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Maternal and Infant Factors Associated With Failure to Thrive in Children With Vertically Transmitted Human Immunodeficiency Virus-1 Infection: The Prospective, P²C² Human Immunodeficiency Virus Multicenter Study

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Abstract

Objective—Many children with human immunodeficiency virus-1 (HIV-1) have chronic problems with growth and nutrition, yet limited information is available to identify infected children at high risk for growth abnormalities. Using data from the prospective, multicenter P²C² HIV study, we evaluated the relationships between maternal and infant clinical and laboratory factors and impaired growth in this cohort.

Methods—Children of HIV-1–infected women were enrolled prenatally or within the first 28 days of life. Failure to thrive (FTT) was defined as an age- and sex-adjusted weight *z* score -2.0 SD. Maternal baseline covariates included age, race, illicit drug use, zidovudine use, CD4⁺ T-cell count, and smoking. Infant baseline predictors included sex, race, CD4⁺ T-cell count, Centers for Disease Control stage, HIV-1 RNA, antiretroviral therapy, pneumonia, heart rate, cytomegalovirus, and Epstein–Barr virus infection status.

Results—The study cohort included 92 HIV-1–infected and 439 uninfected children. Infected children had a lower mean gestational age, but birth weights, lengths, and head circumferences in the 2 groups were similar. Mothers of growth-delayed infants were more likely to have smoked

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The institutions and investigators participating in this study are listed in the “Appendix.”

tobacco and used illicit drugs during pregnancy. In repeated-measures analyses of weight and length or height *z* scores, the means of the HIV-1-infected group were significantly lower at 6 months of age ($P < .001$) and remained lower throughout the first 5 years of life. In a multivariable Cox regression analysis, FTT was associated with a history of pneumonia (relative risk [RR] = 8.78; 95% confidence interval [CI]: 3.59–21.44), maternal use of cocaine, crack, or heroin during pregnancy (RR = 3.17; 95% CI: 1.51–6.66), infant CD4⁺ T-cell count *z* score (RR = 2.13 per 1 SD decrease; 95% CI: 1.25–3.57), and any antiretroviral therapy by 3 months of age (RR = 2.77; 95% CI: 1.16–6.65). After adjustment for pneumonia and antiretroviral therapy, HIV-1 RNA load remained associated with FTT in the subset of children whose serum was available for viral load analysis.

Conclusion—Clinical and laboratory factors associated with FTT among HIV-1-infected children include history of pneumonia, maternal illicit drug use during pregnancy, lower infant CD4⁺ T-cell count, exposure to antiretroviral therapy by 3 months of age (non-protease inhibitor), and HIV-1 RNA viral load.

Keywords

human immunodeficiency virus; children; failure to thrive; growth; malnutrition

Many children with human immunodeficiency virus-1 (HIV-1) infection have chronic problems with linear growth and weight gain.^{1–5} A variety of disturbed growth patterns have been described, ranging from symmetric delays in weight and length or height to severe wasting with normal length or height. The differences in growth patterns probably result from differences in disease manifestations in HIV-1-infected children. In developed countries, both weight and length or height decline in infected children as early as the first month of life.⁴ Sequential follow-up showed that the growth rate in HIV-1-infected children remained below that of exposed but uninfected children.

The exact mechanism of failure to thrive (FTT) has not been identified in the pediatric HIV-1-infected population. Factors that influence growth in all children include energy intake, energy metabolism, gastrointestinal absorption, and psychosocial factors. In HIV-1-infected children, preliminary evidence suggests that dietary intakes are adequate because the majority of these children meet or exceed the recommended daily allowance (RDA) for calories and macronutrients.^{6,7} Some evidence suggests that dietary intakes that are much higher than the RDA can increase the weight of HIV-1-infected children.⁷ Energy metabolism is less well-defined, but some studies suggest that resting energy expenditure in infected children is slightly higher than predicted,⁸ which is also the case in adults with HIV-1 infection.^{9,10} Children with HIV-1 infection are also more likely than noninfected children to have problems absorbing nutrients, which can impair growth.^{11,12} Comorbidities or chronic clinical conditions associated with HIV-1 can influence growth and nutrition by altering any of the aforementioned factors.

Despite the expanding literature on growth and nutrition in children with HIV infection,^{1–5} a comprehensive evaluation of prenatal and postnatal associations with FTT in HIV-1-infected children has not been reported. Knowing those factors may enable clinicians to intervene with closer nutritional surveillance in children at risk for FTT. Alternatively,

children with FTT may be at risk for comorbid conditions associated with FTT. In this report, we analyzed data from a prospective multicenter pediatric HIV study to identify baseline maternal and infant covariates that may be associated with FTT in children with vertically transmitted HIV-1 infection. A secondary objective was to evaluate the effect of HIV-1 on growth from birth through 5 years of age.

Methods

Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV-1 Infection (P²C²) was a prospective study of vertically transmitted HIV-1 infection, with primary emphasis on the cardiopulmonary manifestations. Pregnant HIV-1–infected women were enrolled at 5 sites in the United States: Boston, Massachusetts; Houston, Texas; Los Angeles, California; and New York, New York (2 sites). Recruitment began in May 1990 and continued through January 1994, with follow-up through January 1997. The methods and the study population have been fully described elsewhere.¹³ This report is limited to the 600 infants born to HIV-1–infected women; 432 were enrolled while their mothers were pregnant, and 168 were enrolled before 28 days postpartum.

