institute of Health Sciences, Nazi Boni University, Burkina Faso
[5]Laboratory Service of the University Hospital of Tengandogo, Burkina Faso
[6]Infectious Diseases Department of the Charles de Gaulle Pediatric University Hospital, Burkina Faso
[7]Biochemistry Department of the Yalgado Ouedraogo University Hospital, Burkina Faso
[8]National Public Health Laboratory, Burkina Faso

***Corresponding author:** Fabienne Marie Soudre, Training and Research Unit in Health Sciences, Joseph Ki-Zerbo University, Ouagadougou, P. O. Box: 09 BP 1201 Ouaga 09, Burkina Faso, Tel: + 226 70 45 51 06; Email: fabysoudre@gmail.com

Research Article
Volume 7 Issue 1
Received Date: March 10, 2022
Published Date: April 18, 2022
DOI: 10.23880/pnboa-16000163

Abstract

Introduction: Mother-to-child transmission of HIV is a public health problem for sub-Saharan African countries. Systematic antiretroviral treatment at diagnosis is an important step in the evolution of HIV/AIDS management. However, this treatment can be the cause of hepatic adverse effects. The aim of this study was to evaluate the profile of hepatic cytolysis and cholestasis markers in children living with HIV under ARV treatment at Charles de Gaulle Pediatric University Hospital (CHUP-CDG).

Materials and Methods: This was a descriptive cross-sectional study from February to June 2018 in which markers of cytolysis (AST, ALT, and LDH) and cholestasis (ALP and γGT) were studied in children living with HIV 1 undergoing ARV treatment at CHUP-CDG.

Results: The markers of hepatic cytolysis, ALT, AST and LDH, were elevated in 11.63%, 13.95% and 26.74% of children on ARV treatment, respectively; as were those of hepatic cholestasis (ALP=77.91% and γGT=12.79%). Cytolysis and hepatic cholestasis were more marked in children with CD4 counts below 400/mL. In addition, when the viral load was less than 500 copies/mL and when the duration of treatment was more than 12 months, the proportions of these liver biological disorders were higher in children on ARV treatment.

Conclusion: The disturbances observed on cytolysis and cholestasis markers were slightly elevated, but without serious consequences because they were mostly at low toxicity levels.

Keywords: Hepatic Markers; Cytolysis; Cholestasis; HIV; Antiretroviral; Children

Abbreviations: HIV: Human Immunodeficiency Virus; MTCT: Mother-to-Child Transmission; ARV; Antiretroviral Treatment; WHO: World Health Organization; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; γGT: Gamma Glutamyl Transpeptidase; ALP: Alkaline Phosphatase.

Introduction

The human immunodeficiency virus (HIV) is responsible for nearly 1,500 new infections in children every day, more than 90% of which are in developing countries and most of which are associated with Mother-to-Child Transmission (MTCT) [1]. In 2016, in Burkina Faso, there were approximately 95,000 people living with HIV, of whom 60% had access to antiretroviral treatment (ARV). Prophylaxis as part of MTCT prevention was effective in 91.60% of pregnant women living with HIV. In addition, early ARV treatment in these children is effective in improving their survival [2]. Thus, the World Health Organization (WHO) recommends ARV treatment for any child tested HIV positive regardless of CD4 count and clinical stage [3]. However, this ARV treatment leads to several types of side effects that can be severe. Given the hepatic metabolism of most of the molecules, hepatotoxicity may be considered. Indeed, several physio-pathogenic mechanisms may be at the origin of this hepatic toxicity of ARVs; in particular an immune reaction to the introduction of ARVs, the mitochondrial toxicity of nucleosides, the immune allergy induced by certain molecules and the direct dose-dependent toxicity of some ARVs with hepatic metabolism [4,5]. Hence the interest of this study, which aimed to evaluate the hepatic markers of cytolysis and cholestasis in children living with HIV under ARVs at the Charles de Gaulle University Hospital.

