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This information is current as of November 20, 2006

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Treatment With Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus Type 1–Infected Children Is Associated With a Sustained Effect on Growth

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ABSTRACT. *Introduction.* **Growth failure is a common feature of children with human immunodeficiency virus type 1 (HIV-1) infection. Children who are treated with mono or dual nucleoside analogue reverse transcriptase inhibitor (NRTI) therapy show a temporary increase in weight gain and linear growth rate. In adults, protease-inhibitor-containing antiretroviral therapy is associated with a sustained weight gain and increased body mass index (BMI). Experience with protease inhibitors and growth in children is still limited. The data mainly deal with short-term effects on growth.**

Objective. **To evaluate the effect of highly active antiretroviral therapy (HAART) on growth in children with HIV-1 infection.**

Design and Methods. **We analyzed selected growth parameters, clinical data, and laboratory results as part of a prospective, open, uncontrolled, multicenter study to evaluate the clinical, immunologic, and virologic response to HAART consisting of indinavir, zidovudine, and lamivudine in children with HIV-1 infection. Height and weight were measured at 0, 12, 24, 36, 48, 60, 72, 84, and 96 weeks after initiation of HAART. Information about the children's growth before enrollment in the study was retrieved from the hospital medical records and/or the school doctor or health center. BMI was calculated.** z **Scores were used to express the standard deviation (SD) in SD units from the Dutch reference curves for age and gender. Viral loads and CD4$^+$ T-cell counts were examined prospectively and related to these growth parameters.** z **Scores were also calculated for CD4$^+$ T-cell counts to correct for age-related differences. A** z **score of 0 represents the P50, which is exactly the age/sex-appropriate median. A height** z **score of** -1 **indicates that a child's height is 1 SD below the age- and gender-specific median height for the normal population. Virologic responders were defined as those who either reached an undetectable viral load (<500 copies/mL) or had a >1.5 log reduction in viral load compared with baseline at week 12 after the initiation of HAART, which was maintained during the follow-up period.**

Results. Patients. **Twenty-four patients were included (age: 0.4–16.3 years at baseline), with a median HIV-1 RNA load of 105 925 copies/mL (5.03 log), a median CD4$^+$ T-cell count of 0.586 × 10^9/L (median** z **score: -2.28 SD), a median height** z **score of -1.22, a median weight** z **score of -0.74, and a median baseline BMI** z **score of -0.32. Eleven patients were naive to antiretroviral therapy, and 13 patients had received previous treatment with NRTI monotherapy. Twenty children used indinavir and 4 children used nelfinavir as part of HAART.**

Virologic and immunologic responses to HAART. **Seventeen children were virologic responders, and 7 children were virologic nonresponders. In patients naive to NRTIs, median baseline viral loads were significantly higher than in pretreated patients. However, at weeks 48 and 96, there was no significant difference between the viral loads of both groups. At baseline, there was no significant difference in CD4$^+$ T-cell** z **scores between virologic responders and nonresponders or between naive and pretreated patients. During 96 weeks of HAART, the increase of CD4$^+$ T-cell** z **score was significantly higher in responders than in nonresponders. The increase in CD4$^+$ T-cell** z **score was not significantly different for naive and pretreated patients.**

Height, weight, and BMI z score changes. **We found that there was a trend toward a significantly increased** z **score change during 96 weeks of HAART compared with the** z **score change before HAART initiation for height and weight, but not for BMI.**

Growth and virologic response to HAART. **When the data were analyzed separately for virologic responders and nonresponders, virologic responders showed significant increases in height and weight. The height and weight of virologic nonresponders did not change significantly. The BMI did not change significantly in responders or in nonresponders.**

Growth and immunologic response to HAART. **The increase of weight and BMI** z **scores from baseline correlated positively with the CD4$^+$ T-cell** z **score increase from baseline. It did not correlate with absolute CD4$^+$ T-cell count increase. Height** z **score increase did not correlate with CD4$^+$ T-cell** z **score or with absolute CD4$^+$ T-cell counts.**

Growth and previous NRTI treatment. **The height** z **score decrease from week -48 to baseline was significantly larger in naive than in pretreated patients. The weight and BMI** z **score change from week -48 to baseline was not significantly different for pretreated and naive patients. From baseline to week 96, the height and weight** z **score change increased significantly in naive patients but not in pretreated patients compared with the change from week -48 to baseline. The BMI** z **score did**

not change significantly over 96 weeks of HAART for naive or pretreated patients.

