Lipd Metabolism Abnormalities in Children and Adolescents with HIV/AIDS Treated with Protease Inhibitors

GHEORGHITA JUGULETE[1,2]*, SIMONA IACOB[1,2], MADALINA MERISESCU[1,2], MONICA LUMINOS[1,2]

[1] National Institute of Infectious Diseases Prof. Dr. Matei Bals, 1 Dr. Calistrat Grozovici Str., 021105, Bucharest, Romania

[2]Carol Davila University of Medicine and Pharmacy, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

In this paper we propose to evaluate the lipid metabolism abnormalities in children and adolescents with HIV/AIDS undergoing treatment with protease inhibitors (PIs). There are over 1000 children and adolescents with HIV infection of various stages registered in the Pediatric Department of the National Institute of Infectious Diseases Prof. Dr. Matei Bals. We have carried out a retrospective study on 200 HIV seropositive children without previous lipid metabolism abnormalities in which antiretroviral treatment was initiated. In these patients we have monitored modifications in lipid metabolism secondary to antiretroviral treatment (triglycerides, cholesterol, and lipids). The majorities of abnormalities of the lipid metabolism were not severe and did not require modification or cessation of treatment. 24 months of treatment later, approximately 23.5% of patients treated with 2 NRTI+PI/r had modifications of the lipid metabolism: 34.6% had hypercholesterolemia, 38.4% had hypertriglyceridemia, and 36.9% had an increase of total serum lipids. Lipid metabolism abnormalities have been more significant in patients treated previously with antiretrovirals, especially those who have received PIs, in comparison to naïve patients.

Keywords: lipid metabolism modifications, HIV, child

HIV/AIDS 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, 4,000 of which are still alive [6, 10, 11]. 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. Aside from the obvious benefits, antiretroviral treatment has an array of adverse effects, including changes in the lipid metabolism. Protease inhibitors carry a high rate of lipid abnormalities, particularly ritonavir, lopinavir, and saquinavir [4-6, 11]. 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 lipid metabolism abnormalities in children and adolescents with HIV/AIDS, both naïve and previously treated with ART, without previous metabolic modifications, who have received nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) with or without ritonavir (r) for 24 months.

Experimental part

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).

Patients were split into 2 groups: naive – 22 cases (who previously have not received PIs) and previously treated – 178 cases (children who had been treated previously with ARV containing PIs). 23% were naive to PIs, 47% received 1 PI, and 30% received 2 PIs previously.

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+ Indinavir/ritonavir (IDV/r), and patients received 2 NRTIs + NFV/SQV. In all cases we have monitored age, sex, and triglycerides, cholesterol, total serum lipids.

Stage	A3	B1	B2	B3	C1	C2	C3	Total
2 NRTI+IDV	5	4	7	17	2	1	1	37
2 NRTI+NFV	8	11	18	24	4	3	2	70
2 NRTI+RTV	4	6	8	18	1	1	0	38
2 NRTI +LPV/r	2	5	10	5	2	2	2	28
2 NRTI +IDV/r	3	0	5	10	2	1	1	22
2 NRTI +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

* email: georgejugulete@yahoo.com

All the authors had the same contribution to this article

Results and discussions

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

23.5% of cases presented modification in the lipid metabolism (47 out of 200), predominantly patients previously treated with PIs. The majority of patients presented only mild modifications of laboratory parameters. Only 5 patients required cessation of treatment because of adverse effects (table 1). All 5 cases previously received at least 2 PIs.

Figure 2 reveals how the number of cases with metabolic changes increases proportionally with the number of therapeutic schemes and particularly the number of PIs. Therefore, 64.1% of patients previously treated with 2 PIs had changes in lipid metabolism compared to only 7.7% of naive patients.

Figure 3 shows that the percentages of lipid metabolism parameters are similar, varing between 6 to 9 %; cholesterol has the highest percentage and total serum lipids the lowest.

Regarding the lipid metabolism overall, the studied patient lots presented variable percentages in rises of lipid profile (2-20%) [7, 9, 12]. The most important modifications have been observed in patient lots treated with plain ritonavir, SQV/NFV or IDV/r [2, 8, 16].

