Abstract 690

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LONGITUDINAL EVALUATION OF HYPERLYPIDEMIA IN HIV-INFECTED CHILDREN STARTING THEIR FIRST HAART REGIMEN

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BACKGROUND

Metabolic disorders are common in HIV-infected children treated with HAART. As most HIV-infected children in developed countries are currently being treated with HAART. These metabolic derangements have been assessed mostly in cross-sectional pediatric studies. Furthermore, hyperlipidemia is highly prevalent in HIV-infected children treated with HAART. Nevertheless, there are very few longitudinal studies that have addressed the evolution of plasma cholesterol and triglycerides levels in children treated with HAART. Hyperlipidemia raise concerns for their long-term consequences specially in children because of their likely greater cumulative exposure.

OBJECTIVES

The aim of this study has been to assess the frequency and extent of raised total cholesterol and triglycerides plasma levels before and after the introduction of HAART in a large cohort of HIV-infected children.

We also aimed to determine the possible contribution of each individual antiretroviral drug used.

PATIENTS AND METHODS

Subjects: This is a retrospective longitudinal study examining the frequency, extent and significance of plasma lipid levels in pediatric HIV patients before and during treatment with HAART. Children included in the study were selected out from the Madrid cohort of HIV-infected children. The Madrid cohort was set up in January 03 with prospective data collection according to an standardized protocol. By December 2005, 240 HIV-infected children are being followed in 9 public hospitals in Madrid. All children followed prospectively had clinical assessment, including lipid levels every 3-6 months. Before 2003 data were collected retrospectively by reviewing clinical records. Children followed prospectively had all fasting plasma lipid levels. In the retrospective data collection, most samples were fasting.

Only those children who had baseline plasma cholesterol and triglycerides available before HAART, and longitudinal assessment for at least 12 months with their first HAART regimen were included in the study. Only children starting HAART with 2 NRTI plus either a PI or a NNRTI were included in the analysis. Patients who did not have lipid levels available before HAART were excluded from this study. In addition those children starting HAART with 3 NRTI, 4 drugs or the 3 families of available antiretrovirals were excluded. The local ethics committee was informed of the research study. The period of study was from October 1996 to December 04, to allow for a minimum of 12 months of follow-up. Children were assessed at the last clinic visit during the data collection period. Hyperlipidemia was defined as plasma cholesterol and triglycerides levels above 200 and 170 mg/dl, respectively, at any time point.

Statistical analysis: Student *t* and [chi]^2 were used for comparisons of group means and percentages. Multivariate analysis of risk factors was done by logistic regression to obtain odds ratios and 95% confidence intervals. For analysis of possible risk factors associated with high cholesterol levels, both hypercholesterolemia or an increase greater than 30 mg/dl were considered as the independent variable in univariate and multivariate analysis. Age, sex, CDC clinical and immunological classification, baseline height z-score and weight z-score, time updated CD4 percentage and absolute CD4 counts and viral load were included in univariate analysis. Those variables that were significant ($p<0.05$) in univariate analysis we included in multivariate analysis. Analysis was performed using SPSS version 12.0 and SAS statistical software (version 8.2).

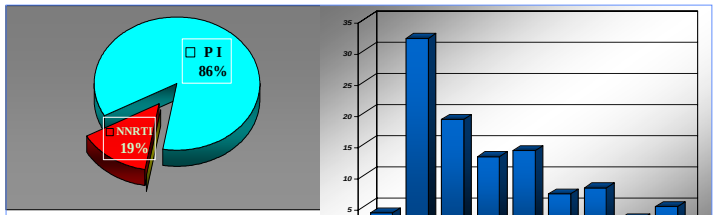
RESULTS

Baseline characteristics of the HIV-infected children included in the study

n: 105	mean ± SD	median (range)
Age (years)	6.3 ± 4.3	5.8 (1 month-18 years)
Body mass index z score (kg/cm^2)	-0.4 ± 1.3	-0.3 (-4.9, 2.54)
CD4 %:	21.4 ± 12.7	21 (1-59)
CD4 % nadir	14.6 ± 10	14 (0.1-41)

	n (%)		
Female	60 (57%)		
Vertical transmission	102 (97%)		
CDC Class C	31 (29.6%)	CDC Class 3	58 (55.2%)

