

Marked Dyslipidemia in Human Immunodeficiency Virus–Infected Children on Protease Inhibitor-Containing Antiretroviral Therapy

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ABSTRACT. *Objective.* To assess the effects of antiretroviral combination therapy that contains protease inhibitor (PI) on carbohydrate and lipid metabolism in human immunodeficiency virus (HIV)-infected children.

Methods. A cross-sectional, descriptive clinical study was conducted in an outpatient clinic. Thirty-seven HIV-infected children who ranged from 1 to 17 years of age received nucleoside reverse transcriptase inhibitor treatment together with PI (PI group, $n = 25$) or without PI (non-PI group, $n = 12$). Age, gender, weight, length, CD4 cell count, and viral load did not differ between groups. Nonfasting total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, glucose, lactate, and blood gases were determined. In addition, c-peptide, insulin, hemoglobin A1c, free fatty acids, lipoprotein a, and apolipoproteins A1 and B were evaluated after fasting. PI and non-PI group values were compared with normal values taken from healthy children.

Results. In nonfasting and fasting conditions, children of the PI group had higher total cholesterol (fasting PI group: 235 ± 71 mg/dL; non-PI group: 176 ± 25 mg/dL, mean \pm standard deviation), triglycerides (156 ± 89 vs 87 ± 31 mg/dL), and LDL cholesterol levels (159 ± 58 vs 113 ± 23 mg/dL) compared with the non-PI group. High-density lipoprotein cholesterol and apolipoprotein A1 levels did not differ in both groups; there was a trend toward higher apolipoprotein B levels in the PI group. After fasting, 8 (47%) of 17 patients in the PI group presented with hypercholesterolemia as a result of an increase of LDL cholesterol and 11 (65%) had hypertriglyceridemia. It is interesting that the non-PI group showed no pathologic deviations. Compared with normal values, lipoprotein a and free fatty acids were increased in the PI and non-PI groups. Glucose, lactate, blood gases, c-peptide, insulin, and hemoglobin A1c were normal in both groups.

Conclusion. PI-containing antiretroviral treatment of HIV-infected children was associated with hypercholesterolemia, hypertriglyceridemia, and an increase of LDL cholesterol. The long-term complications of dyslipidemia are of major concern in the growing HIV-infected child. *Pediatrics* 2002;110(5). URL: <http://www.pediatrics.org/cgi/content/full/110/5/e56>; antiretroviral therapy, HIV infection, dyslipidemia, carbohydrate metabolism.

ABBREVIATIONS. HAART, highly active antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; HIV, human immunodeficiency virus; 3TC, lamivudine; AZT, zidovudine; NFV, nelfinavir; DDI, didanosine; d4T, stavadine; RTV, nintonavir, ABC, abacavir; DDC, zalcitabine; SAQ, saquinavir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein a; HbA1c, hemoglobin A1c.

Highly active antiretroviral therapy (HAART) that consists of protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) in combination with nucleoside reverse transcriptase inhibitors (NRTIs) has led to a dramatic improvement in the prognosis of human immunodeficiency virus (HIV)-infected patients.^{1,2} Suppression of viral replication and reconstitution of immunologic competence are associated with reduction of morbidity and mortality in HIV-infected adults.³ A similar effect has been observed in children, although suppression of viral load and CD4 recovery seem to be somewhat less efficient. Antiretroviral treatment in children requires a different approach from that in adults because of differences in viral dynamics, immune competence, and pharmacokinetics.^{4–6}

Although these new antiretroviral therapies are usually well tolerated, previously unrecognized side effects are becoming more evident with their widespread use and increased duration of treatment.^{2,7,8} In adults, severe and potentially fatal toxicities associated with altered carbohydrate and lipid metabolism have been described and are thought to be more profound in patients who receive PIs.^{9–12} Frequent side effects include hypertriglyceridemia, hypercholesterolemia, insulin resistance, changes of apolipoproteins, elevated free fatty acids, lactic acidemia, impaired glucose tolerance, type 2 diabetes, and lipodystrophy syndrome.^{2,11,13–18}

In children, there is little information about metabolic complications of antiretroviral therapy.^{19–22} Recently, reports have described significant changes of body fat distribution and clinically overt lipodystrophy.^{19,20} Studies on the tolerability and efficacy of PI-containing regimens have mentioned alterations of serum lipids ranging from dyslipidemia in 20% to 50% of children on single PI to >90% on dual PI-containing regimens.^{4,23–25} However, the determination of the precise role of PI on metabolic side effects has been difficult to examine as all of these studies

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lacked PI negative control groups and provided little or no data on carbohydrate metabolism.

