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Stunting and Wasting Are Associated with Poorer Psychomotor and Mental Development in HIV-Exposed Tanzanian Infants[1,2]

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Abstract

Infants born to HIV-infected women are at increased risk of impaired neurodevelopment, but little research has attempted to identify modifiable risk factors. The objective of this prospective cohort analysis was to identify maternal, socioeconomic, and child correlates of psychomotor and mental development in the first 18 mo of life among Tanzanian infants born to HIV-infected women. We hypothesized that child HIV infection, morbidity, and undernutrition would be associated with lower developmental status when taking into consideration maternal health and socioeconomic factors. Baseline maternal characteristics were recorded during pregnancy, birth characteristics were collected immediately after delivery, infant micronutrient status was measured at 6 wk and 6 mo, and anthropometric measurements and morbidity histories were performed at monthly follow-up visits. The Psychomotor Development Index (PDI) and Mental Development Index (MDI) of the Bayley Scales of Infant Development, 2nd edition (BSID-II) were used to assess developmental functioning at 6, 12, and 18 mo of age. Multivariate repeated regression models with time-varying covariates were used to estimate adjusted mean MDI and PDI scores for each level of the variables. A total of 311 infants contributed ≥1 BSID-II assessments for 657 PDI and 655 MDI measurements. Of infants, 51% were male, 23% were born preterm, 7% were low birth weight, and 10% were HIV-positive at 6 wk. Preterm birth, child HIV infection, stunting, and wasting were independently associated with lower PDI and MDI scores. Strategies to lower mother-to-child transmission of HIV, prevent preterm birth, and enhance child growth could contribute to improved child psychomotor and mental development. J. Nutr. 143: 204–214, 2013.

Introduction

It is estimated that >200 million children <5 y living in developing countries fail to reach their developmental potential every year (1). The first 2 y of life are particularly crucial, as the brain undergoes a period of rapid growth characterized by neurogenesis, axonal and dendritic growth, synaptogenesis, cell death, synaptic pruning, myelination, and gliogenesis. These events are cumulative, so any perturbations in a process can have long-term consequences on the brain's structural and functional capacity (2). Several biological, environmental, and psychosocial factors are required for optimal child development. Although it is well accepted that poverty, poor health, and suboptimal care-giving practices heighten a child's risk of developmental delay (3), little research has attempted to identify particular risk factors or quantify their magnitude in the context of maternal HIV infection and its consequences.

Infants born to HIV-infected women in resource-limited settings represent a particularly vulnerable subgroup for a number of reasons. HIV-associated morbidity may hinder a mother's ability to provide adequate care and stimulation to her child. Households affected by HIV are often food insecure (4), which may limit dietary diversity and increase the risk of deficiencies in multiple micronutrients that play an important role in brain development (5–7). Furthermore, if a child is infected with HIV, the virus can invade the central nervous system, destroy neuronal tissue, and impair neurodevelopment (8). Compared with HIV-negative infants, HIV-infected infants consistently perform worse on developmental tests and are at increased risk of developmental delay, impaired fine motor abilities, attention problems, and language deficits (9–11).

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The consequences of poor development are serious. Children who do not reach their developmental potential attend school for a fewer number of years and learn less per year in school, which ultimately lowers their productivity as adults. In fact, each year of schooling increases adult wages by nearly 10% (12). This disparity may impede the economic development of countries where a large number of children are affected. Given the vulnerability of HIV-exposed infants, there is a critical need to identify modifiable risk factors in order to design and target appropriate interventions for optimal early childhood development. The objective of this study was to identify the maternal, socioeconomic, and child correlates of psychomotor and mental development in the first 18 mo of life among Tanzanian infants born to HIV-infected women. We hypothesized that child HIV infection, morbidity, and undernutrition would be associated with lower developmental status when taking into consideration maternal health and socioeconomic factors.

Participants and Methods

Subjects included in this analysis were part of a randomized, double-blind, placebo-controlled trial to examine the effect of maternal multivitamin supplementation on mother-to-child HIV-1 transmission and disease progression. Details of the trial were previously published (13). To summarize, between April 1995 and July 1997, 1078 pregnant women who were infected with HIV-1 and were between 12 and 27 wk of gestation were enrolled in the trial and were randomly assigned to receive a daily oral dose of 1 of 4 regimens [multivitamins (including vitamin B-complex, C, and E) and vitamin A in a 2 × 2 factorial design] from enrollment throughout pregnancy and lactation. In addition, all women and children received standard medical care, which included daily ferrous sulfate and folate supplementation and weekly prophylactic chloroquine phosphate during the antenatal period. Severe anemia was treated with iron supplementation, dietary counseling, and antihelminthic treatment when age appropriate. All children received 100,000 IU of vitamin A at age 6 mo and 200,000 IU (1 IU = 1.05 nmol) every 6 mo thereafter. At the time of the study, antiretroviral therapy was not available to the majority of Tanzanians, including those who participated in this study.

On enrollment, trained study personnel conducted a complete medical examination of all women, took anthropometric measurements, obtained blood samples, and collected information pertaining to demographic characteristics and socioeconomic status. Maternal hemoglobin was also assessed every 6 mo from enrollment. At ~2 mo after delivery, a validated subset of items from the Hopkins Symptom Checklist-25 was used to assess maternal depressive symptoms (14).