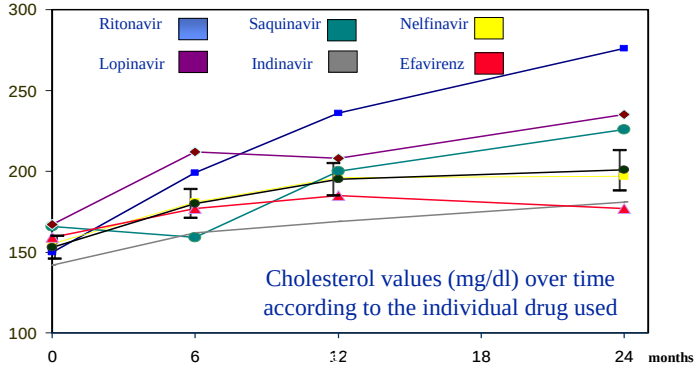
Previous ART	n	Duration in months
Naive	41	
Monotherapy	9	43.5 (1.6-114)
Dual therapy	56	43.4 (1.6-111)



Type of HAART and year of initiation in 105 children

Characteristics of children with and without hypercholesterolemia at baseline

	Hypercholesterolemia	No Hypercholesterolemia	p
Age (years)	6.6 ± 2.9	6.0 ± 4.7	0.69
BMI z score	0.15 ± 0.98	-0.45 ±1.4	0.35
Baseline CD4 %	25 ± 11.8	21 ± 12.7	0.20
HIV-1 RNA(log_{10})	4.1± 1.2	4.5 ± 0.97	0.27
Previous treatment	60%	36%	0.17
Female	70%	45%	0.19
Clinical Stage C	28%	50%	0.23
Immunological Stage 3	40%	57%	0.17



Individual drug comparisons at 24 months

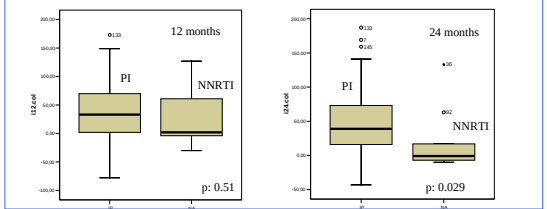
	Ritonavir	Nelfinavir	Indinavir	Saquinavir	Lopinavir/r	Efavirenz
Ritonavir	-					
Nelfinavir	0.051	-				
Indinavir	0.039	0.64	-			
Saquinavir	0.18	0.36	0.58	-		
Lopinavir/r	0.67	0.16	0.16	0.53	-	
Efavirenz	0.013	0.06	0.11	0.27	0.25	-

Proportions of children with hyperlipidemia

n (%)	Baseline	6 m	12 m	24 m	p
Hypercholesterolemia	10 (9.5%)	29 (30%)	37 (42%)	33 (47%)	
(>200 mg/dl) PI	8 (9%)	26 (32%)	33 (45%)	29 (48%)	<0.01 *
NNRTI	2 (13%)	3 (20%)	4 (14%)	4 (10%)	>0.05**
Hypertrigliceridemia	13 (13.7%)	16(17%)	16 (18%)	7 (10%)	>0.05***
(>170 mg/dl) PI	11 (14%)	14 (18%)	13 (18%)	5 (9%)	
NNRTI	2 (13%)	2 (17%)	3 (21%)	2 (22%)	

* p< 0.01. Comparisons of PI at all timepoints from baseline. ** Comparisons of NNRTI at all timepoints from baseline.*** Comparisons of both PI and NNRTI at all time points
Mean baseline Cholesterol level: 153 ± 38.1mg/dl. Triglycerides level: 115 ± 84.7 mg/dl