In this study, we investigated the effects of PI-containing antiretroviral therapy on metabolic disturbances in children by comparing serologic parameters in patients with and without PI treatment. We found significant alterations of lipid metabolism in the majority of children on PI-containing regimens, whereas the lipid metabolism in children on dual-NRTI regimens remained largely unchanged.

METHODS

Patients

Forty-nine HIV-infected children who ranged from 1 to 17 years of age were seen for routine care in the outpatient clinic for immunology at the Children's Hospital of the Heinrich Heine University Düsseldorf between August 2000 and September 2001. Thirty-seven patients were recruited for the study on the basis of the inclusion criteria, which comprised vertical HIV-1 infection, antiretroviral therapy with the current regimen for at least 5 months before onset of the study (representing the minimum duration of therapy on the current regimen in the study group) and documented compliance that was assessed by adherence questionnaire,²⁶ drug levels of PI, and increase of mean corpuscular volume in children on therapy with zidovudine. Twenty-four of 37 children had their last food intake >6 hours before blood was drawn and were included in the fasting group. Twelve children were excluded because of documented noncompliance, failure to meet appointments in the outpatient clinic, or severe clinical illness within 6 months before evaluation. In all cases, informed consent was obtained from either the parents or a person who had the care and custody of the child.

Patients were divided into 2 groups, which were examined at 3 time points within 9 months in a nonfasting ($n = 37$) and once in a fasting ($n = 24$) condition. In the PI group (nonfasting, $n = 25$; fasting, $n = 17$), antiretroviral treatment consisted of 3 drugs, including NRTI and PI (lamivudine [3TC]/zidovudine [AZT]/nelfinavir [NFV], $n = 6$; didanosine [DDI]/stavudine [d4T]/NFV, $n = 6$; AZT/3TC/ritonavir [RTV], $n = 3$; DDI/d4T/RTV, $n = 2$; 3TC/d4T/NFV, $n = 2$; 3TC/abacavir [ABC]/NFV, $n = 2$; AZT/ABC/NFV, $n = 1$; 3TC/d4T/RTV, $n = 1$; zalcitabine [DDC]/saquinavir [SAQ]/NFV, $n = 1$; d4T/3TC/SAQ/RTV, $n = 1$). The non-PI group (nonfasting, $n = 12$; fasting, $n = 7$) consisted of children who had never been treated with PI and received only

dual therapy with NRTIs (3TC/AZT, $n = 9$; 3TC/ABC, $n = 1$; d4T/DDI, $n = 1$; d4T/3TC, $n = 1$).

PI and non-PI groups were comparable concerning age, gender, weight, height, CD4 cell count, and viral load (Table 1). With every visit in the outpatient clinic, these measurements were evaluated prospectively. The CD4 lymphocyte count was assessed by flow cytometry (measured from ethylenediaminetetraacetic blood). The detection limit of quantitative HIV-1 viral load (branched chain DNA assay) was 50 copies/mL (heparinized blood). The worst Centers for Disease Control and Prevention classification that the patients ever achieved showed more children with category B and C in the PI group.²⁷ All subjects were in good health at the time of enrollment. The mean time of exposure to current antiretroviral therapy was significantly longer in the non-PI group. None of the patients was treated with any other drug known to influence glucose or lipid metabolism. Detailed family history did not reveal any disturbances in lipid metabolism except 1 case in which an HIV-infected mother had hyperlipidemia and died after myocardial infarction. In 4 cases, the family history was not available for both parents.

Systematic evaluation of lipodystrophy by a scoring system, anthropometric measurements, dual-energy x-ray absorptiometry, and magnetic resonance imaging was not performed. However, lipodystrophy was suspected in 5 of 25 PI patients on a clinical basis of peripheral lipoatrophy (3 of 5 with facial, buttocks, and/or limb atrophy and/or prominent veins) and/or truncal lipohypertrophy (4 of 5 with breast enlargement and/or abdominal obesity).

