Natural History of Lipid Abnormalities and Fat Redistribution Among Human Immunodeficiency Virus-Infected Children Receiving Long-Term, Protease Inhibitor-Containing, Highly Active Antiretroviral Therapy Regimens

Perdita Taylor, MD*; Carol Worrell, MD*; Seth M. Steinberg, PhD‡; Rohan Hazra, MD*; Shirley Jankelevich, MD*; Lauren V. Wood, MD*; Sheryl Zwerski, RN, MSN, CRNP*; Robert Yarchan, MD*; and Steven Zeichner, MD, PhD*

ABSTRACT. Objective. To characterize the type and frequency of biochemical lipid abnormalities and physical changes in body composition associated with the use of protease inhibitor (PI)-containing antiretroviral therapy among human immunodeficiency virus-infected children treated for up to 6 years.

Methods. A retrospective study of human immunodeficiency virus-infected pediatric patients enrolled in research protocols between August 1995 and December 2001 was performed. All patients who had received a PI for ≥2 years as part of their investigational antiretroviral treatment regimens during the study period were eligible. Of the 110 patients identified as having received PI therapy, 94 met the study criteria.

Results. Of the 94 patients evaluated, 9 patients (10%) developed fat redistribution as well as dyslipidemia, 49 patients (52%) developed dyslipidemia without associated physical changes, and 36 patients (38%) exhibited no elevation of lipid levels or physical signs of fat redistribution. For all 9 patients with fat redistribution, the onset of the physical changes was closely associated with changes during pubertal development. Fat redistribution was also associated with lower viral loads and higher, more sustained levels of dyslipidemia. The onset of dyslipidemia and fat redistribution peaked between 10 and 15 years of age.

Conclusion. Among pediatric patients receiving PI therapy, there seems to be an age range in which children are at greater risk of developing hypercholesterolemia and subsequent fat redistribution, suggesting that unidentified physiologic changes associated with puberty may predispose pediatric patients treated with PI therapy to developing lipodystrophy. Pediatrics 2004; 114:e235–e242. URL: http://www.pediatrics.org/cgi/content/full/114/2/e235; human immunodeficiency virus, protease inhibitor, lipid, fat.

ABBREVIATIONS. HAART, highly active antiretroviral therapy; PI, protease inhibitor; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; AIDS, acquired immunodeficiency syndrome; DEXA, dual-energy x-ray absorptiometry.

HIV-infected children treated with highly active antiretroviral therapy (HAART) regimens that include a human immunodeficiency virus (HIV) protease inhibitor (PI) can exhibit large decreases in plasma HIV RNA concentrations (viral load) and subsequent increases in the number of circulating CD4+ T lymphocytes. These changes have resulted in significant improvements in clinical outcomes and quality of life, dramatically decreasing the risk of serious opportunistic infections, progression to acquired immunodeficiency syndrome (AIDS), and death. For many, HIV disease has been transformed from an acutely life-threatening illness into a manageable chronic disease, allowing children once not expected to survive to live well into adulthood. However, HAART has also been associated with certain undesirable side effects, including gastrointestinal intolerance, high pill burden, mitochondrial toxicities, and lipodystrophy, a syndrome characterized by changes in body habitus attributable to fat redistribution and associated with many metabolic derangements.

Lipodystrophy among adults has been described extensively, and there are indications that it is associated with the use of PIs, with nucleoside reverse transcriptase inhibitor (NRTI) therapy, and perhaps with HIV infection itself. There is not a universally accepted definition of lipodystrophy, but most descriptions of the syndrome define it on the basis of clinical features of fat redistribution, as assessed with patient reports, physical examinations, single-slice, abdominal, computed tomography scans, and/or dual-energy x-ray absorptiometry (DEXA) scans, with an associated range of metabolic abnormalities. The physical features include clinical evidence of ≥1 of the following: fat wasting (lipoatrophy) of the face, extremities, or buttocks and fat accumulation (lipohypertrophy) in the abdomen or over the dorsocephalic spine. The metabolic features include ≥1 of the following: fasting hypertriglyceridemia and/or hypercholesterolemia, fasting C-peptide level elevation, and evidence of abnormal glucose metabolism.
including disorders ranging from abnormal fasting glucose levels to diabetes mellitus.\textsuperscript{2,7} The pathogenesis of antiretroviral agent-associated lipodystrophy syndrome and its direct association with PI therapy are unclear but are likely to be multifactorial.

