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Effect of Maternal Multivitamin Supplementation on the Mental and Psychomotor Development of Children Who Are Born to HIV-1–Infected Mothers in Tanzania

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ABSTRACT

OBJECTIVES. To determine the association between maternal multivitamin supplementation and the mental and psychomotor development of children who are born to HIV-1–infected mothers in Tanzania, as secondary endpoints in a randomized trial that investigated the effect of maternal multivitamin supplementation on HIV-1 vertical transmission and progression.

METHODS. The Bayley Scales of Infant Development, 2nd Edition, were administered at 6, 12, and 18 months of age to a subset of children ($N = 327$). We assessed the effect of vitamin A and multivitamin (vitamins B, C, and E) supplementation using linear regression models and Cox proportional hazard models for the Mental Development Index, the Psychomotor Development Index, and raw scores separately.

RESULTS. Multivitamin supplementation was associated significantly with a mean increase in Psychomotor Development Index score of 2.6 (95% confidence interval: 0.1–5.1). Multivitamins were also significantly protective against the risk for developmental delay on the motor scale (relative risk: 0.4; 95% confidence interval: 0.2–0.7) but not on the Mental Development Index. Vitamin A supplementation had no significant effect on these outcomes.

CONCLUSIONS. Maternal multivitamin supplements provide a low-cost intervention to reduce the risk for developmental delays among infants who are born to HIV-positive mothers in developing countries.

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Key Words
multivitamins, mental development, psychomotor development, supplementation, children, Tanzania

Abbreviations
LBW—low birth weight
BSID-II—Bayley Scales of Infant Development, 2nd Edition
MDI—Mental Development Index
PDI—Psychomotor Development Index
ESR— erythrocyte sedimentation rate
CI— confidence interval
SES—socioeconomic status

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ALTHOUGH STUDIES HAVE sought to improve mental and psychomotor development in children through protein energy[1] and multivitamin child supplements,[2–4] few have examined the effect of maternal supplements on infant development. Nutritional deficiencies are common in children in developing countries.[5] In 1996, 43% of preschool Tanzanian children were stunted (low height for age).[6] Vitamin A, iodine, and iron deficiencies are also prevalent.[7–9] Pepping et al[8] found that vitamin A deficiency was a significant problem in Tanzania, with 1.5% of the preschool age children whom they surveyed having xerophthalmia and 1.6% having Bitot's spots. In addition, children are have HIV-1 infection; antenatal HIV-1 seroprevalence has been ~12% since 1995 in Dar es Salaam.[10] Because multivitamin deficiencies are associated with faster HIV disease progression in adults[11] and higher risk for infant morbidity,[12] they may have a negative impact on the mental and psychomotor development of the child.

Daily consumption of multivitamin supplements by HIV-1–infected pregnant women has been shown to delay significantly the progression of HIV disease.[13] Multivitamin supplements also resulted in significant reductions in the risk for low birth weight (LBW), severe preterm birth, and fetal loss and improved the immunologic profile of the mothers and increased their hemoglobin concentrations.[14] Vitamin A supplementation during pregnancy has also been shown to reduce the risk for preterm delivery among HIV-infected women.[15] Baylin et al[16] demonstrated that vitamin A supplements that are given to HIV-infected mothers during pregnancy and lactation increases serum vitamin A in their infants during the first 6 months of life. Similarly, multivitamin supplements (B, C, and E) increase serum vitamins B_{12} and E.

Improved maternal multivitamin status after supplementation to the mother during the prenatal and postnatal periods could result in improved mental and motor development in the breastfed child through 3 possible mechanisms: (1) by reducing the risk for LBW and prematurity in the prenatal supplement phase, both of which have been shown to be associated with poor neurodevelopment[17–19]; (2) through postnatal supplements to the mothers, which would improve her own health, allowing her to be more interactive with the child; or (3) by improving the child's vitamin status and directly reducing child morbidity.[20] We conducted a randomized trial among HIV-1–infected women and examined the effect of maternal multivitamin or vitamin A supplementation on the mental and psychomotor development of children in Tanzania.