At birth, 3 months, and 6 months, infant peripheral blood was cultured for HIV-1 according to the AIDS Clinical Trials Group consensus protocol for qualitative peripheral blood mononuclear leukocyte HIV-1 cultures.¹⁴ Enzyme-linked immunosorbent assays and Western immunoblot serologic tests were performed when the infants were 15 months old or older; the results were used to confirm HIV-1 infection status. Infants were considered to be HIV-1 infected if they had 2 positive cultures or a positive HIV-1 serologic result at 15 or more months of age, died from an HIV-1–associated condition, or developed acquired immunodeficiency syndrome. Children were considered to be HIV-1 uninfected if they had 2 negative cultures, including 1 at or after 5 months, or if they had a negative antibody test at 15 months of age or older. The noninfected children constituted the comparison population. Because they shared many of the same growth-impairing psychosocial factors with the infected children, we were able to determine the effect of HIV-1 infection on growth patterns. Those who did not meet either criterion were classified as having indeterminate infection status.

Maternal Covariates

HIV-1 infection in the women was confirmed by standard enzyme-linked immunosorbent assay and Western immunoblot serologic testing. Baseline characteristics of the women during pregnancy were evaluated as potential covariates that might have influenced the children's growth. Demographic information (age, race) and a complete history of the pregnancy and delivery, including prescription medications (eg, zidovudine [ZDV]) and illicit drug use, were collected in a standardized fashion from interviews and medical records.¹³ Mothers were asked about use of tobacco as well as cocaine, crack, heroin, methadone, marijuana, nitrate inhalants, phencyclidine, amphetamines, and barbiturates. Lymphocyte subsets were determined during pregnancy using an AIDS Clinical Trial Group-certified laboratory.¹⁴

Infant and Child Covariates

We recorded baseline demographic features (sex and race) and immunologic factors including CD4⁺ T-cell counts at baseline (within the first 6 months of life) and Centers for Disease Control and Prevention (CDC) symptom status as determined by the most severe category by 3 months of life.¹⁵ Two infants with wasting syndrome before 3 months of age were not included in the CDC symptom status analysis. CD4⁺ T-cell counts were expressed as age-adjusted *z* scores.¹⁶ Serum HIV-1 RNA concentration was measured in stored samples by quantitative HIV-1 RNA polymerase chain reaction using Amplicor HIV-1 Monitor test (Roche Diagnostic Systems, Branchburg, NJ); 1 technician performed all assays. The lower limit of detection was 400 copies/mL, as previously described.¹⁷ Because HIV-1 RNA levels rise sharply in the first 2 months of life and then decline gradually through 24 months,¹⁷ the first measurement from each child in this period (2–24 months) was used for analysis. We evaluated left ventricular fractional shortening and mass and heart rate within the first 10 months of life. Respiratory rate was measured over a full minute by a trained observer while the child was awake and breathing quietly. Tachypnea was defined as a respiratory rate at or above the upper 95th percentile for age by 3 months of age.¹⁸ Other baseline covariates included postnatal use of antiretroviral therapy by 3 months of age (no children were on protease inhibitors before age 2 or highly active antiretroviral therapy) and disease progression as previously described.¹⁹ The children were considered to be rapid progressors if they had an acquired immunodeficiency syndrome–defining condition (other than lymphocytic interstitial pneumonitis/pulmonary lymphoid hyperplasia), severe immunosuppression (CDC category 3), or both in the first year of life. Disease progression categories for infants who died before 1 year of age were assigned based on available symptom and immunology data.

All children were evaluated for cytomegalovirus (CMV) infection by 18 months of age using urine culture with standard virologic techniques (shell vial or standard culture) and serology with commercially available enzyme immunoassays.²⁰ A child who had a positive culture at any age or who had a positive serologic test (immunoglobulin G or M) at 12 months of age or older was considered CMV positive. Patients older than 6 months were considered CMV-negative if they had a negative serologic test and no previous positive culture results. Oropharyngeal swab specimens for Epstein–Barr virus (EBV) were obtained by 18 months of age and assayed using standard techniques.²¹

Specific criteria for viral and bacterial pneumonia diagnoses have been previously reported.²² Evidence from bronchial lavage fluid or open lung biopsy was needed for a diagnosis of *Pneumocystis carinii* pneumonia (PCP). Mycobacterial infection was diagnosed when a new radiographic abnormality occurred and a culture from lower-airway secretions or an open lung biopsy specimen showed that the organism was present. If the origin of pneumonia could not be determined, it was designated as not otherwise specified (NOS).

Outcome Measurements

The primary outcome of this study was time to FTT. FTT was defined as an age- and sex-adjusted weight *z* score of -2.0 SD (ie, a weight that falls at or below 2 standard deviations of the age- and sex-adjusted mean of healthy population standards). Recumbent length and

weight were recorded in all children younger than 2 years of age. For those 2 years and older, standing height and weight were recorded. Standard techniques²³ were used in all patients. Length or height and weight were determined at each pulmonary physical examination (every 3 months from birth to 18 months and every 6 months thereafter) and at each cardiac assessment (every 4 months for HIV-1–infected children and every 6 months for uninfected children). Because growth endpoints were not the main outcome measurements for the P²C² HIV protocol, data on parental stature and dietary intake were not available for analysis.

Weight, length or height, and weight for length or height were age and sex adjusted and expressed as *z* scores using the ANTHRO pediatric anthropometry software program.²⁴

Statistical Analyses

Actual gestational age, birth weight, birth length, birth head circumference, and *z* scores for these variables were compared by HIV-1 group with the Wilcoxon rank-sum test. *z* Scores were calculated for birth weight, birth length, and head circumference based on gestational age.²⁵ Baseline weight *z* scores that were available by 3 months of age were compared separately for HIV-1–infected and HIV-1–uninfected infants by maternal characteristics using the Wilcoxon rank-sum test.

