Impact of Protease Inhibitor-Containing Combination Antiretroviral Therapies on Height and Weight Growth in HIV-Infected Children

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ABSTRACT. *Objective.* **To examine beneficial or detrimental effects of protease inhibitor (PI)-containing antiretroviral regimens on height and weight growth in children with human immunodeficiency virus (HIV) infection.**

Methods. **A prospective cohort study was conducted of 906 HIV-infected children, from pediatric research clinics in the United States, who were between 3 months and 18 years of age and who had height and weight assessed in 1995 (before introduction of PIs in this population) and at least once more through 1999. Changes in age- and gender-adjusted height and weight growth associated with PI use were assessed.**

Results. **Compared with a healthy reference population, children were more affected in height (mean *z* score: −0.90 [18th percentile]) than in weight (mean *z* score: −0.42 [34th percentile]) at baseline (1995). Two thirds of children received at least 1 PI during 1996 to 1999. In the multivariate mixed effects regression models adjusted for baseline $\log_{10}$ CD4 cell count, baseline age, gender, and race/ethnicity, the use of PIs was associated with per-year gains of 0.13 *z* scores in height and 0.05 *z* scores in weight relative to the expected growth with non–PI-containing regimens (eg, after 1 year of PI use, a representative 6-year-old boy in our study would be approximately 0.7 cm taller and 0.1 kg heavier than if he had not received PIs). No significant differential effects of PIs on height or weight growth according to specific agents or children's sociodemographic or clinical characteristics were found.**

Conclusions. **Although the use of PI-containing regimens was not associated with growth retardation, it was associated with only small annual increments in height and weight growth in HIV-infected children.** *Pediatrics* **2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e72;** *HIV-1, protease inhibitor, growth, children.*

ABBREVIATIONS. PI, protease inhibitor; HIV, human immunodeficiency virus; PACTG, Pediatric AIDS Clinical Trials Group; HAZ, height-for-age-and-gender *z* score; WAZ, weight-for-age-and-gender *z* score.

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Protease inhibitors (PIs) have been used increasingly in the treatment of human immunodeficiency virus (HIV)-infected children since the mid-1990s. However, little is known about the long-term effects of PI-containing combination antiretroviral therapies on height and weight growth in pediatric populations. HIV-infected children fall behind HIV-uninfected children who are born to HIV-infected mothers in age- and gender-appropriate height and weight in the first few years of life.[1–3] Studies that examined the effect of zidovudine on height and weight gain in HIV-infected children were limited by sample size and produced mixed results.[2,4] Some small clinical studies[5–8] suggested that PI treatments may have beneficial effects on weight and/or height growth in HIV-infected children, but other studies found no improvements in growth associated with the use of PI-containing regimens.[9–11] The hope is that PI treatments may reverse some of the negative effects of HIV disease on growth in children by reducing viral load, improving immune function, and arresting some metabolic and endocrinologic changes, although the exact biological mechanism of their action is not known.[12] High viral load and low CD4 cell counts have been shown to be associated with growth retardation and growth failure in pediatric populations.[13,14] Failure to grow and gain weight are in turn risk factors for mortality in HIV-infected children.[15,16] The use of PI-containing therapies has been associated with clinical improvement and increased survival of HIV-infected children,[17,18] so it also might benefit growth. These analyses were undertaken to examine the effects of PIs on height and weight growth in a large prospective study of 906 HIV-infected children, followed over time as PI treatments were being introduced for pediatric use.