Procedures

At 3 different points of time, several nonfasting parameters of lipid and carbohydrate metabolism were determined. These included lipid parameters such as total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol (serum) and carbohydrate parameters such as glucose and lactate (sodium fluoride tube), which were assessed by enzymatic methods. Blood gases (pH, base excess) were analyzed by specific O₂- and CO₂-sensitive electrodes.

All children were instructed to fast overnight or at least for a period of >6 hours.²⁸ After fasting, additional lipid parameters such as free fatty acids, lipoprotein a (Lp[a]), and apolipoproteins A1 and B as well as carbohydrate parameters such as c-peptide, insulin, and hemoglobin A1c (HbA1c) were evaluated. Lp(a) and apolipoproteins A1 and B (serum) were measured by nephelometric immunoassays, c-peptide (serum) was measured by chemoluminescence immunoassay, insulin (serum) was measured by microbead enzyme immunoassay, HbA1c (ethylenediaminetetra-

TABLE 1. Patient Characteristics

	PI Group		Non-PI Group	
	Nonfasting ($n = 25$)	Fasting ($n = 17$)	Nonfasting ($n = 12$)	Fasting ($n = 7$)
Ethnic origin				
White	9	6	4	2
Black/black-white	15	11	6	4
Asian/Asian-white	1	0	2	1
Age (y)*	7.9 ± 4.9	8.4 ± 4.2	9.3 ± 4.2	9.3 ± 3.7
Gender	17 f, 8 m	12 f, 5 m	8 f, 4 m	5 f, 2 m
Weight (kg)*	26 ± 12	29 ± 11	34 ± 20	34 ± 22
Height (cm)*	122 ± 26	129 ± 24	133 ± 26	135 ± 23
CD4 cells (/μL)*	971 ± 538	864 ± 353	826 ± 197	779 ± 247
Viral load (copies/mL)*	11 279 ± 30 062	16 095 ± 43 668	8469 ± 13 762	3081 ± 3781
Length of current therapy regimen (mo)*	17 ± 12	30 ± 12	34 ± 7	45 ± 7
Therapy regimens				
2 NRTI	—	—	$n = 12$	$n = 7$
2 NRTI + 1 PI	$n = 23$	$n = 15$	—	—
1 NRTI + 2 PI	$n = 1$	$n = 1$	—	—
2 NRTI + 2 PI	$n = 1$	$n = 1$	—	—
CDC classification				
A	14	10	9	4
B	6	3	2	2
C	5	4	1	1

* Values given as mean ± standard deviation.

acetic acid blood) was measured by turbidimetric immunoassay, and free fatty acids (serum) were measured by photometric enzymatic test.

Normal values were taken from the standard reference values of our Clinical Chemistry and Laboratory Research Unit. Normal range was defined as the interval between the 3rd and 97th percentiles of healthy children in the respective age classes (children: 2–11 months, 1–3 or 4–15 years old, adults: ≥ 16 years old). Values above the 97th percentile were considered increased or elevated (eg, hypercholesterolemia).

Statistical Analysis

The distribution of parameters in the PI and non-PI groups was expressed as mean \pm standard deviation. Values for nonfasting condition are represented by the mean of triple patient measurements. Differences between both groups were evaluated by Student *t* test for unpaired samples (Excel 4.0 software; Microsoft, Inc, Redmond, WA). A 2-sided *P* value $< .05$ was considered statistically significant.

RESULTS

Lipid Metabolism

Nonfasting Condition

In each individual, parameter levels measured were stable over time. Variations among the 3 different time points comprised $< 5\%$ in all samples. Patients in the PI group ($n = 25$) displayed higher mean values for total cholesterol (PI group: 211 ± 58 mg/dL; non-PI group: 157 ± 27 mg/dL; $P < .001$), triglycerides (182 ± 130 vs 100 ± 44 mg/dL; $P < .01$), and LDL cholesterol levels (133 ± 51 vs 97 ± 30 mg/dL; $P < .01$) than patients who received only NRTIs ($n = 12$). HDL cholesterol levels (45 ± 10 vs 43 ± 10 mg/dL) did not differ in both groups. Compared with normal values, 8 (32%) of 25 patients in the PI group presented with hypercholesterolemia as a result of an increase in LDL cholesterol, 13 (52%) had hypertriglyceridemia, and 2 (8%) showed a decrease in HDL cholesterol. In contrast, only 2 (17%) of 12 patients in the non-PI group had hypertriglyceridemia. In all cases but 1, hypercholesterolemia was combined with hypertriglyceridemia.

