Biochemical Modifications in HIV-Infected Children and Adolescents Under Antiretroviral Therapy

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In this paper we propose to present the biochemical modifications in children and adolescents with HIV infection/AIDS undergoing antiretroviral therapy (ART). We have carried out a retrospective study on 200 HIV-seropositive children registered in our department, without any prior workup modifications, in which antiretroviral therapy was initiated. In all patients we have monitored serum glucose, amylasemia, natremia, and liver enzymes. Most of the biochemical modifications were mild and moderate and did not necessitate cessation of therapy. In only 2 cases, modifications were severe enough to impose a temporary interruption of the ART: one case with elevated triglycerides and one case with elevated liver enzymes. After 24 months of ART, approximately 11.5% (23/200) of the monitored patients had biochemical modifications: 3.5 % elevated triglycerides, 5% elevated liver enzymes, 2.5 % hyperamylasemia, and 0.5 % hypernatremia. Biochemical modifications were more significant in patients who received prior antiretroviral therapy, particularly those who received protease inhibitors (PIs) in comparison to patients naive to ART.

Keywords: biochemical modifications, HIV, child

HIV infection is an important cause of morbidity and mortality worldwide, especially in developing countries. In Romania, over 12,000 children with HIV/AIDS have been registered, 87.2% of which have received ART [9,10]. From the detection of the first cases of HIV infection, there has been a constant strive to find an effective treatment. The current *gold standard* treatment aims to obtain an undetectable viral load and level of CD4 lymphocytes over 500/mm^3 [6]. Aside from the obvious benefits, antiretroviral treatment has an array of adverse effects, including modifications of biochemical parameters. Protease inhibitors can cause such modifications, particularly ritonavir, lopinavir, and saquinavir [5, 14]. The clinician handling patients with HIV infection is confronted with complex challenges in management of adverse effects of the specific therapy.

In this paper we propose to evaluate the biochemical modifications in children and adolescents with HIV/AIDS, both naïve and previously treated with ART, without previous workup modifications, who have received nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) with or without ritonavir (r) over a period of 24 months.

We have carried out a retrospective study on 200 HIV-seropositive children, aged between 9-18 years, in different stages of clinical evolution, registered in the Pediatric Department of the National Institute of Infectious Diseases Prof. Dr. Matei Bals. According to CDC/WHO clinical and immunological staging, the cases have been classified as: A3 - 22, B1 – 26, B2 – 48, B3 – 76, C1 – 12, C2 – 9, and C3 – 7 (table 1).

Based on the type of ARV, 37 patients received 2 NRTIs + Indinavir (IDV), 70 - 2 NRTIs + Nelfinavir (NFV), 38 – 2 NRTIs + Ritonavir (RTV), 28 - 2 NRTIs+ Lopinavir/ritonavir (LPV/r), 22 - 2 NRTIs+ Indinavirvir/ritonavir (IDV/r), and patients received 2 NRTIs + NFV/SQV. In all cases we have monitored serum glucose, amylasemia, alanine aminotransferase (ALT) and natremia.

Results and discussions

We registered no deaths during the study. 60% of patients were male and the mean age was 16.2 years.

Table 2 shows that the biochemical modifications secondary to ART were 11% (22/200). All 6 lots of HIV-seropositive children had similar biochemical modifications, except serum glucose which was elevated mostly in patients treated with IDV/r.

Table 3 shows a discrepancy between our results and those reported by the authors of a clinical study published in AIDS magazine in 2000. In our study, the biochemical modifications arisen in patients treated with 2 NRTIs +

Stage	A3	B1	B2	B3	C1	C2	C3	Total
2 INRT+IDV	5	4	7	17	2	1	1	37
2 INRT+NFV	8	11	18	24	4	3	2	70
2 INRT+RTV	4	6	8	18	1	1	0	38
2 INRT+LPV/r	2	5	10	5	2	2	2	28
2 INRT+IDV/r	3	0	5	10	2	1	1	22
2 INRT+NFV/SQV	0	0	0	2	1	1	1	5
Total cases	**22**	**26**	**48**	**76**	**12**	**9**	**7**	**200**

Table 1
CDC STAGING OF STUDIED CASES

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All the authors had the same contribution to this article

Table 2
BIOCHEMICAL MODIFICATIONS

Studied lots	Serum glucose > 150 mg/dL (%)	ALT > 2 x N (%)	Amylasemia > 2 x N (%)	Natremia (> 145 mmol/l)
2 NRTIs + IDV	0	5.40 (2/37)	5.40 (2/37)	0
2 NRTIs + NFV	4.28 (3/70)	5.71 (4/70)	0	0
2 NRTIs + RTV	0	5.26 (2/38)	5.26 (2/38)	0
2 NRTIs + IDV/r	13.63 (3/22)	4.54 (1/22)	0	0
2 NRTIs + LPV/r	3.57 (1/28)	3.57 (1/28)	3.57 (1/28)	3.57 (1/28)
2 NRTIs+ NFV/SQV	0	0	0	0

Table 3
COMPARATIVE ASPECTS OF BIOCHEMICAL MODIFICATIONS IN PATIENTS TREATED WITH IDV/r

Test	2 NRTIs + IDV/r	
	Our study (%)	AIDS* study (%)
Serum glucose(>150 mg/dL)	13.63 (3/22)	0
Amylasemia (> 2 x N)	0	0
ALT (> 2 x N)	4.54 (1/22)	1.1
Na^+(> 145 mmol/l)	0	0

*AIDS – Vol. 14, No 9, June 2000.