MATERIALS AND METHODS

Study Population

Pediatric AIDS Clinical Trials Group (PACTG) protocol 219 is a long-term prospective cohort study designed to assess the late effects of in utero and neonatal exposure to antiretroviral drugs in perinatal HIV clinical trials and late effects of antiretroviral treatment in children who are infected with HIV-1. The study is conducted at 87 pediatric clinics across the United States. Participants or their mothers who were HIV-infected while pregnant, must have been enrolled in a PACTG clinical trial before enrollment in PACTG 219. Children who were younger than 3 years had study visits every 6 months, and children who were older than 3 years had visits every 12 months, which included the following

evaluations: sociodemographic characteristics, height and weight, CD4 cell count, and antiretroviral medication use since the previous study visit (in the past 12 months at study enrollment). Body composition, hormone levels, and anthropometric measures other than height and weight were not collected as part of the study. HIV viral load measurements also were not available. The study was approved by the human subjects review boards at each participating institution. Written informed consent was obtained from each child's parent or legal guardian.

In the present analysis, we investigated height and weight growth in HIV-infected children through 18 years of age who were enrolled in PACTG 219 in the pre-PI era and followed over time as PIs were being introduced. To be included in the analysis, a child must have had a study visit in 1995 (referred to as the baseline visit) and at least 1 subsequent visit between 1996 and 1999, both with complete height and weight measurements ($n = 906$). Thus, 97 children who had a visit with complete growth measures in 1995 but no visit with complete growth measures between 1996 and 1999 were excluded.

Measures

Height and weight were obtained according to a standardized protocol. Children up to 24 months of age were measured in the supine position using a standard measuring board. Children who were older than 24 months had their standing heights measured using stadiometers (to the nearest 0.1 cm). Weights were recorded without shoes, clothing, or diapers. One height and weight measurement was recorded per study visit.

Height and weight growth were analyzed in terms of height-for-age-and-gender z scores (HAZ) and weight-for-age-and-gender z scores (WAZ). Z scores, which are standard deviations, represent the departure of an individual's anthropometric measurements from the median values in the appropriate age and gender categories in a reference population. The standard Centers for Disease Control–World Health Organization growth reference based on the National Center for Health Statistics and Fels databases of HIV-uninfected children was used.[19,20] A child with a z score of 0 is at the median (50th) percentile for height/weight for his or her age and gender. Positive changes in z scores indicate improvements in a child's growth relative to the norms. Height and weight measurements with z scores of <-5 or >5 ($<1\%$ of all growth measurements) were considered errors and were excluded from the analyses.

Z scores were used in the analyses because changes in a child's actual height and weight over a period of time cannot be interpreted easily and may represent an average, better or worse growth relative to the expected growth patterns. Changes in z scores over a period of time were converted into corresponding changes in growth percentiles and were presented for hypothetical children having the mean height or weight z score for the study population at baseline. Growth velocities were not used because velocities before (or after) PI treatment could not be determined for many children with only 1 growth measure recorded before (or after) receiving PIs.

Statistical Methods

Univariate analyses were conducted to examine within-individual changes in height and weight z scores between 1) the last 2 visits before a child had a record of PI use and 2) the last visit before PI use and the first visit after initiation of PIs, for all children who began a PI. Individual changes in z scores were standardized to reflect change over a 1-year period and were averaged across all children who began PI treatments in the course of the study. Mean 2-year changes in height and weight z scores also were determined for a subset of children who had growth measures available for at least 2 calendar years after initiating a PI.

Longitudinal within-individual analyses using all available growth measurements for each child also were undertaken to examine the effects of PIs on children's growth. Mixed-effects linear regression models[21–23] with PI use as a time-varying covariate were performed to model separately growth before and after a child received a PI. In these within-individual analyses, each child served as his or her own control. Because the exact dates for the initiation of PI treatments were not available, we chose to model the transition onto PIs at the first study visit when a child was already known to be receiving PIs and performed sensitivity analyses to evaluate the effects of this assumption. At the time of

the first study visit that showed a record of PI use, a typical child may have been exposed to PIs for a period ranging from <1 month to up to 12 months. In all regression analyses, children who did not initiate PI-containing combination therapies (approximately one third of the population) contributed their information to model estimates of growth before PI use.

