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

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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 underling 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 nonnucleoside 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% (±2.8%) at baseline to 36.8% (±5%) at week 24, but increased to 38% (±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%) at 17 and 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%) at 17 and 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.
This study should encourage large randomized trials to investigate simplification strategies in HIV-infected children. *Pediatrics* 2003;111:275–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. Recently, many serious metabolic complications have emerged and are believed to be attributable to antiretroviral therapy. 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. Simplication strategy has been investigated in HIV-infected adults. 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. 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, 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 (± 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 at least 4 consecutive months, receiving a stable PI-containing antiretroviral regimen for at least 6 months 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 ritonavir (29%).
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 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.

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 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/m²) | W-H MAC (cm) | Triceps SF (mm) | Thigh SF (mm) | Fat % | Fat (lb) | LBM (lb) | LBM (%) |
|---------|------------------------|-----------|----------------------|-------------|-------------|-----------|---------------|----------------|----------------|------------|-------------|---------------|--------------|------|--------|--------|--------|--------|
| 1       | 320                    | 314       | 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                    | 134       | 43.2                 | 70          | 64          | 77         | 10.5          | 1.6            | 27.88       | 0.89       | 29          | 32            | 51.4           | 32  | 23.3   | 21      | 37.6   | 33     |
| 3       | <50                    | 139       | 43.9                 | 122         | 122         | 67         | 3.6           | 0.8            | 16.06       | 0.93       | 18.6         | 10            | 34             | 13  | 1.2    | 2       | 22.7   | 38     |
| 4       | <50                    | 190       | 75.7                 | 104         | 52          | 65         | 3.1           | 1.1            | 16.02       | 0.82       | 19           | 11            | 37.7           | 3   | 9.6    | 16      | 20.1   | 34     |
| 5       | <50                    | 250       | 49.8                 | 147         | 208         | 57         | 4.9           | 1.6            | 16.02       | 0.89       | 19.4         | 5             | 24             | 3   | 5      | 2       | ND     | ND     |
| 6       | <50                    | 238       | 52.1                 | 144         | 172         | 68         | 3.7           | 1.5            | 17.17       | 0.94       | 18.4         | 8             | 35             | 2   | 9.8    | 16      | 21     | 34     |
| 7       | 117                    | 32        | 50                   | 134         | 122         | 70         | 84            | 17.8          | 0.86        | 22          | 15            | 34             | 13            | 2.7 | 4      | 31.1   | 43     |
| 8       | <50                    | 201       | 53                   | 106         | 209         | 64         | 68            | 2.6            | 20.11       | 0.79       | 25.2         | 11            | 49.2           | 30  | 22.7   | 23      | 39.5   | 36     |
| 9       | <50                    | 214       | 50.6                 | 135         | 75          | 14.3        | 2.4           | 17.8          | 0.88        | 20          | 8            | 36             | 15            | 10.5 | 18.5   | 21      | 35.7   | 36     |
| 10      | <50                    | 37        | 221                  | 250         | 49          | 147         | 208           | 57             | 16.02       | 0.82       | 19           | 11            | 37.7           | 3   | 9.6    | 16      | 20.1   | 34     |
| 11      | <400                   | 28        | 176                  | 50           | 98          | 138        | 81            | 2.1           | 23.56       | 0.86       | 32.6         | 13            | 63.5           | 39  | 7.1    | 6       | 38.7   | 25     |
| 12      | 1,441                  | 32        | 123                  | 35           | 68          | 100        | 84            | 2.3           | 25.16       | 0.95       | 26.9         | 29            | 47.7           | 27  | 4.6    | 6       | 32.4   | 24     |
| 13      | 50                     | 31        | 237                  | 44           | 154         | 193        | 66            | 10.7          | 17.39       | 0.87       | 20.6         | 7             | 43.6           | 16  | 14.1   | 17      | 29.8   | 36     |
| 14      | <50                    | 215       | 50                   | 133         | 161         | 99          | 59            | 19.5          | 2.47        | 1           | 27.8          | 18            | 48.7           | 22  | 48.5   | 40      | 34.2   | 28     |
| 15      | >400                   | 200       | 67                   | 117         | 78          | 96          | 76.9          | 6.5           | 28.72       | 1          | 33            | 27            | 23.5           | 9   | 28.7   | 20      | 54.3   | 38     |
| 16      | <50                    | 25        | 323                  | 64           | 232         | 136        | 70            | 3.3           | 16.56       | 0.9        | 19.2         | 5             | 36.9           | 6   | 4.6    | 6       | 32.4   | 24     |
| 17      | <50                    | NA        | 259                  | 67           | 180         | 62          | 98            | 1.7           | 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.

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 NRTI. Elavirex has several pharmacodynamic characteristics: it is more tolerable than other PI drugs, has a high (20-30%) rate of drug resistance, and is less well tolerated for wild-type virus. In this study, we were able to show that the PI was switched to elavirex in the simplification trial, in which the PI was switched to elavirex successfully. The accumulated weight of evidence from European and American studies suggests that a switch to a simplified regimen, replacing a PI with efavirenz, is reasonable. This is consistent with several studies of HIV-infected adults who had a good virological control at the time they were enrolled into the simplification trial. This was likely related in part to improved convenience and thereby adherence. To the best of our knowledge, this is the first study involving 13,000 healthy children to assess better the significance of the lipid levels on our patients. There were no significant changes in insulin or C-peptide throughout the study period. In addition, there were no significant changes in insulin or C-peptide in children to evaluate the substitution of PI in a virologically successful regimen with elavirex, a potent once-daily NRTI. Elavirex has several pharmacodynamic characteristics: it is more tolerable than other PI drugs, has a high (20-30%) rate of drug resistance, and is less well tolerated for wild-type virus. In this study, we were able to show that the PI was switched to elavirex in the simplification trial, in which the PI was switched to elavirex successfully. The accumulated weight of evidence from European and American studies suggests that a switch to a simplified regimen, replacing a PI with efavirenz, is reasonable. This is consistent with several studies of HIV-infected adults who had a good virological control at the time they were enrolled into the simplification trial. This was likely related in part to improved convenience and thereby adherence.

DISCUSSION

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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. 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. 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.

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. 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.

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,
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. 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. 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. 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 dysfunction 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.

ACKNOWLEDGMENTS
This study was supported by Dupont Pharmaceuticals. Dr McComsey has received a clinical research grant from Bristol-Myers Squibb.

We thank Drs Michael Lederman, Sally Hodder, and Beth Burtel for insightful comments and all their patients and families for participating in the study.

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Pediatrics 2003;111:e275
DOI: 10.1542/peds.111.3.e275

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*Pediatrics* 2003;111:e275
DOI: 10.1542/peds.111.3.e275

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