Growth and clinical stage of infection. The clinical stage of infection according to the Centers for Disease Control and Prevention classification correlated negatively with the BMI *z* score and the weight *z* score at baseline but not with the height *z* score. Thus, children with the most severe clinical disease had the lowest BMI and weight *z* scores at baseline. The BMI *z* score increased more in children with more advanced clinical infection at baseline, who had lower BMI at baseline. The clinical stage of infection did not correlate with the change in weight *z* score from baseline to week 96.

Conclusions. HAART has a positive influence effect on the growth of HIV-1–infected children. This effect is sustained for at least 96 weeks. Height and weight are favorably influenced in children in whom HAART leads to a reduction of the viral load of at least 1.5 log or to <500 copies/mL and to an increase in the CD4^{+} T-cell *z* score. In contrast to the increase of the BMI in adults on HAART, BMI did not increase in all children effectively treated with HAART. BMI increased more in children with an advanced stage of infection and a poor nutritional status at baseline. Data from pretreated and naive patients were difficult to interpret, because the baseline characteristics of these 2 groups differed too much. *Pediatrics* 2002;109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e25; *human immunodeficiency virus, acquired immunodeficiency syndrome, highly active antiretroviral therapy, protease inhibitor, growth, height, weight, body mass index.*

ABBREVIATIONS. HIV-1, human immunodeficiency virus type 1; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; HAART, highly active antiretroviral therapy; NRTI, nucleoside analogue reverse transcriptase inhibitor; SD, standard deviation.

Growth failure is a common feature of children with human immunodeficiency virus type 1 (HIV-1) infection.[1–8] The cause of this HIV-1–related growth failure is complex. It is not only caused by an inadequate caloric intake, because increases in caloric intake do not seem to increase lean body mass or accelerate the rate of linear growth, but only increase weight and fat mass.[9,10] A correlation with viral load was previously recognized.[11] Abnormal function of the thyroid gland, the somatomedine axis, the lipid metabolism, and abnormal resting energy expenditure may also contribute to the diminished growth.[12,13] Growth seems to be one of the most sensitive indicators of disease progression in children with acquired immunodeficiency syndrome (AIDS). The absence of growth indicates a poor prognosis, also in children who are treated with antiretroviral regimens.[14–19] Poor growth commonly precedes a decline in CD4^{+} T-cell count and the subsequent development of opportunistic infections.[20,21] Several studies have shown that weight gain may be an important indicator of antiretroviral therapeutic efficacy.[22,23] Children who are treated with mono or dual therapy containing zidovudine, didanosine, or zalcitabine show a temporary increase in weight gain and linear growth rate.[24–26] In adults, protease-inhibitor-containing antiretroviral therapy is associated with a sustained weight gain and in-

creased body mass index (BMI).[27] Experience with protease inhibitors and growth in children is still limited; it mainly consists of short-term effects on growth.[28–31] The objective of this study was to evaluate the effect of highly active antiretroviral therapy (HAART) consisting of 1 protease inhibitor and 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) on the long-term growth profile of HIV-1–infected children.

METHODS

Selected growth parameters, clinical data, and laboratory results were analyzed as part of a prospective, open, uncontrolled, multicenter study to evaluate the clinical, immunologic, and virologic response to HAART consisting of indinavir, zidovudine, and lamivudine in children with HIV-1 infection.[32] The study protocol was approved by the medical ethical committees of all the participating centers. Written informed consent was obtained from parents or legal guardians. Children >3 months of age with HIV-1 infection and 1 of the following 2 items: a decreased CD4^{+} T-cell count (<1 year: <1750/mm^3, 1–2 years: <1000/mm^3, 3–6 years: <750/mm^3, >6 years: <500/mm^3) or a HIV-1 viral load >5000 copies/mL were included. Growth data before HAART initiation also needed to be available to be included. Height and weight measurements and blood samples for virologic and immunologic parameters were obtained twice within a month before the start of HAART, and after 12, 24, 36, 48, 60, 72, 84, and 96 weeks of treatment. Height and weight measurements were obtained by a single investigator using the same scales and the same metal measuring rod every time. Information about the children's growth before enrollment in the study was retrieved from the hospital medical records and/or the school doctor or health center. Height and weight measurements obtained closest to 24 and 48 weeks before HAART initiation were entered into the database.

