Growth and Body Composition of Uninfected Children Exposed to Human Immunodeficiency Virus: Comparison with a Contemporary Cohort and United States National Standards

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Objective To compare growth and body composition of uninfected children exposed to HIV with a contemporary HIV-unexposed group and to US references.

Study design Uninfected children exposed to HIV under 2 years were enrolled into a longitudinal observational study and unexposed children under 2 years of age in a cross-sectional evaluation. Weights, lengths, head circumferences, skinfold thicknesses, and arm and thigh circumferences were measured and adjusted for age using Centers for Disease Control and National Health and Nutrition Examination Survey standards. Uninfected children exposed to HIV were compared with an unexposed nearest-neighbor matched comparison group. Uninfected children exposed to HIV were compared by age to Centers for Disease Control standards for growth measures and National Health and Nutrition Examination Survey standards for body composition.

Results One hundred eleven uninfected children exposed to HIV and 82 children not exposed to HIV were evaluated. For the matched comparison for both groups, the mean age was 10 months, 59% were male, and 73% were African American. No statistical differences were found in anthropometric measurements between uninfected children who were or were not exposed to HIV. Uninfected children exposed to HIV were smaller than US standards at birth with mean (SD) weight-for-age and weight-for-length z-scores of −0.39 (1.06); $P = .002$ and −0.35 (1.04); $P = .005$, respectively. Over the first 2 years of life, there was a trend toward increasing weight-for-age z-score, length-for-age z-score, and weight-for-length z-score in uninfected children exposed to HIV. Subscapular and triceps skinfolds among uninfected children exposed to HIV were lower than national standards and there was a trend that mid-upper arm circumference decreased over time.

Conclusions Growth and body composition of uninfected children who were or were not exposed to HIV were similar. Uninfected children exposed to HIV weigh less at birth and show a pattern of slightly accelerated growth in the first 2 years of life. Uninfected children exposed to HIV had less subcutaneous fat and decreasing mid-upper arm circumference over time when compared with US standards. *(J Pediatr 2013;163:249-54)*.

Effective preventive strategies during pregnancy have reduced the risk of mother-to-child transmission of HIV in the US to approximately 1%-2%.[1] Preventive mother-to-child transmission recommendations[2] include antiretroviral (ARV) therapy for all pregnant women with HIV regardless of CD4 lymphocyte count or viral load. Recommended ARV regimens include the use of 2 nucleoside reverse transcriptase inhibitors (NRTI), zidovudine (ZDV) and lamivudine being the preferred agents, in combination with a non-NRTI or a protease inhibitor.[2]

Exposures to HIV and ARVs in utero are postulated to have adverse associations on infant development.[3] NRTIs cross the placenta and inhibit DNA polymerase γ, potentially interfering with fetal mitochondrial DNA synthesis, resulting in short- and long-term mitochondrial depletion and/or dysfunction in some studies,[3] although other studies have not demonstrated these effects.[4-6] Mitochondrial dysfunction is linked to growth abnormalities in other childhood disorders. The extent to which this is true in uninfected children exposed to HIV is not well-defined.

Pre- and postnatal growth can also be influenced by socioeconomic status (SES) and lifestyle factors. Uninfected children exposed to HIV are often born to women of lower SES[7] with a greater prevalence of smoking and illicit drug

ARV	Antiretroviral	NRTI	Nucleoside reverse transcriptase inhibitors
BMI	Body mass index		
CDC	Centers for Disease Control	SES	Socioeconomic status
HCZ	Head circumference-for-age z-score	SFT	Skinfold thickness
		WAZ	Weight-for-age z-score
LAZ	Length-for-age z-score	WLZ	Weight-for-length z-score
MAC	Mid-upper arm circumference	ZDV	Zidovudine
NHANES	National Health and Nutrition Examination Survey		

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use.[7] Few studies have compared uninfected children exposed to HIV with a socioeconomically similar group of infants. Although studies have shown little to no differences in growth among uninfected children exposed to HIV and the general population,[4,8,9] these studies have not evaluated body composition, nor compared growth parameters to a sociodemographically similar group of children.

The objective of this study was to compare anthropometric outcomes of uninfected children exposed to HIV to an age-, race-, and sex-matched group of non-exposed infants from a similar geographic region. We compared serial growth and anthropometric trajectories of uninfected children exposed to HIV with US standards.