Repeated-measures analyses were performed for actual weight, length or height, and weight for length or height and for the *z* scores. A linear model using maximum likelihood estimation and a heterogeneous compound symmetry variance–covariance form among the repeated measurements was fit for each outcome. Covariate adjustment was made for HIV-1 group, age category, and HIV-1 group by age category. The results were summarized by HIV-1 group and age category using model-based means and 95% confidence intervals (CIs) obtained from the repeated-measures model.

Cumulative rates of FTT and mortality were estimated with the Kaplan–Meier method, and 95% CIs for FTT were provided for the first 5 years of life by HIV-1 group. Generalized Wilcoxon tests were used to compare overall FTT incidence among HIV-1–infected children according to baseline clinical characteristics. To estimate the relative risk (RR) of FTT and examine the temporal relationship between pneumonia and FTT, we included each type of pneumonia as a time-dependent nominal covariate (yes/no) in a Cox regression model of time to FTT. The Cox regression model was fit separately for each type of pneumonia. FTT rates by disease progression and HIV-1 group and mortality rates by FTT status were compared using the generalized Wilcoxon test. All tests were 2-sided. A *P* value .05 was considered to indicate statistical significance.

To assess the simultaneous effect of baseline factors on time to FTT, Cox's proportional-hazards regression model was used. Forward and backward stepwise selection was used to choose prognostic factors for the multivariable model. Only factors that were significant at *P* .05 in the univariable analyses were included in the multivariable analyses. The RR and its 95% CI were calculated for each factor in the presence of others in the final model.

Results

Study Cohort Characteristics

The original study cohort was composed of 600 participants: 93 HIV-1–infected and 463 uninfected children plus 44 infants of indeterminate status. We excluded 10 pairs of twins (1 infected infant and 19 uninfected infants), 44 infants of indeterminate HIV-1 status, and 5 HIV-1–uninfected infants without length and weight data. Thus, the final study cohort contained 92 HIV-1–infected and 439 HIV-1–uninfected children, for whom there were 1921 and 4570 study visits, respectively. Ten HIV-1–infected children who received supplemental nutrition from either nasogastric feeding tube, gastrostomy tube, or parenteral nutrition were included in the analyses because the 10 did not differ from the other 82 infected infants in mean weight, length, or weight for length, and FTT was documented before any feeding interventions were started in 8 of the infants and shortly after the interventions were started in the other 2.

Most of the children were black (271/531, 51%) or Hispanic (166/531, 31.3%), and 282 were male (53.1%). There were no differences in sex or race distribution between the infected and uninfected children. Infants were small at birth because mean weight and length z scores were less than zero ($P < .001$) for both HIV-1–infected and uninfected infants. However, birth weight, length, and head circumference (and z scores of these measurements) were similar among the infected and uninfected infants. Gestational age was lower in the infected infants (mean $\pm$ SD, 37.7 weeks $\pm$ 2.9) than in the uninfected infants (38.4 weeks $\pm$ 2.6; $P = .01$). By 3 months of age, all infants were alive, and 17 HIV-1–infected infants had received antiretroviral therapy. All 17 received ZDV, and 5 infants received more than 1 antiretroviral therapy.

Table 1 summarizes baseline weight z scores in both the HIV-1–infected and noninfected infants grouped by maternal covariates. Weight z scores for the HIV-1–infected infants were lower if mothers smoked tobacco during pregnancy ($P = .001$) or used illicit drugs ($P = .007$) during pregnancy. Weight z scores were also lower in the HIV-1–uninfected infants born to mothers who smoked tobacco during pregnancy ($P < .001$) or mothers who used illicit drugs during pregnancy ($P < .001$). Weight z scores among HIV-1–uninfected infants declined as the amount of maternal smoking during pregnancy increased ($P = .004$). Maternal use of crack, cocaine, or heroin was associated with lower weight z scores among the HIV-1–infected infants ($P = .02$) and HIV-1–uninfected infants ($P < .001$).

Longitudinal Analysis of Growth Patterns of HIV-1–Infected and Uninfected Children

Growth patterns (raw and age- and sex-adjusted values) for the HIV-1–infected and uninfected groups are graphed in Fig 1. The HIV-1–infected and uninfected infants were similar in mean weight, length, and weight for length at birth, but the means were significantly lower by 6 months of age for the HIV-1–infected infants ($P = .01$, $P < .001$, and $P < .001$, respectively). By 18 months of age, the HIV-1–infected children were an estimated mean of 1.27 kg lighter and 3.52 cm shorter than the HIV-1–uninfected children. Similar age trends were observed for the mean z scores. The mean z scores for length, weight, and weight for length differed at 3 months ($P = .01$), 6 months ($P < .001$), and 14

months ($P = .03$), respectively. Mean z scores for weight, length, and weight for length at 18 months of age were 0.98, 1.08, and 0.45 SD units lower in the HIV-1–infected children than in the HIV-1–uninfected children. Similar mean differences in z scores persisted through 5 years of age.

Among the HIV-1–infected infants only, mean z scores for length remained low and did not change in the first year of life. Mean weight z scores increased from baseline (0–3 months) to 6 months (3–6 months, $P = .01$) and then declined by 10 months (6–10 months, $P < .001$). Mean weight-for-length z scores increased immediately between birth and 6 months of age ($P < .001$) and then declined over the next 8 months ($P < .001$). Mean z scores for length or height, weight, and weight for length or height tended to increase between 1 and 5 years of age for HIV-1–infected children, but the gradual increases were not statistically significant.

