Height, Weight, and Growth in Children Born to Mothers With HIV-1 Infection in Europe

The European Collaborative Study

ABSTRACT. *Objectives.* **Little is known about the independent long-term effect on growth of exposure to maternal human immunodeficiency virus (HIV) infection. Growth patterns in uninfected children who are born to infected mothers have not been described in detail previously beyond early childhood, and patterns over age for infected and uninfected children have not been based on appropriate general population standards. In vertically HIV-infected children, poor growth has been suggested to be an early marker of infection or progression of disease. However, whether growth faltering is an independent HIV-related symptom or caused indirectly by other HIV clinical symptoms requires clarification. This information is needed to inform the debate on a possible effect of antiretroviral combination therapy on the height of infected children and would provide evidence for the use of specific interventions to improve height. The objective of this study was to describe growth (height and weight) patterns in infected and uninfected children who are born to HIV-infected mothers with respect to standards from a general population and to assess age-related differences in height and weight by infection status, allowing for birth weight, gestational age, gender, HIV-related clinical status, and antiretroviral therapy (ART).**

Methods. **Since 1987, children who were born to HIV-infected mothers in 11 centers in 8 European countries were enrolled at birth in the European Collaborative Study and followed prospectively according to a standard protocol. Height and weight were measured at every visit, scheduled at birth; 3 and 6 weeks; 3, 6, 9, 12, 15, 18, and 24 months; and every 6 months thereafter. Serial measurements of height and weight from birth to 10 years of age of 1403 uninfected and 184 infected children were assessed. We fitted linear mixed effects models allowing for variance changes over age and within-subject correlation using fractional polynomials and natural cubic splines. Growth patterns were compared with British 1990 growth standards and by infection status.**

Results. **Of the 1587 children enrolled, 810 were male and 777 were female; 1403 were not infected (681 boys, 722 girls), and 184 were infected (88 boys, 96 girls). Neither height nor weight was associated significantly with the main effects of HIV infection status at birth, but differences between infected and uninfected children increased with age. Uninfected children had normal growth patterns from early ages. Infected children were estimated to be significantly shorter and lighter than uninfected children with growth differences increasing with age. Differences in growth velocities between the infected and uninfected children increased after 2 years of age for height and after 4 years of age for weight and were more marked in the latter. Between 6 and 12 months, uninfected children grew an estimated 1.6% faster in height and 6.2% in weight than infected children; between ages 8 and 10 years, these figures were 16% and 44%, respectively. By 10 years, uninfected children were on average an estimated 7 kg heavier and 7.5 cm taller than infected children. Growth in uninfected children who were born before 1994, before the widespread use of ART prophylaxis to reduce vertical transmission, did not substantially differ from that of children who were born after 1994. To investigate whether the growth differences between infected and uninfected children were associated with HIV disease progression, we analyzed growth of infected children using the Centers for Disease Control and Prevention (CDC) clinical classification, in 3 groups: no symptoms, mild or moderate symptoms (A and B), and severe symptoms (C or death). Infected children with mild or serious symptoms lagged behind asymptomatic children in both height and weight, and these differences increased with age. Infected children who were born before availability of ART, before 1988, were more likely to reach a weight below the third centile for age than children who were born after 1994 when effective HIV treatment was widely available. Of the 184 infected children, 67 had been weighed and/or measured at least once while on combination (≥2 drugs) ART. Reflecting the longitudinal nature of the European Collaborative Study and the changing availability of HIV treatment, most of these measurements took place after 7 years of age, and therefore analyzing the possible effect of combination therapy on growth is difficult. The *z* scores for height and weight gain improved substantially in several children who received combination therapy regardless of their CDC clinical classification. To increase available information, we pooled all measurements according to CDC clinical classification and presence of combination therapy at the time of the observation. Weight and height significantly improved for severely ill children after combination therapy.**

Conclusion. **Using data from this large prospective European study, we investigated in comparison with general British standards growth patterns in the first 10 years of life of HIV-infected and uninfected children who were born to HIV-infected mothers. The duration of follow-up of uninfected as well as infected children makes this a unique data set. We allowed for repeated measurements for each child and the increase of variability in height and weight with age. Growth faltering may be related to the social environment, and our finding that uninfected children have normal growth, which is unaffected by exposure to maternal HIV infection, is consis-**

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tent with observations that in Europe the HIV-infected population is more like the general population and less socioeconomically disadvantaged than that in the United States. However, HIV-infected children grew considerably slower, and differences between infected and uninfected children increased with age. Growth patterns in asymptomatic infected children were similar to those with only mild or moderate symptoms. However, compared with these 2 groups combined, severely ill children had poorer growth at all ages. Although limited by the small number of children who received combination therapy, severely ill children may benefit from such therapy in terms of improvements in weight and, to a smaller extent, in height. Growth faltering, particularly stunting, may adversely affect a child's quality of life, especially once they reach adolescence, and this should be taken into account when making decisions about starting and changing ART. Additional research will help to elucidate the relationship between combination therapy and improved growth, in particular regarding different regimens and the best timing of initiation for optimizing growth of infected children. *Pediatrics* 2003;111:e52–e60. URL: http://www.pediatrics.org/cgi/content/full/111/1/e52; *HIV infection, growth, weight, height, Europe.*

ABBREVIATIONS. HIV, human immunodeficiency virus; ECS, European Collaborative Study; AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; BMI, body mass index; LME, linear mixed effects; FP, fractional polynomial; ART, antiretroviral therapy; PI, protease inhibitor.