Material and Methods

Characteristics of the Study

This was a descriptive cross-sectional study, which covered the period from February to June 2018, in the Infectious Diseases and Laboratories Department of the Charles de Gaulle Pediatric Hospital Center (CHUP-CDG). The study population consisted of children less than 15 years of age, known HIV type 1 carriers on ARV treatment, regularly followed up in the infectious diseases department and performing their biological check up at the CHUP-CDG laboratory. Children who received hepatotoxic drug treatment (other than ARVs) or who were co-infected (HIV - viral hepatitis) were not included.

As part of their follow-up, we have collected venous blood samples from children in the laboratory. These samples were used to perform the following tests: viral load quantification, TCD4+ lymphocyte count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), Gamma glutamyl transpeptidase (γGT), and alkaline phosphatase (ALP). Hepatic cytolysis was assessed by the grade of elevation of AST, ALT [6], and LDH; cholestasis was estimated by the elevation of ALP and γGT in all children on treatment.

The study equipment consisted of the BD FACSCountTM for TCD4+ lymphocyte count, the COBAS® TaqMan® Systems for viral load quantification, the Indiko Plus® multiparameter automated system for biochemical assays (AST, ALT, LDH, γGT and ALP) and small laboratory equipment (pipettes, centrifuge...). The calibrations and internal quality controls on the automatons were performed according to the internal procedures of the laboratory.

Ethical Consideration

Authorization from hospital management was obtained prior to data collection. A unique identification code was affixed to the samples to preserve the confidentiality of the patient's results. The data were analyzed in strict anonymity.

Statistical Analysis

Data were collected from the patient's clinical records. Data entry and statistical analysis were performed on a computer using Epi Info version 7.2.2.2 and Excel 2010. The Chi-square test was used to compare the percentages and the p significance level was set at 5%.

Results

A total of 86 children with HIV 1 on ARV treatment were included in the study. The sex ratio M/F was 0.95. The age of the patients ranged from 0 to 180 months and the most represented age group was 61-180 months.

Clinically, 40.70% of the children were in clinical stage 2 and almost 56.97% in advanced disease (clinical stage 3 and 4). The Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) regimen was the most used (34.88%). During follow-up, 26.74% (n=23) of children had their treatment changed from the initial regimen. Among the reasons for modification, toxidermia accounted for 17.39%, followed by non-compliance 13.04%. The majority of the treatment regimen related to toxidermia was the combination of AZT+3TC+NVP presented sociodemographic, clinical and therapeutic characteristics (Table 1).

Parameters	Number	Percent (%)
Sex (n=86)		
Male	42	48.84
Female	44	51.16
Age Range (months) (n=86)		
0-12	8	9.3
13-36	6	6.98
37-60	12	13.95
61-180	60	69.77
WHO Clinical Stages (n=86)		
Clinical stage 1	2	2.33
Clinical stage 2	35	40.7
Clinical stage 3	33	38.37
Clinical stage 4	16	18.6
Treatment Regimen (n=86)		
AZT / 3TC / NVP	30	34.88
AZT / 3TC / EFV	18	20.93
ABC / 3TC /LPV/r	15	17.44
ABC / 3TC / EFV	6	6.98
ABC /3TC /NVP	4	4.65
AZT / 3TC / LPV/r	6	6.98
EFV / 3TC / ABC	4	4.65
EFV / FTC / TDF	3	3.49
Duration of Treatment in Months (n=86)		
< 12	15	17.44
Dec-60	33	38.37
61 - 120	38	44.19
Reason for Treatment Change (n=23)		
Withdrawal of D4T from regimens	14	60.87
Toxidermia	4	17.39
Non-compliance	3	13.04
Treatment failure	2	8.7

Table 1: Sociodemographic, clinical and therapeutic characteristics of children on ARVs.

Viral load was less than 500 copies/mL in 65.12% of children on treatment, and 86.05% had a TCD4+ lymphocyte count greater than 400/mL (Table 2). Markers of hepatic cytolysis were elevated in 11.63%, 13.95%, and 26.74% of children on ARV therapy for ALT, AST, and LDH respectively. The majority of children were classified as grade 1 cytolysis for ALT (9.30%) and AST (5.81%). Cholestasis markers showed elevated ALP in 77.91% of children and 12.72% for γGT. Cytolysis and cholestasis markers were higher when TCD4+ lymphocytes were greater than 400/mL, but without a statistically significant relationship (Table 3). These markers were elevated in children with a viral load of less than 500 copies/mL; and when the duration of treatment was greater than 12 months, the proportions of children on ARV therapy with cytolysis and cholestasis were high (Table 4).

