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Impact of Protease Inhibitor Substitution With Efavirenz in HIV-Infected Children: Results of the First Pediatric Switch Study

Grace McComsey, MD*; Nasreen Bhumbra, MD†; Jen-Fu Ma§; Mobeen Rathore, MD||; and Ana Alvarez, MD||

ABSTRACT. *Objective.* Simplification of antiretroviral regimen in human immunodeficiency virus (HIV)-infected children has not yet been investigated. In general, children have a more difficult time maintaining viral suppression because of many factors, including frequent nonadherence and less availability of antiretrovirals in palatable forms. In addition, many serious metabolic complications have emerged in HIV-infected adults and are believed to be attributable to antiretroviral therapy. Some of these complications—hypercholesterolemia, hypertriglyceridemia, and insulin resistance—are believed to be the result of the use of protease inhibitor (PI) therapy, whereas the cause of others, such as lipodystrophy, remains undetermined. Recent reports underline that children experience long-term metabolic abnormalities in the same manner that adults do, and perhaps these consequences are even more worrisome in children secondary to long-term expected survival. We report here the results of the first open-label PI-switch study in HIV-infected children.

Methods. Seventeen children, 24 to 160 months of age (median: 120), were enrolled into the study. All were receiving a stable PI-containing antiretroviral regimen that containing 2 to 3 nucleoside analogue reverse transcriptase inhibitors (NRTIs) in addition to 1 to 2 PIs for a median duration of 21 months (range: 5–50) before study entry. All children had HIV-1 RNA <400 copies/mL at screening; their baseline plasma HIV-1 RNA level had been <400 copies/mL for a median of 13 months (range: 4–55) before study entry. All patients were naïve to non-nucleoside reverse transcriptase inhibitor therapy. Their protease inhibitor(s) was switched to efavirenz while their NRTI therapy was maintained.

Results. All children were heavily pretreated; 88% of the patients had previous NRTIs, and 41% had previous PI use. The most common PI at study entry was nelfinavir (47%), followed by ritonavir (29%), then amprenavir (18%); only 1 was on saquinavir/ritonavir. At study entry, the duration of previous antiretroviral therapy was between 21 and 123 months (median: 88). All patients completed the 48-week study. No acquired immunodeficiency syndrome-defining events occurred. There were no rashes and no changes in liver transaminases. Mild,

transient insomnia and dizziness each occurred in 1 child. Two other subjects (6 and 8 years old) experienced unusual vivid dreams, mostly pleasant, which decreased in intensity and frequency after the first 12 weeks of the study. One subject, a 10-year-old girl, had an episode of generalized seizure at week 6; study drugs were not interrupted, and seizure never recurred. The patient had a strong family history of epilepsy, although she had never experienced previous seizures. No anticonvulsants were given. Sixteen of 17 patients had HIV-1 RNA levels of <50 copies/mL (1 HIV-1 RNA was 61 copies/mL) at week 48. The mean CD4% remained stable initially from a mean of 35.1% ($\pm 2.8\%$) at baseline to 36.8% ($\pm 5\%$) at week 24, but increased to 38% ($\pm 6\%$) at week 48. Fasting triglycerides decreased from a mean of 126 mg/dL (± 50) at baseline to 86 mg/dL (± 45) at week 24 and to 94 mg/dL (± 38) at week 48. At study entry, 12 (71%) of 17 children had triglyceride levels greater than the 95th percentile for age, race, and gender, compared with only 6 (35%) of 17 at week 48. Fasting cholesterol levels decreased from a mean of 203 mg/dL (± 50) at baseline to 173 mg/dL (± 31) at week 24 and to 174 mg/dL (± 27) at week 48. At study entry, 5 (29%) of 17 children had cholesterol levels greater than the 95th percentile for age, race, and gender, compared with only 1 (6%) of 17 at week 48. The decrease in low-density lipoprotein cholesterol was also significant, from a mean baseline of 124 mg/dL (± 42) to 100 mg/dL (± 28) at week 24 and to 105 mg/dL (± 20) at week 48. High-density lipoprotein (HDL) cholesterol did not change significantly, but the changes in cholesterol:HDL ratio, a better marker of atherogenic risk, significantly decreased from a mean baseline of 3.8 (± 0.8) to 3.2 (± 0.7) at week 24 and to 3 (± 0.6) at week 48. Detailed dietary history revealed no significant changes during the study. In addition, none of the patients initiated therapy with lipid-lowering agents. There were no significant changes in insulin or C-peptide throughout the study period. In addition, anthropometric measurements that included mid-thigh and mid-arm circumferences, triceps and thigh skinfolds, and waist:hip ratio were stable throughout the study period. For bioelectrical impedance measurements, lean body mass increased from a mean baseline of 32.1 lb (± 9.3) to 35.7 lb (± 11.4) at week 24 and to 36.5 lb (± 11.5) at week 48. Bioelectrical impedance measurements of fat content were unchanged throughout the study period.