HAART-associated lipodystrophy has not been as extensively studied among children as it has among adults. Recent studies on the emergence and definition of lipodystrophy among HIV-infected pediatric patients receiving HAART demonstrated that lipodystrophy occurs more frequently among children than previously thought but the onset is usually subtle and the manifestations are less severe than those seen among adults.\textsuperscript{9–14} It has also been noted that other antiretroviral drugs, especially stavudine, may play an independent or contributory role in the development of lipodystrophy, as may diet and lifestyle. Although published studies have yielded valuable short-term data on the frequency of lipodystrophy and its association with PI-containing antiretroviral therapy among children, few long-term data exist that establish the risk factors for its development.

In this study, we report longitudinal clinical data for pediatric patients continuously exposed to PI-containing HAART regimens for up to 6 years, and we describe the rate of occurrence of the physical manifestations of fat redistribution and dyslipidemia, as well as the factors associated with their onset. We found 2 potentially significant risk factors for the development of fat redistribution and dyslipidemia among children, ie, pubertal development during PI therapy and the virologic response to HAART. Patients who begin receiving PI-containing HAART as they are going through puberty and perhaps those who begin receiving PIs at a very young age but remain on PI-containing HAART during puberty may have greater risks of developing more severe manifestations of these toxicities.

METHODS

Patients and Case Identification

We reviewed the records of all pediatric patients enrolled in research protocols of the HIV and AIDS Malignancy Branch, National Cancer Institute, who had been treated with a PI between August 1, 1995, and December 31, 2001. Studies included phase I/II protocols investigating the PIs indinavir (along with didanosine and lamivudine) and ritonavir (along with didanosine and didanosine), a pilot study of the immunologic reconstitution of HIV-1-infected children receiving HAART with the combination of ritonavir, nevirapine, and stavudine, a pilot study of interleukin-2, and a long-term observational protocol for patients treated with PIs (in the latter 2 protocols, patients were treated with multiple types of HAART regimens). We identified 110 HIV-infected children who had been on a regimen that included a PI. The eligibility criteria for the study included patients who had been on a PI-containing regimen for \( \geq 2 \) years. With these eligibility criteria, 94 patients were found to be eligible for the retrospective study; 16 patients who had been exposed to PI-containing regimens for \(< 2 \) years were excluded. As part of their research study participation, patients were evaluated routinely with laboratory and physical examinations. All records were reviewed to identify any elevations in serum lipid levels or the development of any physical signs of fat redistribution during the 6-year time period.

The criteria set forth in the 1991 National Cholesterol Education Program report on the management of blood cholesterol levels among children were used to define abnormal lipid levels.\textsuperscript{15} Hypercholesterolemia was defined as a total fasting cholesterol level of \( > 200 \) mg/dL and a low-density lipoprotein cholesterol level of \( > 130 \) mg/dL. Hypertriglyceridemia was defined as a fasting triglyceride level of \( > 140 \) mg/dL. If a laboratory sample was obtained from a patient who had not fasted, then elevated lipid laboratory values were confirmed in the fasting state at the next visit. Data abstraction included age, gender, mode of HIV transmission, complete antiretroviral therapy history, Centers for Disease Control and Prevention classification, CD4\textsuperscript{+} T lymphocyte counts, HIV-1 RNA levels, Tanner stages, and assessments for physical signs of fat redistribution. Fat redistribution was defined primarily with phenotypic criteria noted during protocol-related physical examinations and was considered to be any physical evidence of the following, alone or in combination: changes in body habitus consistent with truncal obesity, peripheral fat wasting, excessive breast enlargement among postpubertal female patients, or dorsocervical fat pad (buffalo hump). Dyslipidemia was defined as \(< 3 \) consecutive cholesterol and/or triglyceride blood levels elevated above the normal levels, with the elevation being defined with the National Cholesterol Education Program criteria for high blood cholesterol and triglyceride levels.