Data pertaining to the infant's birth were collected immediately after delivery at Muhimbili National Hospital, then mothers and their infants were followed up on a monthly basis for a minimum of 18 mo. Gestational age was calculated based on the date of the last menstrual period, obtained at enrollment, and preterm birth was defined as <37 wk gestational age at birth. A research midwife measured the infant's weight to the nearest 10 g using a standard beam balance immediately after birth and low birth weight was defined as <2500 g. At each of these monthly clinic visits, a study nurse conducted a morbidity assessment and asked mothers about the presence of certain symptoms in their child, including cough, fever, difficulty breathing, refusal to eat or breastfeed, and diarrhea during the previous month. Diarrhea was defined as ≥3 watery stools within a 24-h period, acute diarrhea included all periods of ≥1 d but <14 d, and persistent diarrhea included all periods of ≥14 d of diarrhea. The study nurse also inquired about breastfeeding practices and measured the child's weight and length at each monthly clinic visit. Length-for-age (LAZ)[13], weight-for-length (WLZ), and weight-for-age Z-scores were calculated using the 2006 WHO Growth Standards (15). Stunting, wasting, and underweight were defined as binary variables using a cutoff of <−2 Z-scores. Blood samples were obtained from the infants at birth, 6 wk of age, and every 3 mo until 18 mo of age for diagnosis of HIV infection using PCR.

The 6-wk and 6-mo blood samples were used to measure children's micronutrient concentrations. Serum concentrations of vitamins A and E were analyzed using HPLC (16) and serum vitamin B-12 was measured using a competitive magnetic separation assay (Bayer). Plasma selenium was measured using a graphite-furnace atomic absorption spectrophotometric method with deuterium background correction and a reduced palladium modifier, employing a Perkin-Elmer system (17), and ferritin was measured by a particle-enhanced immunoturbidimetric assay (Roche Diagnostics). Hemoglobin was determined using a CBC5 Coulter Counter. For the purposes of this analysis, the following cutoffs were used to define micronutrient deficiencies: 70 μmol/L for serum vitamin A (18), 11.6 μmol/L for serum vitamin E (19), and 150 pmol/L for serum vitamin B-12 (20). A hemoglobin value of 70 g/L was used to define severe anemia (21). Plasma selenium and serum ferritin were categorized according to the median and quartile values, respectively.

The Bayley Scales of Infant Development, 2nd edition (BSID-II) (22) was used to assess the developmental functioning of a subset of infants 6–18 mo of age. Due to logistical and personnel constraints, we selected infants who attended clinic on Mondays or Fridays and had an identification number that ended in an odd-numbered digit. The BSID-II consists of 3 scales: mental, motor, and behavior rating; however, only the Mental Development Index (MDI) and Psychomotor Development Index (PDI) were performed in this study. A Kiswahili translation of all instructions to the child was used during each assessment. Tests were scheduled to be administered at ~6, 12, and 18 mo by 1 of 2 trained Tanzanian nurses who were unaware of the HIV status of the children. Infants who were acutely ill were not tested, but their mothers were asked to return them for testing once they recovered.

Statistical analyses. For this analysis, we included all 311 singleton children in the subset who had at least one MDI or PDI measure and covariate data available. Only singleton births were included, because twins are at greater risk of impaired development. We used MDI and PDI as outcome measures, as these are conversions of the raw BSID-II scores compared with a standardized and representative sample of U.S. children that has a mean score of 100. Any assessment for which the achieved raw score "fell off" the development index range (i.e., <50) was represented by a value of 49 in the analyses.

Descriptive statistics were used to summarize baseline characteristics of the study population. Frequencies were reported for categorical variables and the mean ± SD for continuous variables. The difference in mean MDI and PDI scores between each level of the potential correlates and associated 95% CIs was estimated using repeated-measures regression models with exchangeable correlation matrices (23). These models used data from all children at all time points, accounted for intra-subject correlation between measures, and adjusted for the child's age at time of BSID-II assessment. The maternal hemoglobin concentration and the child's HIV status, micronutrient concentrations, morbidity history, and anthropometric status varied over the course of follow-up; therefore, we included all available time-updated data on these variables in the analysis.

To identify correlates of psychomotor and mental development, we first identified key variables that comprehensively reflected maternal demographics and health status, household socioeconomic status, and important characteristics pertaining to the infant's birth, morbidity history, and micronutrient and anthropometric status. We fit separate, univariate, age-adjusted models between each of these variables and each outcome. We then constructed age-adjusted multivariate models that included all variables that were significant at $P < 0.20$ in the univariate analyses. A priori, we decided to retain child sex, prematurity, time-varying HIV status, and maternal study regimen, regardless of their significance, as these variables are important from a biological perspective. Given the potential for collinearity between the various types of respiratory and diarrheal morbidities, we included "cough + fever" and "diarrhea" as representative variables in the multivariate models if multiple forms of each type of morbidity were significant in the

[13] Abbreviations used: BSID-II, Bayley Scales of Infant Development, 2nd edition; LAZ, length-for-age Z-score; MDI, Mental Development Index; PDI, Psychomotor Development Index; WLZ, weight-for-length Z-score.

univariate analyses. We were also aware that hemoglobin, ferritin, and hypochromic microcytosis would likely be collinear if they were all included in the multivariate model. Therefore, we decided to include only hemoglobin, because it is a general and commonly used measure of anemia. Likewise, we included stunting and wasting, but not underweight, in the multivariate model if all 3 variables were significant in the univariate analysis, as stunting and wasting reflect chronic and acute undernutrition, respectively, but underweight does not distinguish between the 2 and is correlated with both. Missing indicator variables were used in the multivariate models for covariates with missing data (24). We used the test for trend to estimate P values for variables with ≥3 categories. Values in text are mean ± SD or difference in mean scores (95% CI). Significance was based on a P value < 0.05.