Multivariate regression models adjusted for confounding and included the following covariates: child's age at baseline, gender, race/ethnicity, baseline $\log_{10}$ CD4 cell count, and interaction terms for these factors with time. The Centers for Disease Control and Prevention pediatric immunosuppression categories based on CD4 cell count and age, or relative CD4 cell count (CD4%) categories[24] also were considered in univariate and some exploratory multivariate analyses. The possibility of differential effects of PIs on height and weight z scores according to the calendar year of first PI record, child's age and immunosuppression category at baseline, and the major categories of PI treatments also were investigated by including interaction terms. All analyses were conducted using SAS version 6.12 (SAS, Inc, Cary, NC).

RESULTS

Patient Characteristics

The baseline (1995) sociodemographic, clinical, and growth characteristics of the study population are summarized in Table 1. Approximately half of children were boys. The majority of children were between 3 and 10 years of age. The racial/ethnic composition of the sample was 48% black/non-Hispanic, 35% Hispanic, 16% white/non-Hispanic, and 1% of other race/ethnicity. Approximately one third of children were in each of moderate, severe, and not immunosuppressed categories based on age and CD4 cell count at baseline (Table 1) or based on CD4% (data not shown). Ninety-nine percent of children had been treated with nucleoside analog reverse transcriptase inhibitors (primarily zidovudine), 9% had received nonnucleoside reverse transcriptase inhibitors, and 1% had no record of antiretroviral use in 1995. For 829 children (92%), HIV infection was acquired perinatally; 49 (5%) had other risk factors for acquiring HIV infection; and for the remaining 28 (3%), the mode of HIV acquisition was unknown or uncertain. Between 1996 and 1999, 55 children (6%) died and an additional 93 (10%) were lost to follow-up. Participants had a median of 5 (range: 2–8) height and weight assessments during the study period; those who received PIs had a median of 2 (range: 1–5) height and weight assessments after starting PI treatment.

HIV-infected children were more affected in height (mean at the 18th percentile) than in weight (mean at the 34 percentile) at baseline (Table 1). Univariate analyses indicate that girls had somewhat higher mean gender-adjusted height and weight z scores at baseline than boys. Younger and less immunosuppressed children also had higher mean height and weight z scores than children who were older and/or had more severe HIV disease. Small univariate differences in height and weight z scores by racial/ethnic subgroups were attributable primarily to confounding by other demographic and clinical factors. In the adjusted baseline regression analyses, only younger age, female gender, and none/moderate level of immunosuppression were significantly associated with higher height and weight z scores.

TABLE 1. Characteristics of the Study Population at Baseline (1995) (n = 906)

Characteristic	n	%	Mean Height z Score (Q1–Q3)*	Mean Height Percentile	Mean Weight z Score (Q1–Q3)*	Mean Weight Percentile
Overall	906	100	−0.9 (−1.7, −0.1)	18	−0.4 (−1.2, 0.3)	34
Gender						
Male	458	51	−1.1 (−1.8, −0.2)	14	−0.5 (−1.3, 0.2)	31
Female	448	49	−0.7 (−1.5, 0.1)	24	−0.3 (−1.1, 0.4)	38
Age at baseline (y)						
<3	163	18	−0.9 (−1.7, −0.1)	18	−0.5 (−1.2, 0.3)	31
3–<6	309	34	−0.7 (−1.4, 0.1)	24	−0.3 (−1.1, 0.5)	38
6–<10	273	30	−0.9 (−1.6, 0.0)	18	−0.3 (−1.1, 0.4)	38
≥10	161	18	−1.3 (−2.1, −0.5)	10	−0.8 (−1.4, 0.1)	22
Race/ethnicity						
White/non-Hispanic	147	16	−1.1 (−1.9, −0.3)	14	−0.6 (−1.4, 0.2)	27
Black/non-Hispanic	433	48	−0.8 (−1.5, −0.0)	21	−0.4 (−1.2, 0.4)	34
Hispanic	314	35	−1.0 (−1.7, −0.1)	16	−0.4 (−1.1, 0.4)	34
Other	12	1	−0.8 (−1.4, 0.1)	21	−0.5 (−1.2, 0.3)	31
CDC pediatric immune suppression category†						
None	297	33	−0.7 (−1.3, 0.1)	24	−0.1 (−1.0, 0.5)	46
Moderate	308	34	−0.7 (−1.5, 0.2)	24	−0.3 (−1.1, 0.5)	38
Severe	274	30	−1.4 (−2.1, −0.5)	8	−0.9 (−1.7, −0.1)	18
Missing	27	3	−0.9 (−1.3, −0.2)	18	−0.4 (−0.7, 0.2)	34