Three groups of patients were identified on the basis of evidence of physical changes associated with fat redistribution, with or without dyslipidemia. Detailed physical examinations of these patients occurred at uniform intervals, generally every 3 months, as mandated by the patients’ protocols, and data were recorded in a database (maintained with FileMaker Pro software, Filemaker, Inc, Santa Clara, CA) in a uniform structured manner, via direct entry by the health care provider into computerized physical examination forms. We defined 3 groups of patients on the basis of the appearance of dyslipidemia and fat redistribution: 1 included patients with dyslipidemia and physically apparent changes associated with fat redistribution (fat wasting of the face, extremities, or buttocks or fat accumulation in the abdomen or over the dorsocervical spine). Group 2 included patients with dyslipidemia only and no observed physical changes. Group 3 included patients without evidence of either dyslipidemia or fat redistribution.

Statistical Analyses

The probability of developing lipodystrophy or dyslipidemia was determined by using the Kaplan-Meier method,\textsuperscript{16} from the date on which the PI was first used until the date on which the outcome being evaluated was noted. For patients who did not develop the outcome under evaluation, follow-up monitoring was conducted at the date on which the PI was no longer used. These analyses were performed by both excluding patients whose lipid values were known to be elevated before initiation of a PI-containing therapy and including those patients. Analyses that categorized patients into 4 age groups (0 to \(< 5 \) years of age, 5 to \(< 10 \) years of age, 10 to \(< 15 \) years of age, and \( > 15 \) years of age) were also performed, with the pairwise significance of the difference in the probability of developing high lipid levels between groups being determined with the Mantel-Haenszel method.\textsuperscript{17}

The 3 groups of patients were compared by using several continuously measured parameters (CD4\textsuperscript{+} T lymphocyte counts from baseline through year 5, HIV-1 RNA levels from baseline through year 5, changes in CD4\textsuperscript{+} T lymphocyte counts from baseline to year 1 through year 5, changes in HIV-1 RNA levels from baseline to year 1 through year 5, at the start of PI therapy, number of years of PI therapy, and number of years of NRTI therapy). All pairwise comparisons between groups were made by using the Wilcoxon rank sum test. The 58 patients with lipid abnormalities, including those with lipodystrophy and those with dyslipidemia only, were pooled, and immunologic and virologic results were compared with those for patients with normal lipid levels and no changes in body habitus with the Wilcoxon rank sum test. Because a large number of tests were performed on continuously measured parameters and because the continuously measured variables are probably not independent, a simple interpretation to account for multiple comparisons was used. Any \( P \) value between \( .01 \) and \( .05 \) was considered representative of a trend toward statistical significance, whereas any result with a \( P \) value of \(< .01 \) was interpreted as statistically significant. All \( P \) values were 2-sided.
RESULTS

General Results

Ninety-four patients treated with PI therapy met our criteria for inclusion in this study. The median age at the onset of PI therapy was 8.9 years, the median duration of PI therapy was 4.4 years, and the median duration of prior NRTI therapy was 4.6 years for the patients in this cohort. Of these, a total of 9 patients (10%) developed both physical changes associated with fat redistribution and dyslipidemia (group 1). There were 49 patients (52%) who exhibited dyslipidemia without notable physical changes in body habitus (group 2) and 36 patients (38%) who demonstrated no evidence of dyslipidemia or altered body habitus associated with PI therapy during the study period (group 3). The demographic and clinical data for all 94 patients are presented in Table 1.