Biological Characteristics		Number	Percent (%)
TCD4+ lymphocyte count (/mL)			
≤399		12	13.95
>400		74	86.05
Viral load (copies /ml)			
<500		56	65.12
≥500		30	34.88
Markers of cytolysis and cholestasis			
ALT	Normal	76	88.37
	High	10	11.63
AST	Normal	74	86.05
	High	12	13.95
LDH	Normal	63	73.26
	High	23	26.74
ALP	Normal	19	22.09
	High	67	77.91
γGT	Normal	75	87.21
	High	11	12.79
Grade of Hepatic Cytolysis			
ALT	<50 IU/L	78	90.7
	50 – 100 IU/L (Grade 1)	8	9.3
AST	<50 IU/L	81	94.19
	50 – 100 IU/L (Grade 1)	5	5.81

Table 2: Biological characteristics of children on ARV treatment.

Markers of cytolysis and cholestasis by TCD4+ lymphocyte count				
CD4/mL		**≤399**	**>400**	**p**
ALT (%)	Normal	12.79	75.58	0.78
	High	1.16	10.47	
AST (%)	Normal	10.46	75.58	0.07
	High	3.49	10.47	
LDH (%)	Normal	10.46	62.8	0.57
	High	3.49	23.25	
ALP (%)	Normal	4.65	17.44	0.14
	High	9.3	68.61	
γGT (%)	Normal	11.62	75.58	0.53
	High	2.33	10.47	
Markers of cytolysis and cholestasis by viral load				
Viral load copy/mL		**<500**	**≥500**	**p**
ALT (%)	Normal	58.14	30.23	0.99
High	6.98	4.65		

AST (%) High	Normal	59.3	26.74	0.06
	5.82	8.14		
LDH (%) High	Normal	50	23.25	0.59
	15.12	11.63		
ALP (%) High	Normal	15.12	6.98	0.73
	50	27.9		
γGT (%) High	Normal	58.14	29.07	0.43
	6.98	5.81		

Table 3: Profile of cytolysis and cholestasis markers according to TCD4+ lymphocyte count and viral load.

Markers of Cytolysis and Cholestasis by duration of Treatment					
		< 12 months	**12 – 60 months**	**60- 120 months**	**p**
ALT	Normal	14 (16.28%)	27 (31.39%)	35 (40.70%)	0.32
	High	01 (01.16%)	06 (06.98%)	03 (03.49%)	
AST	Normal	12 (13.95%)	29 (33.72%)	33 (38.37%)	0.75
	High	03 (03.49%)	04 (04.65%)	05 (05.81%)	
LDH	Normal	13 (15.12%)	18 (20.93%)	32 (37.21%)	0.02
	High	02 (02.32%)	15 (17.44%)	06 (6.98%)	
ALP	Normal	05 (05.81%)	06 (6.98%)	08 (09.30%)	0.49
	High	10 (11.62%)	27 (31.39%)	30 (34.88%)	
γGT	Normal	13 (15.12%)	28 (32.56%)	37 (43.02%)	0.84
	High	02 (02.32%)	05 (05.81%)	01 (01.16%)	

Table 4: Evolution of cytolysis and cholestasis markers according to the duration of ARV treatment.