We constructed curves that depicted mean MDI and PDI, by age, over the entire follow-up period, and stratified these by HIV status using unadjusted, restricted cubic spline models (25). Automated stepwise selection with entry and retain criteria of $P < 0.05$ was used for the placement of 8 knots in each curve (26). We used the likelihood ratio test to test for nonlinearity, comparing the model with only the linear term to the model with the linear and restricted cubic spline terms.

All analyses were performed using SAS software version 9.2 (SAS Institute). Written informed consent was obtained from all mothers and Institutional Review Board approval was granted by Muhimbili University of Health and Allied Sciences, the Tanzanian National AIDS Control Program, and the Harvard School of Public Health.

Results

Study population. Among the 1078 women enrolled in the parent trial, there were 1042 known birth outcomes, of which 939 were singleton live births. Of the 837 infants who were alive at 6 mo of age, 311 contributed one or more BSID-II assessments to this analysis and had covariate data available. More specifically, 96, 86, 127, and 2 infants contributed 1, 2, 3, and 4 PDI measures, respectively, and 98, 84, 127, and 2 infants contributed 1, 2, 3, and 4 MDI measures, respectively. **Table 1** shows baseline maternal, socioeconomic, and infant characteristics of the BSID-II subgroup (n = 311). Approximately one-half of mothers were 25 y or older, 11% were in stage 2 or higher of HIV infection, more than three-quarters had at least one prior pregnancy, and almost 90% had at least 5 y of education. More than 12% had >5 people eating in the same household and 40% spent <500 TShs (~USD 0.80 at the time of the study) on food per person per day. Of the infants, just over one-half were male, almost one-quarter were born preterm, and <10% were born with a low birth weight. At 6 wk, approximately 1 in 10 infants were HIV positive and the prevalences of stunting, wasting, and underweight were 11.5, 2.7, and 0.5%, respectively.

The distributions of these characteristics did not significantly differ from those of singleton infants from the parent trial who were not selected for inclusion in the BSID-II subgroup, except for maternal disease stage and infant Apgar score. A lower percentage of infants in the BSID-II subgroup had mothers with an HIV disease stage ≥2 (10.9 vs. 17.8%) and fewer infants had an Apgar score ≤7 at 5 min after birth (2.5 vs. 8.9%). Furthermore, baseline characteristics did not significantly differ between infants who contributed only one BSID-II assessment and those who contributed ≥2, with the exception of maternal hemoglobin and infant vitamin E concentrations, which were lower among infants with only one BSID-II assessment.

Correlates of psychomotor development. The mean PDI score across all ages was 90.5 ± 15.2. None of the maternal or socioeconomic characteristics were significantly associated with psychomotor development in the multivariate analysis (**Table 2**). Among the child characteristics that were assessed, preterm birth, HIV infection, stunting, and wasting were associated with significantly lower PDI scores in the multivariate model. The mean PDI was 3.6 points lower (95% CI= −7.1, −0.1) in preterm than in term infants (P = 0.04) and 5.9 points lower (95% CI = −8.9, −2.3) in HIV positive than in negative infants (P = 0.0001). The effect of gestational age was not modified by low birth weight (P-interaction = 0.71). The mean PDI was 4.5 points lower (95% CI= −7.6, −1.3) among stunted children compared with children whose LAZ was ≥−2 (P = 0.0006). Wasting was even more deleterious: mean PDI was 8.9 points lower (95% CI = −14.2, −3.6) among children with a WLZ <−2 compared with ≥−2 (P = 0.0009).

Correlates of mental development. The mean MDI score across all ages was 89.4 ± 13.9. As with psychomotor development, gestational age at birth, infant HIV status, stunting, and wasting were the only significant, independent correlates of MDI in the multivariate analysis (**Table 3**). The mean MDI was 3.2 points lower (95% CI = −5.7, −0.7) among preterm than among term infants (P = 0.01); however, the effect of gestational

TABLE 1 Baseline characteristics of 311 HIV-exposed Tanzanian infants and their mothers[1]

Maternal characteristics	
Age ≥25 y	154 (49.5)
HIV stage at baseline ≥2	34 (10.9)
ESR at baseline ≥81 mm/h	66 (23.1)
Mid-upper arm circumference,[2] *cm*	25.6 ± 2.9
Postpartum hemoglobin,[3] *g/L*	107 ± 17.8
Prior pregnancies, *n*	
0	74 (24.0)
1–2	143 (46.4)
≥3	91 (29.6)
Formal education ≥5 y	276 (88.8)
Housewife	223 (71.7)
Has a partner	274 (88.1)
Socioeconomic characteristics	
>5 people eating in the household	39 (12.5)
Household spends ≤500 TSh/person/d on food[4]	109 (39.8)
Child characteristics	
Male sex	159 (51.1)
Born <37 wk gestational age	70 (22.5)
Birth weight <2500 g	22 (7.1)
Head circumference ≤32.0 cm at birth	14 (5.0)
Apgar score ≤7 at 5 min after birth	7 (2.5)
HIV positive at 6 wk	32 (10.3)
Micronutrient status at 6 wk[5]	
Serum vitamin A, *μmol/L*	0.48 ± 0.17
Serum vitamin E, *μmol/L*	15.8 ± 7.2
Serum vitamin B-12, *pmol/L*	335 ± 171
Plasma selenium, *μmol/L*	0.86 ± 0.24
Serum ferritin, *pmol/L*	526 ± 335
Anthropometric status at 6 wk[6]	
LAZ	−0.43 ± 1.22
WLZ	0.51 ± 1.06
WAZ	0.11 ± 1.04

[1] Values are *n* (%) or mean ± SD, *n* = 311. ESR, erythrocyte sedimentation rate; LAZ, length-for-age Z-score; WLZ, weight-for-length Z-score; WAZ, weight-for-age Z-score.
[2] Mid-upper arm circumference was measured during pregnancy, *n* = 309.
[3] Maternal hemoglobin was assessed within 2 mo after delivery, *n* = 279.
[4] 500 TSh was equivalent to ~USD 0.80 at the time of the study.
[5] *n* for serum vitamin A, serum vitamin E, and plasma selenium = 241; *n* for serum vitamin B-12 = 226; *n* for serum ferritin = 232.
[6] *n* for LAZ = 218; *n* for WLZ = 210; *n* for WAZ = 222.