Conclusion. This is the first study in children to evaluate the substitution of PI in a virologically successful regimen with efavirenz, a potent once-daily nonnucleoside reverse transcriptase inhibitor therapy. We were able to show significant improvement in fasting total cholesterol, low-density lipoprotein cholesterol, triglycerides, and, more important, the cholesterol:HDL ratio. In addition, switching to an efavirenz-containing regimen was well tolerated and successfully maintained virologic suppression in all HIV-infected children in this study.

From the *Rainbow Babies and Children's Hospital, Center for AIDS Research, Case Western Reserve University, Cleveland, Ohio; †Medical College of Ohio, Toledo, Ohio; §Bristol-Myers Squibb, Plainsboro, New Jersey; and ||University of Florida Health Science Center, Jacksonville, Florida. This study was partly presented at the Eighth Conference on Retroviruses and Opportunistic Infections; February 4–8, 2001; Chicago, IL. Received for publication Aug 5, 2002; accepted Oct 18, 2002. Reprint requests to (G.M.) Department of Pediatrics, Division of Infectious Diseases, Rainbow Babies and Children's Hospital, 11100 Euclid Ave, Cleveland, OH 44106. E-mail: mcomsey.grace@clevelandact.org PEDIATRICS (ISSN 0031 4005). Copyright © 2003 by the American Academy of Pediatrics.

This study should encourage large randomized trials to investigate simplification strategies in HIV-infected children. *Pediatrics* 2003;111:e275–e281. URL: <http://www.pediatrics.org/cgi/content/full/111/3/e275>; HIV, AIDS, simplification, lipodystrophy, switch studies, metabolic complications.

ABBREVIATIONS. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor; BIA, bioelectrical impedance; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

The advent of highly active antiretroviral therapy (HAART) has led to significant improvement in mortality and morbidity of human immunodeficiency virus (HIV)-infected individuals.¹ Recently, many serious metabolic complications have emerged and are believed to be attributable to antiretroviral therapy.^{2,3} The most common metabolic abnormalities encountered are hypercholesterolemia, hypertriglyceridemia, and insulin resistance. Other abnormalities include peripheral fat wasting, visceral fat accumulation, and hypertension. After much debate in the past few years on the causes of these complications, the spotlight remains on the protease inhibitors (PIs) as being the main culprit in most of these abnormalities, mainly the dyslipidemias and insulin resistance. Even a short-course administration of these agents to HIV-uninfected healthy volunteers has led to significant dyslipidemias and insulin resistance.^{4,5}

Simplification strategy has been investigated in HIV-infected adults.^{6–10} Patients who have been treated successfully with PIs may choose to switch to nonnucleoside reverse transcriptase inhibitor (NNRTI)- or exclusive nucleoside analogue reverse transcriptase inhibitor (NRTI)-based regimens to decrease short-term side effects, to prevent or reverse long-term toxicity, or to simplify therapy and improve adherence and quality of life.^{9–11} In general, children have a more difficult time maintaining viral suppression because of many factors, including frequent nonadherence and less availability of antiretrovirals in palatable forms. Recent reports underline that children experience long-term metabolic abnormalities in the same manner that adults do,^{12–17} and perhaps these consequences are even more worrisome in children secondary to long-term expected survival. We report here the results of the first open-label PI-switch study in HIV-infected children. The objectives of this study were to evaluate the virologic and immunologic effect of PI substitution with efavirenz in HIV-infected children, the metabolic changes associated with this substitution, and the safety and tolerability of efavirenz in this population.

METHODS

Patients

Children were enrolled in the study when they fulfilled the following criteria: HIV-1 infection as confirmed by enzyme-linked immunosorbent assays and Western blot. In addition, all children younger than 18 months had to have documentation of 2 positive HIV-1 polymerase chain reaction assays. Other inclusion criteria

were age 1 to 18 years, plasma HIV-1 RNA of <400 copies/mL for at least 4 consecutive months, receiving a stable PI-containing antiretroviral regimen for at least 6 months before study entry, and no previous NNRTI therapy. Patients with known opportunistic infections must have had no acute symptoms of infection within the last month before study entry and must have been receiving a stable approved antimicrobial therapy. Written informed consent was obtained from each patient's legal guardian before enrollment. This study was approved by the Institutional Review Boards at the University Hospitals of Cleveland (Cleveland, OH), the Medical College of Ohio (Toledo, OH), and the University of Florida Health Science Center (Jacksonville, FL).