* Q1 and Q3: Values for first and third quartiles of the distribution.
† CDC immune suppression category based on CD4 cell count and age.

Use of PIs Over Time

A total of 605 children (67%) received at least 1 PI between 1996 and 1999. The majority of children first used a PI in 1997 or 1998 (Table 2). Children who first received a PI in 1996 or 1997 had lower mean CD4 cell count and lower height and weight z scores at their last pre-PI study visit than children who first received a PI in 1998 or 1999. Also, children who began PI treatments in any given calendar year had lower CD4 cell counts and lower height and weight z scores than children who did not begin PIs in the same year (data not shown). Thus, children who had more advanced HIV disease received PI-containing combination treatments before healthier children.

Five PIs were in use at the PACTG sites by 1999, including, in order of decreasing frequency of use in our study population, nelfinavir (43%), ritonavir (38%), indinavir (11%), saquinavir (11%), and amprenavir (3%). Of the 605 children who received a PI during the period 1996 to 1999, 60% received 1 PI only; the remaining 40% received 2 or more PIs either sequentially or in combination. Although 40% of children switched from 1 type of PI to another, only 30 (5%) of 605 patients who initiated PI(s) subsequently discontinued use of any PI. Although the reasons for switching PIs (eg, toxicity, virologic failure) were not recorded, children who were older, had lower CD4 counts, and/or had lower height and

weight z scores at baseline were more likely to receive more than 1 PI.

Unadjusted Changes in z Scores Among Children Who Initiated PIs

Individual height and weight z scores before and after the last visit before PI use were examined for the whole population and for subgroups of children according to sociodemographic characteristics and baseline CD4 immunosuppression category (data not shown). There was variability in response to PIs among children and no clear pattern of improvement or reduction in height or weight z scores after the receipt of PIs in the entire population and in various subgroups.

Mean changes in height and weight z scores before and during PI use are shown in Table 3. These results indicate that children experienced a small mean decrease in height and weight z scores in a 1-year period before PI use. During the first year of PI use, children continued to lag behind in age- and gender-appropriate height (mean decline in z score: 0.01) but showed small improvements in weight (mean improvement in z score: 0.05). However, over a 2-year period on PIs, the population as a whole experienced small mean improvements in height and weight z scores (0.11 in both cases).

Because children who initiated PIs in earlier calen-

TABLE 2. Characteristics* of Children Who Received PIs by Calendar Year of the First Record of PI Use (n = 605)

Year of First PI Use	n (%)	Mean Age (Year)	Mean CD4 Cell Count (CD4%)	Mean Height z Score	Mean Weight z Score
1996†	51 (8)	8.9	241 (10)	−1.7	−1.2
1997	220 (36)	7.9	471 (17)	−1.1	−0.6
1998	225 (37)	8.0	584 (22)	−1.0	−0.3
1999	109 (18)	8.3	582 (24)	−0.7	−0.2

* Clinical and demographic characteristics at the last study visit before initiation of PIs.
† Mean CD4 cell count, CD4%, height z score, and weight z score were significantly lower for children who began PIs in 1996 to 1997 compared with those who began PIs in 1998 to 1999 (P < .001 for all).