TABLE 2 Maternal, socioeconomic, and child correlates of PDI scores in HIV-exposed children in Tanzania[1]

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean PDI (95% CI)	P[4]	Difference in mean PDI (95% CI)	P[4]
Maternal characteristics					
Age, y					
<25	329	Ref	0.70		
≥25	328	0.55 (−2.24, 3.35)			
HIV stage at baseline					
1	586	Ref	0.15	Ref	0.83
≥2	71	−3.59 (−8.46, 1.29)		−0.50 (−5.15, 4.15)	
ESR at baseline,[5] mm/h					
<81	521	Ref	0.13	Ref	0.34
≥81	136	−2.98 (−6.80, 0.84)		−1.53 (−4.67, 1.61)	
Hemoglobin,[5] g/L					
≥110	370	Ref	0.65		
85–109	238	1.01 (−1.26, 3.29)			
<85	49	−0.38 (−4.96, 4.20)			
Mid-upper arm circumference, cm					
<22.0	39	Ref	0.83		
≥22.0	613	0.68 (−5.34, 6.70)			
Prior pregnancies, *n*					
0	155	Ref	0.94		
1–2	297	0.60 (−2.87, 4.08)			
≥3	200	0.20 (−3.50, 3.89)			
Formal education, y			0.24		
<5	74	Ref			
≥5	583	3.24 (−2.22, 8.69)			
Housewife					
No	189	Ref	1.00		
Yes	468	−0.004 (−3.19, 3.19)			
Has a partner					
No	82	Ref	0.40		
Yes	575	−1.82 (−6.09, 2.44)			
Elevated level of depressive symptoms					
No	537	Ref	0.29		
Yes	108	1.58 (−1.33, 4.49)			
Socioeconomic characteristics					
People eating together in the household, *n*					
≤5	575	Ref	0.75		
>5	82	−0.72 (−5.05, 3.61)			
Household spends >500 TSh/person/day on food[6]					
No	236	Ref	0.56		
Yes	341	0.89 (−2.11, 3.90)			
Child characteristics					
Sex					
Female	316	Ref	0.11	Ref	0.13
Male	341	2.27 (−0.52, 5.06)		1.89 (−0.54, 4.31)	
Gestational age at birth, wk					
≥37	509	Ref	0.003	Ref	0.04
<37	148	−5.38 (−8.97, −1.80)		−3.61 (−7.12, −0.10)	
Birth weight, g					
≥2500	606	Ref	<0.0001	Ref	0.25
<2500	51	−9.76 (−14.2, −5.36)		−2.65 (−7.15, 1.86)	
Head circumference at birth, cm					
>32.0	576	Ref	0.002	Ref	0.17
≤32.0	29	−10.9 (−17.8, −3.93)		−4.34 (−10.6, 1.91)	
Apgar score at 5 min					
>7	586	Ref	0.16	Ref	0.25
≤7	16	−8.47 (−20.39, 3.45)		−5.69 (−15.47, 4.09)	

(Continued)

TABLE 2 *Continued*

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean PDI (95% CI)	P[4]	Difference in mean PDI (95% CI)	P[4]
Duration of exclusive breastfeeding,[5] mo					
≥3	486	Ref	0.11	Ref	0.42
<3	191	2.32 (−0.54, 5.17)		1.04 (−1.50, 3.59)	
HIV status[5]					
Negative	519	Ref	<0.0001	Ref	0.0001
Positive	139	−7.53 (−10.83, −4.23)		−5.87 (−8.86, −2.87)	
Child micronutrient status[5]					
Serum vitamin A, μmol/L					
≥0.70	112	Ref	0.40		
<0.70	529	−1.36 (−4.54, 1.83)			
Serum vitamin E, μmol/L					
≥11.6	470	Ref	0.10	Ref	0.32
<11.6	171	2.73 (−0.49, 5.96)		1.56 (−1.49, 4.61)	
Serum vitamin B-12, pmol/L					
≥150	538	Ref	0.77		
<150	44	0.96 (−5.40, 7.32)			
Plasma selenium,[7] μmol/L					
≥Median	312	Ref	0.73		
<Median	322	−0.50 (−3.29, 2.29)			
Serum ferritin,[8] pmol/L					
Q1	147	Ref	0.71		
Q2	134	2.10 (−1.83, 6.02)			
Q3	136	−0.06 (−4.22, 4.09)			
Q4	136	−0.39 (−4.52, 3.73)			
Hemoglobin, g/L					
≥70	609	Ref	0.009	Ref	0.09
<70	44	−6.07 (−10.7, −1.49)		−3.61 (−7.75, 0.54)	
Hypochromic microcystosis (moderate and severe)					
No	532	Ref	0.10	–	
Yes	101	−2.78 (−6.09, 0.54)		–	
Cumulative child morbidity episodes,[5,9]					
Cough alone					
0	54	Ref	0.06	–	
1 to 2	193	−2.70 (−6.47, 1.06)		–	
3 to 4	173	−2.81 (−7.05, 1.42)		–	
≥5	237	−5.45 (−10.4, −0.47)		–	
Cough and fever					
0	263	Ref	0.01	Ref	0.22
1	182	0.33 (−2.40, 3.06)		1.00 (−1.57, 3.57)	
2	98	−0.51 (−3.93, 2.91)		1.04 (−2.42, 4.50)	
≥3	114	−5.99 (−10.0, −1.96)		−3.19 (−6.95, 0.57)	
Cough and difficulty breathing, chest retractions, or refusal to eat					
0	431	Ref	0.01	–	
1	162	−0.80 (−3.80, 2.19)		–	
≥2	64	−6.73 (−11.1, −2.41)		–	
Diarrhea					
0	272	Ref	0.46		
1	173	0.67 (−2.17, 3.51)			
2	95	−1.06 (−4.86, 2.74)			
≥3	117	−1.40 (−5.65, 2.85)			
Acute diarrhea					
0	279	Ref	0.41		
1	175	−0.07 (−2.86, 2.72)			
2	94	−2.32 (−6.27, 1.63)			
≥3	109	−1.20 (−5.48, 3.07)			