Table 4
COMPARATIVE ASPECTS OF BIOCHEMICAL MODIFICATIONS IN PATIENTS TREATED WITH LPV/r

Test	2 NRTIs + LPV/r	
	Our study (%)	M98-863 study
Serum glucose(>150 mg/dL)	3.57 (1/28)	2 %
Amylasemia (> 2 x N)	3.57 (1/28)	3 %
ALT (> 2 x N)	3.57 (1/28)	4 %
Na^+(> 145 mmol/l)	3.57 (1/28)	3 %

IDV/r were significant comparing to results obtained by foreign authors. We have noticed that the said authors did not report modifications of the serum glucose levels and the percentage of patients with elevated liver enzymes was fourfold. Amylasemia and natremia were not modified in our study or in the AIDS study. These differences could be explained by the fact that the AIDS study had higher numbers of patients compared to the number enrolled in our study [2, 11].

Comparing M98-863 study with data from personal research regarding biochemical modifications in children treated with therapeutic schemes containing LPV/r, it is observed that data is similar except hyperglycemia which is twice as frequent in our study (table 4) [3, 5, 15].

Modifications of serum glucose and natremia in patients treated with 2 NRTIs and IDV reported in the Merck study were insignificant compared to our study. We also noticed important differences regarding liver enzymes, twofold in our study compared to six fold in the Merck study (table 5).

A comparative study between our study and the Abbott study show that data regarding alanine aminotransferase are comparable statistically; increased amylasemia was more frequent in our study. No foreign authors have reported modifications of serum glucose levels or natremia in patients treated with 2 NRTIs + RTV (table 6) [11, 16].

Analyzing Agouron 511, a double blind, randomized study, carried out on 316 patients, separated into 2 lots, one treated with 2 NRTIs + NFV and the other one with 2 NRTIs, has showed that during the 48 weeks of the study no amylasemia or natremia modifications were reported, only slight elevations of serum glucose and liver enzymes. We also have not registered any modifications in amylasemia or natremia levels in patients treated with 2 NRTIs + NFV, although elevation of serum glucose and liver enzyme levels were twice as frequent (table 7) [8,12].

Analysis of the cohort study Swiss HIV revealed that the authors did not report any modifications of biochemical parameters (serum glucose, amylasemia, liver enzymes) in patients treated with 2 NRTIs + SQV/NFV, which was similar to our study [1].

Conclusions

On the course of the study we have registered biochemical modifications in 11.5% in all cases. Most cases had grade 1 and 2 biochemical modifications, and only 2

Test	2 NRTIs + IDV	
	Our study (%)	Merck study (%)
Serum glucose(>150 mg/dL)	0	1.6
Amylasemia (> 2 x N)	5.40 (2/37)	0.9
ALT (> 2 x N)	5.40 (2/37)	2.6
Na^+(> 145 mmol/l)	0	0

Table 5
COMPARATIVE ASPECTS OF BIOCHEMICAL MODIFICATIONS IN PATIENTS TREATED WITH IDV

Test	2 NRTIs + RTV	
	Our study (%)	Abbott study (%)
Serum glucose(>150 mg/dL)	0	0
Amylasemia (> 2 x N)	5.26 (2/38)	0
ALT (> 2 x N)	5.26 (2/38)	6
Na^+(> 145 mmol/l)	0	0

Table 6
COMPARATIVE ASPECTS OF BIOCHEMICAL MODIFICATIONS IN PATIENTS TREATED WITH RTV

Test	2 NRTIs + NFV	
	Our study (%)	511 study (%)
Serum glucose(>150 mg/dL)	4.28 (3/70)	2
Amylasemia (> 2 x N)	0	0
ALT (> 2 x N)	5.26 (2/38)	3
Na^+(> 145 mmol/l)	0	0

Table 7
COMPARATIVE ASPECTS OF BIOCHEMICAL MODIFICATIONS IN PATIENTS TREATED WITH NFV

cases necessitated cessation of ART. No deaths were registered on the duration of the study.

The most important changes in serum glucose levels were observed in patients treated with 2 NRTIs + IDV/r and fewer in patients who received 2 NRTIs + NFV or LPV/r. The other lots did not present any changes in serum glucose levels. One case had severe hyperglycemia reversible after ART cessation.

All monitored lots had modifications of the liver enzymes, except the lot treated with 2 NRTIs + SQV/NFV. ALT elevations were minimal (3-5% of all cases); one single case presented with significantly elevated ALT (x 5N) and required cessation of ART.

Amylasemia was modified in the lots treated 2 NRTIs + IDV, LPV/r or RTV. Natremia was elevated in one single case which received 2 NRTIs + LPV/r. Modifications were minimal and reversible.

With few exceptions, biochemical modifications we have observed on the course of the ART in children and adolescents with HIV/AIDS compare to those reported by authors in various international specialty studies.

Aside from obvious benefits, antiretroviral treatment has adverse effects, some severe, which have to be taken into consideration when choosing a therapeutic scheme for these patients.

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