There is a lack of evidence to substantiate the suggestion that exposure to maternal human immunodeficiency virus (HIV) infection during fetal life may affect growth. Growth patterns in uninfected children who are born to mothers with HIV-1 infection have not been described in detail previously beyond early childhood, and patterns for infected and uninfected children have not been related to appropriate general population standards.

Growth faltering in vertically HIV-infected children may be an early marker of infection or progression of disease.[1,2] However, although poor growth in HIV-infected children has been reported,[1,3–7] this has been limited to early childhood, and it is unclear what happens after 5 years of age. Whether growth faltering is an independent HIV-related symptom or caused indirectly by other HIV clinical symptoms is not yet clarified.[3]

In a previous paper,[3] we reported significant but small differences in growth in the first 4 years of life between uninfected and symptomatic infected children who were born to HIV-1–infected mothers who were enrolled in the prospective European Collaborative Study (ECS).[8] We now extend this previous work using data obtained from children in the ECS up to 10 years of age, to evaluate growth patterns of both infected and uninfected children who were born to HIV-1–infected mothers with respect to standards from a general population.[9] In addition, we assess age-related differences in height and weight by HIV infection status, allowing for birth weight, gestational age, gender, HIV-related clinical status, and treatment.

METHODS

In the ECS, children who were born to women who were known to be infected with HIV at the time of delivery were examined at birth, at 3-month intervals to 24 months of age, and at least every 6 months thereafter for infected children and yearly for uninfected children, according to a standard protocol.[3,8] Parental consent was obtained before enrollment in the ECS, and the study was approved by local ethics committees.

By October 2001, 1587 children had been enrolled in the 11 pediatric centers of the ECS. The number of observations ($n = 280$) for ages above 10 years was limited, and, given the rapid and variable growth in puberty starting soon after this age, the analysis was restricted to the 12 735 observations below 10 years of age. Infection in the child was defined by persistence of HIV antibody beyond 18 months, the detection of the virus or antigen on 2 or more occasions, or the diagnosis of acquired immunodeficiency syndrome (AIDS).[10] At each visit, each child was allocated a Centers for Disease Control and Prevention (CDC) clinical category, based on clinical symptoms and signs.[10] Treatment was categorized into no therapy, monotherapy, or combination therapy with 2 or more drugs.[8]

Growth standards for height, weight, and body mass index (BMI; weight divided by height squared) based on a general British population[9] were used to obtain z scores for each measurement according to age and gender, which were adjusted for gestational age. Linear mixed effects (LME) models fitted with restricted maximum likelihood were used. For the original measurements, the linear predictors specifying the fixed effects for age were obtained using fractional polynomials (FP).[11] FPs up to order 5 were fitted, and the optimal form was determined using the gain in deviance with respect to the straight line model.

With the use of nonparametric smoothers, the trends of the z scores across combinations of gender and HIV infection status differed more than those of the untransformed measurements. Accordingly, we used natural cubic splines to define the linear predictors for the z transformed values. The model selection for the fixed effects was based on the Akaike Information Criterion. Once a suitable linear predictor (including interactions) was obtained using only random intercepts, more complex models were incorporated for the random effects. The model selection for this part of the mixed models was done via likelihood ratio tests. We modeled the response variables directly, and the variance of the error terms was modeled with a power function of age. We also accounted for within-subjects serial correlation.

All calculations were done in S-Plus 6.0 (Data Analysis Division, MathSoft Inc, Seattle, WA) in a Unix environment using the function LME.[12] We used the LMS method to obtain the z scores values.[13]

RESULTS

Of the 1587 children enrolled in the pediatric arm of the ECS, 810 were male and 777 were female; 1403 were not infected (681 boys, 722 girls), and 184 were infected (88 boys, 96 girls). Figure 1 shows the height and weight measurements by HIV infection status, with infected children seeming to grow more slowly than uninfected children. The measurements' coefficients of variation increased with age, especially in infected children. This, as well as the longitudinal and irregular nature of the data, was taken into account in the following analyses.