Comparative analysis of the lots shows that patients treated with NFV/SQV or ritonavir were the most affected, followed by those treated with IDV or LDV/r. Minimal modifications of total cholesterol were patients receiving IDV/r or NFV (fig. 4).

Also, we have observed a discrepancy in the results obtained in this study and those reported by authors of a study published in AIDS magazine in 2000. In our study, metabolic abnormalities were not as significant in comparison to the results obtained by foreign authors, where more than 40% of patients enrolled in the study had increased levels of cholesterol and triglycerides.

The same group of patients treated with NFV/SQV or RTV had the most increase in triglycerides levels. Although,

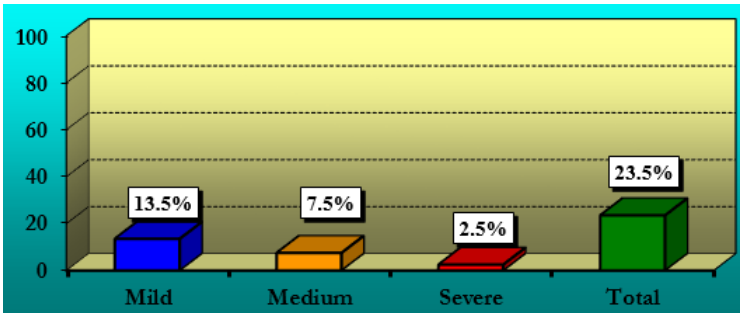

Fig. 1. Classification of metabolic abnormalities according to severity

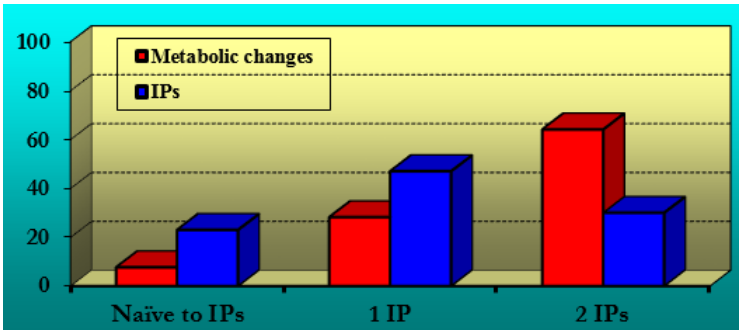

Fig. 2. Distribution of metabolic abnormalities according to previous therapy

Studied lot	Triglycerides > 500 mg/dL (%)	Cholesterol > 300 mg/dL (%)	Lipids > 900 mg/dL(%)
2 NRTIs + IDV	5.40 (2/37)	10.81 (4/37)	2.71 (1/37)
2 NRTIs + NFV	4.28 (3/70)	5.71 (4/70)	2.85 (2/70)
2 NRTIs + RTV	15.78 (6/38)	13.15 (5/38)	10.52 (4/38)
2 NRTIs + IDV/r	13.63 (3/22)	4.54 (1/22)	9.09 (2/22)
2 NRTIs + LPV/r	7.14 (2/28)	10.71 (3/28)	7.14 (2/28)
2 NRTIs + NFV/SQV	20 (1/5)	20 (1/5)	20 (1/5)