Fasting Condition

To exclude that the changes in lipid metabolism were merely the result of recent food intake, we performed the analysis in the fasting condition. Again, in the PI group ($n = 17$), we found higher mean values for total cholesterol (235 ± 71 vs 176 ± 25 mg/dL; $P < .01$), triglycerides (156 ± 89 vs 87 ± 31 mg/dL; $P < .01$), and LDL cholesterol levels (159 ± 58 vs 113 ± 23 mg/dL; $P < .01$) compared with the non-PI group ($n = 7$). No significant difference was observed in HDL cholesterol levels between both groups (48 ± 13 vs 47 ± 6 mg/dL). Similar to the nonfasting condition, 8 (47%) of 17 patients in the PI group presented with hypercholesterolemia as a result of an increase in LDL cholesterol, 11 (65%) presented with hypertriglyceridemia, and 2 (12%) showed a decrease in HDL cholesterol. In all cases, hypercholesterolemia and hypertriglyceridemia were present simultaneously. It is interesting that in the fasting non-PI group, no pathologic deviations were found (Figs 1 and 2).

Compared with normal values mean fasting levels for apolipoprotein A1 (147 ± 27 vs 142 ± 18 mg/dL)

and apolipoprotein B (106 ± 41 vs 85 ± 21 mg/dL) were not increased. There was a trend toward higher apolipoprotein B levels in the PI group as compared with non-PI group as 6 of 15 PI patients showed an increase of apolipoprotein B (2 samples were not available for apolipoprotein B analysis; Fig 2). Because apolipoprotein B is specifically found in LDL, conditions with raised serum concentrations of LDL are expected to be associated with increased serum apolipoprotein B levels.²⁸ In all 6 cases with elevated apolipoprotein B, hypercholesterolemia and increased LDL cholesterol level were present simultaneously.

Increased Lp(a) was found in both PI and non-PI group patients; 50% of all children had Lp(a) above the laboratory 97th percentile of normal distribution. Mean Lp(a) levels did not differ between groups (45 ± 58 vs 43 ± 36 mg/dL).

Compared with normal values, elevated free fatty acids were measured in both groups. However, free fatty acids were significantly higher in the PI group compared with the non-PI group (0.76 ± 0.27 vs 0.54 ± 0.11 mmol/L; $P < .001$).

Carbohydrate Metabolism

Nonfasting and Fasting Conditions

Nonfasting glucose (84 ± 11 vs 83 ± 9 mg/dL), lactate (1.8 ± 0.5 vs 1.4 ± 0.4 mmol/L), and blood gases assessed at 3 time points and fasting glucose (85 ± 10 vs 87 ± 3 mg/dL), lactate (1.2 ± 0.3 vs 1.2 ± 0.6 mmol/L), and blood gases showed normal levels in both the PI and non-PI groups and did not differ between groups. The same holds true for the fasting c-peptide (1.6 ± 0.7 vs 1.4 ± 0.6 μ g/L), insulin (6.2 ± 3 vs 8.5 ± 5 mU/L), and HbA1c ($5.2 \pm 0.8\%$ vs $5.4 \pm 0.3\%$) levels.

DISCUSSION

To our knowledge, this is the first controlled study specifically analyzing metabolic side effects of PI-containing antiretroviral therapy as opposed to NRTI-only regimens in HIV-infected children. Similar to adults, metabolic abnormalities seem to be more profound in those who receive PIs.

The study design does not allow one to draw conclusions about whether PI alone may be associated with dyslipidemia or whether there is a potentiating effect by combining PI with nucleoside inhibitors. Processes that lead to changes of metabolic parameters are likely to be multifactorial, and there is lipodystrophy in patients who have never received PI.^{13,14} Furthermore, it has to be taken into account that patients were not randomized to PI therapy and that the study was based on a small number of HIV-infected children. We cannot exclude confounding by variables that were not assessed but differed between groups, and on the basis of our data, it is difficult to separate the roles of drug regimen and disease severity. However, the main clinical, immunologic, and virologic parameters did not differ significantly between the groups except for a longer mean time of exposure to antiretroviral therapy in the non-PI group and a higher Centers for Disease