Trial Design and Treatment

This was a prospective, open-label, multicenter trial. At study entry, the PIs were switched to efavirenz, at weight-dependent doses, as recommended by the manufacturer. Patients were maintained on their preentry NRTIs throughout the duration of the study. Efavirenz was provided by Dupont Pharmaceuticals (Wilmington, DE) in a form of 200-, 100-, and 50-mg capsules. Parents of children younger than 5 years were informed to open the capsules and mix the content very well in grape jelly.

Clinical Endpoints and Laboratory Measurements

Evaluations were performed at baseline and at weeks 2, 6, 12, 18, 24, 32, 40, and 48. At each evaluation, patients underwent a complete medical history and a physical examination that included weight, height, and blood pressure measurements. Laboratory evaluations included serum glucose, blood chemistries, complete blood counts, creatine kinase, total bilirubin, aspartate transaminase, amylase (and, if elevated, lipase), flow cytometric measurements of CD4 and CD8, and HIV-1 RNA using the ultrasensitive assay (linear range 50–75 000 copies/mL). In addition, metabolic evaluations were obtained at study entry and every 12 weeks thereafter. These included C-peptide, insulin, complete lipid profile, and bioelectrical impedance (BIA) and anthropometric measurements, including mid-thigh and mid-arm circumferences, triceps and thigh skinfolds, and waist:hip ratio. All these metabolic evaluations were obtained after at least 8 hours of fasting.

Statistical Methods

Mean change from baseline for clinical laboratory evaluations were assessed for statistical significance using a 2-sided paired *t* test. Quantitative data were expressed in terms of means (\pm standard deviation) unless otherwise specified. Qualitative variables were expressed as percentages. *P* < .05 was considered statistically significant.

RESULTS

Patients' Characteristics

Seventeen children, age 24 to 160 months (median: 120), were enrolled into the study. Fifty-nine percent (10 of 17) were girls, 88% (15 of 17) were black, and 12% (2 of 17) were white. All children acquired HIV by vertical transmission. All were receiving a stable PI-containing antiretroviral regimen for a median duration of 21 months (range: 5–50) before study entry. All children had HIV-1 RNA <400 copies/mL at screening; their baseline plasma HIV-1 RNA level had been <400 copies/mL for a median of 13 months (range: 4–55). In 1 child, repeat HIV-1 RNA at study entry was 1441 copies/mL. The median CD4% was 35% (range: 31–42) at study entry. The median CD4% nadir (before the initiation of any antiretrovirals) was 21% (range: 0–42), and the median pre-HAART HIV-1 RNA was 15 395 copies/mL (range: 1066 to >750 000). All children were heavily pretreated, but they had never received any NNRTI therapy. The most common PI at study entry was nelfinavir (47%), followed by zidovudine (29%), then

amprenavir (18%); only 1 was on saquinavir/ritonavir at study entry. The cumulative duration of previous antiretroviral therapy (before study entry) was between 21 and 123 months (median: 88); 88% of the patients had previous NRTIs and 41% had previous PI use (before the entry antiretroviral regimen). Tables 1 and 2 summarize the baseline characteristics of all 17 patients. At study entry, their PIs were switched to efavirenz while their NRTIs were maintained.

Clinical Evaluations

All patients completed the 48-week study. One child, a 24-month-old girl, was unable to swallow the intact capsule of efavirenz. Therefore, for this child, the efavirenz capsule was opened and mixed with grape jelly. No acquired immunodeficiency syndrome-defining events occurred. Mild, transient insomnia for the initial 4 weeks of the study occurred in a 10-year-old child; another 10-year-old described transient dizziness at week 2. Two other subjects (6 and 8 years old) experienced unusual vivid dreams, mostly pleasant, which decreased in intensity and frequency after the first 12 weeks of the study but persisted throughout the study period. One subject, a 10-year-old girl, had an episode of generalized seizure at week 6; study drugs were not interrupted, and seizure never recurred. The patient had a strong family history of epilepsy, although she had never experienced previous seizures. No anticonvulsants were given.