Virologic responders were defined as those who either reached an undetectable viral load (<500 copies/mL) or had a >1.5 log reduction in viral load compared with baseline at week 12 after the initiation of HAART, which was maintained during the follow-up period.

The BMI was calculated from height and weight values as defined by BMI = weight (kg)/(height (m)).^{2} BMI provides an indication of the nutritional status of the patients. Compared with the 2 other measurements for weight-for-height, ie, kg/m and kg/m^3, BMI has the desired lower correlation with height and higher correlation with weight and skinfold thickness.[33] *z* Scores were used to express the deviation in standard deviation (SD) units from the Dutch reference curves for age and gender.[34,35] The *z* scores for weight, height, and BMI were calculated by means of the SDS software program (version 2.0, Erasmus University, Rotterdam, the Netherlands). Reference growth curves were not available for most countries from which the patients originated. Therefore, Dutch reference growth curves were used. Because we only discuss change in *z* scores over time and not absolute *z* scores, this does not present any problems. *z* Scores were also calculated for CD4^{+} T-cell counts to correct for age-related differences.[36] A *z* score of 0 represents the P50, which is exactly the age/sex-appropriate median. A height *z* score of −1 indicates that a child's height is 1 SD below the age- and gender-specific median height for the normal population.

The viral load was measured using the Roche Amplicor HIV-1 Monitor test (Roche, Branchburg, NJ).[37] CD4^{+} T-cell counts were obtained by standard flow cytometric methods. Statistical calculations were performed with the SPSS statistical analysis software program (SPSS Inc, Chicago, IL, version 10.0). The relations between growth parameters, CD4^{+} T lymphocyte counts, CD4^{+} *z* scores, and viral loads were analyzed using the Wilcoxon signed-rank test, Mann-Whitney *U* test, and Spearman rank correlation test. All *P* values are 2-tailed.

RESULTS

Population Characteristics

Patients

Twenty-four HIV-1–infected children were included. They all completed at least 96 weeks of

HAART. Baseline characteristics of these 24 children are presented in Table 1. The median age of the children was 5.2 years (range: 4.6 months–16.3 years). Eleven patients were not previously treated and 13 had received previous treatment with NRTIs, mostly zidovudine mono therapy for an average of 30 months (range: 8.4–106.2 months). Pretreated children were significantly older at baseline than NRTI-naive children ($P = .002$), with a median age of 7.4 years and 2.0 years, respectively. Twenty children received HAART containing indinavir and 2 NRTIs and 4 children received HAART containing nelfinavir and 2 NRTIs. In 5 children, indinavir was changed to nelfinavir and in 1 child to indinavir and ritonavir and later to nevirapine because of a viral load rebound after a median duration of 48 weeks. In 2 other children, indinavir was changed to nelfinavir because of long-term side effects.

Virologic Response

The median baseline plasma viral load of 5.03 $\log_{10}$ copies/mL (range: 2.43–5.88) decreased to less than 2.70 $\log_{10}$ copies/mL by week 48 and remained below the level of detection until at least week 96. In patients naive to NRTIs ($N = 11$) median baseline viral loads were significantly higher than in pretreated patients ($N = 13$; $P = .02$). However, at weeks 48 and 96, there was no significant difference between the viral loads of both groups (Table 2).

Seventeen children were virologic responders and 7 children virologic nonresponders.

Immunologic Response

Absolute $CD4^+$ T-cell counts per age group are shown in Fig 1A. The median baseline $CD4^+$ T-cell z score was -2.28 SD (range: -13.75–0.26). At base-

line, there was no significant difference between virologic responders and nonresponders or between naive and pretreated patients ($P > .05$). During 96 weeks of HAART, the increase of $CD4^+$ T-cell z score was significantly higher in responders than in non-responders ($P = .008$; Fig 1B). The increase in $CD4^+$ T-cell z score was not significantly different for naive and pretreated patients ($P > .05$).