The time to the development of fat redistribution or dyslipidemia during PI therapy was calculated from the PI therapy start date until the date on which the physical or laboratory abnormality was noted or until the patient was no longer receiving a PI, if neither developed. The median time from the start of PI therapy until the development of dyslipidemia was 7.3 months (among 49 patients with dyslipidemia; range: 0-47 months) and the time until the development of physical signs of fat redistribution was 31.7 months (among 9 patients with lipodystrophy; range: 7.7-67.1 months). The probability of developing fat redistribution, as a function of months after institution of PI therapy, is depicted in Fig 1. Viral loads after 2 and 3 years of therapy were significantly lower among patients with fat redistribution and dyslipidemia (group 1), compared with the group with dyslipidemia alone (group 2) (Table 1). When changes in CD4+ cell counts from baseline levels were evaluated, results for group 1 alone and groups 1 and 2 together suggested trends toward statistical significance, in comparison with group 3, for years 2 and 3 of the study, but this was not seen when absolute values were compared. No significant differences between group 2 and group 3 with respect to viral loads or CD4+ cell counts were noted at any time point. No significant differences between any of the groups with respect to gender, duration of PI treatment, or duration of prior NRTI treatment were noted.

Clinical Results

Of the 9 patients who developed physical changes consistent with fat redistribution, 2 had truncal obesity only (ages at the time of the physical changes

TABLE 1. Demographic Variables

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1, Children with Fat Redistribution and Dyslipidemia</th>
<th>Group 2, Children with Dyslipidemia Only</th>
<th>Group 3, Children with No Fat Redistribution or Dyslipidemia</th>
<th>P Values for Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
<td>No.</td>
<td>Group 1 vs Group 2</td>
</tr>
<tr>
<td>No.</td>
<td>9</td>
<td>49</td>
<td>36</td>
<td>.07</td>
</tr>
<tr>
<td>Gender, female/male</td>
<td>7/2</td>
<td>20/29</td>
<td>14/22</td>
<td>.38</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>6 vertical, 3 transfusion</td>
<td>39 vertical, 1 unknown, 9 transfusion</td>
<td>8.9 (1.7–18.5)</td>
<td>.64</td>
</tr>
<tr>
<td>Median age at PI start, y (range)</td>
<td>9.8 (6.0–14.0)</td>
<td>8.0 (0.5–17.9)</td>
<td></td>
<td>.017</td>
</tr>
<tr>
<td>Initial PI used to treat patient</td>
<td>Indinavir</td>
<td>1</td>
<td>19</td>
<td>.01</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>7</td>
<td>19</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median years of PI therapy (range)</td>
<td>3.4 (2–6.4)</td>
<td>4.5 (2.0–6.4)</td>
<td>.69</td>
<td>.44</td>
</tr>
<tr>
<td>Median years of prior NRTI therapy (range)</td>
<td>5.3 (0.4–7.5)</td>
<td>4.3 (0.7–8.9)</td>
<td>.47</td>
<td>.32</td>
</tr>
<tr>
<td>Median CD4+ cell count (range)</td>
<td>527 (0–665)</td>
<td>226 (0–2022)</td>
<td>356 (0–1706)</td>
<td>.97</td>
</tr>
<tr>
<td>Start of PI</td>
<td>660 (7–1450)</td>
<td>605 (10–2237)</td>
<td>592 (3–1888)</td>
<td>.90</td>
</tr>
<tr>
<td>1 y of PI</td>
<td>863 (0–1333)</td>
<td>607 (4–2913)</td>
<td>556.5 (0–1619)</td>
<td>.43</td>
</tr>
<tr>
<td>3 y of PI</td>
<td>868 (0–1205)</td>
<td>575 (4–2340)</td>
<td>590 (0–1302)</td>
<td>.33</td>
</tr>
<tr>
<td>4 y of PI</td>
<td>759 (239–1084)</td>
<td>577 (3–2296)</td>
<td>554 (4–1881)</td>
<td>.31</td>
</tr>
<tr>
<td>5 y of PI</td>
<td>610 (23–619)</td>
<td>592 (16–1901)</td>
<td>576 (5–1776)</td>
<td>.62</td>
</tr>
<tr>
<td>Median HIV RNA, log_{10} copies/mL (range)*</td>
<td>4.7 (2.8–5.8)</td>
<td>4.9 (3.3–6.2)</td>
<td>5.1 (3.3–6.4)</td>
<td>.30</td>
</tr>
<tr>
<td>Start of PI</td>
<td>2.3 (2.3–5.5)</td>
<td>4.1 (2.3–6.7)</td>
<td>4.0 (2.3–5.6)</td>
<td>.042</td>
</tr>
<tr>
<td>1 y of PI</td>
<td>2.3 (1.69–4.8)</td>
<td>2.3 (1.69–5.8)</td>
<td>3.6 (1.8–6.2)</td>
<td>.010</td>
</tr>
<tr>
<td>2 y of PI</td>
<td>1.69 (1.69–4.7)</td>
<td>4.2 (1.69–5.9)</td>
<td>3.7 (1.69–6.7)</td>
<td>.009</td>
</tr>
<tr>
<td>3 y of PI</td>
<td>1.69 (1.69–5.6)</td>
<td>3.8 (1.69–6.0)</td>
<td>3.2 (1.69–5.0)</td>
<td>.19</td>
</tr>
<tr>
<td>4 y of PI</td>
<td>1.69 (1.69–5.3)</td>
<td>3.8 (1.69–5.2)</td>
<td>3.0 (1.69–5.6)</td>
<td>.64</td>
</tr>
</tbody>
</table>