Predicted Height and Weight and Their Velocities

The final models for height and weight included terms for birth weight, gestational age at delivery, HIV status, gender, and interactions between the FPs on age and the last 2 factors. For the adjusted z scores, they included the same covariates, plus the interactions between HIV status and gender and the spline terms. In both cases, the random effects included an intercept and all of the age-related terms,

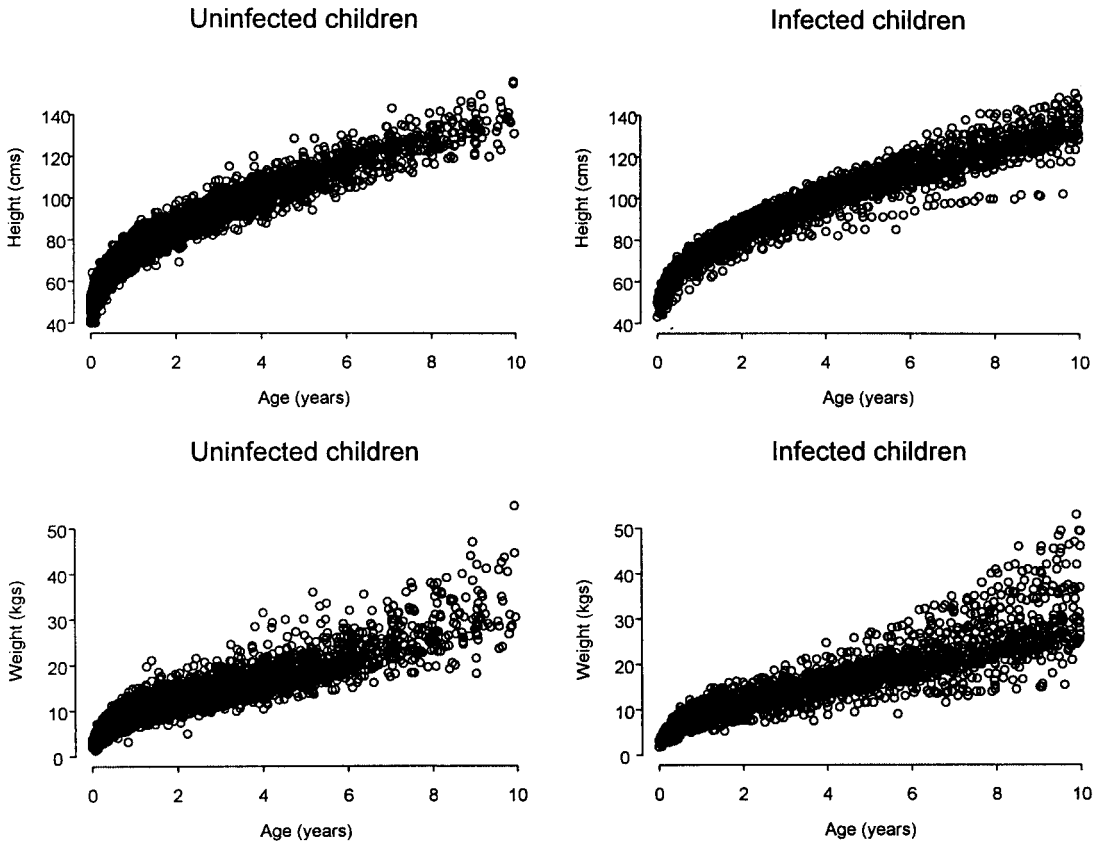

Fig 1. Observed height and weight by infection status.

the age-related changes in variance were modeled with a power function, and a within-subjects autoregressive process was included. Table 1 shows summary statistics for the predicted height and weight of infected and uninfected children at selected ages. Neither height nor weight was associated significantly with the main effects of HIV infection status at birth ($P = .57$ and .06, respectively), but differences between infected and uninfected children increased with age ($P < .0001$). Uninfected children were significantly taller and heavier from very early ages, and by 10 years of age, they were estimated to be almost 7 kg (22%) heavier and 7.5 cm (5.6%) taller than infected children. The interaction between HIV infection status and gender was not significant for either height or weight, and this was excluded from the final models.

Differences in growth velocities between the infected and uninfected children increased after 2 years of age for height and after 4 years of age for weight and were more marked in the latter. The predicted velocities and their standard deviations for height and weight by infection status were calculated from the final LME models and are shown in Table 2. Between 6 and 12 months, uninfected children grew an estimated 1.6% and 6.2% faster in height and weight, respectively, than infected children; between 3 and 4 years and between 8 and 10 years, these figures were 10.7% and 10.8% and 16% and 44%, respectively.