METHODS

Study Design and Population

Children in this study were born to mothers who were part of a randomized, double-blinded, placebo-controlled trial of vitamin supplements (multivitamins and vitamin A in a 2 × 2 factorial design) among HIV-1–infected pregnant women in Dar es Salaam, Tanzania. The primary endpoints of this trial were to examine the effect of maternal vitamin supplementation on mother to child HIV-1 transmission and disease progression. A secondary endpoint was to examine the role of maternal vitamin supplementation on child mental and psychomotor development. Pregnant women who were between 12 and 27 weeks' gestation at the time of randomization and had HIV-1 infection were eligible for entry into the trial. HIV-1 serostatus was tested using an enzyme-linked immunosorbent assay, and positive results were confirmed by Western blot. HIV-1–positive women were excluded when they were classified to have AIDS on the basis of the World Health Organization definition.[21] At the time of the study, antiretroviral treatment was not available to the majority of Tanzanians, including those who participated in this study.

During enrollment for each pregnant woman, a number of characteristics were captured in response to questions asked by the counselor as part of a structured questionnaire interview. Enrolled women were followed up at the study clinic at Muhimbili National Hospital monthly during pregnancy and with their infants after delivery for a minimum of 18 months. It was hypothesized that pharmacologic doses were needed, ie, that HIV-infected individuals needed intakes in multiples of the RDA to achieve adequate plasma nutrient values. Women received a daily dose during pregnancy and continued after delivery, throughout follow-up, 1 of the following regimens: vitamin A (30 mg of β-carotene plus 5000 IU preformed vitamin A); multivitamins excluding vitamin A (20 mg of B_1, 20 mg of B_2, 25 mg of B_6, 100 mg of niacin, 50 μg of B_{12}, 500 mg of C, 30 mg of E, and 0.8 mg of folic acid); multivitamins including vitamin A, all formulated in 2 tablets; or 2 tablets of placebo. At delivery, women who were taking vitamin A supplementation received an additional oral dose of vitamin A (200 000 IU), and the others received an extra dose of placebo. At each monthly visit to the study clinic, used bottles were exchanged for new bottles, and the remaining pills were counted. All children, regardless of maternal regimen assignment, were given vitamin A 100 000 IU at 6 months and 200 000 IU every 6 months thereafter as per national guidelines in Tanzania. Children had postnatal exposure to the trial supplements through their mothers' breast milk. Data used in this article were collected within this framework.

All women gave informed consent to participate in the study according to a strict protocol that was approved by the institutional review boards for Muhimbili University College of Health Sciences, the Tanzanian National AIDS Control Program, and Harvard School of Public Health. These boards also approved the study protocol.

Measures

The Bayley Scales of Infant Development, 2nd Edition[22] (BSID-II), was used to assess the current developmental functioning of children aged 6 to 18 months in this study. The BSID-II consists of 3 scales: mental, motor, and behavior rating scale. Only the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) were considered in this study. The BSID-II was administered at 6, 12, and 18 months to a subset of the infants who were born from first-study pregnancies, attended clinic on Mondays or Fridays, and had an identification number that ended in an uneven digit. A Kiswahili translation of all of the instructions to the child was used during each assessment. Tests were administered by 1 of 2 trained Tanzanian nurses, who were masked to the HIV-1 status of the children. Test administration occurred at the beginning of the clinic visit for each child. Children who were acutely ill were not tested, but their mothers were asked to return with them once they had recovered.

Statistical Analysis

BSID-II raw scores signify the number of individual items that a child passes on either the MDI or the PDI. The MDI and the PDI are conversions of these raw scores, compared with a standardized and representative sample of US children. Any assessment for which the achieved raw score "fell off" the development index range (ie, <50) was represented by a value of 49 in analyses. The MDI and PDI and their associated raw scores each were considered separately as outcomes for analyses. The analyses of raw mental and motor scores were considered in an effort to differentiate between a delay in achieving new developmental capacities and losing previously acquired capacities, as well as to avoid making representation of children who had raw scores that did not convert to a score within the scaled score range. Only singleton births were included in the analyses because twins are at greater risk and have different mental and psychomotor development than singletons.

For longitudinal analyses, linear regression models were fitted for each of the outcomes separately using all available data. In each case, additional confounders were considered. Given the factorial design, we examined the effect of multivitamin versus no multivitamin supplementation and of vitamin A versus no vitamin A supplementation on child mental and psychomotor development. Each supplement was also considered a possible modifier of the effect of the other supplement by adding an interaction term. LBW (<2500 g), the child's HIV-1 status, maternal CD4 count at baseline (CD4 <200 cells/mm^3), maternal total lymphocyte count at baseline (1340 cells/μL, representing the lowest quartile), maternal erythrocyte sedimentation rate (ESR; 81 mm/hour, representing the highest quartile) at baseline, duration of supplementation during pregnancy (the difference between gestational age at enrollment and gestational age at delivery), and timing of the initiation of treatment during pregnancy (as a continuous covariate) all were considered as potential modifiers of the effect of maternal supplementation as well.