The efavirenz-containing regimen was associated with improvement of the children's quality of life as assessed by parents' self-report, as well as improvement in adherence, as judged by the number of missed doses (evaluations done in 10 patients only; mean of 1% missed doses vs 16% at study entry).

Clinical and laboratory results are shown in Table 3. Systolic and diastolic blood pressure remained stable throughout the study period. Body weight remained stable at week 24, from a mean of 41.4 kg (± 18.2) at baseline to 43.1 kg (± 18) at week 24 ($P > .05$), but increased significantly at week 48 to 45.3 kg (± 18.5 ; $P = .001$). Height steadily increased throughout the study period, from a mean baseline of 135.2 cm (± 20) to 137.7 cm (± 19) at week 24 ($P < .001$) and to 140.8 cm (± 18.4) at week 48 ($P < .001$). Body mass index did not significantly change after 48 weeks.

Laboratory Evaluations

At week 48, 16 of 17 patients had HIV-1 RNA levels of < 50 copies/mL; 1 patient had HIV-1 RNA of 61 copies/mL at week 48. The mean CD4% remained stable initially from a mean of 35.1% (± 2.8) at baseline to 36.8% (± 5) at week 24 ($P > .05$) but increased to 38% (± 6) at week 48 ($P = .03$). Because the absolute CD4 cell count is age dependent, the CD4 changes on study are shown only as changes in CD4%, rather than in absolute CD4 cell count. Liver and pancreatic enzymes did not change significantly.

Fasting triglycerides (Fig 1) decreased from a mean of 126 mg/dL (± 50) at baseline to 86 mg/dL (± 45) at week 24 ($P < .05$) and to 94 mg/dL (± 38) at week 48 ($P < .05$). We used data generated from studies in-

TABLE 1. Baseline Characteristics of Study Participants

Patient	Race	Gender	Age (Months)	Current Antiretrovirals	Cumulative Duration of NRTI Before Entry (Months)	Cumulative Duration of PI Before Entry (Months)	No. of Previous NRTIs	No. of Previous PIs	Duration of Preentry HAART Regimen (Months)	Nadir CD4%	CD4% at the Start of Study Entry HAART	CD4% at the Study Entry	HIV RNA at the Start of Study Entry HAART	Duration of RNA < 400 Before Study Entry (Months)
1	B	M	79	d4T/3TC/abacavir/amprenavir	62	35	2	1	5	0	28	36	6285	4.5
2	B	M	100	ddl/abacavir/ritonavir/saquinavir	28	35	3	1	13	28	30	34	3312	5
3	B	M	113	d4T/3TC/nelfinavir	66	7	1	0	15	24	33	32	2668	5.5
4	B	F	97	d4T/ddl/nelfinavir	24	24	0	0	24	37	24	35	28791	23
5	B	F	24	d4T/ddl/ritonavir	23	23	2	1	11	42	49	40	$> 750\ 000$	9
6	W	F	130	d4T/3TC/ritonavir	109	25	2	1	24	10	20	35	54582	21
7	W	M	81	d4T/3TC/nelfinavir	115	21	1	0	21	0	1	32	479038	18
8	B	F	160	abacavir/3TC/ritonavir	11	23	3	1	5	17	29	34	1066	4
9	B	F	152	d4T/ddl/nelfinavir	24	24	0	0	24	28	28	33	25931	7.5
10	B	F	89	d4T/ddl/nelfinavir	38	23	2	0	23	2	4	35	15395	22
11	B	F	120	d4T/ddl/nelfinavir	88	38	3	0	38	23	23	42	39969	6
12	B	F	120	combivir/ritonavir	112	44	1	0	9	20	32	31	ND	8
13	B	F	132	combivir/nelfinavir	123	38	1	0	5	6	23	31	2149	36.5
14	B	F	120	d4T/3TC/amprenavir	120	41	2	2	25	21	24	35	3020	13
15	B	M	144	combivir/amprenavir	118	39	1	1	18	12	16	42	162868	23
16	B	M	120	d4T/3TC/ritonavir	117	48	2	0	18	21	24	31	ND	55
17	B	M	130	d4T/3TC/nelfinavir	95	50	2	0	50	38	44.8	39	1643	37