Table 2
CHANGES OF LIPID METABOLISM

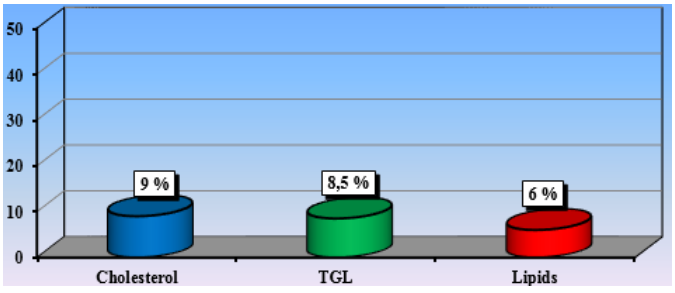

Fig. 3.Modifications of lipid metabolism

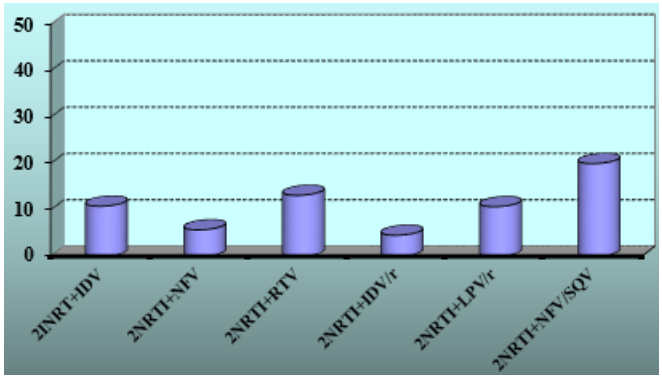

Fig. 4. Modifications of cholesterol

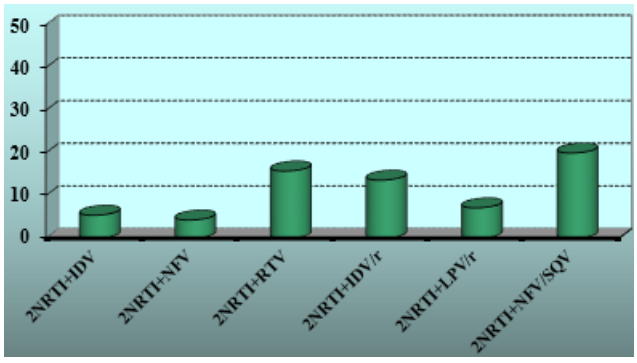

Fig. 5. Modifications of triglycerides

comparing with the modifications of total cholesterol, patients who received IDV/r or LPV/r had more significant triglycerides modifications. Patients treated with plain PIs (NFV or IDV) had minimal modifications of triglycerides (fig. 5).

A comparative assessment of study M98-63 with the data from our study regarding biochemical modifications in children treated with therapeutic schemes with LPV/r, has revealed the fact that the data is similar, except hyperlipidemia which is not present in the cases of foreign authors [1, 14].

Regarding changes of the total serum lipids we have noticed that lots treated with NFV/SQV, IDV/r or RTV had the most significant modifications and patients that received IDV or NFV had minimal rises in total serum lipids levels (fig. 6).

Metabolic abnormalities reported in the Merck study are insignificant in comparison with our study, where the biochemical modification is between 2-10%. We noticed that other authors did not report modifications of lipid metabolism [12].

A comparative analysis between data obtained in our study and the authors of the Abbott study show that the data is comparable statistically, except the modification of total lipids, which are more frequent in our study [14].

We have observed mild modifications in lipid metabolism (10%) in all studied lots, without significant discrepancies. These modifications are correlated with the clinical onset of lipodystrophy and/or lipoatrophy.

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 lipid metabolism abnormalities were reported, except some small modification in patients from both lots. These modifications did not require cessation of ARV. It has been observed that the biochemical modifications are similar

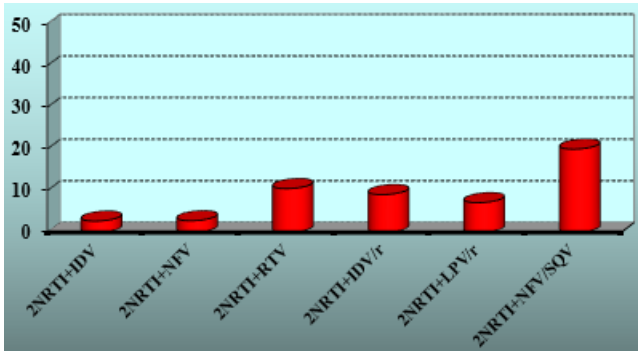

Fig. 6. Modifications of total lipids

to those in our study, except the levels of cholesterol, which have been higher in the 511 study [13].

Analysis of the cohort study Swiss HIV revealed similar modifications of the lipid metabolism with those from our study [15, 16].

Conclusions

All patient lots had lipid metabolism abnormalities in variable proportions, in accordance to the type of PI used. Also, the patient's medical history has a definitive role: previous PI treatment increases the risk of developing lipid metabolism abnormalities. Therefore, most evident modifications took place in patients previously treated with PIs. Also, we have observed that in the cases where 2 IPs were used, changes in the lipid metabolism were more significant.

We have not registered any severe modifications of lipid metabolism that necessitated cessation or change of therapy, or any deaths.