TABLE 1. Predicted Height and Weight at Selected Ages by Infection Status

Age (Months)	Height (cm)				Weight (kg)			
	Infected		Uninfected		Infected		Uninfected	
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*
1	51.81 ± 0.34	50	52.65 ± 0.12	457	3.69 ± 0.07	50	3.90 ± 0.03	457
3	59.19 ± 0.21	115	60.22 ± 0.08	878	5.26 ± 0.07	115	5.72 ± 0.02	878
6	65.52 ± 0.19	146	66.46 ± 0.07	1069	6.84 ± 0.07	146	7.45 ± 0.03	1069
12	73.34 ± 0.24	142	74.45 ± 0.08	971	8.95 ± 0.10	142	9.66 ± 0.03	971
24	83.72 ± 0.30	127	85.34 ± 0.12	661	11.68 ± 0.13	127	12.43 ± 0.06	661
36	92.04 ± 0.35	111	94.06 ± 0.15	547	13.87 ± 0.16	111	14.59 ± 0.08	547
48	99.51 ± 0.43	99	101.63 ± 0.18	432	15.96 ± 0.21	99	16.67 ± 0.10	432
72	112.10 ± 0.61	79	115.70 ± 0.39	155	19.93 ± 0.36	79	21.86 ± 0.23	155
96	123.68 ± 0.90	56	128.29 ± 0.69	73	25.09 ± 0.67	56	28.24 ± 0.57	73
120	134.54 ± 1.32	39	142.08 ± 1.23	38	31.33 ± 1.23	39	38.28 ± 1.17	38

SD indicates standard deviation.

TABLE 2. Predicted Height and Weight Velocities by Infection Status

Age (Months)	Uninfected			Infected		
	Velocity	SD	*N*	Velocity	SD	*N*
Height						
1–3	32.48 cm/y	5.04	452	31.42 cm/y	7.29	55
3–6	25.24 cm/y	3.03	836	25.62 cm/y	3.85	115
6–12	15.88 cm/y	1.26	928	15.62 cm/y	1.87	142
12–24	10.92 cm/y	0.73	641	10.25 cm/y	0.88	131
24–36	8.82 cm/y	0.76	542	8.01 cm/y	0.96	115
36–48	7.89 cm/y	0.82	428	7.12 cm/y	1.05	102
48–72	7.08 cm/y	0.83	153	6.35 cm/y	0.98	81
72–96	6.49 cm/y	0.80	72	5.73 cm/y	0.85	57
96–120	6.30 cm/y	0.81	37	5.42 cm/y	0.84	40
Weight						
1–3	7.77 kg/y	1.22	452	6.94 kg/y	1.47	55
3–6	7.10 kg/y	0.96	836	6.42 kg/y	1.17	115
6–12	4.45 kg/y	0.56	928	4.19 kg/y	0.72	142
12–24	2.81 kg/y	0.43	641	2.68 kg/y	0.46	131
24–36	2.23 kg/y	0.42	542	2.07 kg/y	0.45	115
36–48	2.17 kg/y	0.47	428	1.96 kg/y	0.52	102
48–72	2.51 kg/y	0.68	153	2.04 kg/y	0.70	81
72–96	3.18 kg/y	1.08	72	2.43 kg/y	0.99	57
96–120	4.27 kg/y	1.38	37	2.95 kg/y	1.25	40

Comparison With the 1990 British Standards

Figure 2 shows the predicted *z* scores for height, weight, and BMI by gender and HIV infection status, corresponding to the mean values of birth weight and gestational age. Gestational age and birth weight were significantly associated with all the *z*-transformed values ($P < .0001$), as were all of the interactions between age and HIV infection status. There were no significant main effects of gender, and the interaction between gender and infection status by height was also not significant, indicating that within infection status category, boys and girls had similar growth patterns. Girls were overall heavier than boys ($P < .01$), although there were no significant interactions between gender and any of the age terms in the model. HIV status's main effect and all of its interactions with the age terms, except for the first one, were significant ($P < .0001$). BMI was significantly affected by the main effects of gender and HIV status and was the only *z* score variable with a significant interaction between HIV and gender ($P = .002$), indicating that the gender differences within infection status groups were larger in the uninfected than in the infected children.

The patterns for uninfected children suggest that their growth is unaffected by exposure to maternal HIV infection. Growth in uninfected children who were born before 1994, before the widespread use of antiretroviral therapy (ART) prophylaxis to reduce vertical transmission, did not substantially differ from that of children who were born after 1994. Growth in infected children substantially and increasingly deviates with age from the norm in both height and weight.

Effect of HIV Clinical Status on Growth

To investigate whether the growth differences between infected and uninfected children were associated with HIV disease progression, we analyzed