Factors Associated With Failure to Thrive in HIV-Infected Children

Cumulative rates of FTT and 95% CIs for the 92 HIV-1–infected children and 439 uninfected children are shown in Fig 2. By 3 months of age, 20.8% (95% CI: 12.5%–29.1%) of HIV-1–infected children had weight z scores below -2.0 SD. By 1 year of age that percentage had increased to 37.3% (95% CI: 27.1%–47.4%). Cumulative rates of FTT in the HIV-1–infected group were 42.2% at 2 years of age and 50.1% at 5 years of age. For the uninfected children, 11.0% (95% CI: 8.0%–13.9%) had weight z scores below -2.0 SD at 3 months of age, with 15.7% (95% CI: 12.3%–19.2%) below -2.0 SD at 2 years of age ($P < .001$ for the comparison between infected and uninfected children). Although mean weight z scores were lower for HIV-1–uninfected infants born to mothers who smoked tobacco during pregnancy or mothers who used crack, cocaine, or heroin, the FTT rates were not different based on these maternal characteristics.

Table 2 summarizes univariable results for FTT among the HIV-1–infected children by baseline characteristics. Use of crack, cocaine, or heroin during pregnancy was associated with FTT ($P = .008$), but smoking tobacco during pregnancy, alcohol use during pregnancy, maternal age, ZDV use during pregnancy, and maternal CD4 count were not associated with FTT. Cumulative FTT was higher for infants with any pneumonia by 9 months of age ($P = .007$) and for those with higher HIV-1 RNA levels. Among the subset of 65 children whose serum was available for viral load determination, FTT rates were higher in those with HIV-1 RNA levels above 100 000 copies/mL than in those with lower viral burden ($P = .02$ and $P = .01$ when analyzed as a continuous variable). Infants with lower CD4⁺ T-cell count z scores ($P = .12$ when dichotomized at -1 SD and $P = .02$ when fitting a Cox regression model using actual z scores) and those with higher heart rates ($P = .05$) also had higher FTT rates. Cumulative FTT rates were not higher ($P = .11$) for infants in the most severe CDC symptom category by 3 months of age, but only 5 infants had CDC class C symptoms. Sex, race, clinical center, left ventricular mass and fractional shortening, respiratory rate, and EBV and CMV infection status at 18 months were not associated with FTT. In 6 of 7 children with *Mycobacterium avium intracellulare* complex, the complex was identified after FTT. There were 3 HIV-1–infected children with encephalopathy before 3 months of age, but only 1 had encephalopathy before FTT.

The association between FTT and pneumonia was analyzed in 2 ways. First, HIV-1-infected infants were categorized into 2 subsets by pneumonia status at 9 months of age (the criterion was any notation of PCP, viral pneumonia, bacterial pneumonia, or pneumonia NOS). There were 18 HIV-1-infected infants with pneumonia by 9 months of age (8 with PCP). They were more likely to have experienced growth failure than infants and children without pneumonia (69.7% vs 29.5% at 9 months, $P = .007$). Secondly, time to the first episode of any kind of pneumonia by 5 years of age was defined as a time-dependent covariate, and then a Cox regression analysis was performed. Children who developed pneumonia had a RR of FTT of 5.06 (95% CI: 2.20–11.7). Similar results were found for PCP, but no difference was found for viral pneumonia and pneumonia NOS. Bacterial pneumonia was identified in only 2 children.

Table 3A provides the results from Cox regression analyses for 82 children (38 with FTT). Factors independently associated with FTT were first pneumonia episode; maternal use of crack, cocaine, or heroin during pregnancy; lower CD4⁺ T-cell count; and any antiretroviral therapy by 3 months of age. In a separate analysis of 75 children that included heart rate z score as a covariate in addition to the factors in Table 3, the association between heart rate and FTT approached statistical significance (RR = 1.26 per 1 SD increase; 95% CI: 0.97–1.64; $P = .08$).

HIV-1 RNA remained associated with FTT after adjustment for pneumonia and antiretroviral therapy (Table 3B), but only 65 children were available for this analysis. Maternal use of crack, cocaine, or heroin and infant CD4⁺ T-cell count z score did not remain associated with FTT in the HIV-1 RNA subset analysis.

Morbidity and Mortality

Figure 3 shows the cumulative mortality for HIV-1-infected children. Children with FTT had higher mortality rates than the children without FTT (36.3% mortality at 36 months compared with 14.3%; $P = .02$). Figure 4 demonstrates that children who were classified as rapid progressors also had higher rates of FTT (64.5% at 36 months compared with 27.1%; $P < .001$ by the log-rank test).

Discussion

In this study, we have shown that weight and length or height for HIV-1-infected children fall below those of a socioeconomically similar group of children without HIV-1 by 6 months of age. Analyzing simple weight measurements enabled us to determine that maternal illicit drug use during pregnancy, the child's CD4⁺ T-cell count, history of pneumonia, and exposure to antiretroviral therapy were significantly associated with FTT in HIV-1-infected children. In a smaller subset analysis, HIV-1 RNA level was also associated with FTT.

Growth and nutritional problems in HIV-1-infected children were recognized even before HIV-1 was isolated in the early 1980s.^{26,27} Reports from Africa initially called HIV-1 the “slim disease.”²⁸ Although several reports have characterized growth patterns for HIV-1-infected children,^{1–5} few have reported important both prenatal and postnatal clinical or

biochemical associates of growth problems.²⁹ Simple longitudinal analyses of weight and length or height have shown that stable HIV-1–infected children experience a nearly proportionate decline in both length or height and weight but maintain nearly normal ratios of weight for length or height.^{2–5} As children become sicker, wasting becomes more clinically obvious. By controlling for the multiple potential confounders that can affect growth, some studies, including the Women and Infants Transmission Study, showed that HIV-1 itself influences both height and weight.⁴ In the Women and Infants Transmission Study, maternal and neonatal factors were evaluated only at baseline, yet the authors recognized the importance of evaluating postnatal events.