TABLE 3. Changes in Height and Weight z Scores Before and After Receiving PIs

Year of First PI Use	During 1 Year Before Starting PIs*		During 1 Year After Starting PIs†		During 2 Years After Starting PIs‡	
	n	Mean Change (95% CI)	n	Mean Change (95% CI)	n	Mean Change (95% CI)
Height						
All	434	−0.09 (−0.13, −0.04)	535	−0.01 (−0.05, 0.02)	337	0.11 (0.05, 0.18)
1996–1997	190	−0.10 (−0.16, −0.03)	238	−0.10 (−0.16, −0.05)	186	0.03 (−0.06, 0.12)
1998–1999	244	−0.08 (−0.14, −0.01)	297	0.06 (0.02, 0.10)	161	0.21 (0.13, 0.29)
Weight						
All	437	−0.01 (−0.06, 0.04)	544	0.05 (0.01, 0.10)	351	0.11 (0.04, 0.19)
1996–1997	193	−0.06 (−0.13, 0.01)	244	0.04 (−0.04, 0.11)	188	0.07 (−0.04, 0.18)
1998–1999	244	0.03 (−0.03, 0.10)	300	0.07 (0.01, 0.13)	163	0.17 (0.07, 0.27)

* Mean 1-year change up to the last visit pre-PI.
† Mean 1-year change from last pre-PI visit to first on-PI visit in the following year (eg, from 1996 to 1997).
‡ Mean 2-year change from last pre-PI visit to second on-PI visit (eg, from 1996 to 1998).

dar years had different clinical characteristics than children who initiated PIs in the later calendar years (Table 2) and potentially could have different growth responses to treatment, analyses also were stratified by calendar year of first use of a PI (Table 3). Children who began PI treatment in 1998 or 1999 experienced greater positive changes in height and weight z scores over 1-year and 2-year periods than children who began PI treatment in 1996 or 1997 (Table 3). In addition, the mean change in height z score over 2 years was substantially larger than the mean change over the first year of PI use, suggesting that there may be a lag in height growth response before the effects of PI treatment are fully observed.

Changes in z Scores Associated With PI Use: Longitudinal Analyses for All Children

In the unadjusted regression analyses, the estimated mean annual improvements in growth associated with PI use were 0.10 z scores in height ($P < .001$) and 0.03 z scores in weight ($P = .15$). After adjustment for gender, race/ethnicity, $\log_{10}$ CD4 cell count, and child's age at baseline (1995), use of PIs was associated with a mean increase in height z score of 0.13 per year (on average 3.7 percentiles; $P < .001$) and a mean increase of 0.05 weight z scores per year (on average 1.9 percentiles; $P = .03$). These estimates can be interpreted as annual increments in height and weight z scores while receiving PIs, relative to the expected annual changes in z scores when not (yet) receiving PIs (but generally receiving other antiretroviral treatments). Depending on a child's growth trajectory before receiving PIs, these small improvements may either contribute to some "catch-up" growth or translate to a slower rate of decline in gender- and age-appropriate height and weight. The significant multivariate predictors of better height growth over time before/without receiving PIs were younger age at baseline, higher baseline $\log_{10}$ CD4 cell count, male gender, and being non-Hispanic, whereas only younger age at baseline was a significant predictor of better weight growth before initiation of PIs. Similar findings were obtained in analyses adjusting for time-varying $\log_{10}$ CD4 cell count (varying up to last visit pre-PI use) instead of the baseline $\log_{10}$ CD4 cell count, or baseline immunosuppression category based either on CD4 cell count or on CD4% (data not shown).