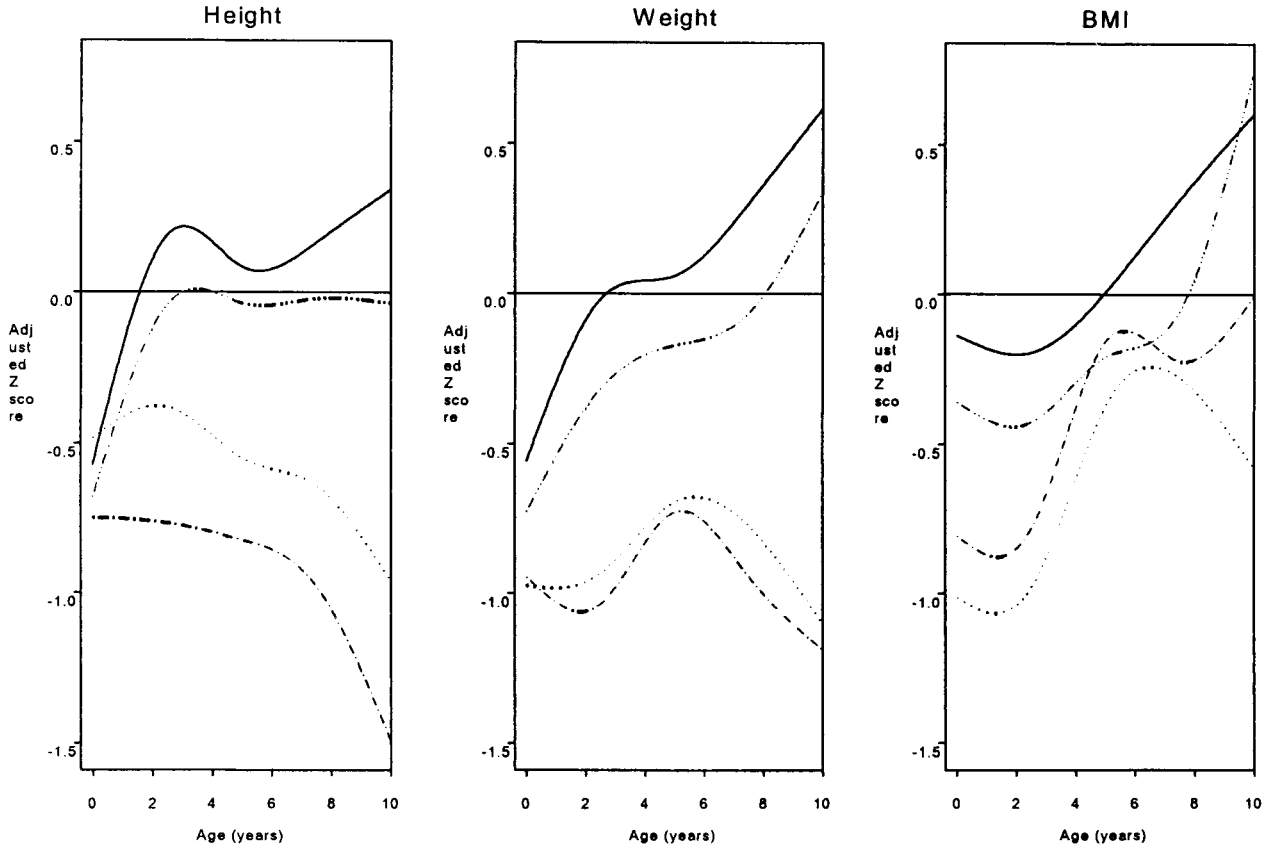

Fig 2. Predicted *z* scores for height, weight, and BMI by gender and infection status. ___, uninfected girls; __. . . __, uninfected boys; . . . . . , infected girls; _._._, infected boys.

TABLE 3. Predicted Height and Height Velocity for Infected Children by CDC Clinical Category

Age (Months)	Predicted Height (cm)							Age (Months)	Predicted Height Velocity (cm/y)						
	Asymptomatic		AB		*P* Value	CD			Asymptomatic			AB			*P* Value
	Mean ± SD	*n*	Mean ± SD	*n*		Mean ± SD	*n*		Velocity (cm/y)	SD	*n*	Velocity (cm/y)	SD	*n*	
1	51.45 ± 2.39	42	51.84 ± 1.75	7	.30	50.18	1	1–3	32.84	6.70	43	29.2	7.25	10	.07
3	59.16 ± 2.12	82	59.08 ± 2.35	31	.56	57.95	1	3–6	24.90	6.37	82	22.42	8.46	31	.07
6	65.74 ± 2.32	94	64.96 ± 2.52	48	.04	63.60	1	6–12	15.32	2.48	93	14.57	3.00	45	.07
12	73.55 ± 2.90	91	72.85 ± 3.12	47	.10	69.88 ± 1.07	2	12–24	10.25	1.00	86	9.65	1.15	42	.00
24	84.11 ± 3.35	84	83.01 ± 3.80	41	.06	76.70	1	24–36	8.36	0.99	78	8.06	1.43	38	.12
36	92.55 ± 3.77	74	91.16 ± 4.14	36	.40	NA	0	36–48	7.34	0.93	70	6.85	1.26	34	.02
48	100.32 ± 3.83	66	98.09 ± 5.04	33	.01	NA	0	48–72	6.37	1.16	53	5.89	1.29	29	.05
72	113.21 ± 5.12	50	111.12 ± 6.03	29	.06	NA	0	72–96	5.97	0.82	36	5.92	1.10	23	.43
96	125.21 ± 6.01	33	123.58 ± 7.67	23	.20	NA	0	96–120	5.69	0.89	25	5.31	0.92	16	.10
120	136.64 ± 8.34	23	133.24 ± 8.79	16	.11	NA	0								

NA indicates not applicable.