The average absolute effects of supplementation on mental and motor outcomes at 6, 12, and 18 months were calculated separately. The timing of assessments was not always according to schedule, so the data were grouped for these analyses around the scheduled time points. Repeat assessments were not used in these analyses. Instead, the assessment that was performed closest to the scheduled assessment time was used.

Any observed difference in mental and psychomotor development scores over 6 to 18 months between groups defined by vitamin A supplementation is more likely attributable to vitamin A supplementation in the first 6 months because all children received vitamin A supplements at 6, 12, and 18 months. For this reason, particular attention was paid to the effect of vitamin A supplementation on mental and motor outcomes at 6 months. The empirical variance was used to estimate 95% confidence intervals (CIs) for all results from longitudinal analyses to reflect that the data are repeated measures within individuals.

Cox proportional hazards regression models were used to investigate the effect of maternal supplementation on time to an index score <70, where an index score of <70 represents "developmental delay." All analyses were determined a priori and were performed using SAS version 6.12 (SAS, Inc, Cary, NC).

RESULTS

Figure 1 shows the inclusions and exclusions from the study population. The characteristics of the women who agreed to enroll in the trial were similar to the characteristics of all of the HIV-positive women who had been counseled and tested in terms of their age; BMI and mid-upper arm circumference; marital status; gestational age of their fetus at enrollment; and their partner's age, education, and occupation. These women were also similar in terms of their socioeconomic status (SES), considering money spent on food per person per day in the household and maternal education as 2 proxies for SES.

Of the infants who were alive at 6 months, 327 contributed 1 or more BSID-II assessments to this study at different ages, for a total of 681 assessments for analysis. The mothers of 169 of the children who had at least 1 BSID-II assessment received multivitamin supplements versus 158 who received no multivitamin supplement; 180 mothers received vitamin A supplements compared with 147 women who did not receive a vitamin A supplement. Four of these children, each with 1 assessment, had either an MDI or a PDI but not both. Eleven other children had 1 assessment for which either the raw