Comparison of PI and NNRTI increases at 12 and 24 months



Characteristics of children and outcome of cholesterolemia according to the individual drug used

	n	Age (y.)	%CD4	baseline Cho	Δ Cho 6 m	Δ Cho 12 m	Δ Cho 24 m	HIV-RNA(log_{10})
Overall *	105	5.9 (0.1-18)	21	150 (66-258)	23 (-79,166)	33 (-78,188)	39 (-43,187)	4.6 (2.6-6.8)
PI * *	91	5.6 (0.1-18)	21	150 66-258)	24.5 (-79,166)	38 (-78,188)	39 (-43,187)	4.7 (2.-6.8)
Ritonavir	14	4.0 (0.7-8.4)	23	139 (104-258)	32 (-40,134)	73 (-8,188)	80.5 (14,187)	5.1 (4.1-6.0)
Nelfinavir	42	4.7 (0.1-18)	27	155 (66-252)	31 (-43,110)	39 (-78,140)	39 (-43,141)	4.4 (2.7-6.8)
Indinavir	19	9.3 (2.6-13.9)	12	140 (99-191)	24.5 (-51,121)	17 (-21,85)	28.5 (-16,97)	4.9 (2.6-5.6)
Saquinavir	8	7.3 (2.1-11.1)	11	162 (122-230)	-5 (-79,61)	19 (-15,64)	9.5 (17,22)	4.9 (2.7-5.7)
Lopinavir/r	7	1.2 (0.1-9.8)	22	175 (106-256)	39.5 (-44,166)	51.5 (-35,149)	93.5(-13,159)	4.4 (3.4-5.9)
NNRTI* *	15	9.4 (0.1-12.4)	21	152 (72-223)	12.0 (-10,139)	16.0 (-30,181)	-1 (-10,133)	4.0 (2.6-5.9)
Efavirenz	13	9.4 (2.4-12.4)	20	153 (96-223)	3 (-10,179)	2 (-30,127)	-1 (-10,133)	3.9 (2.6-5.6)
Nevirapine	2	0.4 (0.1-0.7)	30	94 (72-115)	89.5 (65,114)	125 (70,181)	NA	5.9 (5.6-6.2)

Cho: Cholesterol values in median and range * p< 0.05 at all different timepoints compared with baseline value
** p : 0.7; 0.51; and 0.029 at 6, 12 and 24 months, respectively. NA: Not available

There was no difference in the proportion of patients with hypercholesterolemia at 12 months with regard to virological response: 33% in children who achieved a viral load <400 cp/ml vs. 44% in those with HIV-RNA above this level (p:0.49).

Analysis of risk factors for Hypercholesterolemia or Δ > 30 mg/dl form baseline

Risk factors	Univariate	Adjusted odds ratio (95% CI) Multivariate
Female vs male	1.17 (0.48-2.84)	
Age (per year increment)	0.85 (0.76-0.96)	0.92 (0.76-1.13)
Baseline weight z-score (per 1 SD higher)	0.83 (0.60-1.13)	
Baseline height z-score (per 1 SD higher)	0.63 (0.43-0.91)	1.03 (0.47-2.23)
Baseline BMI z score (per 1 SD higher)	0.65 (0.44-0.95)	0.68 (0.31-1.51)
Baseline % CD4	1.03 (0.99-1.07)	
Viral load > 10^5 cop/ml	4.02 (1.48-10.9)	6.4 (1.55-27.05)
Prior Tx with NRTI	0.68 (0.28-1.64)	3.6 (0.8-16.74)
CDC Class C vs. Non-C	1.35 (0.49-3.69)	
CDC Class 3 vs. Non 3	0.49 (0.2-1.19)	
PI exposure	0.65 (0.18-2.29)	

CONCLUSIONS

- **In the Madrid cohort, HIV-infected children experience increases in cholesterolemia with most PI-containing regimens.**
- **Ritonavir and lopinavir/ritonavir are associated with the greatest raises in plasma cholesterol in the first 2 years of HAART**
- **In this study, a higher viral load at baseline has been independently associated with hypercholesterolemia after HAART**