Growth in Human Immunodeficiency Virus–Infected Children Receiving Ritonavir-Containing Antiretroviral Therapy

Sharon A. Nachman, MD; Jane C. Lindsey, ScD; Stephen Pelton, MD; Lynne Mofenson, MD; Kenneth McIntosh, MD; Andrew Wiznia, MD; Kenneth Stanley, PhD; Ram Yogev, MD

Background: Human immunodeficiency virus (HIV)–infected children often suffer from impaired growth. Highly active antiretroviral therapy (HAART) successfully reduces HIV 1 (HIV-1) RNA to 400 copies/mL or less in many children.

Objectives: To determine if age- and sex-adjusted growth z scores correlate with HIV-1 RNA level and if control of viral load for 48 and 96 weeks results in improved growth in children receiving highly active antiretroviral therapy.

Design: Secondary analysis of the cohort of children receiving ritonavir nested in a randomized, open-label, clinical trial.

Subjects and Methods: The Pediatric AIDS Clinical Trials Group Protocol 338 enrolled clinically stable, antiretroviral therapy–experienced, HIV-infected subjects aged 2 through 17 years. Using data from subjects randomized to ritonavir-containing regimens (n = 197), the association of growth z scores and HIV-1 RNA levels were examined.

Main Outcome Measures: Age- and sex-adjusted weight and height z scores.

Results: Enrollment weights were comparable with age- and sex-adjusted norms, but subjects receiving ritonavir-containing antiretroviral therapy were significantly shorter (mean z score, −0.57 [29th percentile]; 95% confidence interval, −0.73 to −0.40). Higher HIV-1 RNA levels correlated with lower growth z scores (P < .01). Subjects achieving and maintaining HIV-1 RNA of 400 copies/mL or less through 48 and 96 weeks experienced worse growth than subjects with a less controlled viral load.

Conclusions: In this pediatric cohort, a significant decline in height and weight z scores was found despite control of viral replication. Further studies of growth are necessary to assess if nutritional and hormonal adjuvants to highly active antiretroviral therapy should be considered to improve growth in HIV-infected children.

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MPAIRED SOMATIC growth is a well-documented complication of human immunodeficiency virus 1 (HIV-1) infection in children. In perinatal infection, linear growth in particular seems to be affected more than weight growth and can be apparent within the first few months of life. Several studies have documented that impaired growth is predictive of HIV-related disease progression, and in one study, disturbances in linear (but not weight) growth correlated with high viral load in perinatally infected infants. Antiretroviral therapy has been shown to improve growth in some but not all studies. These studies, however, were primarily reported prior to the introduction of highly active antiretroviral therapy and the use of protease inhibitors (PIs), with which HIV-1 RNA levels in many children were brought to levels beneath the quantification limits of current assays.

The Pediatric AIDS Clinical Trials Group (PACTG) Protocol 338 was designed to evaluate the safety, tolerance, and virologic efficacy of changing antiretroviral treatment to either dual nucleoside analogue therapy or a 2- or 3-drug regimen containing the PI ritonavir in clinically and immunologically stable, PI-naive children. Although this clinical trial was not designed to look at growth as a primary outcome, it provides an opportunity to examine the correlation of weight and height growth with HIV-1 RNA levels at study enrollment and growth over time in children with persistent reductions in viral load for 1 and 2 years after the initiation of therapy with a PI.

RESULTS

ENROLLMENT CHARACTERISTICS

One hundred ninety-seven subjects started 1 of the 2 PI-containing treatment com-
SUBJECTS AND METHODS

STUDY DESIGN AND DATA

The PACTG Protocol 338 enrolled 297 clinically and immunologically stable subjects aged from 2 through 17 years (stable CD4 count or percentage in Centers for Disease Control and Prevention immune category 1 or 2 during the 4 months prior to study enrollment and with no new Centers for Disease Control category C diagnoses in the 12 months prior to study enrollment). All had received continuous antiretroviral therapy for at least 16 weeks before study enrollment and had no exposure to combination therapy of zidovudine and lamivudine, non-nucleoside reverse transcriptase inhibitors, or PIs. Participants were randomized to 1 of 3 treatment combinations: zidovudine and lamivudine; zidovudine, lamivudine, and ritonavir; or stavudine and ritonavir. The primary objectives of the study were to evaluate the safety and tolerance of the 3 regimens and to compare the change in plasma HIV-1 RNA copy number between enrollment and study weeks 12 and 48. Follow-up was subsequently extended from the initially planned 48 to 120 weeks. Height and weight were measured every 4 weeks, following standardized instructions outlined in PACTG manuals. Toxic effects were graded according to the National Institute of Allergy and Infectious Diseases Division of AIDS Standardized Toxicity Table for Grading of Pediatric Adverse Experiences (April 1994). Gastrointestinal tract grade 2 or higher toxic effect included appetite loss, weight loss, nausea (moderately decreased intake to inability to ingest food or fluid for >24 hours), vomiting (≥1 episode per day for at least 3 days), and diarrhea (liquid stools to dehydration requiring intravenous therapy or hypotensive shock). The study was approved by the institutional review boards at the sites and informed consent was obtained from all legal guardians and/or participants.