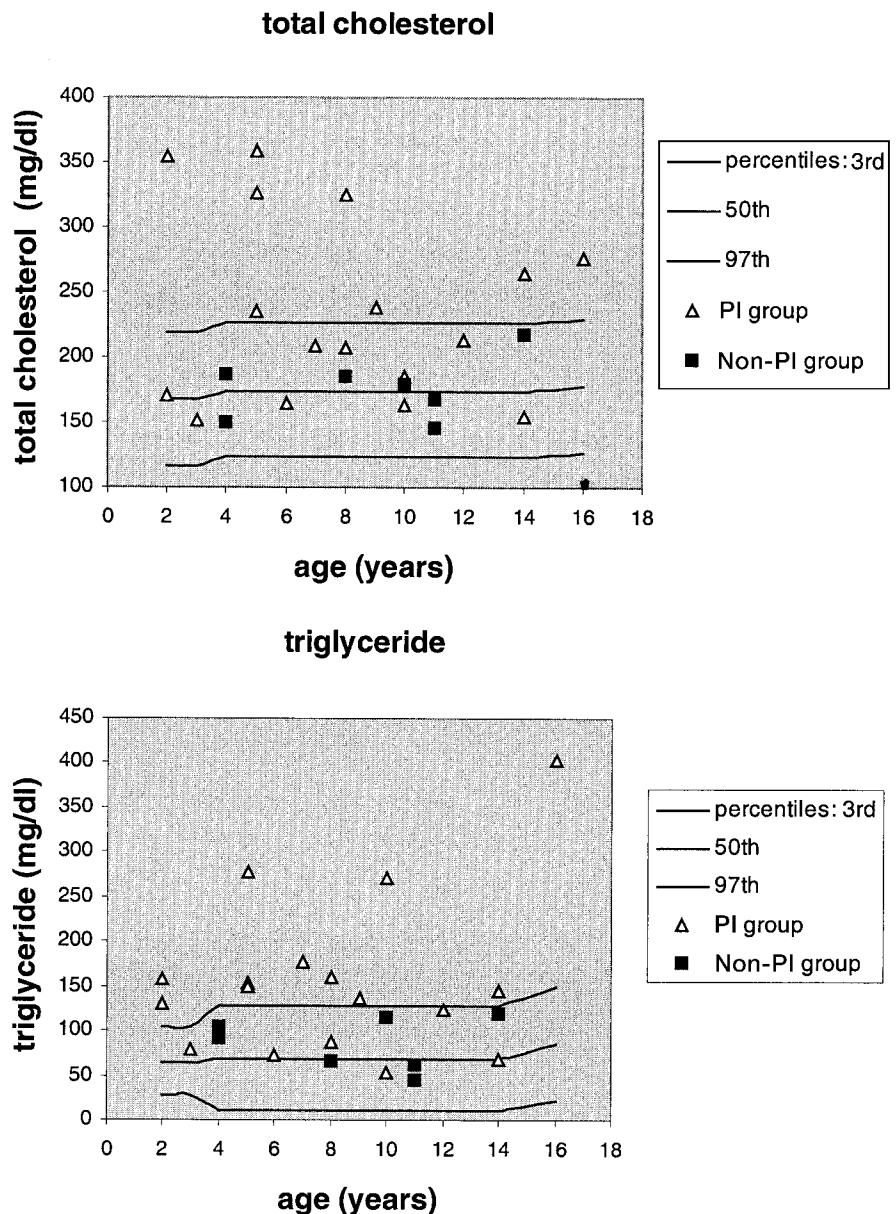


Fig 1. Individual fasting total cholesterol (upper) and triglyceride (lower) concentrations of HIV-infected children in the PI group ($n = 17$) with treatment regimens containing PIs and the non-PI group ($n = 7$) with dual NRTI therapy. Solid lines represent the 3rd, 50th, and 97th percentiles of normal values for age.

Control and Prevention category as reference to initial disease severity in a few PI patients (Table 1).