Many factors probably interact to cause growth problems among HIV-1–infected children. The 4 most cited factors are low energy intake, gastrointestinal malabsorption, increased energy expenditure, and psychosocial issues. The extent to which any of these factors adequately explains growth abnormalities in this group of children has not been well-studied. Preliminary evaluations of diet intake in stable HIV-1–infected children have shown that although the majority of children ingest most macronutrients at or above the RDA,^{6,7} their weights and lengths or heights are below those of age- and sex-matched control children. Diets that contained calories and macronutrients in amounts greater than that suggested by the RDA were associated with greater weights, suggesting that malabsorption or increased energy requirements contribute to the growth abnormalities. Unfortunately, energy expenditure was not simultaneously measured in those studies. Abnormal gastrointestinal absorption of carbohydrate, fat, and protein in children with HIV-1 infection has been well-described, yet there are conflicting reports of its association with growth problems in these children.^{11,12} In the above-cited studies,⁷ diarrhea was more prevalent in the smaller children, but gastrointestinal absorption was not formally evaluated.

Psychosocial factors must also be considered for any child with impaired growth. Factors such as an unstable home environment and inadequate emotional and social support have been shown to contribute to growth problems in both HIV-1–infected³⁰ and non-HIV-1–infected children via many mechanisms, including growth hormone deficiencies.^{31,32} Children with HIV-1 infection are more likely to live with parents who are ill, who have limited access to social services and support, and who have ongoing problems with drug and substance abuse.³³ Our result mirrors those of Moye et al,⁴ who found maternal crack and cocaine use during pregnancy to be a predictor of growth and nutritional problems for the child. This finding is not unique for HIV-1; it has been reported in other non-HIV-1 cohorts.³⁴ Children born to drug-using women often are small, suggesting that drugs have a prenatal effect, but the postnatal home environment is likely to influence growth as well. Our finding that 15.7% of the uninfected children experienced FTT by 2 years of age also suggests that environmental factors also affected growth. Unfortunately, our study did not have a comparison group of children without exposure to HIV-1, which could have helped us differentiate between the effects of social factors and HIV-1 exposure.

Increased energy use can affect growth for all children. Even an asymptomatic chronic viral infection can affect energy use and predispose children to secondary infections, which can alter energy use patterns. These infections can increase or shunt effective use of energy substrates from normal, healthy growth patterns to abnormal ones, as occurs in many

children with chronic illness, including cystic fibrosis, inflammatory bowel disease, congenital heart disease, and childhood cancer.^{35–37} Our study determined that time to pneumonia and lower CD4⁺ T-cell count are significantly associated with FTT. In addition, HIV-1 RNA load was also associated with FTT. These findings support the hypothesis and early findings that higher HIV-1 loads and secondary infections are associated with growth problems in these children. It is possible that other unmeasured factors, such as serum cytokines, which may change with viral load and can alter metabolism, contribute to the growth changes associated viral load and CD4 counts.

Few studies have evaluated energy use in children with HIV-1, and small sample sizes limit the interpretation of the results.^{8,38–40} In adults with HIV-1 infection, even those with minimal symptoms have a resting energy expenditure that increases with advancing HIV-1 stage.^{9,10} Few studies have evaluated total energy expenditure in adults or children,^{39–41} yet total energy expenditure does not appear to be different between HIV-1-infected children with growth failure, as defined by a linear growth velocity of less than the 5th percentile,^{39,40} and those without growth failure.

Antiretroviral therapy (nonprotease inhibitor) was independently associated with FTT in our cohort, although it may be a surrogate for more advanced disease. This association has been found in other studies.^{4,7} ZDV, in particular, alters mitochondrial metabolism⁴² and may have direct nutritional effects in addition to acting as a surrogate marker for more advanced HIV-1 disease. Additional studies should focus on the effects of ZDV and other antiretroviral therapy on nutritional status.

This study did not evaluate the effects of protease inhibitor or highly active antiretroviral therapy on growth in children with HIV-1 because the cohort was recruited and followed before the therapy became widely available. Yet there is evidence that protease inhibitor therapy positively influences nutritional status, including improving body composition.⁴³ There may have been other factors, such as neurologic deficits, that can influence growth yet were not recorded in the study because it was not designed with growth changes as a primary outcome. However, this study included a large, systematically studied group of HIV-1–infected infants, tracked from birth with close follow-up of important clinical variables. In addition, the multicenter, national distribution of black, Hispanic, and white children makes this study more generalizable to children throughout the world than any single or regional study.

Our study provides important preliminary data that can help providers identify HIV-1–infected children who are at risk for FTT or who may develop comorbid conditions as a result of FTT. We hope that knowledge of these associations will enable practitioners to intervene earlier with closer nutritional surveillance or earlier institution of supplemental feedings to prevent additional morbidity and mortality in these children. Likewise, FTT may be associated with comorbid conditions such as pneumonia. The clinician should be aware of potential medical complications associated with FTT. Future studies should evaluate growth and long-term nutritional consequences of highly active antiretroviral therapies in children and should test nutritional interventions in high-risk children.