Height, Weight, and BMI z Score Changes

Using data from all patients regardless of virologic response and previous treatment, the effects of HAART on growth were determined. We found that the height z score decreased in the 48 weeks before HAART initiation with a median (range) of -0.088 SD (-1.88–1.17) to a median of -1.22 SD at baseline. From baseline to 96 weeks after the initiation of HAART the height z score increased with a median (range) of 0.20 SD (-0.72–1.29) to a median of -0.95 SD. The weight z score decreased from week -48 to baseline with a median (range) of -0.041 SD (-4.10–1.96) to a median of -0.74. From baseline to week 96 the weight z score increased with a median of 0.34 SD (-0.83–2.13) to a median of -0.60. The BMI z score change from week -48 to baseline decreased with a median (range) of -0.12 SD (-4.10–1.96) to a median of -0.32 SD. From baseline to week 96 the median (range) BMI z score change was 0.28 SD (-1.75–3.60) to a median of 0.19 SD. We found that there was a trend toward a significantly increased z score change during 96 weeks of HAART compared with the z score change before HAART initiation for height ($P = .052$) and weight ($P = .056$), but not for BMI ($P = .627$).

Growth and Virologic Response to HAART

The median change in height z score decreased in the 48 weeks before HAART initiation. Children with a higher viral load at baseline showed a larger decrease ($P < .0001$) of the height z score in the 48 weeks before HAART initiation than children with a lower viral load. From baseline to week 96 height z score and weight z score changes increased significantly in virologic responders, but not in nonresponders compared with the change from week -48 to baseline (Fig 2A–D).

BMI z score did not increase significantly over 48 or 96 weeks of HAART in responders or in nonresponders. (Fig 2, E and F) However, the BMI z score change increased significantly more in virologic responders than in nonresponders to HAART ($P = .024$ after 96 weeks).

Growth and Immunologic Response to HAART

During 96 weeks of HAART, the change in height z scores from baseline did not correlate with the change in $CD4^+$ T-cell z scores or absolute $CD4^+$ T-cell counts.

The change in weight z scores from baseline correlated positively with the change in $CD4^+$ T-cell z scores at week 24 ($r = 0.693$; $P < .0001$), 36 ($r = 0.543$; $P = .007$), 48 ($r = 0.628$; $P = .001$), 60 ($r = 0.540$; $P = .009$), 84 ($r = 0.496$; $P = .019$) and 96 ($r = 0.408$; $P = .048$). The change in weight z scores only correlated

TABLE 1. Baseline Characteristics of Study Patients ($n = 24$)

Median age in years (range)	5.2 (0.4–16.3)
Sex (male/female), n	11/13
Race/ethnicity, n	
Nonwhite	19
White	5
Route of acquisition, n	
Vertical	16
Blood products	4
Unknown	4
CDC classification*, n	
N 1/2	2/3
A 1/2/3	2/3/4
B 1/2	1/4
C 2/3	2/3
No previous treatment, n	11
Previous treatment with, n	
zidovudine	11
zidovudine/zalcitabine	2
$\log_{10}$ copies of HIV RNA/mL plasma, median (range)	5.03 (3.42–5.87)
$CD4^+$ cell count in 10^9/L, median (range)	0.586 (0.010–3.580)
$CD4^+$ z score in SD, median (range)	-2.28 (-13.75–0.26)
z Score in SD, median (range)	
Height	-1.22 (-3.84–1.25)
Weight	-0.74 (-3.13–2.26)
BMI	-0.32 (-3.88–2.03)

* Clinical and immunologic categories as defined by the US Centers for Disease Control and Prevention (CDC).[38]

TABLE 2. Viral Load at Baseline, 48 Weeks and 96 Weeks after HAART Initiation in Log copies per mL, Median (25th and 75th Percentile)

Patients	Baseline	Week 48	Week 96
All	5.03 (4.29–5.60)	<2.70 (<2.70–<2.70)	<2.70 (<2.70–3.29)
Naive	5.41 (5.16–5.85)*	<2.70 (<2.70–<2.70)	<2.70 (<2.70–2.85)
Pretreated	4.47 (4.09–4.93)*	<2.70 (<2.70–2.76)	<2.70 (<2.70–3.47)
Responders	5.16 (4.32–5.66)	<2.70 (<2.70–<2.70)†	<2.70 (<2.70–<2.70)‡
Nonresponders	4.94 (4.24–5.29)	<2.70 (<2.70–3.80)†	3.29 (3.08–4.34)‡