Discussion

The majority of patients were female (51.16%) with a sex ratio of 0.95. Our results were close to those of Djadou KE, et al. [7] in Togo, who found a female predominance of 53%. The most represented age group was 61 to 180 months with 69.77% of children on ARV treatment against only 09.30% for children under 12 months. Children over 5 years of age (60 months) were the most numerous, which shows the need to reinforce diagnosis and early follow-up of mothers in order to avoid mother-fetal transmission. Indeed, mother-to-child transmission of HIV is the main mode of contamination in pediatrics, with an additional risk linked to breastfeeding. The majority of children was followed in the city of Ouagadougou because of its accessibility and enhanced technical facilities compared to other cities in Burkina Faso. Clinically, at inclusion, the majority of children had clinical stage 2 (40.70%), while 18.60% had severe symptoms (clinical stage 4). Our results were comparable to those of Djadou KE, et al. [7] in Togo who found 18.18% of children infected at clinical stage 4 at inclusion; however, our figures were higher than those of Oumar AA ,et al. [8] who found 11.1% of children at clinical stage 4 in Segou [7,8]. Late diagnosis and management of children, especially at stages when they develop opportunistic diseases, are factors related to these high rates of children with severe symptoms at inclusion.

In first-line treatment, the proposed triple therapy (two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor) complied with national protocols in 75.58% of cases [3]. This combination therapy resulted in sustained inhibition of viral replication in the child, thus promoting immune reconstitution. Combinations of Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) and Zidovudine (AZT) + Lamivudine (3TC) + Efavirenz (EFV) were the most used with proportions of 34.88% and 20.93% respectively; as the new therapeutic recommendations in first line treatment replace Stavudine (D4T) by Zidovudine (AZT) due to its toxicity. During the follow-up of the children, the therapeutic regimen was modified in 26.74% of the cases. Among the reasons for these modifications, toxidermia was the most represented with 17.39% of children. A cohort study of children undergoing ARV treatment in Togo showed a 25% incidence of toxidermia [9]. Several authors have shown an

involvement of the Nevirapine molecule in this toxidermia, but also the cutaneous sensitivity of young children [10]. Non-compliance with treatment was present in 13.04% of children, which could lead to the appearance of mutations, compromising the use of certain antiretrovirals.

An immune deficiency (13.95%) was observed in children under ARV treatment; while the majority (86.05%) had a CD4 count above 400/mL. Authors found in Togo, 67.7% absence of immune deficiency after 12 months of treatment and 81.9% after 24 months [11]. As most authors believe, there is immune reconstitution after at least six months of effective treatment for patients on triple therapy. The viral load was less than 500 copies/mL in 65.12% of children on ARV treatment. Indeed, several authors have shown a beneficial effect of ARVs on the health of HIV-infected African children, under the condition of a good therapeutic compliance responsible for a durable suppression of viral replication and a very low risk of rebound [12].

The profile of liver cytolysis markers showed elevated levels of ALT, AST and LDH in 11.63%, 13.95% and 26.74% of children on ARV treatment, respectively. This hepatic cytolysis was more pronounced in children who had CD4 counts above 400/mL. In addition, when the viral load was below 500 copies/mL, then the proportions of cytolysis were high. In addition, high rates of cytolysis were observed in children with treatment duration of more than 12 months. The level of hepatic cytolysis was low (grade 1) in 9.30% of children on ARV treatment according to ALT and 5.81% according to AST. Several authors have shown that a good tolerance of the patient to ARV treatment favors a progressive decrease in the grade of liver toxicity over time [13-15]. However, some authors associated this increase in aminotransferases (ALT and AST) with the increase in viral load [16]. Similarly, asymptomatic elevation of blood lactates was frequent during treatment with nucleoside reverse transcriptase inhibitors, which reflected mitochondrial toxicity related to the combination of Stavudine (d4T) + didanosine (DDI), the early interruption of which allowed clinical and biological recovery [17].

Hepatic cholestasis (intra or extrahepatic) is usually observed in the face of increased ALP, which is the result of increased synthesis of the enzyme by the epithelial cells of the bile ducts and increased γGT. Nearly 77.91% of children on treatment had elevated ALP versus 12.79% who had elevated γGTs. The proportions of children on ARV treatment in whom liver cholestasis could be suspected increased when the CD4 count was above 400/mL (elevated ALP =68.6% and elevated γGT=10.46%). On the other hand, the lower the viral load (less than 500 copies/mL), the higher the rates of children on treatment with hepatic cholestasis (high ALP =50% and high γGT=6.98%). In addition, after 12 months of ARV treatment, markers of hepatic cholestasis increased in children.