P values of <.01 were considered significant, and .01 < P < .05 indicated a trend. P values were determined with Mehta’s version of Fisher’s exact test for r × c contingency tables.

* Assessed with the Roche Amplicor test for plasma HIV RNA concentration; with the lower limit of detection being 2.3 log_{10} copies/mL until April 2000 and 1.69 log_{10} copies/mL thereafter.
were 10.1 and 18.6 years), 4 had truncal obesity and
dorsocervical fat pads (ages at the time of the physi-
cal changes were 9.1, 11.0, 11.6, and 14.6 years), and
3 developed a combination of truncal obesity, dorso-
cervical fat pads, and lipoatrophy of the extremities
(ages at the time of the physical changes were 13.5,
14.0, and 16.5 years). No patients exhibited lipoatro-
phy alone. All 9 patients (7 female patients and 2
male patients) with physical signs of fat redistribu-
tion first exhibited the changes in association with
pubertal development. That is, the phenotypic
changes became apparent in physical examinations
sometime during the transition between Tanner
stages 1 and 4. Moreover, no patients were in Tanner
stage 1 when they developed lipodystrophy. Four
patients had transitioned from Tanner stage 1 to
stage 2 at the time when their phenotypic changes
were first noted. Two patients had transitioned from
Tanner stage 2 to stage 3 at the time of their pheno-
typic changes, and 3 patients had transitioned from
Tanner stage 3 to stage 4. None of the patients in the
lipodystrophy group (group 1) started PI therapy
after Tanner stage 4. A description of the Tanner
stages in relation to the start of PI therapy and the
development of physical signs of fat redistribution
for the 9 patients with fat redistribution is given in
Table 2.

The majority of patients (6 of 9 patients) who de-
veloped physical changes consistent with fat redis-
tribution developed those changes within the first 3
years after the inclusion of a PI in their antiretroviral
therapy (median time: 31.7 months). There were,
however, 3 patients who developed the phenotypic
changes well into their PI course (ie, 57.0, 57.8, and
67.1 months). Of interest, these 3 patients all had
received ≥1 round of a PI-containing HAART regi-
men but were not virologic responders until their
second or third regimens. For these 3 patients, phys-
ical signs of fat redistribution occurred later in their
PI-containing regimen histories, compared with the
other patients in this group, and coincided with the
periods during which virologic responses occurred.
The probability of developing lipodystrophy (fat re-
distribution and dyslipidemia) in different Tanner
stages is depicted in Fig 2. Also of interest for this
cohort is the fact that 22 of 49 patients (45%) in group
2 (patients with dyslipidemia only) remained at Tan-
nier stage 1 during the entire period of the study,
possibly accounting for the lower numbers of phys-
ical changes associated with fat redistribution in this
group.