LABORATORY METHODS

The HIV-1 RNA copy number was assessed at preenrollment, enrollment, and study weeks 4, 12, 24, 36, 44, 48, and every 12 weeks thereafter. The HIV-1 RNA was measured using a nucleic acid sequence-based amplification assay according to the manufacturer’s instructions (NucliSens Assay; Organon Teknika, Durham, NC). All assays were performed by a single laboratory participating in the Division of AIDS Virology Quality Assurance program.12 Assay results were adjusted using the Virology Quality Assurance program’s external standards as previously described.13 The lower limit of assay quantitation was 400 copies/mL. Lymphocyte subsets were evaluated at preenrollment; enrollment; study weeks 4, 8, 12, and every 12 weeks thereafter. Assays were performed by clinical site laboratories participating in the National Institute of Allergy and Infectious Diseases Flow Cytometry Quality Assurance Program.14

STATISTICAL METHODS

The goal of this analysis was to assess the effect of highly active antiretroviral therapy on height and weight growth over at least 48 weeks. Subjects assigned to the dual non-nucleoside reverse transcriptase inhibitors zidovudine and lamivudine arm, most of whom discontinued their assigned therapy after 24 weeks of treatment, were excluded from this study. Weights and heights were analyzed using age- and sex-adjusted z scores based on norms derived from children not infected with HIV.15 A child with a z score of 0 is at the mean (equivalent to the 50th percentile) for weight and height for his or her age and sex. If a child was growing at a steady rate (tracking along their enrollment percentile), their change in z score from baseline would be 0. Positive changes in z scores would indicate improvements in growth relative to their age and sex. Results are shown on the z score scale and transformed to the percentile scale for cross-sectional summaries.

The association of HIV-1 RNA levels with growth z scores at study enrollment was examined using analysis of variance.16 To assess the effect of virologic suppression on growth over 48 weeks, subjects were initially classified into the following groups: (1) those who had achieved and maintained HIV-1 RNA levels of <400 copies/mL or less at weeks 24 and 48 and who had continued to take their originally assigned therapy, (2) those receiving his or her original treatment with HIV-1 RNA levels between 401 copies/mL and 10 000 copies/mL at weeks 24 and 48, (3) subjects receiving his or her assigned treatment and with at least one HIV-1 RNA level higher than 10 000 copies/mL, and (4) subjects who discontinued his or her assigned treatment before week 48. Subjects could have experienced dose reductions in groups 1 and 2, but they could not have had their study treatment permanently discontinued to be in these groups. Similar groupings were applied to subjects with 96 weeks of follow-up. Changes in z scores were graphed by virologic response group.

Mixed-effects models17 were used to compare the changes from baseline in age- and sex-adjusted weight and height z scores by virologic response group. In these models, groups 3 and 4 were collapsed into 1 group since the profiles of changes were similar and both groups reflected, in some sense, treatment failure (eg, toxic effects, clinical end points, intolerance, or compliance problems). Models included main effects for sex, race or ethnicity, treatment group, CD4 percentage, height and weight z scores, HIV-1 RNA copy number, Centers for Disease Control disease category, age (all measured at study enrollment), whether the subject experienced any grade 2 or higher gastrointestinal tract toxic effects during the first 24 weeks, or whether their dose was reduced during the first 24 weeks. A stepwise procedure was used to find the most parsimonious model. Least squares means were used to test for significant changes from enrollment within the 3 HIV-1 RNA level response groups averaged over the other covariates in the model. The groups were also compared with respect to the rates of dose reductions and incidence of grade 2 or higher gastrointestinal tract toxic effect using χ² tests.16 All significance levels are 2-sided and not adjusted for multiple comparisons. All analyses were performed using SAS Version 6.12 (SAS Institute Inc, Cary, NC).
CORRELATION OF HIV-1 RNA LEVELS AND GROWTH z SCORES AT STUDY ENROLLMENT