Conclusion

The liver marker profile of cytolysis and cholestasis in HIV-positive children on ARV treatment showed a high proportion of liver cytotoxicity for a TCD4+ lymphocyte count above 400/mL, a viral load below 500 copies/mL. This shows the importance of biological monitoring which, in addition to helping in the decision to start the initial treatment, also makes it possible to evaluate its effectiveness and the appearance of any intolerance. The disturbances observed were slight, marked by an increase in most parameters, but without serious clinical consequences.

References

1. Antiretroviral therapy of HIV infection in infants and children. WHO.

2. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, et al. (2008) Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. N Engl J Med 359(21): 2233-2244.

3. Ministerial Committee for the fight against HIV/AIDS in Burkina Faso. Standards and protocols for the medical care of people living with HIV in Burkina Faso.

4. Gervais A (2009) Hepatotoxicite des antiretroviraux. Hepato-Gastro Oncol Dig 16(2): 93-99.

5. Leclercq P, Roudiere L, Viard J (2004) Complications graves des traitements antiretroviraux. Reanimation 13(3): 238-248.

6. OMS (1992) International Adverse Drug Reaction Surveillance: Adverse Reaction Terminology. Uppsala: WHO Collaborating Center for International Drug Monitoring.

7. Djadou KE, Azoumah DR, Saka B, Douti K, Koudaya K, et al. (2012) Follow-up of HIV-infected children receiving antiretroviral therapy in a rural area of Togo. Medecine et Sante Tropicales 22(3): 283-286.

8. Oumar AA, Katile D, Maiga B, Toure A, Drabo M, et al. (2016) Evaluation de l'observance therapeutique aux antiretroviraux chez l'enfant a Segou, Mali. Antropo 35: 83-89.

9. Takassi OE, Djadou KE, Adi P, Guedenon KM, Fiawoo M, et al. (2017) Evolution clinique et biologique de cohortes d'enfants sous traitement antiretroviral au Togo. Journal de la Recherche Scientifique de l'Universite de Lome

19(3): 615-621.

10. Pitche P, Drobacheff-Thiebaut C, Gavignet B, Mercier M, Laurent R (2005) Toxidermie a la nevirapine. Annales de Dermatologie et de Venereologie 132(12): 970-974.

11. Atakouma DY, Tsolenyanu E, Gbadoe A, Gbetoglo V, Lawson–Evi K, et al. (2007) Traitement antiretroviral des enfants infectes par le VIH/sida a Lome (Togo): premiers resultats. Archives de Pediatrie 14(10): 1178-1182.

12. Coetzee D, Boulle A, Hildebrand K, Asselman V, Van Cutsem G, et al.(2004) Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. AIDS. 18: S27-S31.

13. Martinez E, Blanco JL, Arnaiz JA, Mocroft A, Cruceta A, et al. (2001) Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 15(10): 1261-1268.

14. Aurpibul L, Bunupuradah T, Sophan S, Boettiger D, Wati DK, et al. (2015) Prevalence and Incidence of Liver Dysfunction and Assessment of Biomarkers of Liver Disease in HIV-Infected Asian Children. Pediatr Infect Dis J 34(6): e153-e158.

15. Gray D, Nuttall J, Lombard C, Davies M, Workman L, et al. (2010) Low rates of hepatotoxicity in HIV-infected children on anti-retroviral therapy with and without isoniazid prophylaxis. J Trop Pediatr 56(3): 159-165.

16. Mouhari-Toure A, Patassi A, Nabroulaba KT, Djadou KE, Edou K, Nyametso D, et al. (2011) Profil biologique des patients adultes infectes par le VIH a l'initiation du traitement antiretroviral au Togo. Medecine et Maladies Infectieuses 41(5): 229-234.

17. Coutet J, Durupt F, Penaud JF, Durupt S (2005) Hyperlactatemie symptomatique chez des patients infectes par le VIH et traites par antiretroviraux : mise au point a partir de trois nouveaux cas. Journal de Pharmacie Clinique 24(1): 47-51.