**Laboratory Results**

**Lipid Levels**

Of the 94 patients who were retrospectively eval-
uated for this study, a total of 58 (62%) developed
dyslipidemia (elevated cholesterol and/or triglycer-
ite levels); 9 of the 58 patients (16%) with consist-
tently high lipid levels developed physical signs of
fat redistribution, and 49 of the 58 patients (84%) exhibited dyslipidemia alone. For the 58 patients
who developed dyslipidemia, lipid values were gen-
erally not statistically significantly different between
the fat redistribution group (group 1) and the dys-
lipidemia group (group 2) at any time point. How-
ever, the elevations in total cholesterol and triglycer-
ite levels that we observed for group 1 seemed to be
higher, especially during the first 3 years of therapy
(Table 3). The time until the development of abnor-
mal plasma lipid values was calculated from the start
of the PI-containing therapy until the date on which
elevated lipid levels were first noted for a patient or
until the end of the study period, if elevated levels
never developed.
Lipid Levels in Relation to PI Therapy

As previously stated, the median time to the appearance of elevated lipid levels after the initiation of PI therapy was 7.3 months. When patients with a history of elevated cholesterol levels were excluded from the analysis, the median time to the appearance of elevated lipid levels increased to 12.9 months. With respect to specific PI therapies, a greater fraction of patients with lipodystrophy were treated with ritonavir as the initial PI, compared with those in the other 2 groups.

Lipid Levels in Relation to Age

When all patients were grouped according to age, children who began their PI therapy between the ages of 10 and 15 years seemed to be more likely to develop elevated cholesterol or triglyceride levels with time, compared with children who began PI therapy at other ages (Fig 3). When patients with dyslipidemia before PI therapy were excluded from the analysis, a significant difference was noted between children in the 10- to 15-year age group and those >15 years of age (P = .0058). Patients who began PI therapy at <15 years of age generally developed dyslipidemia within the first 12 months of therapy and maintained elevated lipid levels throughout the course of the study. Two of 9 patients (22%) who began PI-containing regimens at ≥15 years of age demonstrated preexisting dyslipidemia, but no new cases of dyslipidemia developed in this age group during the course of the study.

DISCUSSION

Although lipodystrophy, fat redistribution, and dyslipidemia have been described for HIV-infected children, primarily those treated with PIs, the cause and natural history of the disorders are not well understood. Several pediatric studies reported incidences of lipodystrophy ranging from 18 to 33%,9,11,13 but risk factors have not been defined for this population. For adults, the literature is larger and the incidences range widely (estimates of 1–80%). It has been suggested that several factors may contribute to the risk of developing these toxicities, including age, weight, baseline body mass index, diet, severity and duration of HIV infection, antiretroviral agents used, duration of antiretroviral therapy, suppression of viremia, and history of lipid abnormalities.19 With respect to lipid abnormalities in HIV disease, the occurrence of hypertriglyceride-
mia among HIV-infected patients clearly preceded the use of PIs in antiretroviral regimens. However, after the widespread introduction of PIs, there has been a direct association of elevated total cholesterol levels and the extent of fat redistribution with the use of PIs in antiretroviral therapy.20

A cross-sectional cohort study by Melvin et al10 examined 23 children who had been treated with HAART for at least 6 months and 12 children treated with NRTI therapy alone. In this cohort, 65% of the PI-treated children had total cholesterol values of >95th percentile for age, whereas none of the control children had cholesterol levels that were elevated to that degree. When body habitus changes were evaluated via DEXA and anthropometric measurements, there were no significant differences between the 2 groups. It is interesting to note that, in that study, most of the PI-treated patients (79% in the PI-treated group) were in Tanner stage 1 or 2. However, there was 1 patient in this group who developed hypertriglyceridemia, insulin resistance, and abnormal body composition, ie, an 18-year-old female patient who was in Tanner stage 5 and had been receiving a PI-containing regimen since 15 years of age. A retrospective study by Cheseaux et al14 evaluated laboratory data for 66 PI-treated children and found that PI-treated children had elevated plasma cholesterol levels similar to those seen for children with familial hypercholesterolemia. In this group, treatment with ritonavir was associated with doubling of plasma levels of total cholesterol and triglycerides.