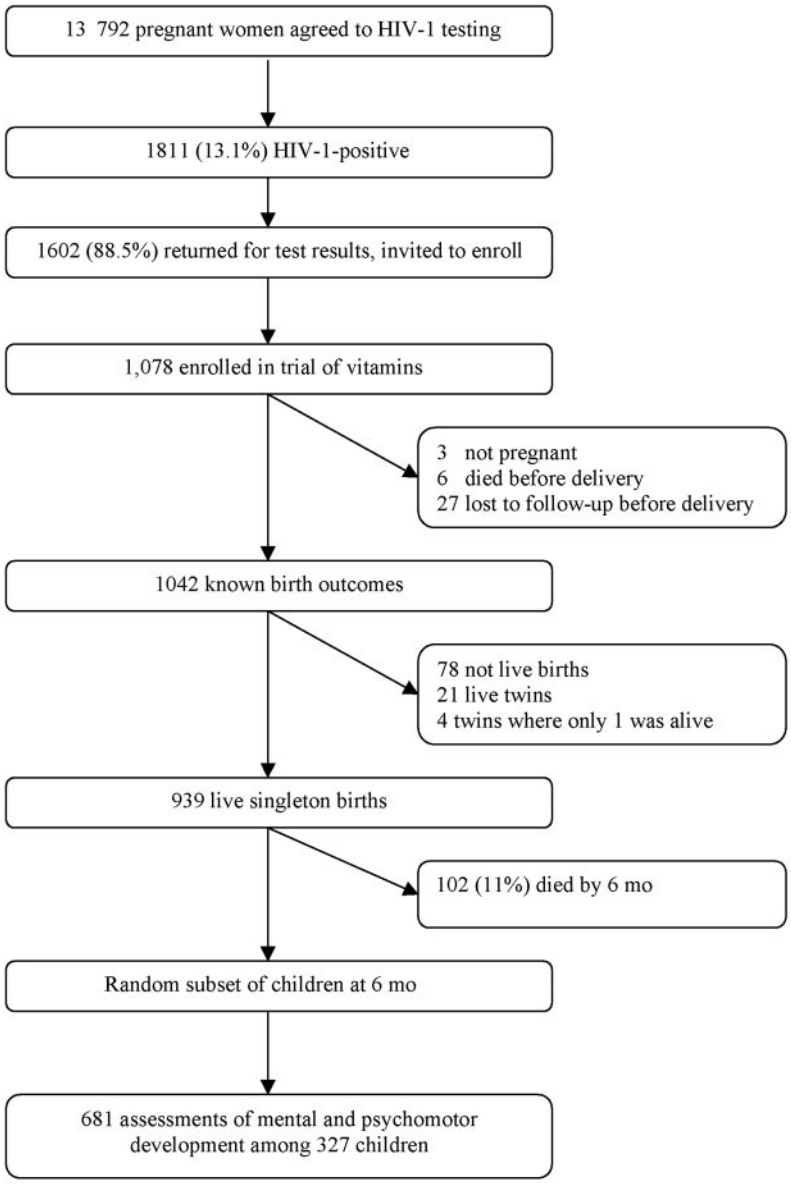

FIGURE 1
Flowchart of selection for study population.

mental or raw motor score could not be scaled and were assigned a value of 49 for analyses. Considering raw scores over time, only 2 children were observed to have had a decrease in raw score during the study. In both cases, the decrease was in mental score. One child lost 2 items in the mental raw score between the age of 7 and 12 months, whereas the other child lost 1 item in the mental raw score between the age of 12 and 13 months.

Breastfeeding was almost universally adopted in this population. The percentage of children who were alive and breastfeeding was 95% at 6 months, 92% at 12 months, and 79% at 18 months.[23] The median adherence to maternal supplementation between randomization and delivery was 96% (mean 91%) and 92% (mean 88%) at 30 weeks postpartum and did not differ significantly between groups.[14] Median compliance was 89% at 12 months, 84% by 18 months, and 84% by 24 months.[24]

Table 1 shows the distributions of maternal and child characteristics between groups that were defined by the type of supplementation received and that these distributions were similar. There were also no significant differences, at the 5% level, between groups in terms of biochemical markers, specifically maternal vitamin A, vitamin E, and selenium status at baseline (not presented in Table 1). As expected on the basis of our previous report,[14] comparing the 2 groups defined by supplementation, children whose mothers received multivitamin supplements were significantly less likely to have LBW (<2500 g; $P = .02$). The only significant difference between those who received vitamin A sup-

TABLE 1 **Characteristics of Children and Their Mothers According to Maternal Supplement Assignment**