Protease inhibitors constitute a therapeutic class of high importance for the HIV seropositive patient, having high effectiveness reflected in the low mortality rates after the introduction of PIs in the ARV. Still, when we decide to establish a therapeutic scheme in a patient with HIV/AIDS we have to take into consideration the patient's medical history, particularly previous treatments (prior/actual treatments, dyslipidemia, and other associated comorbidities).

References

1.*** A Phase III, Randomised, Double-blind Trial of ABT-378/r+Stavudine and Lamivudine vs. Nelfinavir +d4T/3TC Handout Accompanyig the Oral Presentation,The M98-863 Study Group

2.ANANWORANICH J., RUXRUNGTHAM K., SIANGPHOE U., et all l- A Prospective Cohort Study of Efficacy and Safety of 2 NRTIs plus once-daily Ritonavir boosted-Saquinavir Hard Gel Capsule (SQV-HGC/r) at 24 weeks – XV International AIDS Conference (IAC), 11 – 16 July 2004, Bangkok, Thailand, Poster TuPeB4469.

3.ERON J. J.R., YENI P., GATHE J. Jr. et al. - The KLEAN Study of fosamprenavir-ritonavir vs. Lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomized non-inferiority trial. Lancet 2006; 368: 476-482

4.DOROS, G.,OLARIU,C.,ARDELEAN,A.M., STROESCU,R.,GAFENCU, M.,Relevance of the Cardiac Biomarkers in Children with Heart Disease Admitted for Severe Cardiac Pathology Rev. Chim.(Bucharest), **68**, no. 4, 2017, p. 748

5.HOETELMANS R.M.V., PISCITELLI S.C., HILL A.M., A Guide to Protease Inhibitor Boosting

6.JUGULETE G. – Infectia HIV/SIDA la copil, Aspecte clinic-imunologice si virusologice ale terapiei antiretrovirale, Editura Bren 2016.

7.JUGULETE G.,IACOB, S., MERISESCU, M., LUMINOS, M., Biochemical modifications in HIV-infected children and adolescents under antiretroviral therapy, Rev. Chim. (Bucharest), **68**, no. 11, 2017, in press

8.KIRK O., KATZENSTEIN T.L., GERSTOFT J., MATHIESEN L., NIELSEN H., PEDERSEN C., LUNDGREN J.D. - Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. AIDS 1999; 13:F9-16.
9.LUMINOS M., MERISESCU M., SCHIOPU S., OSMAN E., OTELEA D., JUGULETE G. - Biological and lipid metabolism abnormalities in children and teenagers with HIV/AIDS undergoing antiretroviral treatment - Monduzzi Editore, International Proceedings Division, May 2014, Pag. 57 – 61.
10.MARDARDARESCU M., et al. - Continuum of HIV/AIDS care - between myth and reality – Conferinta Nationala de Boli Infectioase, Timisoara, 2016-08-15
11.MARDARESCU M., Evoluia infeciei HIV/SIDA în România update 31 decembrie 2015 - CNLAS - Compartimentul pentru Monitorizarea si Evaluarea Infectiei HIV/SIDA în Romania-INBI Prof.Dr.M.Bals (www.cnlas.ro)
12.PHAIR J.P., SCHAPIRO J.M.- Use of Boosted Protease Inhibitor – Based Reginens in Treatment-Experienced Patients
13.SAAG M.S., TEBAS P., et al. for the Viracept Collaborative Study Group - Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511) - AIDS: 19 October 2001 - Volume 15 - Issue 15 - pp 1971-1978
14.SAEZ X. – LIORENS et al - Lopinavir/ritonavir in HIV-positive Children - The Pediatric Infectious Disease Journal, Vol 22, November 2003, pg. 216 - 224.
15.ALBOT M. D., Boosted protease inhibitor based regimens - HIV infection, Search date April 2008
16.WALMSLEY S., RUXRUNGTHAM K., SLIM J. et all. - The Gemini Study: saquinavir/r vs. lopinavir plus emtricitabine/ tenofovir as initial therapy in HIV-1- infected pacients. European AIDS Clinical Society.Madrid, Nov 2007[Abstract PS1/4]

Manuscript received: 25.04.2017