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Appendix

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References

1. Miller TL, Evans SJ, Orav EJ, McIntosh K, Winter HS. Growth and body composition in children infected with the human immunodeficiency virus-1. *Am J Clin Nutr.* 1993; 57:588–592. [PubMed: 8460616]
2. Arpadi SM, Horlick MN, Wang J, Cuff P, Bamji M, Kotler DP. Body composition in prepubertal children with human immunodeficiency virus type 1 infection. *Arch Pediatr Adolesc Med.* 1998; 152:688–693. [PubMed: 9667542]
3. Saavedra JM, Henderson RA, Perman JA, Hotton N, Livingston RA, Yolken RH. Longitudinal assessment of growth in children born to mothers with human immunodeficiency virus infection. *Arch Pediatr Adolesc Med.* 1995; 149:497–502. [PubMed: 7735401]
4. Moye J, Rich KC, Kalish LA, et al. Natural history of somatic growth in infants born to women infected by human immunodeficiency virus. *J Pediatr.* 1996; 128:58–69. [PubMed: 8551422]
5. McKinney RE, Robertson RW. the Duke Pediatric AIDS Clinical Trials Unit. Effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr.* 1993; 123:579–582. [PubMed: 8410511]
6. Miller TL, Awnetwant EL, Evans S, Morris VM, Vazquez IM. Gastrostomy tube supplementation for HIV-infected children. *Pediatrics.* 1995; 96:696–702. [PubMed: 7567333]
7. Miller TL, Evans SE, Vasquez I, Orav EJ. Dietary intake is an important predictor of nutritional status in HIV-infected children. *Pediatr Res.* 1997; 41:85A.
8. Henderson RA, Talusan K, Hutton N, Yolken RH, Caballero B. Resting energy expenditure and body composition in children with HIV infection. *J Acquir Immune Defic Syndr.* 1998; 19:150–157.
9. Hommes MJT, Romijn JA, Endert E, Sauerwein HP. Resting energy expenditure and substrate oxidation in human immunodeficiency virus (HIV)–infected asymptomatic men: HIV affects host metabolism in the early asymptomatic stage. *Am J Clin Nutr.* 1991; 54:311–315. [PubMed: 1830451]
10. Suttman U, Ockenga L, Hoogstraal L, et al. Resting energy expenditure and weight loss in human immunodeficiency virus–infected patients. *Metabolism.* 1993; 42:1173–1179. [PubMed: 8412772]
11. Miller TL, Orav EJ, Martin SR, et al. Malnutrition and carbohydrate malabsorption in children with vertically transmitted human immunodeficiency virus-1 infection. *Gastroenterology.* 1991; 100:1296–1302. [PubMed: 2013374]
12. Yolken RH, Hart W, Oung I, Schiff C, Greenon J, Perman JA. Gastrointestinal dysfunction and disaccharide intolerance in children infected with human immunodeficiency virus. *J Pediatr.* 1991; 118:359–363. [PubMed: 1999774]
13. The P²C² HIV Study Group. The pediatric pulmonary and cardiovascular complications of vertically transmitted human immunodeficiency virus (P²C² HIV) infection study: design and methods. *J Clin Epidemiol.* 1996; 49:1285–1294. [PubMed: 8892497]
14. Hollinger F, Bremer J, Myers L, Gold J, McQuay L. The NIH/NIAID/DAIDS/ACTG Virology Laboratories. Standardization of sensitive human immunodeficiency virus coculture procedures and establishment of a multicenter quality assurance program for the AIDS Clinical Trials Group. *J Clin Microbiol.* 1992; 30:1787–1794. [PubMed: 1629336]
15. Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency syndrome in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep.* 1994; 43:1–10.

16. Mofenson LM, Bethel J, Moye J, Flyer P, Nugent R. for the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. Effect of intravenous immunoglobulin (IVIG) on CD4+ lymphocyte decline in HIV-infected children in a clinical trial of IVIG infection prophylaxis. *J Acquir Immune Defic Syndr*. 1993; 6:1103–1113. [PubMed: 8105072]
17. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. *N Engl J Med*. 1997; 336:1337–1342. [PubMed: 9134873]
18. Rusconi F, Castagneto M, Gagliardi L, et al. Reference values for respiratory rate in the first three years of life. *Pediatrics*. 1994; 94:350–355. [PubMed: 8065862]
19. Shearer WT, Lipshultz SE, Easley KA, et al. Alterations in cardiac and pulmonary function in pediatric rapid human immunodeficiency virus type 1 disease progressors. *Pediatrics*. 2000; 105(1) Available at: www.pediatrics.org/cgi/content/full/105/1/e9.
20. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1–infected women. *N Engl J Med*. 1999; 341:77–84. [PubMed: 10395631]
21. Jenson H, McIntosh K, Pitt J, et al. Natural history of primary Epstein-Barr virus infection in children of mothers infected with human immunodeficiency virus type-1. *J Infect Dis*. 1999; 179:1395–1404. [PubMed: 10228060]
22. Kattan M, Platzker A, Mellins RD, et al. for the P2C2 HIV Study Group. Respiratory diseases in the first year of life in children born to HIV-1–infected women. *Pediatr Pulmonol*. 2001; (31):267–276. [PubMed: 11288208]
23. Lohman, TG.; Roche, AF.; Martorell, R. Anthropometric Standardization Manual. Champaign, IL: Human Kinetics; 1988.
24. ANTHRO Software for Calculating Pediatric Anthropometry, Version 1.01. Atlanta, GA: Centers for Disease Control and Prevention; 1990.
25. Babson SG, Benda GI. Growth graphs for the clinical assessment of infants of varying gestational age. *J Pediatr*. 1976; 89:814–820. [PubMed: 978333]
26. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequency, detection, and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*. 1984; 124:500–503. [PubMed: 6200936]
27. Barre-Sinoussi F, Chermann JC, Fey F, et al. Isolation of T-cell lymphotropic retrovirus from a patient at risk for AIDS. *Science*. 1983; 220:868–871. [PubMed: 6189183]
28. Serwadda D, Mugerwa RD, Sewankambo NK, et al. Slim disease: a new disease in Uganda and its association with HTLV-III infection. *Lancet*. 1985; 2:849–852. [PubMed: 2864575]
29. Carey VJ, Yong F, Frenkel L, McKinney R. Enhancing the prognostic value of bodily growth histories in HIV-positive pediatric cohorts. *Int Conf AIDS*. 1996 Jul 7–12.11:134. abstract.
30. Missmer S, Speigelman D, Gorbach SL, Miller TL. Predictors of change in the functional status of children with human immunodeficiency virus infection. *Pediatrics*. 2000; 106(2) Available at: <http://www.pediatrics.org/cgi/content/full/106/2/e24>.
31. Money J. The syndrome of abuse dwarfism (psychosocial dwarfism or reversible hyposomatotropism). *Am J Dis Child*. 1977; 131:508–513. [PubMed: 857651]
32. Boulton TJ, Smith R, Single T. Psychosocial growth failure: a positive response to growth hormone and placebo. *Acta Paediatr*. 1992; 81:322–325. [PubMed: 1606393]
33. Children whose mothers are infected with HIV. Communicable disease report. *Commun Dis Rep CDR Wkly*. 1995; 5:111.
34. Lifschitz MH, Wilson GS, Smith EO, Desmond MM. Fetal and postnatal growth of children born to narcotic-dependent women. *Pediatrics*. 1983; 102:686–690.
35. Salman EK, Haymond MW, Bayne E, et al. Protein and energy metabolism in prepubertal children with sickle cell anemia. *Pediatr Res*. 1996; 40:34–40. [PubMed: 8798243]
36. Stallings VA, Zemel BS, Davies JC, Cronk CE, Charney EB. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. *Am J Clin Nutr*. 1996; 64:626–634.