Factor	No Multivitamins, *N* (%)	Multivitamins, *N* (%)	*P*[a]	No Vitamin A, *N* (%)	Vitamin A, *N* (%)	*P*[b]
Overall	158	169		147	180	
Maternal factors						
HIV stage at baseline			.28			.60
1	136 (86.1)	152 (89.9)		131 (89.1)	157 (87.2)	
≥2	22 (13.9)	17 (10.1)		16 (10.9)	23 (12.8)	
CD4			.98			.74
<200	15 (9.5)	17 (10.1)		15 (10.2)	17 (9.4)	
200–500	87 (55.1)	94 (55.6)		78 (53.1)	103 (57.2)	
>500	45 (28.5)	47 (27.8)		44 (29.9)	48 (26.7)	
Missing	11 (7.0)	11 (6.5)		10 (6.8)	12 (6.7)	
Age, y			.55			.03
<20	18 (11.4)	23 (13.6)		20 (13.6)	21 (11.7)	
20–24	66 (41.8)	61 (36.1)		46 (31.3)	81 (45.0)	
25–29	46 (29.1)	59 (34.9)		58 (39.5)	47 (26.1)	
≥30	28 (17.7)	26 (15.4)		23 (15.7)	31 (17.2)	
Marital status			.85			.27
Single	19 (12.0)	21 (12.4)		15 (10.2)	25 (13.9)	
Monogamous	87 (55.1)	98 (58.0)		92 (62.6)	93 (51.7)	
Polygamous	13 (8.2)	10 (5.9)		9 (6.1)	14 (7.8)	
Cohabiting	39 (24.7)	40 (23.7)		31 (21.1)	48 (26.7)	
Education			.44			.42
None	13 (8.2)	9 (5.3)		10 (6.8)	12 (6.7)	
Low	8 (5.1)	7 (4.1)		9 (6.1)	6 (3.3)	
Elementary	125 (79.1)	133 (78.7)		117 (79.6)	141 (78.3)	
Secondary	12 (7.6)	20 (11.8)		11 (7.5)	21 (11.7)	
Quintiles of money spent			.91			.11
Median = 233	20 (12.7)	17 (10.1)		24 (16.3)	13 (7.2)	
Median = 333	24 (15.2)	26 (15.4)		21 (14.3)	29 (16.1)	
Median = 400	15 (9.5)	13 (7.7)		13 (8.8)	15 (8.3)	
Median = 500	43 (27.2)	48 (28.4)		42 (28.6)	49 (27.2)	
Median = 750	43 (27.2)	38 (22.5)		31 (21.1)	50 (27.8)	
Missing	13 (8.2)	27 (16.0)		16 (10.9)	24 (13.3)	
ESR			.51			.81
≥81 mm/h	30 (19.0)	37 (21.9)		31 (21.0)	36 (20.0)	
<81 mm/h	128 (81.0)	132 (78.1)		116 (79.0)	144 (80.0)	
Child factors						
Gender			.16			.52
Male	87 (55.1)			78 (53.1)	89 (49.4)	
Female	71 (44.9)	89 (52.7)		69 (46.9)	91 (50.6)	
<37 wk gestation			.13			.65
Yes	42 (26.6)	33 (19.5)		32 (21.8)	43 (23.9)	
No	116 (73.4)	136 (80.5)		115 (78.2)	137 (76.1)	
Small for gestational age			.12			.49
Yes	15 (9.5)	8 (4.7)		12 (8.2)	11 (6.1)	
No	136 (86.1)	144 (85.2)		125 (85.0)	155 (86.1)	
Missing	7 (4.4)	17 (10.1)		10 (6.8)	14 (7.8)	
LBW (<2500 g)			.02			.79
Yes	17 (10.8)	6 (3.6)		11 (7.5)	12 (6.7)	
No	134 (84.8)	146 (86.4)		126 (85.7)	154 (85.6)	
Missing	7 (4.4)	17 (10.1)		10 (6.8)	14 (7.8)	
Child died by, cumulative			.11			.73
6 mo	0 (0)	0 (0)		0 (0)	0 (0)	
12 mo	10 (6.3)	3 (1.8)		7 (4.8)	6 (3.3)	
18 mo	17 (10.8)	10 (5.9)		13 (8.8)	14 (7.8)	
Alive at 18 mo	141 (89.2)	159 (94.1)		134 (91.2)	166 (92.2)	

A total of 327 children had at least 1 BSID-II assessment.

[a] χ^2 test comparing nonmissing data between the 2 groups defined by multivitamin use.

[b] χ^2 test comparing nonmissing data between the two groups defined by vitamin A use.

plementation and those who did not was that mothers in the latter group tended to be slightly older ($P = .03$).

Tables 2 and 3 show mean mental and motor scores, respectively, by supplementation group at 6, 12, and 18 months, as well as the results of longitudinal analyses. In multivariate analyses, multivitamin supplementation

TABLE 2 **Mean Scores for the MDI and Raw Mental Scores by Supplementation Groups at 6, 12, and 18 Months of Age and Overall**

Developmental Outcome	No Multivitamins	Multivitamins	*P*	No Vitamin A	Vitamin A	*P*
MDI						
6 mo						
N	137	140		121	156	
Mean (95% CI)	97.2 (95.8 to 98.5)	98.5 (97.2 to 99.9)	.17	97.1 (95.7 to 98.5)	98.4 (97.1 to 99.7)	.20
12 mo						
N	87	108		92	103	
Mean (95% CI)	91.8 (88.9 to 94.5)	90.2 (87.6 to 92.9)	.44	89.7 (86.7 to 92.7)	92.0 (89.5 to 94.5)	.24
18 mo						
N	74	93		73	94	
Mean (95% CI)	82.0 (79.0 to 85.1)	78.4 (75.6 to 81.2)	.09	79.3 (75.7 to 82.8)	80.6 (78.1 to 83.1)	.55
Univariate MDI (95% CI)[a]	Reference	−1.1 (−3.3 to 1.0)	.30	Reference	1.2 (−1.0 to 3.4)	.28
Multivariate MDI (95% CI)[ab]	Reference	−0.7 (−2.7 to 0.3)	.51	Reference	1.3 (−0.7 to 3.2)	.20
Raw mental score[c]						
6 mo	64.4 (63.6 to 65.2)	64.4 (63.5 to 65.2)	.93	64.0 (63.1 to 64.9)	64.7 (63.9 to 65.5)	.25
12 mo	85.4 (83.8 to 86.9)	84.7 (83.3 to 86.2)	.55	83.9 (82.2 to 85.6)	86.0 (84.7 to 87.3)	.05
18 mo	104.4 (102.8 to 106.1)	103.1 (101.7 to 104.6)	.25	103.9 (102.1 to 105.7)	103.6 (102.2 to 105.0)	.79
Univariate raw mental score (95% CI)[a]	Reference	0.3 (−1.7 to 2.2)	.77	Reference	1.5 (−0.4 to 3.5)	.13
Multivariate raw mental score (95% CI)[ab]	Reference	−0.2 (−1.2 to 0.7)	.64	Reference	0.7 (−0.3 to 1.6)	.19