Enrollment height and weight z scores by enrollment HIV-1 RNA copy number are given in Table 2. Significantly impaired age- and sex-adjusted weight was observed only for subjects with enrollment HIV-1 RNA levels higher than 100000 copies/mL (mean z score, −0.53; 95% CI, −0.30 to −0.09). The subjects who discontinued their original treatment or who had no control of their viral load (groups 3 and 4) had very similar profiles over the 48 weeks. The largest declines were seen in the subjects with the best virologic control, where weight z scores remained below enrollment levels through 48 weeks, with an average decline from enrollment of −0.16 (95% CI, −0.30 to −0.09). The profiles for groups 3 and 4 were similar for both changes in weight and height z scores. In addition, both groups represent treatment failure, in the sense that group 3 had an inadequate response to their antiretroviral treatment regimen and group 4 subjects had discontinued the study treatment due to virologic control failure.

WEEK 48 CHANGES IN GROWTH z SCORES FROM STUDY ENROLLMENT

The entire cohort (n = 197) showed significant declines in age- and sex-adjusted weight from week 4 through 48.
were toxic effects (n=14), clinical end points (n=7), at the request of the subject or investigator (n=29), and miscellaneous other reasons (n=5). These 2 groups were combined in the mixed-models stepwise regression. The most parsimonious model for changes in weight z scores from baseline included enrollment HIV-1 RNA levels (P=.05), whether the subject experienced a gastrointestinal tract grade 2 or higher toxic effect within the first 24 weeks (P<.001), and an interaction term between group defined by level of virologic control and time (P=.04). Average over the 48 weeks, subjects experiencing a toxic effect of the gastrointestinal tract declined −0.14 (95% CI, −0.07 to −0.21) z score units more than those not experiencing this kind of toxic effect. Subjects with the best virologic control showed significant declines from baseline from week 8 through week 48. By week 48, the group with the best virologic control had declined a mean of −0.20 (95% CI, −0.30 to −0.10), the group with moderate control a mean of −0.15 (95% CI, −0.28 to −0.02), and the group either with no virologic control or who discontinued their original treatment had no significant declines (mean z score, −0.02; 95% CI, −0.11 to 0.07).

The most parsimonious model for changes in height over time included marginally significant interactions between time and age at enrollment (P=.03) and time and group defined by level of virologic control (P=.03). By week 48 only children older than 10 years at enrollment had significant declines (mean z score, −0.18; 95% CI, −0.29 to −0.06). The group with the best virologic control showed significant declines in height growth after week 36. By week 48 they had declined a mean of −0.12 (95% CI, −0.21 to −0.03), with the other 2 groups showing no significant declines from baseline.

**WEEK 96 CHANGES IN GROWTH z SCORES FROM STUDY ENROLLMENT**

Of the 197 subjects randomized to the ritonavir-containing arms, 37 achieved and maintained HIV-1 RNA levels of 400 copies/mL or less and 19 HIV-1 RNA levels between 401 copies/mL and 10000 copies/mL through 96 weeks of therapy. These represent subsets of the subjects defined in the week 48 analysis. In addition, fifty subjects had at least one HIV-1 RNA level higher than 10000 copies/mL and 91 subjects had discontinued their originally assigned treatment by week 96. Profiles of the changes in weight and height z scores are shown in Figure 2. Changes in height z scores followed similar patterns up to week 48 as for the week 48 cohorts discussed in the “Week 48 Changes in Growth z Scores From Study Enrollment” subsection of the “Results” section. Patterns were also similar for changes in weight z scores with the exception of group 2, which showed more improvement from week 36 than for the analogous week 48 group 2. With only 19 subjects, this group showed the greatest variability and the differences are likely because of group selection factors.

Age- and sex-adjusted weight remained relatively stable in all groups except those with the best virologic control. This group showed significant declines from baseline at both weeks 48 (mean z score, −0.27; 95% CI, −0.38 to −0.16) and 96 (mean z score, −0.25; 95% CI, −0.42 to −0.08). Similar results were seen for changes in height z scores, with week 48 and 96 changes in this group of −0.16 (95% CI, −0.25 to −0.07) and −0.23 (95% CI, −0.38 to −0.09) respectively.