Methods

Uninfected children exposed to HIV under 2 years of age were sequentially enrolled into a single-site and observational study on growth and body composition at the University of Miami HIV Screening Program between June 2006 and December 2009. Study visits followed the HIV screening protocol[10] where uninfected children exposed to HIV were evaluated at approximately 2 and 6 weeks and 4, 12, 18, and 24 months of age. However, there was some deviation in this proposed schedule because of individual variation in adhering to recommended timing of clinical visits. Laboratory protocol included serial virological testing with HIV-1 DNA polymerase chain reaction assays during the first 6 months of life, and immunologic assays using enzyme-linked immunosorbent assays and Western blot assay to confirm reactive screening test results after 1 year of age. Children were determined to be uninfected if they were HIV antibody-negative on 2 separate determinations after 12 months of age and HIV virus or antigen was never detected. Children with HIV were excluded from the analysis.

The HIV-unexposed group was a convenience sample of children, age birth to 2 years with similar demographic and SES characteristics. They were recruited from either an urban general pediatric outpatient practice at the University of Miami or from 5 local urban day-care centers in Miami-Dade County. Recruitment letters were sent to the parents explaining the study procedures and requesting their attendance for consenting process. This group was not known to be infected or exposed to HIV because there are well established and mandated screening programs in Miami-Dade County.

Children with known congenital, chromosomal, or metabolic anomalies were excluded from the study. The Human Subjects Research Office at the University of Miami approved the research protocol, and informed consent from the parent or legal guardian was obtained.

For the uninfected children exposed to HIV, all data were collected during nutrition assessments as part of routine clinical care during the previously defined screening time points. Clinical data included birth weight, length, and gestational age. HIV-1 DNA polymerase chain reaction and enzyme-linked immunosorbent assay results were collected to identify HIV infection status. Maternal information collected at enrollment included sociodemographic information, prepregnancy weight and height, and ARV prophylaxis during pregnancy. Maternal CD4 lymphocyte count nearest to delivery was abstracted from the newborn hospital discharge note. For the HIV-unexposed group, demographic data, including date of birth, race, and ethnicity, were collected through parent or guardian interview. No clinical data or neonatal characteristics were available for this group.

Weight, recumbent length, and head circumference were measured by standardized procedures.[11] Weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), and head circumference-for-age (HCZ) z-scores were generated according to Centers for Disease Control (CDC) standards.[12] Regional body measurements including mid-upper arm circumference (MAC), mid-thigh circumference, and skinfold thickness (SFT) were measured according to standardized procedures.[11] Triceps, biceps, subscapular, and mid-thigh SFT were measured using Lange caliper (Cambridge Scientific, Cambridge, Maryland). All measurements, except SFT, were taken to the nearest 0.1 centimeter. SFT were taken to the nearest 0.1 millimeter. Body measurements were taken on the right side of the body. Triplicate measurements for all body measurements were taken and the mean was recorded. Triceps and MAC measurements were used to derive arm muscle circumference.[13] Similarly, mid-thigh SFT and mid-thigh circumference measurements were used to derive thigh muscle circumference.[14] Z-scores for MAC, and triceps and subscapular SFT were generated.[11,15] WAZ, LAZ, and HCZ for only uninfected premature infants exposed to HIV (less than 37 weeks gestation) were adjusted for prematurity and calculated using population-appropriate updated growth chart for prematurity.[16] Information regarding prematurity was not available for the infants not exposed to HIV. All regional body measurements (circumferences and skinfolds) were performed by one trained dietician (D.N.).

Statistical Analyses

The primary statistical methodology consisted of a comparison between the uninfected children exposed to HIV to a within study HIV-unexposed matched comparison group. Matches were determined individually for each unexposed case by choosing an uninfected children exposed to HIV that was closest to an unexposed individual (ie, nearest-neighbor) over the multivariate space as defined by the matching variables. Euclidean distance was the metric chosen to quantify similarity. The HIV-unexposed comparison group, who were initially selected from the same socioeconomic demographic, were chosen so that the 2 groups had the same race/sex proportions with near identical age distributions. Of the 111 original uninfected children exposed to HIV, 82 matches were possible. When the dependent measure of interest was continuous, the 2 groups were compared using Student *t* test. Fisher exact test was used when the dependent variable was dichotomous.

Uninfected children exposed to HIV were also compared with CDC growth charts for classical growth measures and