* Significant difference, $P = .02$.
† Significant difference, $P = .024$.
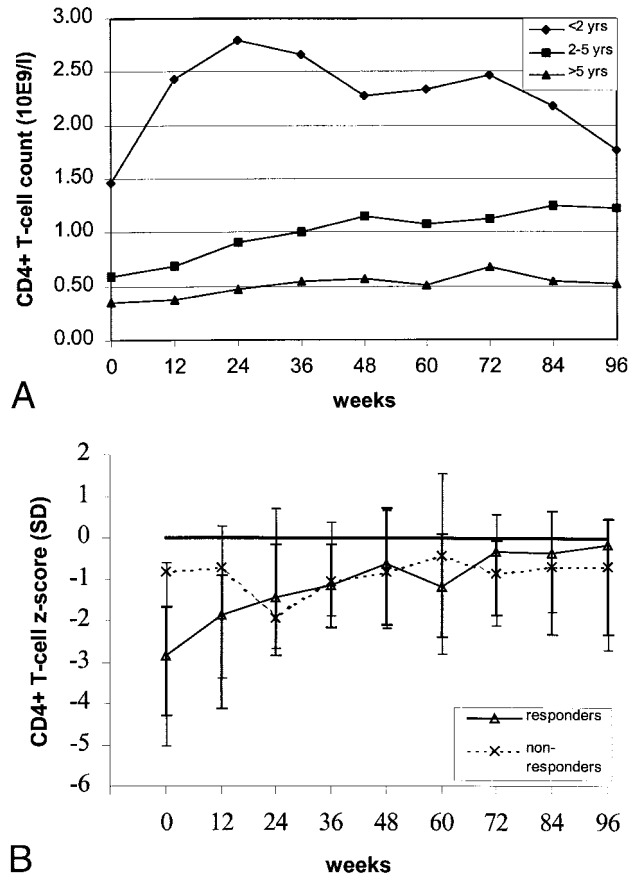‡ Significant difference, $P < .0001$.

Fig 1. A, CD4$^+$ T-cell count change in different age categories during 96 weeks of HAART. B, CD4$^+$ T-cell z score change in responders and nonresponders during 96 weeks of HAART.

with the change in absolute CD4$^+$ T-cell counts at week 36 ($r = 0.439$; $P = .032$).

The change in BMI z scores correlated positively with the change in CD4$^+$ T-cell z scores at al time points from week 12 onwards except at week 84: week 12 ($r = 0.476$; $P = .019$), 24 ($r = 0.671$; $P < .0001$), 36 ($r = 0.508$; $P = .011$), 48 ($r = 0.592$; $P = .003$), 60 ($r = 0.443$; $P = .039$), 72 ($r = 0.520$; $P = .013$), 84 ($r = 0.369$; $P = .091$) and 96 ($r = 0.501$; $P = .013$). The change in BMI z scores did not correlate with change in absolute CD4$^+$ T-cell counts.

Growth and Previous NRTI Treatment

The height z score decrease from week −48 to baseline was significantly larger in naive (−0.41 SD) than in pretreated (−0.04 SD) patients ($P = .007$). From baseline to week 96, the height z score change

increased significantly in naive patients ($P = .033$) but not in pretreated patients compared with the change from week −48 to baseline.

The weight and BMI z score change from week −48 to baseline was not significantly different for pretreated and naive patients. The weight z score change increased significantly over 96 weeks of HAART for naive patients ($P = .026$) but not for pretreated patients.

The BMI z score did not change significantly over 96 weeks of HAART for naive or pretreated patients. There was no significant difference between naive and pretreated patients either.

Growth and Clinical Stage of Infection

The clinical stage of infection according to the Centers for Disease Control and Prevention classification[38] correlated negatively with the BMI z score at baseline. Thus, children with the most severe clinical disease had the lowest BMI z scores at baseline. The BMI z score increased more in children with more advanced clinical infection at baseline, who had lower BMI at baseline.

The clinical stage of infection at baseline also correlated negatively with weight z score but not with the height z score. Children with advanced clinical infection had lower weight for their age and gender at baseline. The clinical stage of infection did not correlate with the change in weight z score from baseline to week 96 ($P > .05$).

DISCUSSION

The results of this study indicate that children with HIV-1 infection show a trend to an increase in height and weight ($P = .052$, $P = .056$, respectively) after the initiation of HAART. However, when the children were divided into virologic responder and nonresponder groups, the responders showed significant increases in height and weight, whereas nonresponders did not. The BMI did not change significantly in responders or in nonresponders, although it increased more in responders than in nonresponders. Increasing CD4$^+$ T-cell counts favorably influenced weight and BMI. Clinical stage of infection was also correlated with the increase of BMI from baseline to week 96 of HAART. BMI z scores increased more in children with an advanced clinical stage of infection at initiation of HAART. The energy expenditure previously needed to combat infection was possibly used for catch-up growth. CD4$^+$ T-cell z scores then relate to BMI and weight only indirectly.