(Continued)

TABLE 2 *Continued*

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean PDI (95% CI)	P[4]	Difference in mean PDI (95% CI)	P[4]
Persistent diarrhea					
0	621	Ref	0.44		
≥2	36	2.50 (−3.80, 8.79)			
Watery diarrhea					
0	425	Ref	0.10	Ref	0.20
1	156	−1.31 (−4.23, 1.61)		−1.69 (−4.44, 1.06)	
≥2	76	−3.47 (−7.67, 0.72)		−2.07 (−6.15, 2.01)	
Child anthropometric status[5]					
Stunting					
No	532	Ref	<0.0001	Ref	0.006
Yes	121	−7.04 (−10.5, −3.55)		−4.47 (−7.63, −1.31)	
Wasting					
No	620	Ref	<0.0001	Ref	0.0009
Yes	36	−13.3 (−18.8, −7.71)		−8.89 (−14.2, −3.62)	
Underweight					
No	534	Ref	<0.0001	–	
Yes	122	−12.7 (−16.8, −8.54)		–	

[1] n represents the number of observations used in the analysis. ESR, erythrocyte sedimentation rate; PDI, Psychomotor Development Index; TSh, Tanzanian Shillings.
[2] Adjusted for child age at time of developmental assessment.
[3] Additionally adjusted for parent study treatment regimen and child age. A dash indicates that, although the variable was significant at $P < 0.2$ in the univariate analysis, it was not included in the multivariate model.
[4] For variables with ≥3 categories, P value was estimated using a test for trend.
[5] Time-updated variable.
[6] 500 TSh was equivalent to ~USD 0.80 at the time of the study.
[7] The median plasma selenium concentration at 6 wk and 6 mo was 0.86 μmol/L.
[8] At 6 wk: Q1 = 6.07–299 pmol/L, Q2 = 300–466 pmol/L, Q3 = 467–704 pmol/L, Q4 >704 pmol/L; at 6 mo: Q1 = 6.29–37.8 pmol/L, Q2 = 37.9–82.7 pmol/L, Q3 = 82.7–164 pmol/L, Q4 >164 pmol/L.
[9] An episode was defined if the symptom was reported during the 4 wk prior to the visit.

age was not modified by low birth weight ($P = 0.34$). The mean MDI was 2.5 points lower (95% CI = −4.9, −0.2) among HIV positive than negative infants ($P = 0.03$). Infants who were stunted at the time of developmental assessment had an MDI that was 4.0 points lower (95% CI = −6.7, −1.3) than their nonstunted counterparts, on average ($P = 0.003$). The mean MDI was 6.5 points lower (95% CI = −10.5, −2.4) among wasted infants compared with infants with a WLZ ≥−2 ($P = 0.002$).

Change in developmental status over time. **Figure 1** illustrates deterioration in both psychomotor and mental development over time among this population of infants born to HIV-infected women; however, the rate of decline was greater among HIV-infected infants, particularly in the case of psychomotor development. PDI decreased linearly with increasing age among HIV-infected and -uninfected infants (P, test for linear relation <0.0001). The decline in MDI was also linear among HIV-uninfected infants; however, among HIV-infected infants, the association was nonlinear (P, test for curvature = 0.05). The mean PDI among HIV-negative infants was ~96 at 6 mo of age, which declined to a low of 88 at the end of follow-up. HIV-positive infants started lower than their HIV-negative peers with a mean of 91 at 6 mo of age but declined to 76 by the end of follow-up. The decline in MDI was steeper among both groups of children compared with PDI. At 6 mo of age, the mean MDI was almost equivalent at ~98 and 97 among HIV-negative and -positive infants, respectively. Although the rate of decline was greater among HIV-positive infants, the mean MDI eventually increased so that both groups finished with a mean MDI of ~77 at the end of the follow-up period. However, the wide CIs reflect the small number of subjects with measurements at 18 mo of age.

Discussion

In this analysis, we assessed maternal, socioeconomic, and child correlates of psychomotor and mental development in a cohort of 311 Tanzanian infants born to HIV-infected women. This cohort of HIV-exposed children is one of the largest with longitudinal measurements of infant development. Our ability to collect anthropometric and morbidity data at frequent, monthly intervals enabled us to model these exposures in a time-varying way. We hypothesized that a child's HIV status, morbidity history, and nutritional status would be most closely related to his or her developmental status after accounting for maternal and socioeconomic characteristics. However, in multivariate analyses, we found that only 4 child characteristics were associated with lower MDI and PDI scores: HIV infection, preterm birth, stunting, and wasting. The finding that stunting and wasting exert independent effects on both psychomotor and mental development is particularly novel.