TABLE 4. Predicted Weight and Weight Velocity for Infected Children by CDC Clinical Category

Age (Months)	Predicted Weight (kg)							Age (Months)	Predicted Weight Velocity (kg/y)						
	Asymptomatic		AB		*P* Value	CD			Asymptomatic			AB			*P* Value
	Mean ± SD	*n*	Mean ± SD	*n*		Mean ± SD	*n*		Velocity (kg/y)	SD	*n*	Velocity (kg/y)	SD	*n*	
1	3.73 ± 0.52	42	3.70 ± 0.29	7	.58	3.11	1	1–3	6.99	1.42	43	6.02	1.27	10	.02
3	5.32 ± 0.69	82	5.10 ± 0.76	31	.08	5.04	1	3–6	6.36	1.67	82	5.43	1.95	31	.00
6	7.01 ± 0.86	94	6.48 ± 0.94	48	.00	7.00	1	6–12	4.20	0.88	93	3.91	0.95	45	.04
12	9.16 ± 1.14	91	8.62 ± 1.25	47	.00	8.79 ± 1.27	2	12–24	2.72	0.53	86	2.60	0.52	42	.12
24	11.95 ± 1.52	84	11.38 ± 1.60	41	.03	9.47	1	24–36	2.14	0.55	78	2.09	0.61	38	.34
36	14.05 ± 1.86	74	13.57 ± 1.70	36	.09	NA	0	36–48	1.96	0.63	70	1.74	0.57	34	.04
48	16.21 ± 2.25	66	15.33 ± 2.09	33	.02	NA	0	48–72	1.98	0.87	53	1.60	0.71	29	.02
72	20.13 ± 3.54	50	18.98 ± 3.00	29	.06	NA	0	72–96	2.45	1.09	36	1.90	0.90	23	.02
96	25.67 ± 5.19	33	23.32 ± 4.63	23	.04	NA	0	96–120	3.06	1.56	25	1.97	1.15	16	.01
120	32.63 ± 9.02	23	27.29 ± 7.25	16	.02	NA	0								

NA indicates not applicable.

growth of infected children using the CDC clinical classification, in 3 groups: no symptoms, mild or moderate symptoms (A and B), and severe symptoms (C or death; Tables 3 and 4). Infected children with mild or serious symptoms lagged behind asymptomatic children in both height and weight, and these differences increased with age.

Figure 3 shows the predicted adjusted *z* scores for the infected children by CDC clinical classification categories, which were introduced as a time-dependent covariate. The height *z* scores indicated a common velocity of standardized height decay and no significant difference in the intercepts. The only significant difference ($P = .035$) was found in the intercepts between the severely ill group and the asymptomatic infected children, with children with evidence of severe clinical symptoms starting at a lower *z* score at birth, and this difference had become larger by 10 years of age. In other words, HIV infection affects growth, particularly in the presence of AIDS conditions.

In the *z* scores for weight, the 3 groups had significantly ($P < .001$) different intercepts, starting at −0.75, −1.1, and −1.6 standard deviations for the asymptomatic, mild/moderate symptomatic, and severely ill groups, respectively. For BMI, the curves were parallel with the only significant difference being in the intercepts with respect to the severely ill children.

HIV Treatment and Growth Patterns of Infected Children

Infected children who were born before availability of ART, before 1988, were more likely to reach a weight below the third centile for age than children who were born after 1994, when effective HIV treatment was widely available. However, for children with poor weight gain, with 1 measurement below the third centile, the age at which this occurred was not influenced by period of birth (data not shown).

Of the 184 infected children, 67 had been weighed and/or measured at least once while on combination (≥2 drugs) ART (range: 1–14; median: 4 observations). Reflecting the longitudinal nature of the ECS and the changing availability of HIV treatment, most of these measurements took place after 7 years of age, and therefore analyzing the possible effect of combination therapy on growth is difficult. In particular, the number of measurements while on combination treatment by CDC clinical category became small (414, 118, and 5 for asymptomatic, mild/moderately symptomatic and severely ill, respectively).