[a] Using linear regression models; 95% CI estimates use the empirical variance to reflect that the data are repeated measures within individuals.
[b] Adjusted for age at test, test administrator, prematurity, maternal CD4 at baseline, money spent per day per person for food (SES), and child's HIV-1 status before assessment.
[c] The sample size for raw scores was the same as for index scores at each time point.

TABLE 3 **Mean Scores for the PDI and Raw Motor Scores by Supplementation Groups at 6, 12, and 18 Months of Age and Overall**

Developmental Outcome	No Multivitamins, mean (95% CI)	Multivitamins, mean (95% CI)	*P*	No Vitamin A, mean (95% CI)	Vitamin A, mean (95% CI)	*P*
PDI						
6 mo						
N	137	140		121	156	
Mean (95% CI)	92.8 (90.6 to 94.9)	95.9 (94.0 to 97.7)	.03	93.2 (90.8 to 95.5)	95.2 (93.5 to 97.0)	.17
12 mo						
N	87	109		93	103	
Mean (95% CI)	90.6 (86.8 to 94.5)	95.4 (92.0 to 98.9)	.07	92.0 (88.6 to 95.4)	94.5 (90.6 to 98.3)	.35
18 mo						
N	75	93		72	96	
Mean (95% CI)	88.5 (85.2 to 91.9)	86.2 (83.3 to 89.1)	.29	87.0 (83.0 to 90.9)	87.4 (85.0 to 89.9)	.84
Univariate PDI (95% CI)[a]	—	2.0 (−0.7 to 4.7)	.14	—	1.2 (−1.5 to 4.0)	.38
Multivariate PDI (95% CI)[ab]	—	2.6 (0.1 to 5.1)	.04	—	2.0 (−0.5 to 4.5)	.12
Raw motor score[c]						
6 mo	41.6 (40.6 to 42.6)	41.7 (40.8 to 42.6)	.90	41.1 (40.1 to 42.2)	42.0 (41.2 to 42.9)	.18
12 mo	62.8 (61.5 to 64.1)	64.2 (63.3 to 65.2)	.09	62.8 (61.7 to 64.0)	64.3 (63.2 to 65.3)	.07
18 mo	72.6 (71.6 to 73.5)	72.2 (71.5 to 73.0)	.56	72.4 (71.4 to 73.5)	72.3 (71.7 to 73.0)	.83
Univariate raw motor score (95% CI)[a]	—	1.2 (−0.4 to 2.7)	.13	—	1.0 (−0.6 to 2.6)	.22
Multivariate raw motor score (95% CI)[ab]	—	0.8 (0.02 to 1.6)	.04	—	0.5 (−0.3 to 1.3)	.26

[a] Using linear regression models; 95% CI estimates use the empirical variance to reflect that the data are repeated measures within individuals.
[b] Adjusted for age, test administrator, prematurity, maternal CD4 at baseline and BMI, and child's HIV-1 status and gender.
[c] The sample size for raw scores was the same as for index scores at each time point.

had a significant effect on motor scores, increasing the PDI score by 2.6 points (95% CI: 0.1–5.1) on average over the period of 6 to 18 months compared with the group that received no multivitamin supplements and increasing the raw score by 0.8 items (95% CI: 0.02–1.6). Multivitamin supplementation did not significantly affect mental scores. Vitamin A supplementation was not significantly associated with a change in either mental or psychomotor function.