TABLE 2. Baseline Characteristics of Study Participants

Patient	HIV RNA at Study Entry	AST (U/L)	Cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	Insulin (IU/mL)	C-Peptide (ng/mL)	BMI (kg/cm ²)	W-H	MAC (cm)	Triceps SF (mm)	MTC (cm)	Thigh SF (mm)	Fat (lb)	Fat %	LBM (lb)	LBM (%)
1	320	29	141	49	75	81	74	7.9	1.1	19.16	0.86	22	15	39.5	15	2.7	4	31.1	43
2	<50	25	134	43.2	70	84	77	10.5	1.6	27.88	0.89	29	32	51.4	31	23.3	21	27.6	33
3	<50	35	190	43.9	122	122	67	3.6	0.8	16.06	0.93	18.6	10	34	13	1.2	2	32.7	38
4	<50	36	190	75.7	104	52	65	3.1	1.1	16.58	0.82	19	11	37.7	3	9.6	16	20.1	34
5	<50	42	250	49.8	147	208	57	4.9	1.6	16.02	0.96	14.9	5	23	4	ND	ND	ND	ND
6	<50	27	238	52.1	144	172	68	3.7	1.5	17.17	0.93	18.4	8	35	2	9.8	16	21	34
7	117	32	161	52.8	90	91	76	5.5	3	15.43	0.96	16	9	30.5	11	ND	ND	ND	ND
8	<50	27	201	53	106	209	64	6.8	2.6	20.11	0.79	25.2	11	49.2	ND	24.9	23	39.5	36
9	<50	29	201	50.6	135	115	75	14.4	2.4	30.14	0.79	34.5	24	55	45	72.2	47	36.7	24
10	<50	37	221	70.8	134	80	79	6.5	1.3	17.59	0.88	20	8	36	15	10.5	18	21.5	37
11	<400	28	176	50	98	138	81	21.1	2.6	30.86	0.8	32.6	32	63.5	39	70.4	45	38.7	25
12	1,441	33	123	35	68	100	84	9.3	2.3	25.16	0.95	26.9	29	47.75	27.5	46	41	30	27
13	<50	31	237	44	154	193	66	10.7	3.7	17.59	0.87	20.6	7	43.6	15	14.1	17	29.8	36
14	<50	32	215	50	133	161	59	19.5	2.9	27.47	1	27.8	18	48.7	22	48.5	40	34.2	28
15	<400	32	200	67	117	78	96	76.9	6.5	28.72	1	33	27	23.5	49	28.7	20	54.3	38
16	<50	25	323	64	232	136	70	3.3	1.7	16.55	0.9	19.2	5	36.9	6	4.6	6	32.4	45
17	<50	NA	259	67	180	62	98	13	2.6	21.12	0.85	27	11	45.8	11	7.1	6	ND	ND

TG indicates triglycerides; BMI, body mass index; W-H, waist to hip ratio; MAC, mid-arm circumference; SF, skinfold; MTC, mid-thigh circumference; LBM, lean body mass; ND, not done.

volving >13 000 healthy children to assess better the significance of the lipid levels on our patients.¹⁸ At study entry, 12 (71%) of 17 children had triglyceride levels greater than the 95th percentile for age, race, and gender, compared with only 6 (35%) of 17 at week 48. All 5 children who entered the study with triglyceride levels within normal limits for age, race, and gender maintained it at week 48.

Cholesterol levels (Fig 2) decreased from a mean of 203 mg/dL (± 50) at baseline to 173 mg/dL (± 31) at week 24 ($P < .05$) and to 174 mg/dL (± 27) at week 48 ($P < .05$). At study entry, 5 (29%) of 17 children had cholesterol levels greater than the 95th percentile for age, race, and gender, compared with only 1 (6%) of 17 at week 48. Similar to the triglycerides results, all 12 children who entered the study with cholesterol levels within normal limits for age, race, and gender maintained it at week 48.

The decrease in low-density lipoprotein (LDL) cholesterol was also significant, from a mean baseline of 124 mg/dL (± 42) to 100 mg/dL (± 28) at week 24 ($P < .05$) and to 105 mg/dL (± 20) at week 48 ($P < .05$). High-density lipoprotein (HDL) cholesterol did not change significantly, but the changes in cholesterol:HDL ratio, a better marker of atherogenic risk,¹⁹ significantly decreased from a mean baseline of 3.8 (± 0.8) to 3.2 (± 0.7) at week 24 ($P < .05$) and to 3 (± 0.6) at week 48 ($P < .001$). Detailed dietary history revealed no significant changes during study. In addition, none of the patients initiated therapy with lipid-lowering agents.