Additional analyses were conducted to investigate any possible differential effects of PI treatments on height and weight growth, depending on the calendar year of first PI record, the age and immunosuppression category of the child, and broad mutually exclusive categories of PI treatment: nelfinavir only (21%), ritonavir only (15%), another PI or various PI combinations (31%), and no PI treatment (33%). These analyses indicated that the per-year increments in z scores associated with PI use were somewhat greater in children who first received PIs in 1998 or 1999 (mean increase of 0.16 HAZ and 0.07 WAZ) compared with children who first received PIs in 1996 or 1997 (mean increase of 0.12 HAZ and 0.04 WAZ), but the differences were not statistically significant ($P > .2$ for both). There also were no significant differences in height and weight growth responses according to the type of PI used, immunosuppression category, or age of the child at baseline in the analyses adjusted for other covariates.

DISCUSSION

PI-containing antiretroviral combination therapies have been shown to significantly reduce plasma HIV-RNA levels, increase CD4 cell counts, and prolong life in adults[25,26] and children.[17,18,27] However, their use has been associated with metabolic and morphologic complications in adults,[28,29] and their effect on other clinical outcomes in children has not been widely studied. In this large observational study of 906 HIV-infected children, we observed small mean increases in height z score of 0.13 per year (3.7 percentiles) and in weight z score of 0.05 (1.9 percentiles) per year, associated with the use of PIs relative to the growth before initiation of PIs. These changes translate to small improvements in the actual height and weight measures for both genders and across the spectrum of ages. For example, for a 6-year-old boy with height z score of −0.9 and weight z score of −0.4 (mean baseline population values in Table 1), the estimated annual gains in z scores associated with PI use correspond to additional increments of 0.7 cm and 0.13 kg in the first year. Similarly, for a 3-year-old girl with the same baseline values, these annual gains would translate to an additional 0.5 cm and 0.08 kg after 1 year on PI-containing therapy.

Our analyses focus on within-individual compar-

isons of height and weight measures before and after receiving PIs. In these analyses, each child serves as his or her own control to reduce variability and control for the influence of some unmeasured factors (eg, genetic predisposition, possibly socioeconomic and nutritional status) on growth before and after PI use. However, as with any observational study, confounding by indication,[30] resulting from the fact that HIV-infected children who were selected to receive PI treatment earlier had on average lower CD4 cell counts and worse growth measures than children who did not receive a PI until later or not at all and thus might have worse prognosis and poorer responses to PIs, might still exist. Confounding by indication was stronger in the early years of the study (1996 and 1997), when children with the most advanced HIV disease were selected to receive PI treatments. It is important to adjust for factors, such as CD4 cell count, that predict the receipt of PIs to control for confounding by indication and obtain more reliable estimates of the PI effects on growth. Plasma HIV viral load measurements, which also may be used for indication of PI-containing therapy, were not available for this analysis. Nonetheless, the estimates of the effect of PIs on growth were similar in the adjusted and unadjusted regression models, and therefore our general conclusion that PI use is associated with beneficial but small effects on growth seems valid.

PI-containing combination therapies may have both positive effects on height and weight growth due to improvements in metabolism and nutrient absorption and negative effects resulting from diarrhea, nausea/vomiting, and loss of appetite.[8,31,32] Considering that some PIs have serious metabolic and gastrointestinal adverse effects, it is reassuring that we did not detect large mean decrements in height or weight after PI use in our study population as a whole or according to specific types of PIs. Metabolic complications of PIs, including body fat distribution and bone density abnormalities, only recently have been recognized in children,[33] and these conditions were not ascertained systematically in our study population between 1995 and 1999.

This is, to our knowledge, the largest longitudinal study examining the impact of PI-containing regimens on height and weight growth in HIV-infected children, which adds to the limited available data from small clinical studies with short follow-up times. For example, in a study of 27 children, Nadal et al[7] found a mean increase in height z score of 0.34 after 24 weeks of treatment with ritonavir-containing regimen, whereas Thuret et al[9] found no significant improvement in height and weight z scores in 22 children who received ritonavir combination therapy for 1 year. In another case series of 27 HIV-infected children, mean height and weight z scores increased by 0.26 and 0.18, respectively, after an average of 20 months on antiretroviral regimen including a PI.[5] Although our and the previously mentioned studies found small or no effects of PI-containing therapies on growth in children with antiretroviral experience, it is possible that the effects of initial PI-containing

combination therapy on growth in antiretroviral-naïve children could be more pronounced.