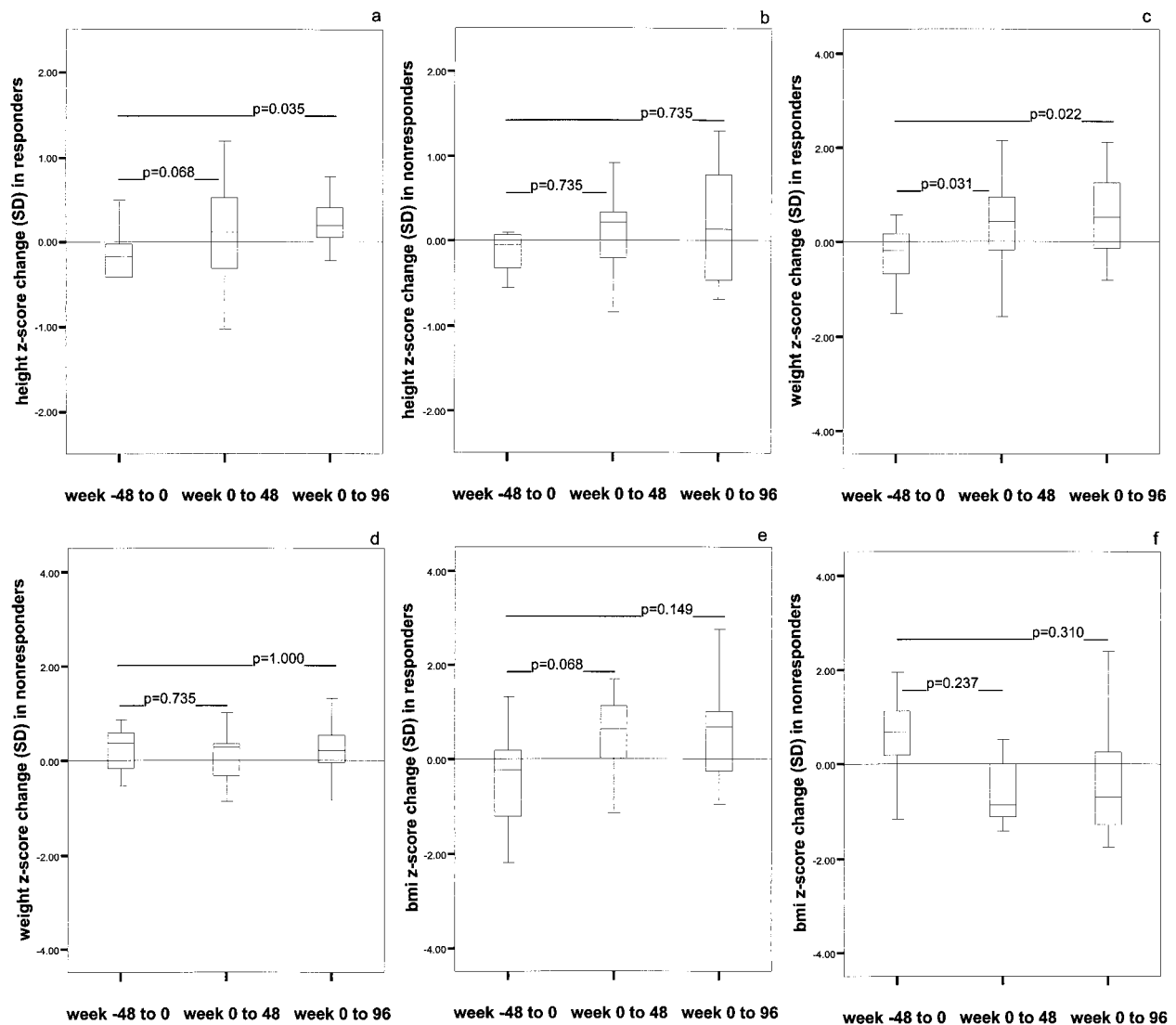In HIV-1–infected adults receiving HAART, BMI

Fig 2. Growth before and during HAART in (A, C, and E) responders and (B, D, and F) nonresponders.