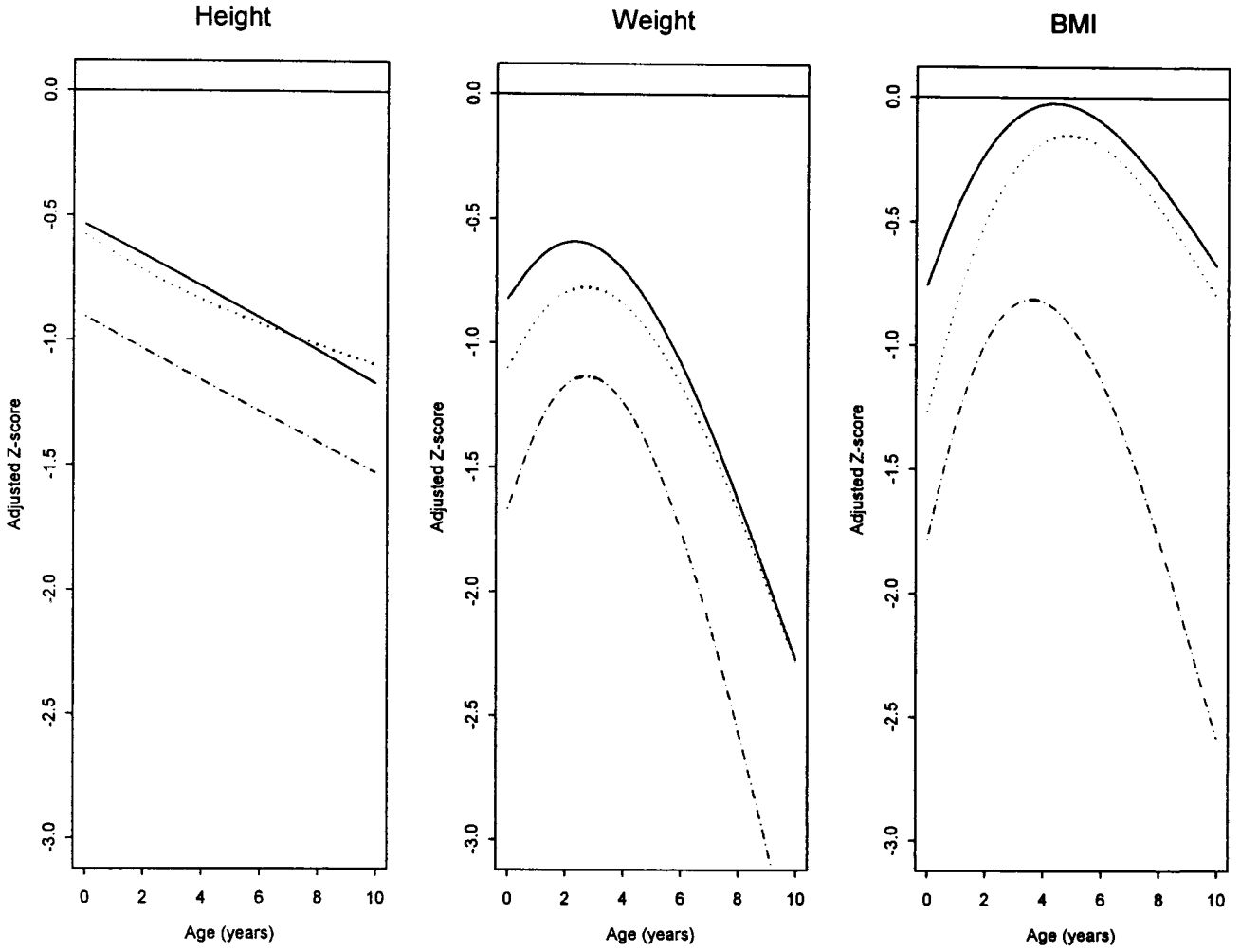

Fig 3. Predicted *z* scores for height, weight, and BMI for infected children by CDC clinical classification categories. ___, asymptomatic children; . . . . . mild/moderate symptomatic children; _._._, severely ill children.

The *z* scores for height and weight gain improved substantially in several children who received combination therapy regardless of their CDC clinical classification. In some cases, there was an increase larger than 1 *z* score in height and weight during a 2-year period after initiation of combination therapy. The numbers of children were too small to analyze formally for changes in growth with respect to age, so we describe the changes pooling all measurements according to CDC clinical classification and presence of combination therapy at the time of the observation.

Forty-three children had severe disease (category C or D) at least once (range: 1–12; median: 1), only 2 of whom received combination therapy—1 child twice, the other once. To evaluate the effect of combination treatment (no treatment and monotherapy were combined into 1 group) interacting with clinical CDC category, we considered the *z* scores as being independent of age and considered only measurements without any reference to individuals (Table 5). Significant differences ($P < .001$) were observed for the *z* scores of height and weight measurements of severely ill children by treatment, with larger measurements under combination therapy. For the measurements of children with asymptomatic and mild/moderate disease at the time, these contrasts were not significant.

DISCUSSION

Using data from this large prospective European study, we investigated in comparison with general British standards growth patterns in the first 10 years of life of HIV-infected and uninfected children who were born to HIV-infected mothers. The duration of follow-up of uninfected as well as infected children makes this a unique data set. We allowed for repeated measurements for each child and the increase of variability in height and weight with age.

Our findings reveal no major differences in growth between uninfected children who were born to HIV-infected women and children in the general population, consistent with the limited literature available. A small Italian study that investigated BMI in the first 6 months of life in infants who were born to HIV-infected mothers reported no substantial differences between the uninfected children and a reference group born at the same hospital.[5] In a South African cohort study that included nearly 150 children who were born to HIV-infected mothers, uninfected children had slightly lower weights for age and lengths for age than the population standards in later infancy (from 9 months of age), but this was reportedly probably attributable to environmental and economic conditions.[1] Growth faltering may be related to the social environment, and our finding that uninfected children have normal growth is consistent with previous work suggesting that in Europe the HIV-infected population is more like the general population and less socioeconomically disadvantaged than that in the United States[8] (S. Fiore, personal communication, January 2002). The lack of an effect on growth of exposure to prophylactic ART is reassuring.