In line with national guidelines, vitamin A was provided starting at 6 months. At 6 months, vitamin A was found to be significantly associated with a 2.8-point increase (95% CI: 0.4–5.2) in PDI and a 1.1-item increase (95% CI: 0.3–1.9) in raw motor score in multivariate regression analyses (not presented in Table 3) that included the same covariates that were found to be important for these outcomes in the overall analyses. There was no association between vitamin A supplementation and mental scores at 6 months.

Table 4 reports the results of Cox proportional hazards models that were used to investigate the effects of the supplements on time to developmental delay. The results of multivariate analyses indicate that multivitamin supplements were significantly protective against

TABLE 4 **Effect of Supplements on Time to Developmental Delay (<70)**

Factor	No Multivitamins	Multivitamins	No Vitamin A	Vitamin A
MDI <70				
N (%)	23/158 (14.6)	32/169 (18.9)	26/147 (17.7)	29/180 (16.1)
RR (95% CI)[a]	1.0	1.3 (0.8–2.2)	1.0	0.7 (0.4–1.2)
RR (95% CI)[b]	1.0	1.3 (0.7–2.4)	1.0	0.7 (0.4–1.3)
PDI <70				
N (%)	25/158 (15.8)	19/169 (11.2)	22/147 (15.0)	22/180 (12.2)
RR (95% CI)[a]	1.0	0.5 (0.3–1.0)	1.0	0.6 (0.3–1.2)
RR (95% CI)[c]	1.0	0.4 (0.2–0.7)	1.0	0.6 (0.3–1.2)

Using Cox proportional hazards regression models.

[a] Univariate analyses.

[b] Adjusted for prematurity, test administrator, maternal CD4 at baseline and SES, and child's HIV-1 status.

[c] Adjusted for prematurity, test administrator, maternal CD4 and BMI at baseline, child's gender, and child's HIV-1 status.

the risk for developmental delay on the motor scale (relative risk: 0.4; 95% CI: 0.2–0.7; $P = .004$) but not on the mental scale. Vitamin A supplementation was not protective against the risk for developmental delay on either scale.

Maternal ESR group at baseline was an important modifier of the effect of multivitamin supplementation on motor scores in this study. Among children who were born to women with high ESR (≥81 mm/hour), their raw motor scores were 3.4 items (95% CI: 1.5–5.2) higher for children whose mother received multivitamin supplementation compared with those whose mother did not receive multivitamin supplements. The corresponding comparison between the 2 multivitamin supplementation groups among children who were born to mothers with low ESR (<81 mm/hour), raw motor scores differed by 0.3 items (95% CI: −0.7 to 1.2; $P = .004$ for interaction). Considering the PDI, among children who were born to mothers with high ESR, multivitamin supplementation was associated with a 7.1-point (95% CI: 1.1–13.0) increase in score, whereas among children who were born to mothers with low ESR, scores differed by 1.6 points (95% CI: −1.4 to 4.6; $P = .11$ for interaction). ESR group did not modify the effect of multivitamin supplementation on mental scores. Maternal CD4 count at baseline, maternal total lymphocyte count at baseline, duration of multivitamin supplementation, the timing of initiation of supplementation, the child's HIV-1 status, and the child's birth weight were not significant modifiers of the effect of multivitamin supplementation on mental or motor function.

The interaction between the 2 supplements was significant for raw motor scores but not for motor index scores. Among those who did not receive vitamin A supplementation, multivitamin supplements were associated with 2.0-item (95% CI: 0.5–3.4) increase in raw motor score, compared with those who did not receive multivitamin supplements. Meanwhile, among children whose mothers received vitamin A supplementation, multivitamin supplements were associated with a 0.01-item (95% CI: −1.0 to 0.9; $P = .03$ for interaction) decrease in raw motor score compared with those who did not receive multivitamin supplements. For the PDI, $P = .23$ for interaction, although the same trend of a suggested effect of multivitamin supplementation only among those who did not take vitamin A supplementation simultaneously was observed. Vitamin A supplementation did not modify the effect of multivitamin supplementation on mental scores.