There were no significant changes in insulin or C-peptide throughout the study period. In addition, anthropometric measurements that included mid-thigh and mid-arm circumferences, triceps and thigh skinfolds, and waist:hip ratio were stable throughout the study period. For BIA measurements, lean body mass (Fig 3) increased from a mean baseline of 32.1 lb (± 9.3) to 35.7 lb (± 11.4) at week 24 ($P < .05$) and to 36.5 lb (± 11.5) at week 48 ($P < .001$). BIA measurements of fat content were unchanged throughout the study period.

DISCUSSION

To the best of our knowledge, this is the first study in children to evaluate the substitution of PI in a virologically successful regimen with efavirenz, a potent once-daily NNRTI.

Efavirenz has several pharmacodynamic characteristics that makes it more tolerant of occasional breaches in compliance: a long half-life of 40 to 55 hours, coupled with a high (20–30 \times) ratio of free drug plasma trough levels to the IC₉₀ for wild-type virus.²⁰ In this study, we were able to show maintenance of virologic suppression in all children who enrolled into this simplification trial, in which the PI was switched to efavirenz. This was likely related in part to improved convenience and, thereby, adherence. This is consistent with several studies of HIV-infected adults who had a good virologic control at the time they were enrolled into the simplification study.⁶ The accumulated weight of evidence from European and American studies suggests that a switch to a simplified regimen, replacing a PI with

TABLE 3. Changes in Metabolic, Immunologic, and Virologic Parameters

Parameter (Mean [\pm SD], Median, Range)	Study Entry	Week 24	Week 48
Systolic blood pressure	103 (\pm 11); 100, 90–120	108 (\pm 13), 108, 90–129	106 (\pm 9), 107, 90–127
Diastolic blood pressure	64 (\pm 7), 63, 52–80	64 (\pm 4), 65, 51–80	66 (\pm 6), 67, 55–75
Total cholesterol (mg/dL)	203 (\pm 50), 201, 123–323	173 (\pm 31), 180.5, 113–223	174 (\pm 27), 175, 126–217
LDL cholesterol (mg/dL)	124 (\pm 42), 122, 68–232	100 (\pm 28), 103, 51–153	105 (\pm 20), 102, 66–138
HDL cholesterol (mg/dL)	54 (\pm 11), 51, 35–76	56 (\pm 11), 52, 39–78	61 (\pm 10), 61, 42–84
Triglycerides (mg/dL)	126 (\pm 50), 115, 52–209	86 (\pm 45), 71, 36–202	94 (\pm 38), 81, 49–172
Cholesterol: HDL ratio	3.8 (\pm 0.8), 3.8, 2.5–5.4	3.2 (\pm 0.7), 3.1, 2.2–4.6	3 (\pm 0.6), 3, 2.2–4.2
Glucose (mg/dL)	74 (\pm 11), 74, 57–98	84 (\pm 8.6), 83, 69–99	81 (\pm 11), 81, 59–104
Insulin (IU/mL)	13 (\pm 17), 8, 3–77	14 (\pm 16), 9, 2–60	13 (\pm 10), 12, 2.5–34
C-peptide (ng/mL)	2.3 (\pm 1.3), 2.3, 0.8–6.5	2.5 (\pm 2.1), 1.6, 0.7–9.2	2.8 (\pm 2.1), 2.6, 0.9–8.5
BMI (kg/cm ²)	21.4 (\pm 5.6), 19.2, 15.4–30.9	21.5 (\pm 5.4), 20.2, 15.6–30.3	21.7 (\pm 5.5), 22.1, 15.1–31.9
Fat (%)	21 (\pm 15), 18, 1.9–47	25 (\pm 13), 21, 6.4–47.3	23 (\pm 13), 21, 5–49
Fat (lb)	27 (\pm 24), 18.7, 2.3–70.4	29 (\pm 21), 22.95, 5.2–52.3	28 (\pm 22), 18.6, 3.9–81.9
Lean body mass (%)	34 (\pm 6), 35, 24–45	34 (\pm 6), 34, 23.5–43	35 (\pm 6), 35, 22.5–46
Lean body mass (lb)	32 (\pm 9), 31.8, 20–54	36 (\pm 11), 36, 20.5–57	36 (\pm 11), 35.5, 21–61
Waist-to-hip	0.89 (\pm 0.01), 0.89, 0.79–1	0.91 (\pm 0.07), 0.89, 0.83–1.1	0.91 (\pm 0.07), 0.89, 0.74–1
MAC (cm)	24 (\pm 6), 22, 14.9–34.5	24 (\pm 6), 24.45, 15–35.5	24 (\pm 6), 24.2, 16–34.5
Triceps skinfold (mm)	16 (\pm 10), 11, 5–32	17 (\pm 8), 15, 6–33	16 (\pm 9), 13, 4–35
Mid-thigh circumference (cm)	41 (\pm 11), 39.5, 23–63.5	44 (\pm 9), 45.5, 25.5–57	43 (\pm 9.5), 45.1, 27–58
Thigh skinfold (mm)	19 (\pm 15), 15, 2–49	20 (\pm 10), 18, 6–40	19 (\pm 11), 17, 5–47
CD4 %	35 (\pm 3), 35, 31–40	37 (\pm 5), 34.5, 30–48.3	38 (\pm 6), 37, 31–48.9
% with HIV-1 RNA <400 cps/mL	94%	100%	100%
% with HIV-1 RNA <50 cps/mL	59%	100%	94%