As expected, HIV-infected children had lower PDI and MDI scores compared with their HIV-exposed, uninfected peers. The persistence of this association in the multivariate models suggests that HIV infection may have extended deleterious effects beyond the pathways of morbidity and undernutrition. Our results build upon findings from earlier studies of HIV-exposed children in sub-Saharan Africa. Drotar et al. (10) demonstrated that by 12 mo of age, 30% of HIV-infected Ugandan infants demonstrated motor abnormalities and 26% had cognitive abnormalities, whereas the respective prevalence among HIV-exposed, uninfected infants was 11 and 6%. In Rwanda, Msellati et al. (27) also reported lower gross and fine motor scores among HIV-infected infants compared with HIV-

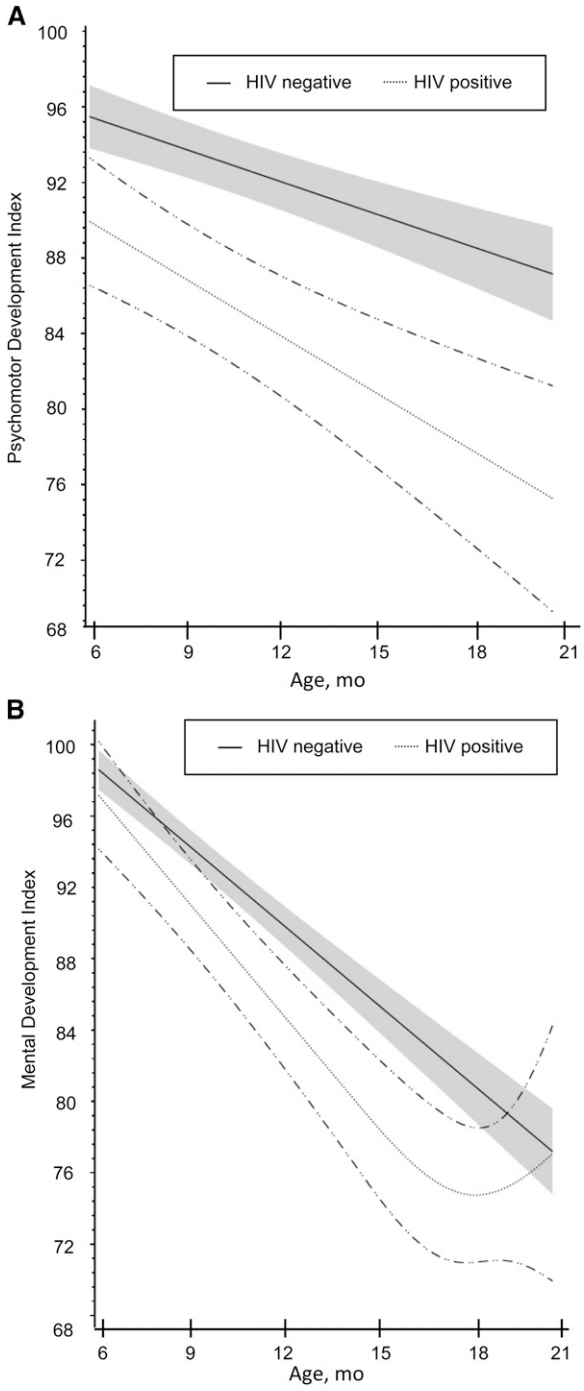

FIGURE 1 Changes in PDI score (*A*) and MDI score (*B*) of Tanzanian infants (n = 311) by age and HIV status. MDI, Mental Development Index; PDI, Psychomotor Development Index.

exposed, uninfected infants at 12 mo of age. Likewise, the prevalence of social and motor deficits was higher among a small group of HIV-infected Zairian infants compared with HIV-exposed uninfected and HIV-unexposed infants (28). However, these previous studies employed relatively basic statistical techniques and reported only unadjusted mean values comparing HIV-infected and HIV-exposed uninfected children. By performing more detailed multivariate modeling and controlling for the presence of several other significant correlates of infant development, we are able to report estimates for HIV that are less likely to be confounded.

We also found that although child gestational age and weight at birth were both significantly associated with psychomotor and mental development in univariate analyses, only gestational age retained significance and drastically attenuated the effect of low birth weight in multivariate models. Although several clinical studies have examined the association between preterm birth and infant development in industrialized settings (29–31), few studies have investigated the interplay between low birth weight and prematurity in developing countries, where both conditions are more prevalent (32). Our study considered both variables as separate correlates and also explored potential effect modification. Although the interaction term was not significant in either the PDI or MDI multivariate model, additional research with a larger sample size is called for to better understand the interaction between gestational age and birth weight in their relationship with infant development.

Our finding that mean PDI and MDI were ~4 points lower in stunted children than in nonstunted children reinforces previous evidence linking chronic undernutrition to impaired development (33,34). In fact, the 2007 Lancet series on child development in developing countries used stunting as 1 of 2 factors to indicate impaired development (1). The adverse effects of early childhood stunting on cognitive development can persist through childhood and even adolescence. A recent cohort study of 3000 children from Vietnam found that a 1-SD higher height-for-age Z-score at 1 y of age was associated with a 0.25-SD higher log score on the Peabody Picture Vocabulary Test and a 0.2-SD higher score on the cognitive achievement test at age 5 y (35). The aforementioned study from Peru found that at 9 y of age, children who had a LAZ <-3 at age 2 y scored 10 points lower on the Wechsler Intelligence Scale for Children-Revised test than children who had not been severely stunted (36). Similarly, research from Jamaica revealed that children who were stunted at 9–24 mo of age had lower arithmetic, spelling, word reading, and reading comprehension than nonstunted children at age 11–12 y (37). A follow-up study later found that these deficits persisted at age 17–18 y (38).