We did not detect statistically significant differences in height and weight responses according to the type of PI treatment received (only ritonavir, only nelfinavir, or other PI or combination). However, our ability to examine growth changes according to specific PI treatments was limited because a large proportion of children (40%) switched PIs in the course of the study. In addition, different PI agents were introduced for use in this pediatric population in different calendar years, and formulations are not always available for younger children. Consequently, the associations between growth and specific PIs are subject to confounding by calendar time, age, and severity of disease.

Although the increases in height and weight z scores per year associated with the use of PIs were very small, if these small per-year changes could be sustained over a few years of PI use, then the longer-term effects of PIs on growth may be more clinically significant. Even in the absence of catch-up growth in some children after the receipt of PIs, it is possible that a progressive decline in age-appropriate height and weight was arrested in some children. Children in our population had mean height and weight z scores well below the 50th percentile at baseline, and some also seemed to be falling behind in age-appropriate height and weight, as evidenced by negative changes in z scores before PI treatment (Table 3). This suggests that initiation of PI treatments at a younger age, before a child becomes severely growth impaired, may increase chances for normalization of attained growth. Although the per-year improvements in z scores associated with PI use did not depend on age, children in our study generally began PIs when they were older (Table 2); therefore, the effects of early initiation of potent PI-containing regimens on growth in younger children need to be explored further.

Findings of lower height z scores than weight z scores at baseline (Table 1) and over time before the introduction of PIs (Table 3) suggest that HIV disease has a more pronounced effect on height than weight growth. These findings also suggest that children may have had more opportunity to improve in height than weight growth and therefore might explain why we find somewhat greater beneficial effects of PI treatments on height than weight in this study. Some previous studies in HIV-infected children who received no antiretrovirals, monotherapy, or combination therapy excluding PIs also found that height may be more affected than weight growth.[1,2,15,34]

In the multivariate models presented here, the initiation of PI treatment was assumed to occur at the first visit when the use of PIs was reported, to maximize our ability to detect any potential effect of PIs on growth. This assumption was made because the exact dates of initiation of PI treatments were not available; only the time interval between study visits when a child began PI treatment was known. In alternative regression analyses, when the start of the PI therapy was taken to be the date of last visit before

PI use first was reported, the effect of PIs on weight growth was similar. The effect on height growth still was beneficial but smaller and potentially underestimated for 2 reasons: 1) some children may not receive PIs for up to several months from the time of the last pre-PI study visit, and 2) the effects of PIs, especially on height growth, may be delayed. It is possible that as a result of some misclassification of exposure (initiation of PI use) and measurement error in height and weight, our findings may somewhat underestimate the positive changes in height and weight z scores associated with PI use. However, it is unlikely that these factors would mask a large effect of PIs on growth after 1 or 2 years of PI use in this population as a whole. More immediate effects of PIs on height and weight may be different and could not be evaluated in this study because height, weight, and treatment history were assessed at annual intervals.

Our study suggests that PI-containing combination therapies improve growth in children during the first year or 2 of use, but only to a small extent. The increments in age-appropriate height and weight attributed to PI use indeed were modest and probably would not lead to normalization of attained height or weight in the majority of growth-impaired children in our population. However, the use of PI-containing combination therapies was not associated with retardation in height or weight growth from side effects of these therapies. Examination of the effects of HIV and its treatments on growth in children over longer periods of time is warranted. Additional PACTG studies are being conducted to investigate the effects of antiretroviral and hormonal treatments on growth and body composition of HIV-infected children and to evaluate complications of PI therapies in pediatric populations.

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