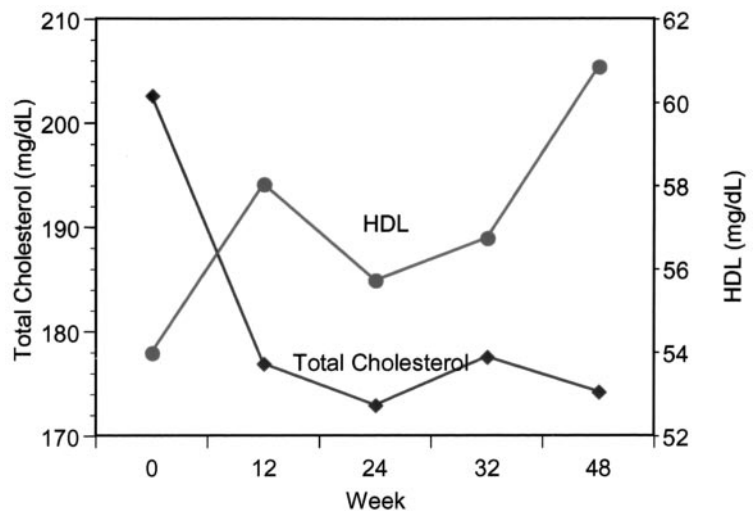


Fig 1. Mean fasting triglycerides, LDL cholesterol, and cholesterol:HDL ratio.

abacavir, efavirenz, or nevirapine, is successful in maintaining virologic suppression in patients who initiated their PI-based HAART without previous mono- or dual-NRTI therapy. Remarkably in this study, all children were able to maintain virologic suppression, despite a history of heavy previous exposure to NRTIs.

Derangement in lipid and glucose metabolism has been sparsely reported in children and adolescents infected with HIV.^{12,13,15,17} Treating lipid derangements has proved to be difficult even in HIV-infected adults. The standard lipid-lowering agents, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins,” must be used cautiously because of the potential for serious drug–drug interactions when used in conjunction with protease inhibitors.²¹ Only limited data are available on the use of statins in HIV-uninfected children, and to date, no data are available on their use in HIV-infected children. As in the adult HIV population, PI

therapy has the greatest association with dyslipidemia in children.^{12,13}

In studies of HIV-infected adults, lipid abnormalities have generally shown significant improvement when the PI was switched to either abacavir or nevirapine, whereas the lipid effect of the switch to efavirenz is more controversial.^{6,7,10} To date, no data are available for HIV-infected children. We were able to show for the first time significant improvement in fasting total cholesterol, LDL cholesterol, triglycerides, and, more important, of the cholesterol:HDL ratio with PI switch to NNRTI. The cholesterol:HDL ratio is an excellent predictor of future ischemic heart disease.¹⁹ The issues of both PI-induced dyslipidemias and their management are even more problematic in the pediatric population. Many children likely will require antiretroviral therapy for decades, and strict adherence to a low-fat diet is difficult in this age group.

We had used fasting insulin and C-peptide as markers of insulin resistance. Despite some pitfalls,

Fig 2. Mean total cholesterol and HDL cholesterol.