**INFLUENCE OF THE TOXIC EFFECTS TO THE GASTROINTESTINAL TRACT AND DOSE REDUCTIONS ON CHANGES IN WEIGHT AND HEIGHT GROWTH**

One possible explanation for the decline in weight z scores (and subsequent decline in height z scores) in the subjects with the best virologic control is that this group managed to take the drug despite experiencing toxic effects that could influence adequate caloric intake. To address this we compared the 3 groups (combining groups 3 and 4) defined by virologic control at week 48 with respect to (1) their rates of dose reductions during the first 24

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**Figure 1.** Mean (95% pointwise confidence intervals) indicate the changes from baseline in weight (A) and height (B) z scores by level of virologic control achieved through 48 weeks on study. HIV-1 indicates human immunodeficiency virus 1.
weeks and (2) their rates of gastrointestinal tract grade 2 or higher toxic effects. Of the 60 subjects with the best virologic control, 10% had at least one dose reduction during the first 24 weeks compared with 14% in the moderate virologic control group and 26% in the third or other group. This difference was statistically significant (p = .001, \chi^2 test). In contrast, there were no differences in the rates of grade 2 or higher toxic effects in the 3 groups (28% vs 26% vs 34%, p = .55 for decreasing levels of virologic control).

**COMMENT**

Several natural history studies have shown that children born to HIV-infected women are shorter and weigh less than a comparison population of children born to women who are not infected with HIV; however, those infants who are ultimately shown to be uninfected “catch up” with their peers by the first few years of life.2,18,19 Infants who were infected with HIV had progressive decrements in growth compared with uninfected infants born to HIV-infected women as well as uninfected control children; the results of some studies (primarily in HIV-infected children who do not receive antiretroviral therapy) suggest that height may be more affected than weight growth.5-7 There have been mixed reports of the effect of zidovudine treatment on weight and height growth of HIV-infected children.4,5,7,9,10,11 Carey et al.6 found that height growth velocity was more impaired than weight growth of HIV-infected children.4,5,7 Carey et al.6 found that height growth velocity was more impaired than weight growth in a cohort of participants receiving antiretroviral therapy in 4 PACTG clinical trials. In the current study, all subjects (median age, 7.2 years) had been exposed to therapy with non-nucleoside reverse transcriptase inhibitors and had normal weight relative to age- and sex-adjusted norms at study enrollment, but were significantly shorter than their non-HIV-infected peers with an average height at the 29th percentile. These data suggest that height growth continues to be more affected than weight growth in the era of monotherapy or combination therapy with non-nucleoside reverse transcriptase inhibitors. Weight and height z scores were negatively correlated with enrollment HIV-1 RNA level. However, significantly impaired height z scores were seen in all subjects with enrollment HIV-1 RNA levels of 400 copies/mL or less but significantly impaired weight z scores were only observed in subjects with enrollment HIV-1 RNA levels higher than 100 000 copies/mL at study enrollment, suggesting that height may be more sensitive to virologic status than weight. These data are consistent with those reported by Pollack et al,3 in which linear but not weight growth was correlated with the level of postnatal viremia in perinatally infected infants.

It is hoped that one benefit of achieving and sustaining low viral loads with effective treatments will be improvement in weight and height growth. Weight gain has been documented in some small studies in HIV-infected adults.20,21 However, this weight gain may be secondary to changes in fat mass with no change in lean body mass.20 In addition, loss of body cell mass has continued to be observed in infected adults receiving PIs.22 Data regarding the effects of PI-containing potent antiretroviral therapy on the growth of HIV-infected children is limited. Of the 7 studies that mention growth response to PI therapy, 5 reported some improvement in weight23-27, however, 2 studies reported no change in weight and height growth.28,29 These individual studies involved only a few patients, and it is difficult to compare them with the subjects in our study because of the differences in design and patient populations when evaluating growth changes. In the current study, contrary to expectation, age- and sex-adjusted weight declined an average of –0.08 (95% CI, –0.15 to –0.01) units over the first 48 weeks. In the subgroup of subjects who achieved and maintained virologic control with HIV-1 RNA levels of 400 copies/mL or less through 48 weeks, weight z scores declined an average of –0.20 (95% CI, –0.30 to –0.09). Although no significant declines in height z scores were observed in the entire cohort during the first 48 weeks of the study, the subgroup with the best virologic control...
Children infected with HIV often suffer from impaired growth. Highly active antiretroviral therapy was administered in 2 treatment arms of the PACTG Protocol 338, which effectively reduced viral load in a high proportion of subjects. The hope was that control of viral replication would allow improved growth in these children.