increased significantly more in responders than in nonresponders, but BMI also increased significantly overall in responders and in nonresponders. BMI increase consisted mainly of increased fat mass. Lean body mass did not increase significantly.[27] We are not aware of any previously published studies on the influence of HAART on BMI in HIV-1–infected children. However, in a recent study in HIV-1–infected children, protease inhibitors were found to cause a significant increase in weight-for-height and a dramatic improvement in lean body mass over a short interval and had no immediate influence on fat mass, although there was a trend toward increased fat mass, with longer follow-up time.[28] This suggests that in the children whose BMI increased in our study, namely the children with an advance stage of clinical infection and responders to HAART with a high increase in CD4^{+} T-cell count, lean body mass also increased. The difference of the effect of HAART on body composition between children and adults could be attributed to the fact that children are still growing so their metabolism is different, but additional research is needed.

Height did not increase significantly in responders until week 96, whereas weight already increased significantly at week 48. This is a normal reaction to the correction of a growth-retarding disorder: catch-up growth first affects weight followed by height.[39]

At the initiation of HAART, viral loads correlated negatively with height *z* score change in the previous year and the clinical stage of infection correlated negatively with BMI *z* score and weight *z* score. Children with high viral loads and severe clinical infection also had poor grow parameters. These are all associated with a poor prognosis. Although the number or percentage of CD4^{+} T cells has a larger influence on prognosis, increasing growth rates also contribute to a better prognosis.[16,18,19,22,23]

Height and weight *z* score change over 96 weeks compared with *z* score change in the 48 weeks before HAART initiation increased more in responders than in nonresponders. It also increased more in naïve patients than in pretreated patients. Although this could be interpreted as a confounder, it is more likely to be the result of previous antiretroviral therapy. Pretreated patients seem to have already reached a

higher height z score change during the 48 weeks before HAART initiation. This may have been caused by the treatment with NRTIs. Weight z score change in the 48 weeks before HAART initiation was not significantly different between naive and pretreated patients. We concluded from the observation that weights increased in naive patients and not in pretreated patients. However, a difference was observed in baseline viral load and age: pretreated patients were significantly older and had a significantly lower viral load. This complicates the comparison between these 2 groups of patients.

Similar results in height and weight gain as observed by our group were reported in 3 other studies on the effects of HAART in children.[28,30,31] However, the follow-up time of these studies was only 24 weeks. A positive influence on growth has been observed as a result of NRTI mono therapy or dual therapy during this same period.[14,22,24,40–46] The effect on growth of mono therapy cannot be sustained after 24 weeks of treatment. There is no data that supports that dual therapy has a sustained effect on growth beyond 24 weeks. The current study shows that the positive effects of HAART on growth can be sustained for at least 96 weeks. Therefore, the effect on growth lasts longer in patients receiving HAART than in patients receiving mono or duo reverse transcriptase inhibitor therapy. There seems to be a relation between the time that an antiretroviral therapy is successful in the suppression of viral load and the time that the positive effect on growth by this therapy can be maintained. Ogino et al[22] also raised this point when they described the effect of zidovudine resistance on growth.

Dreimane et al[29] retrospectively reviewed 27 HIV-1–infected children receiving HAART for a mean follow-up time of 20 months. They also found increased z scores for height and height-velocity, but not for weight. This difference in findings may be attributed to the low number of responders to HAART in their study (10 of 27) compared with the high number of responders (17 of 24) in our study. It could also be attributed to the fact that they used another protease inhibitor. Unfortunately, they did not mention which protease inhibitor was used in their patients. Miller et al[28] found that ritonavir had a weaker effect on weight with a stronger effect on height compared with indinavir and nelfinavir.

CONCLUSION

HAART has a positive effect on height and weight in children with HIV-1 infection. This effect is sustained for at least 96 weeks and is associated with the successful application of HAART, resulting in long-term viral load reduction of at least 1.5 log copies/mL or viral load suppression below 500 copies/mL and an increase of $CD4^+$ T-cell counts. The sustained effects of HAART on growth may positively influence the child's quality of life and will predictably contribute to a better prognosis. The mechanism of increased growth during antiretroviral therapy is yet unknown. Contrary to the BMI increase in adults treated with HAART, BMI in children does not increase in all patients successfully treated with HAART, but only in those with a low BMI at initiation of HAART. More research is needed to investigate whether those factors causing growth failure in children with HIV-1 infection—caloric intake, thyroid and growth hormones, lipid metabolism, and resting energy expenditure—also play a role in the recovery of growth parameters during HAART.

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