Dyslipidemia in HIV-infected children of the PI-containing group is in sharp contrast to children in the non-PI group who had no detectable fasting hyperlipidemia. The results in nonfasting and fasting conditions are very similar. Nonfasting lipid parameters may be helpful for screening metabolic abnormalities in younger children as they are more easily available. Even in the fasting condition, there is a surprisingly high percentage of children in the PI group who presented with hypercholesterolemia (47%) and hypertriglyceridemia (65%, $n = 24$). Moreover 6 patients in the PI group showed an increase of apolipoprotein B with simultaneous presence of hypercholesterolemia. This is an interesting finding as defective metabolism of apolipoprotein B has recently been postulated to play a central role in PI-associated dyslipidemia.¹⁵ Fasting free fatty acids were also significantly higher in the PI group com-

pared with non-PI group. A correlation between an increase of free fatty acids and antiretroviral therapy in adults has been mentioned.¹⁶ However, the observed increase of free fatty acids compared with normal values in both groups may be a physiologic phenomenon and may validate that the children were indeed fasting.²⁸ Although the majority of the children in the PI group demonstrated alterations in lipid metabolism, it remains unclear why a subset of children showed normal values for triglycerides and cholesterol. Genetic, pharmacokinetic, virologic, or immunologic factors may protect these children. Dyslipidemia may still develop in these children after a longer treatment duration or may be more pronounced with drug dosing and may be more pronounced in children with higher PI levels.^{16,25}

In the present study, no interference of antiretroviral therapy with carbohydrate metabolism was seen in any HIV-infected child. In lipodystrophic children described by Jacquet et al,²⁰ there was a

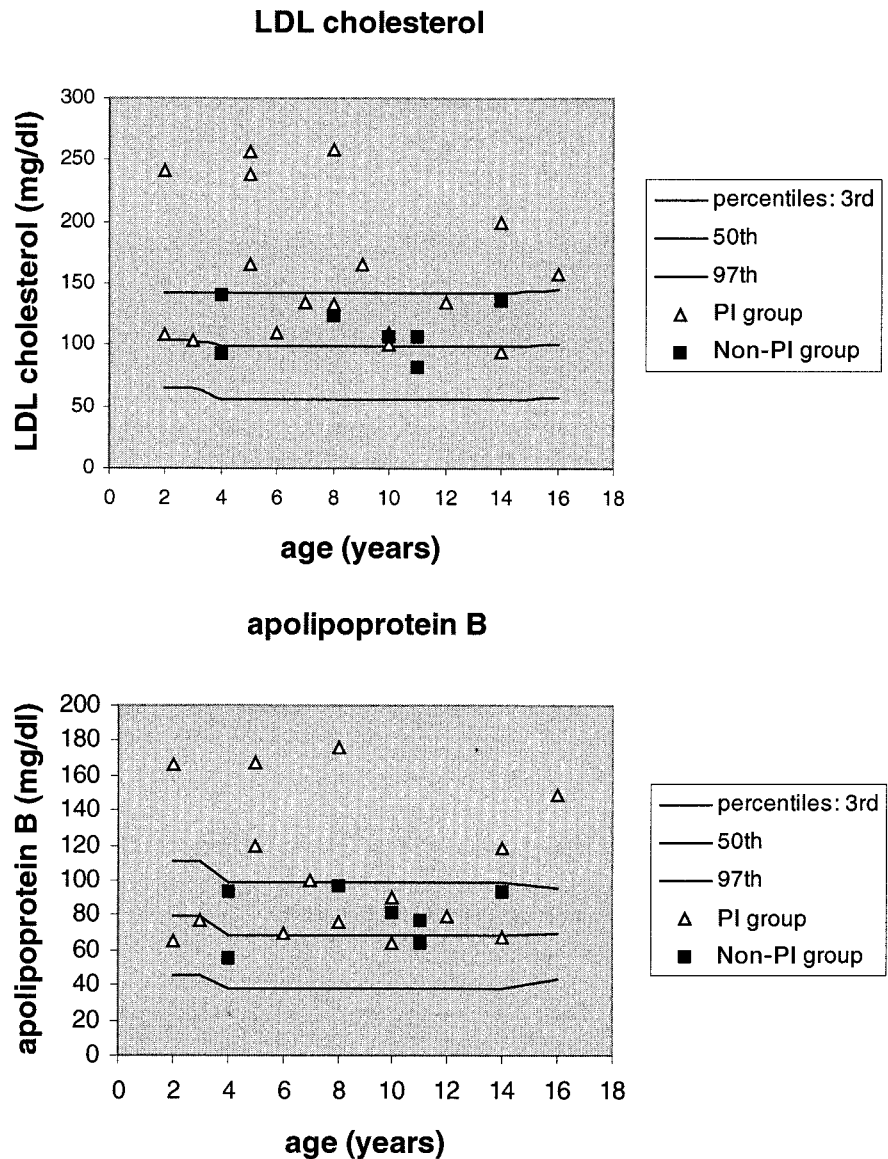


Fig 2. Individual fasting LDL cholesterol (upper) and apolipoprotein B (lower) concentrations of HIV-infected children in the PI group ($n = 17$) with treatment regimens containing PIs and the non-PI group ($n = 7$) with dual NRTI therapy. Solid lines represent the 3rd, 50th, and 97th percentiles of normal values for age.