This secondary analysis of the cohort of children on ritonavir-containing treatment regimens confirmed that at enrollment children with higher enrollment viral loads were shorter and weighed less than children with more controlled viral loads. Children who achieved the best virologic response during the study, showed the worst growth profiles over 48 and 96 weeks. The results show that further studies of growth are necessary even in children receiving therapies that effectively bring viral replication under control.

Three recent articles describe changes in growth in children starting or changing therapy with PIs. Miller et al\textsuperscript{20} found increases in weight and weight-for-height $z$ scores in 45 HIV-infected children initiating any type of PI therapy followed up for a median of 2.4 years. Dreimane et al\textsuperscript{31} reported on 27 children who switched therapy and were followed up for an average of 20.4 months. They observed increases in height $z$ scores and improvements in height velocity. Both studies included children with advanced disease and did not differentiate between the types of PI therapy used. Buchacz et al\textsuperscript{32} reported small but statistically significant improvements in weight and height $z$ scores in a cohort study with children starting PI therapy in all stages of disease. In our study we focused on relatively asymptomatic children initiating ritonavir who achieved and maintained undetectable viral load for 48 or 96 weeks. In both the 48- and 96-week analyses, the subgroup with the best virologic control showed significant declines in weight $z$ scores from week 8, but significant declines in height growth only from week 36 onward. It is unclear why relative weight loss stabilized after week 16 and height loss did not (Figure 1). It is possible that the initial decrease in weight $z$ scores reflects the ritonavir-related toxic effects of the gastrointestinal tract (eg, nausea) in those children most compliant with their therapy (and thereby having the best virologic response), with subsequent resolution of these toxic effects, resulting in no further relative weight loss. The short-term effects on weight growth and the longer-term effects on height growth are consistent with observations in a WHO study in non–HIV-infected children, where investigators found that wasting could develop but also recover rapidly, whereas height growth represented the accumulated effect of wasting that might not be evident for a longer period.\textsuperscript{33}

Our conclusions are based on a small subset of subjects, and the study was not designed to examine growth as a primary end point. Using changes from baseline in $z$ scores rather than calculating growth velocities, which require minimum intervals of 24 weeks between measurements (and for which we had no prestudy treatment values for comparison), allowed us to identify both short- and long-term alterations in weight and height growth. Since the study had no control group of untreated HIV-infected subjects and since there is very little published in the literature on similarly aged-infected children, it is unknown if the growth patterns shown in these subjects are better or worse than would have been expected without treatment, and the changes in growth factors we are reporting may not be generalizable to other highly active antiretroviral therapy therapies or patient populations. It is clear, however, that although the subjects with controlled viral load may not have experienced very large declines in height growth, there was no evidence during 2 years of follow-up that they were catching up to growth levels in non–HIV-infected children.

The cause of growth failure among HIV-infected children has not been well delineated, and many factors including hypermetabolism, poor oral intake, malabsorption, and/or hormonal changes may be involved.\textsuperscript{22} Fontana et al\textsuperscript{30} reported no preferential reduction in fat-free body mass of HIV-infected children, suggesting that inadequate caloric intake could be the main cause of growth failure rather than excess catabolism. Similar results were reported by Henderson et al,\textsuperscript{34} who found that resting caloric expenditure was not significantly increased in HIV-infected children compared with uninfected children, but the mean caloric intake was significantly lower in HIV-infected children with growth failure compared with uninfected children. These results supplement our findings and suggest that further study of nutritional support and hormonal adjuvants in addition to the use of highly active antiretroviral therapy therapy is warranted in improving growth among HIV-infected children.

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From the Department of Pediatrics, State University of New York Health Science Center at Stony Brook (Dr Nachman); Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Mass (Drs Lindsey and Stanley); Department of Pediatrics, Boston Medical Center (Dr Pelton); Pediatric, Adolescent and Maternal AIDS Branch, National Institute of Child Health and Human Development, National Institutes of Health, Rockville, Md (Dr Mofenson); Department of Pediatrics, Children's Hospital, Boston (Dr McIntosh); Department of Pediatrics, Jacobi Hospital, Einstein Medical Center, Bronx, NY (Dr Wiznia); and the Department of Pediatrics, Children's Memorial Hospital, Northwestern University, Chicago, Ill (Dr Yogev).

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Corresponding author and reprints: Sharon A. Nachman, MD, Department of Pediatrics, State University of New York Health Science Center at Stony Brook, Stony Brook, NY 11794-8111 (e-mail: snachman@notes.cc.sunysb.edu).

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