37. Hankard R, Gottrand F, Turck D, Carpentier A, Romon M, Farriaux JP. Resting energy expenditure and energy substrate utilization in children with Duchenne muscular dystrophy. *Pediatr Res.* 1996; 40:29–33. [PubMed: 8798242]
38. Alfaro MP, Siegel RM, Baker RC, Heubi JE. Resting energy expenditure and body composition in pediatric HIV infection. *Pediatric AIDS and HIV Infection: Fetus Adolesc.* 1995; 6:276–280.
39. Arpadi SM, Cuff PA, Kotler DP, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. *J Nutr.* 2000; 130:2498–2502. [PubMed: 11015480]
40. Johann-Liang R, O'Neill L, Cervia J, et al. Energy balance, viral burden, insulin-like growth factor-1, interleukin-6 and growth impairment in children infected with human immunodeficiency virus. *AIDS.* 2000; 14:683–690. [PubMed: 10807191]
41. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med.* 1995; 333:83–88. [PubMed: 7777033]
42. Mhiri C, Baudrimont M, Bonne G, et al. Zidovudine myopathy: a distinctive disorder associated with mitochondrial dysfunction. *Ann Neurol.* 1991; 29:606–614. [PubMed: 1892364]
43. Miller TL, Mawn BE, Orav EJ, et al. The effect of protease inhibitor therapy on growth and body composition in human immunodeficiency virus type 1-infected children. *Pediatrics.* 2001; 107(5) Available at: <http://www.pediatrics.org/cgi/content/full/107/5/e77>.

Abbreviations

HIV-1	human immunodeficiency virus-1
FTT	failure to thrive
RDA	recommended daily allowance
P²C²	Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection study
ZDV	zidovudine
CDC	Centers for Disease Control and Prevention
CMV	cytomegalovirus
EBV	Epstein-Barr virus
PCP	<i>Pneumocystis carinii</i> pneumonia
NOS	not otherwise specified
CI	confidence interval
RR	relative risk

Fig 1.

Longitudinal changes in growth patterns in children born to HIV-1-infected women. The time trend lines are the model-based means and 95% CIs graphed according to age and HIV status. A, B, and C, Weight (kg), height (cm), and weight for height for HIV-1-infected children ($N = 92$) and HIV-1-uninfected children ($N = 439$). D, E, and F, z Scores for weight, height, and weight for height for HIV-1-infected children ($N = 92$) and HIV-1-uninfected children ($N = 439$).

Fig 2. Cumulative rates of failure to thrive (FTT) and 95% CIs by HIV-1 status. A, 92 HIV-1–infected children; B, 439 HIV-1–uninfected children.

Fig 3. Cumulative rates of mortality by FTT status among 92 HIV-1-infected children. Children with FTT ($N = 42$) had higher mortality rates than did children without FTT ($N = 50$, $P = .02$).

Cumulative Rates of FTT for HIV-1-Infected Children (n=90) By Disease Progression

Fig 4. Cumulative rates of FTT by disease progression among 92 HIV-1-infected children. Rapid progressors (RP, $N = 45$) had higher FTT rates than non-rapid progressors ($N = 47$, $P = .001$).