A study by Jaquet et al9 evaluated 39 HIV-infected children who were receiving antiretroviral treatment; clinical and metabolic changes associated with fat redistribution were seen for 13 children (33.3%). Of those children, 11 were receiving HAART therapy, 8 with truncal obesity, 3 with peripheral wasting, and 2 with combined lipodystrophy (observed only among adolescents). The study did note that clinical forms of lipodystrophy were less severe among children before the onset of puberty. However, because it was cross-sectional, the study could not evaluate in a longitudinal manner whether the onset of lipodystrophy was associated with pubertal development for individual patients. In our study, we did not observe any patients with lipodystrophy alone. As in the study by Jaquet et al9, we identified older patients with both lipoatrophy and lipohypertrophy, suggesting that older age may be related to more severe effects of fat redistribution. A study by Arpadi et al11 used DEXA scans to objectively assess lipodystrophy, by measuring regional body fat mass, for 28 children between the ages of 4 and 12 years with perinatally acquired HIV infection. Lipodystrophy was found for 8 children (29%), only 1 of whom had clinically apparent disease. A similar study was performed by Brambilla et al,13 using DEXA and magnetic resonance imaging studies; those authors found excessive truncal and cervical fat accumulation, in addition to lipodystrophy, for 6 of 34 HIV-infected children (18%). Longitudinal follow-up monitoring of 37 HIV-positive children and 54 matched control subjects showed an increase in lean mass, peripheral fat loss, and central fat accumulation for all HIV-infected children, using DEXA and magnetic resonance imaging.21 These studies help
confirm that lipodystrophy occurs at a relatively high frequency among HIV-infected children and that the risk of developing lipodystrophy increases during the year of follow-up monitoring.

In our cohort, we observed a 10% prevalence of fat redistribution for the entire cohort and a 62% dyslipidemia prevalence. This cohort represents one of the earliest pediatric populations exposed to PI therapy, with some of the most extensive longitudinal experience available. Like any retrospective study, our study has limitations. Many of the clinical and laboratory data were collected before the description of lipodystrophy and dyslipidemia as complications associated with antiretroviral therapy, especially among children. Consequently, clinical features suggesting lipodystrophy might have been under-reported by providers because the providers were not looking for them. In addition, assessment of the phenotypic manifestations of lipodystrophy with physical examinations is inherently subjective and may differ among different providers. However, another explanation for our low prevalence rate could be that approximately one-half of our patients with dyslipidemia (group 2) were still in Tanner stage 1 of pubertal development; there seems to be an association between pubertal development and the risk of developing lipodystrophy. A strength of our study is the length of the observation period for a relatively large number of patients and the long-term, longitudinal nature of the data, which enabled us to examine the effects of pubertal maturation as a risk factor for the development of fat redistribution and dyslipidemia among patients treated with PI-containing HAART.

When attempting to assess what could be significant risk factors for the development of lipodystrophy among HIV-infected children, we performed pairwise comparisons of several continuously measured parameters (Table 1).

In our study, univariate analyses showed that the duration of PI therapy and the length of antiretroviral exposure were not significant risk factors for the development of lipodystrophy among children, with P values of > .01 consistently. We found a statistically significant association between the virologic response to PI therapy and lipodystrophy, comparing group 1 with groups 2 and 3, with P values of < .01 for years 2 to 4 of PI therapy (Table 1). This may suggest that more effective exposure to the PI, attributable, for example, to varying pharmacokinetic parameters or adherence, predisposes patients to the development of lipodystrophy. This association might have been apparent only for the first 3 years of PI-containing HAART, because many of the patients in group 1 (5 of the 9 patients) were involved in a research study that started in 1998. Therefore, these patients started their PI-containing HAART regimens later than did patients in groups 2 and 3 and had only 3 years of data available for analysis.