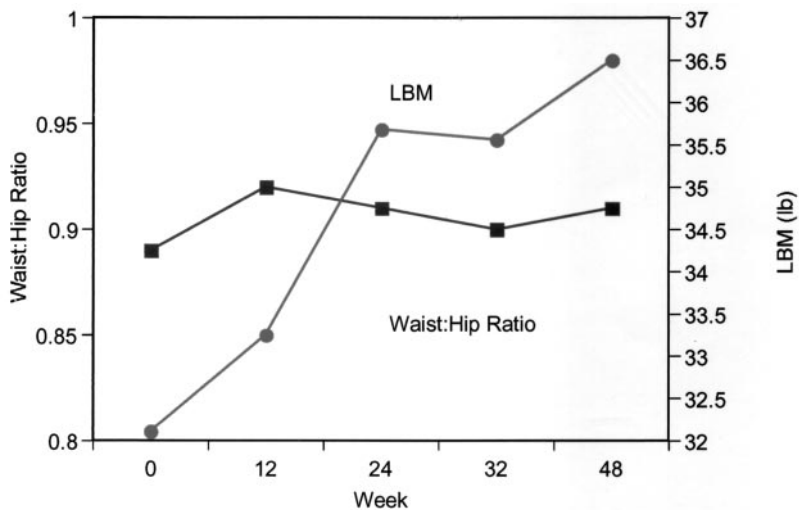
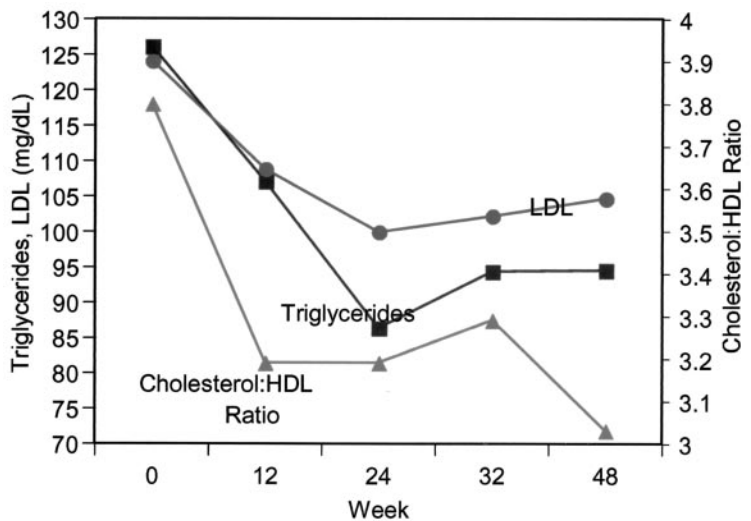


Fig 3. Mean waist:hip ratio and lean body mass.

these markers are widely used for this purpose, because the gold standard clamps techniques or even oral glucose tolerance tests are very cumbersome and impractical to use in most clinical settings. Consistent improvement in insulin sensitivity was seen on switching from PI to either NNRTI or abacavir in HIV-infected adults. Our study participants did not exhibit any significant abnormalities in their fasting insulin and C peptide, despite recent reports of frequent occurrence of insulin resistance in this population.^{15,22,23} These parameters did not change significantly throughout the study. Similar to adult studies, we failed to show evidence of body fat changes, as measured by BIA and standardized anthropometrics, after 48 weeks of PI discontinuation. Although we recognize that these measurements may have been confounded by normal physical development and growth, our observation is consistent with data from HIV-infected adults who were switched to efavirenz, nevirapine, or abacavir. In general, although patients tend to report subjective improvement in their body composition, objective measurements have failed to show evidence of reversal of body fat abnormalities.^{6,10,24} In all of these studies, the lack of significant objective improvement

in body composition abnormalities supports the possible role of NRTI, and not PI, in the generation of these abnormalities.^{25,26} In other words, these findings support the present hypothesis that antiretroviral-induced metabolic abnormalities may not be a consequence solely of PI but possibly of NRTI-induced mitochondrial dysfunction²⁵ or even of HIV infection itself, directly or indirectly through cytokine dysregulation. We recognize the limitations of this study, in particular the small sample size and the open-label, single-arm design. In addition, body composition was measured only by BIA and anthropometrics, both insensitive in detecting small changes in fat over time. This study should encourage large randomized trials to investigate simplification strategies in HIV-infected children.

CONCLUSION

This is the first reported simplification or switch study that included HIV-infected children. We were able to show that PI substitution with efavirenz was able to maintain virologic control successfully in a group of HIV-infected children, despite significant previous antiretroviral experience. At the same time, we show a modest decrease in fasting triglyceride,

LDL cholesterol, and cholesterol:HDL ratio levels. More important, this strategy of simplification may be a successful way to improve adherence and quality of life of the HIV-infected pediatric population, which experience the low availability of antiretrovirals in palatable forms.

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