Although some trials have examined the effectiveness of providing food supplements to nutritionally compromised children on developmental outcomes, our study is one of the few to reveal that acute undernutrition in infancy and early childhood can have a deleterious effect on development that is independent from stunting. Berkman et al. (36) did not find a significant association between WLZ in infancy and Wechsler Intelligence Scale for Children-Revised scores at age 9 y, and although Santos et al. (34) reported an inverse association between wasting and Weschler Pre-School and Primary Scale of Intelligence scores at age 5 y in univariate analyses, their multivariate analyses accounted for HAZ only and not WHZ. By taking full advantage of the monthly anthropometric measurements of children in our study and modeling stunting and wasting as time-varying covariates prior to developmental assessment, our analysis captured the effects of declining nutritional status on development.

Our study has both strengths and limitations. We were able to obtain measures of psychomotor and mental development at multiple ages from a large sample of infants born to HIV-infected women. We also collected data on a comprehensive set of maternal, socioeconomic, and child characteristics, of which many were assessed at multiple time points, allowing for time-varying analysis of important risk factors. Although we obtained repeated measures on nearly 70% of infants, the size of this subset of infants was not sufficient enough to conduct a longitudinal analysis of determinants of change in developmental status over time. Infants were not selected for the BSID-II in a

TABLE 3 Maternal, socioeconomic, and child correlates of MDI scores in HIV-exposed children in Tanzania[1]

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean MDI (95% CI)	P[4]	Difference in mean MDI (95% CI)	P[4]
Maternal characteristics					
Age, y					
<25	329	Ref	0.96		
≥25	328	0.05 (−1.96, 2.05)			
HIV stage at baseline					
1	586	Ref	0.60		
≥2	71	−0.72 (−3.41, 1.97)			
ESR at baseline,[5] mm/h					
<81	521	Ref	0.06	Ref	0.16
≥81	136	−2.43 (−5.00, 0.14)		−1.59 (−3.81, 0.63)	
Hemoglobin,[5] g/L					
≥110	370	Ref	0.52		
85–109	238	0.78 (−0.90, 2.46)			
<85	49	0.16 (−3.39, 3.70)			
Mid-upper arm circumference, cm					
<22.0	39	Ref	0.77		
≥22.0	613	−0.62 (−4.84, 3.61)			
Prior pregnancies, *n*					
0	155	Ref	0.86		
1–2	297	0.39 (−2.22, 3.01)			
≥3	200	0.28 (−2.46, 3.03)			
Formal education, y					
<5	74	Ref	0.56		
≥5	583	1.14 (−2.73, 5.01)			
Housewife					
No	189	Ref	0.50		
Yes	468	−0.79 (−3.09, 1.52)			
Has a partner					
No	82	Ref	0.62		
Yes	575	−0.70 (−3.48, 2.08)			
Elevated level of depressive symptoms					
No	537	Ref	0.66		
Yes	108	−0.52 (−2.85, 1.80)			
Socioeconomic characteristics					
People eating together in the household, *n*					
≤5	575	Ref	0.30		
>5	82	−1.60 (−4.62, 1.41)			
Household spends >500 TSh/person/day on food[6]					
No	236	Ref	0.08	Ref	0.07
Yes	341	1.90 (−0.26, 3.05)		1.82 (−0.13, 3.77)	
Child characteristics					
Sex					
Female	316	Ref	0.36	Ref	0.65
Male	341	0.95 (−1.08, 2.97)		0.42 (−1.38, 2.21)	
Gestational age at birth, wk					
≥37	509	Ref	0.004	Ref	0.01
<37	148	−3.66 (−6.12, −1.20)		−3.21 (−5.67, −0.74)	
Birth weight, g					
≥2500	606	Ref	0.003	Ref	0.60
<2500	51	−5.06 (−8.41, −1.70)		−1.09 (−5.19, 3.01)	
Head circumference at birth, cm					
>32.0	576	Ref	0.11	Ref	0.92
≤32.0	29	−4.40 (−9.84, 1.04)		0.24 (−4.44, 4.92)	
Apgar score at 5 min					
>7	586	Ref	0.18	Ref	0.19
≤7	16	−6.87 (−17.0, 3.23)		−5.12 (−12.8, 2.59)	

(Continued)