Poor growth observed in vertically infected children should be interpreted in the context of their social environment, and here we were able to use the uninfected children as appropriate controls. In the ECS, growth faltering in terms of both weight and height was associated with vertically acquired HIV infection at least up to 10 years of age, extending previous findings from the ECS[3] and others,[2,4–6] which were limited to early childhood. Differences in growth patterns between infected and exposed but uninfected children not only persisted but also significantly increased with age. Although there was no difference in birth weight by HIV infection status, at 3 months of age, infected children were already an estimated 460 g lighter than uninfected children. Differences in weight increased sharply after the second year of life, reaching an estimated 7 kg by 10 years of age. Height differed significantly between infected and uninfected children, but less so than for weight. By 10 years of age, uninfected children were an estimated 7.5 cm taller than infected children.

HIV infection may interfere with sexual maturation,[14] and more information is needed regarding the interaction between faltering growth and onset of puberty in infected adolescents. We did not have enough observations above 10 years of age to study the effect, if any, of vertically acquired HIV infection and treatment on the onset of puberty. However, the mean rate of decrease for height velocity between 8 and 10 years of age of the uninfected children was closer to 0 than that of the infected ones, which might suggest that the latter group may have a delayed pubertal growth spurt. This needs additional investigation.

High RNA viral load and HIV-related symptoms are likely to contribute to slower growth in infected children. In our study, growth patterns in asymptomatic infected children were similar to those with

TABLE 5. *Z* Scores of the Infected Children by Therapy and CDC Clinical Status

	No Therapy or Monotherapy			Combination Therapy			*P* Value
	Mean *z* Score	Standard Error	*N*	Mean *z* Score	Standard Error	*N*	
Height							
Asymptomatic	−0.406	0.029	1622	−0.449	0.075	200	.296
Mild/moderate	−0.695	0.047	768	−1.132	0.177	74	<.001
Serious/death	−2.133	0.17	88	−0.354	0.321	3	<.001
Weight							
Asymptomatic	−0.366	0.031	1622	−0.241	0.082	200	.077
Mild/moderate	−0.898	0.053	768	−0.901	0.194	74	<.001
Serious/death	−2.660	0.194	88	0.232	0.232	3	<.001

only mild or moderate symptoms. However, compared with these 2 groups combined, severely ill children had poorer growth at all ages. Johann-Liang et al[15] found advanced HIV clinical disease and severe immunosuppression to be more common in infected children with growth impairment than in those with normal growth, but the direction of the relationship remains unclear. HIV RNA level has also been identified as a significant predictor of weight growth failure.[16]

Our results suggest that children who were born in a period when effective ART was widely available were less likely to reach weight below the third centile than children who were born when only monotherapy with zidovudine was the norm. It is of interest to note our suggestion that use of combination therapy in severely ill children may be associated with improvements in weight and, to a smaller extent, in height. However, we had only a very limited number of observations available for infected children on combination therapy reflecting the time frame of data collection in the ECS,[8] and reasons for treatment initiation were not recorded. Although a short-term beneficial effect of double therapy with nucleoside analogues on growth has been reported elsewhere,[17] protease inhibitor (PI)-containing regimens have most commonly been linked to improvements in growth in HIV-infected children.[6,18,19] Two studies from Switzerland reported an increase in height in infected children associated with a PI-containing regimen, which tended to be more marked for children who achieved undetectable viral load after treatment and/or for those with more advanced clinical disease at baseline.[20,21] However, in a study of 906 infected children, only small annual increments in height and weight were found to be associated with PI-containing regimens compared with non-PI regimens.[22] It is likely that differences in age at initiation of therapy are crucially associated with probability of growth improvement. The only way to investigate this further is through a randomized, controlled trial.

High HIV replication and/or the resulting immune response may affect metabolism, which in turn has an impact on growth, and reducing viral load through highly active ART leading to improvements in growth fits with this hypothesis. However, the reduction in clinical symptoms of HIV disease after initiation of effective ART could also play a key role. A small number of studies of HIV-infected children have suggested that reduced energy intake may be an important factor relating to growth faltering.[15,23]

It has been suggested that HIV-infected children may benefit from growth hormone therapy,[2] but evidence for both the need for and any positive effect of such therapy is limited to small studies on children with failure to thrive and advanced HIV disease.[24] Even less is known about the possible effect of growth hormone in HIV-infected children in the era of combination therapy. In our study, nearly 30% of infected children had failure to thrive, but this was more common in the early years of the study, when effective ART was not available, and occurred mostly in children who had other AIDS-defining symptoms and were younger than 1 year. Growth faltering, particularly stunting, may adversely affect a child's quality of life, especially once they reach adolescence, and this should be taken into account when making decisions about starting and changing ART. Additional research on large data sets relating to infected children on therapy will help to elucidate the relationship between combination therapy and improved growth, in particular regarding different regimens and the best timing of initiation of therapy for optimizing growth of infected children.

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