There was a statistically significant association between the age at which the patients were treated and the risk of developing hypercholesterolemia (Fig 3). Patients who began PI-containing HAART between 10 and 15 years of age were more likely to develop hypercholesterolemia than were other age groups (10-15-year age group, compared with the 5-10-year age group, P = .059; 10-15-year age group, compared with the ≥15-year age group, P = .016). Therefore, receiving PI therapy in the age range of 10 to 15 years (the years of pubertal development) and sustained control of viremia in response to PI therapy seem to be significantly associated with the development of fat redistribution and dyslipidemia. This may suggest that PI therapy in the setting of the hormonal changes that occur during puberty may predispose pediatric patients to the development of lipid disorders. It may also suggest that prolonged viral suppression may be a surrogate marker of maximal adherence and/or favorable pharmacokinetic parameters and thus maximal sustained exposure to PIs and other antiretroviral drugs in highly active regimens.

The psychosocial effects of alterations in body habitus associated with lipodystrophy and the resulting potential effects on adherence have been described in the adult HIV literature.22 Because HIV-infected children will now probably survive long into adulthood, the long-term risks for the development of premature cardiovascular disease attributable to prolonged dyslipidemia associated with antiretroviral therapy warrant additional studies to assess the relationship between puberty and the development of lipid abnormalities in association with antiretroviral therapy. Visceral fat accumulation, hyperlipidemia, and insulin resistance dramatically increase the risks for diabetes mellitus, heart disease, and stroke, and these abnormalities have been reported for HIV-infected adults.19,23,24 A study by Hadigan et al25 showed that the 10-year heart disease risk estimate was significantly increased among HIV-infected persons with fat redistribution and that subjects with primary lipoatrophy demonstrated the highest 10-year heart disease risk estimate. A better understanding of the pathogenesis of HIV-related dyslipidemia and lipodystrophy might suggest strategies that could reduce the risks of cardiovascular disease and other disorders related to hyperlipidemia among HIV-infected children and adults.

ACKNOWLEDGMENTS

We thank the clinic staff for their help with the study and our patients and their families for their participation.

REFERENCES


http://www.pediatrics.org/cgi/content/full/114/2/e235 e241

Downloaded from http://pediatrics.aappublications.org/ by guest on November 8, 2017
Natural History of Lipid Abnormalities and Fat Redistribution Among Human Immunodeficiency Virus-Infected Children Receiving Long-Term, Protease Inhibitor-Containing, Highly Active Antiretroviral Therapy Regimens
Perdita Taylor, Carol Worrell, Seth M. Steinberg, Rohan Hazra, Shirley Jankelevich, Lauren V. Wood, Sheryl Zwerski, Robert Yarchoan and Steven Zeichner

Pediatrics 2004;114;e235
DOI: 10.1542/peds.114.2.e235

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/114/2/e235

References
This article cites 24 articles, 2 of which you can access for free at:
http://pediatrics.aappublications.org/content/114/2/e235.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub
HIV/AIDS
http://classic.pediatrics.aappublications.org/cgi/collection/hiv:aids_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Natural History of Lipid Abnormalities and Fat Redistribution Among Human Immunodeficiency Virus-Infected Children Receiving Long-Term, Protease Inhibitor-Containing, Highly Active Antiretroviral Therapy Regimens
Perdita Taylor, Carol Worrell, Seth M. Steinberg, Rohan Hazra, Shirley Jankelevich, Lauren V. Wood, Sheryl Zwerski, Robert Yarchoan and Steven Zeichner

*Pediatrics* 2004;114:e235
DOI: 10.1542/peds.114.2.e235

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/114/2/e235