Table 1
Weight z Scores in HIV-1–Infected and Uninfected Infants Grouped by Maternal Covariates

	HIV-1–Infected Infants Weight z Score*				HIV-1–Uninfected Infants Weight z Score*			
	n	Mean ± SD	Median	P Value	n	Mean ± SD	Median	P Value
Used zidovudine during pregnancy								
Yes	26	−0.76 ± 1.33	−0.53	.98	137	−0.52 ± 1.37	−0.40	.62
No	59	−0.72 ± 1.31	−0.63		254	−0.36 ± 1.21	−0.36	
Smoked tobacco during pregnancy								
Yes	33	−1.24 ± 1.18	−1.02	.001	143	−0.64 ± 1.05	−0.63	<.001
No	51	−0.36 ± 1.23	−0.17		242	−0.25 ± 1.34	−0.14	
Amount smoked during pregnancy								
None	51	−0.36 ± 1.23	−0.17	.005	242	−0.25 ± 1.34	−0.14	.004
Less than ½ pack per day	13	−1.55 ± 1.46	−1.14		49	−0.53 ± 1.25	−0.48	
Less than 1 but more than ½ pack	12	−1.31 ± 0.99	−1.11		55	−0.70 ± 0.97	−0.59	
1 pack or more per day	8	−0.62 ± 0.72	−0.35		38	−0.67 ± 0.86	−0.86	
Regular tobacco smoker								
Yes	35	−1.16 ± 1.28	−1.02	.003	154	−0.56 ± 1.13	−0.55	.005
No	49	−0.38 ± 1.19	−0.19		233	−0.29 ± 1.32	−0.14	
Drank alcohol during pregnancy								
Yes	15	−0.64 ± 0.94	−0.63	.65	74	−0.48 ± 1.25	−0.56	.25
No	68	−0.69 ± 1.33	−0.53		307	−0.38 ± 1.26	−0.34	
Used illicit drugs during pregnancy								
Yes	28	−1.16 ± 1.11	−0.95	.007	116	−0.73 ± 1.07	−0.75	<.001
No	55	−0.44 ± 1.27	−0.34		271	−0.26 ± 1.30	−0.19	
Crack, cocaine, or heroin use during pregnancy								
Yes	21	−1.25 ± 1.24	−0.87	.02	89	−0.83 ± 1.03	−0.90	<.001
No	62	−0.49 ± 1.22	−0.44		298	−0.27 ± 1.29	−0.22	
Ever used illicit drugs								
Yes	48	−0.94 ± 1.30	−0.72	.09	210	−0.49 ± 1.24	−0.48	.03
No	36	−0.39 ± 1.18	−0.37		176	−0.29 ± 1.27	−0.15	

* z Scores based on the first available measurement at 0 to 3 months of age.

Cumulative Rates of FTT among 92 HIV-1–Infected Children According to Baseline Clinical Characteristics (Univariable Analysis)

Table 2

Characteristic	n	FTT		Cumulative FTT (%) ± SE		P Value
		n	%	n	1 Year	
All children	92	42	45.7		37.3 ± 5.2	
Sex						
Male	44	21	47.7		42.5 ± 7.2	.66
Female	48	21	43.8		32.5 ± 6.9	
Race or ethnicity						
White	14	3	21.4		22.9 ± 11.7	.15
Black	41	22	53.7		46.0 ± 8.1	
Hispanic	32	15	46.9		32.7 ± 8.5	
Other	5	2	40.0			
Pneumonia by 9 mo						
No	74	29	39.2		29.5 ± 5.4	.007
Yes	18	13	72.2		69.7 ± 11.2	
Any antiretroviral therapy by 3 mo						
No	75	32	42.7		33.3 ± 5.6	.02
Yes	17	10	58.8		53.7 ± 12.3	
HIV-1 RNA (copies/mL) (2–24 mo)						
100K	32	10	31.3		18.8 ± 6.9	.02
>100K	33	20	60.6		45.6 ± 8.7	
CD4 count z score by 6 mo						
–1	43	22	51.2		44.3 ± 7.9	.12
>–1	46	18	39.1		28.6 ± 6.7	
Heart rate z score by 10 mo						
1	37	12	32.4		28.3 ± 7.6	.03
>1	45	25	55.6		40.5 ± 7.4	
Illicit drug use by mother during pregnancy						
No	55	23	41.8		30.5 ± 6.4	.10
Yes	30	16	53.3		49.0 ± 9.5	

Characteristic	n	FTT		Cumulative FTT (%) ± SE		P Value
		n	%	1 Year		
Crack, cocaine, or heroin use during pregnancy						
No	62	25	40.3	29.0 ± 6.0		.008
Yes	23	14	60.9	57.9 ± 10.5		
Most severe CDC symptom by 3 mo						
Asymptomatic	58	27	46.6	36.3 ± 6.5		.11
Mild	16	6	37.5	31.3 ± 11.6		
Moderate	11	4	36.4	27.3 ± 13.4		
Severe	5	3	60.0	60.0 ± 21.9		
CMV status by 18 mo						
Uninfected	22	7	31.8	22.7 ± 8.9		.41
Infected	40	18	45.0	38.3 ± 7.8		
EBV status by 18 mo						
Uninfected	28	16	57.1	42.9 ± 9.4		.10
Infected	25	8	32.0	28.0 ± 9.0		

Table 3
Multivariable Analysis of Factors Associated with FTT for Children Infected with HIV-1

Effect	RR	95% CI	P Value
A: 82 HIV-1–infected children (38 with FTT) Crack, cocaine, or heroin use by mother during pregnancy (yes/no)	3.17	1.51–6.66	.002
CD4 count z score (per 1 SD decrease)	2.13	1.25–3.57	.005
Pneumonia (yes/no, time-dependent)	8.78	3.59–21.44	<.001
Any antiretroviral therapy by 3 mo (yes/no)	2.77	1.16–6.65	.02
B: 65 HIV-1–infected children (30 with FTT) HIV-1 RNA (high/low)*	2.30	1.05–5.04	.04
Pneumonia (yes/no, time-dependent)	4.11	1.51–11.25	.01
Any antiretroviral therapy by 3 mo (yes/no)	2.97	1.21–7.29	.02

* High HIV-1 RNA: RNA > 100K; low HIV-1 RNA: RNA ≤ 100K.