TABLE 3 *Continued*

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean MDI (95% CI)	P[4]	Difference in mean MDI (95% CI)	P[4]
Duration of exclusive breastfeeding,[5] mo					
≥3	486	Ref	0.27		
<3	191	1.16 (−0.92, 3.23)			
HIV status[5]					
Negative	519	Ref	0.01	Ref	0.03
Positive	139	−3.40 (−6.06, −0.74)		−2.53 (−4.86, −0.21)	
Child micronutrient status[5]					
Serum vitamin A, μmol/L					
≥0.70	112	Ref	0.67		
<0.70	529	−0.57 (−3.20, 2.06)			
Serum vitamin E, μmol/L					
≥11.6	470	Ref	0.11	Ref	0.16
<11.6	171	1.72 (−0.39, 3.83)		1.60 (−0.63, 3.84)	
Serum vitamin B-12, pmol/L					
≥150	538	Ref	0.11	Ref	0.28
<150	44	3.02 (−0.69, 6.72)		3.39 (−0.12, 6.90)	
Plasma selenium,[7] μmol/L					
≥Median	312	Ref	0.74		
<Median	322	−0.35 (−2.39, 1.70)			
Serum ferritin,[8] pmol/L					
Q1	147	Ref	0.76		
Q2	134	0.33 (−2.44, 3.10)			
Q3	136	0.20 (−2.65, 3.05)			
Q4	136	−0.83 (−3.99, 2.32)			
Hemoglobin, g/L					
≥70	609	Ref	0.20		
<70	44	−2.83 (−7.20, 1.54)			
Hypochromic microcystosis (moderate and severe)					
No	532	Ref	0.04	Ref	0.26
Yes	101	−2.87 (−5.56, −0.18)		−1.41 (−3.87, 1.04)	
Cumulative child morbidity episodes,[5,9]					
Cough alone					
0	54	Ref	0.27		
1 to 2	193	−2.46 (−5.12, 0.20)			
3 to 4	173	−1.51 (−4.38, 1.36)			
≥5	237	−3.19 (−6.77, 0.39)			
Cough and fever					
0	263	Ref	0.05	Ref	0.44
1	182	−0.09 (−2.23, 2.06)		0.03 (−2.03, 2.09)	
2	98	1.54 (−1.22, 4.30)		2.48 (−0.23, 5.19)	
≥3	114	−4.37 (−7.60, −1.13)		−2.50 (−5.60, 0.60)	
Cough and difficulty breathing, chest retractions, or refusal to eat					
0	431	Ref	0.31		
1	162	−0.98 (−3.52, 1.57)			
≥2	64	−1.49 (−5.17, 2.18)			
Diarrhea					
0	272	Ref	0.88		
1	173	−0.75 (−0.04, 1.54)			
2	95	−0.02 (−2.85, 2.80)			
≥3	117	−0.36 (−3.66, 2.94)			
Acute diarrhea					
0	279	Ref	0.94		
1	175	−0.49 (−2.74, 1.75)			
2	94	−0.60 (−3.50, 2.29)			
≥3	109	0.08 (−3.30, 3.46)			

(Continued)

TABLE 3 *Continued*

		Univariate results[2]		Multivariate results[3]	
	n[1]	Difference in mean MDI (95% CI)	P[4]	Difference in mean MDI (95% CI)	P[4]
Persistent diarrhea					
0	621	Ref	0.16	Ref	0.76
≥2	36	−2.19 (−5.27, 0.89)		−0.52 (−3.87, 2.83)	
Watery diarrhea					
0	425	Ref	0.42		
1	156	1.11 (−1.10, 3.31)			
≥2	76	0.86 (−2.47, 4.18)			
Child anthropometric status[5]					
Stunting					
No	532	Ref	<0.0001	Ref	0.003
Yes	121	−6.32 (−9.27, −3.37)		−4.03 (−6.73, −1.33)	
Wasting					
No	620	Ref	0.0004	Ref	0.002
Yes	36	−9.24 (−14.4, −4.11)		−6.47 (−10.5, −2.42)	
Underweight					
No	534	Ref	<0.0001		
Yes	122	−8.31 (−11.9, −4.68)			

[1] n represents the number of observations used in the analysis. ERS, erythrocyte sedimentation rate; MDI, Mental Development Index; TSh, Tanzanian Shillings.
[2] Adjusted for child age at time of developmental assessment.
[3] Additionally adjusted for parent study treatment regimen and child age. A dash indicates that, although the variable was significant at $P < 0.2$ in the univariate analysis, it was not included in the multivariate model.
[4] For variables with ≥3 categories, P value was estimated using a test for trend.
[5] Time-updated variable.
[6] 500 TSh was equivalent to ~USD 0.80 at the time of the study.
[7] The median plasma selenium concentration at 6 wk and 6 mo was 0.86 μmol/L.
[8] At 6 wk: Q1 = 6.07–299 pmol/L, Q2 = 300–466 pmol/L, Q3 = 467–704 pmol/L, Q4 >704 pmol/L; at 6 mo: Q1 = 6.29–37.8 pmol/L, Q2 = 37.9–82.7 pmol/L, Q3 = 82.7–164 pmol/L, Q4 >164 pmol/L.
[9] An episode was defined if the symptom was reported during the 4 wk prior to the visit.

completely random manner and substantial loss to follow-up did occur; therefore, infants contributing multiple BSID-II assessments may have been healthier or socioeconomically better off than their peers. However, our comparison of baseline characteristics revealed few differences from the overall study population. Unfortunately, detailed data on mother-child interactions and caregiving practices were not obtained, which would help elucidate potential pathways through which some correlates exert their effect on psychomotor and mental development. Furthermore, although child morbidity was frequently assessed, we recognize that the use of monthly symptom recalls and pictorial diaries may not fully capture a child's complete morbidity history. Finally, this analysis does not include a comparison group of HIV-uninfected infants born to HIV-uninfected women; however, the standardized MDI and PDI measures provide a frame of reference for "healthy" development.

In conclusion, child HIV status, gestational age at birth, stunting, and wasting were significant, independent correlates of mental and psychomotor development among infants born to HIV-infected women in Tanzania. Strategies to lower the rates of mother-to-child transmission of HIV, prevent preterm birth, and promote childhood growth could enable more children to reach their developmental potential.

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C.M.M. and C.P.D. wrote the paper; C.M.M. and D.S. performed statistical analysis; W.W.F. and G.M. designed the research; G.M., K.P.M., R. Kisenge, and D.C.B. conducted the research; R. Kupka provided technical inputs to the paper; and C.P.D. had primary responsibility for final content. All authors read and approved the final manuscript.

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