higher fasting insulinemia and insulin:glucose ratio than in the nonlipodystrophic group, suggesting insulin resistance. At present, the clinical significance of these findings is unclear as neither impaired glucose tolerance nor type 2 diabetes was observed in these children.

In our patients, we did not observe lactic acidosis, but it has been reported in infants after treatment with AZT for perinatal transmission prophylaxis and may be associated with a potentially fatal syndrome in NRTI experienced adults.^{8,13,14,29} It cannot be excluded that in a larger sample size and over a longer observation period lactic acidosis may develop in children on antiretroviral therapy.

What are the long-term consequences of the observed alterations in lipid metabolism? Apart from pancreatitis and cholelithiasis, the lipodystrophy syndrome is a major concern.^{8-10,12} The largest published series on clinical lipodystrophy by Jaquet et al²⁰ comprises 13 HIV-infected children, 11 of whom received PI-containing regimens. Recently, dual-energy x-ray absorptiometry and magnetic resonance

imaging in 34 HIV-infected children including 6 children with lipodystrophy documented abnormal fat distribution in all children on PI-containing regimens, even in the absence of lipodystrophy.¹⁹ Laboratory values may facilitate the early detection of toxicity and may help to prevent serious morbidity and mortality.⁸ Arpadi et al³⁰ described an association between lipodystrophy and high viral load or low CD4 cell count. In our study, abnormalities in lipid metabolism were not correlated with viral load or CD4 cell count (data not shown). Although the exact predictive value of serum parameters is still controversial, dyslipidemia might reflect a subclinical alteration of adipose tissue and may allow detection of patients who are at risk of developing lipodystrophy.^{11,12,20} Our 5 patients with signs of lipodystrophy were on PI-containing regimens and had dyslipidemia. The use of sensitive imaging methods is planned to examine our patients for lipodystrophy and validate our clinical impression.

Premature atherosclerosis and coronary artery disease are other concerns in adult patients on PI-con-

taining HAART.^{8,9,31,32} In adults, high Lp(a) levels and various combinations of increased lipid parameters have been postulated to be associated with an increased risk for coronary heart disease.³¹ In children, premature atherosclerosis may be difficult to detect. The present study revealed increased Lp(a) in the whole population without differences between the PI and non-PI groups. This has to be interpreted with caution. Lp(a) concentration is known to be substantially determined by genetic factors. The average level of Lp(a) is higher in black Americans than in whites, suggesting that ethnic differences and Lp(a) concentration varies over an enormous range.¹¹ The majority of our patients with elevated Lp(a) are of African descent. Moreover, Lp(a) seems to be elevated in HIV-infected adults before therapy.³³ Therefore, it cannot be excluded that genetic factors and the HIV infection itself rather than side effects of the antiretroviral therapy may be associated with increased Lp(a) levels.

There is no evidence that HAART in children can be paused safely, and it is not recommended to switch therapy frequently in children.^{5,6,24} Therefore, PI-containing therapy may have to be continued for a long period. However, in adults, serum lipid abnormalities vanished with discontinuation of PIs.³⁴ In our own experience, change of HAART combination in 2 cases by exclusion of PI and inclusion of NNRTI led to a 40% decrease in triglycerides, cholesterol, and LDL cholesterol in 2 patients during the first 2 months after the switch. It remains to be investigated whether NNRTI-containing regimens do not result in metabolic alterations while having the same potent effect of viral load suppression and immune reconstitution as PI.

CONCLUSION

We found normal carbohydrate metabolism but a high frequency of dyslipidemia in children on PI-containing therapy. It should be pointed out that children in our cohort who were naive to PI did not show dyslipidemia. Large cooperative pediatric studies are needed to determine precisely the risk factors associated with metabolic toxicity. A systematic registration and understanding of these abnormalities in children and a careful evaluation of treatment strategy are necessary to prevent long-term deleterious consequences of dyslipidemia in the growing HIV-infected child.

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