Maternal CD4 count at baseline was an important modifier of the effect of vitamin A supplementation on infant mental and psychomotor development. Among children whose mother's CD4 count at baseline was <200 cells/mm^3, vitamin A supplementation was associated with a 10.2-point (95% CI: 4.8–15.5) increase in MDI and a 12.1-point (95% CI: 4.2–20.0) increase in PDI compared with those who did not receive vitamin A supplements. Among children whose mother's CD4 count at baseline was ≥200 cells/mm^3, vitamin A supplementation was associated with a 0.5-point (95% CI: −1.6 to 2.5; $P = .0009$ for interaction) increase in MDI and a 1.0-point (95% CI: −1.6 to 3.6; $P = .009$ for interaction) increase in PDI compared with the group that did not receive vitamin A supplements. The same pattern of effect modification by maternal CD4 count at baseline was observed when the raw mental ($P = .004$ for interaction) and motor scores ($P = .05$ for interaction) were considered. Maternal total lymphocyte count at baseline, multivitamin supplementation, the child's HIV-1 status, the child's birth weight, timing of initiation, and duration of supplementation during pregnancy were not significant modifiers of the effect of vitamin A supplementation on mental or motor function. Considering modifiers of vitamin A supplementation at 6 months, maternal CD4 count was a significant modifier of the effect of vitamin A supplements on motor scores ($P = .009$), with the effect of vitamin A supplements apparent only among children whose mothers had CD4 <200 cells/mm^3 at baseline, as seen in the overall analyses.

DISCUSSION

Maternal multivitamin supplementation (vitamins B, C, and E) was associated with a significant increase in mo-

tor scores. Multivitamin supplementation of HIV-1–infected pregnant women is increasingly practiced in Tanzania and other sub-Saharan African countries because it has been shown that such maternal supplementation delays HIV progression,[13] as well as reduces LBW, severe preterm birth, small for gestational age, and the risk for fetal death.[14] With this program in place, an increase of 2.6 PDI points associated with multivitamin supplementation may not be significant for an individual child but may have important consequences at the population level, particularly if a large segment of the population is exposed. Even a small shift to the right in the distributions of mental and motor function indices has a large effect on the tails of the distributions. An increase of 2.6 points in the average motor index of a population results in a 35% reduction of the number of individuals who have an index score <70 and would require greater educational resources, medical care, and other social supports.[25] This is consistent with our analyses that demonstrated a significant reduction in risk for developmental delay on the motor scale associated with multivitamin supplementation.

The design of this study does not permit the effects of prenatal and postnatal multivitamin supplementation to be distinguished because all of the women received the supplements throughout. Neither is it possible to know which nutrient produced the beneficial effect observed because they all were in the same tablet. B-complex vitamin supplements,[26] as well as riboflavin supplementation specifically,[27,28] have previously been associated with improvements in arm-hand steadiness tests, a measure of fine motor skills. This improvement may be mediated through riboflavin's effect on pyridoxine metabolism. Vitamin C, another component of our multivitamin supplementation, has been shown to improve absorption of dietary iron[29,30] and may help to avoid iron deficiency anemia in children. Such anemia is associated with developmental delays.[31,32]

Psychomotor development improvements may have been through reducing the risks of LBW and being small for gestational age during the prenatal supplement phase. As Table 1 demonstrated, a significantly smaller proportion of children whose mothers received multivitamin supplements had LBW (<2500 g). However, LBW was not a significant effect modifier of the effect of maternal multivitamin supplementation on motor scores in this study. Another potential mechanism during the prenatal supplement phase is through the reduction of mother-to-child transmission of HIV-1, which has been associated with developmental delays, particularly psychomotor delays, as well as neurologic complications and immune dysfunction. However, multivitamin supplements were associated only with mother-to-child transmission in this population among children who were born to women who were immunologically or nutritionally compromised.[24]

In addition, improvements in the mother's immune status[13] may result in less morbidity, more energy, and ability to stimulate her child, resulting in improvements in developmental scores. In a similar way, improvement of child multivitamin status throughout the supplement period, including observed increases in serum vitamins B_{12} and E in these children,[16] may also be associated with reduced morbidity, particularly among initially nutritionally deficient children,[33] and as a result affect their mental and psychomotor development.[34] Both vitamins E and C are antioxidants that are believed to enhance immune responses and phagocytosis. Children who have increased morbidity may lack energy and withdraw from contact with their peers and environment.[35,36] Also, mothers who coddle less mobile infants may further hinder their growth and independence.[35,36] Finally, the mother of a sick child may engage in less responsive communication with the child and thereby deprive him or her of social interaction.[35–37]

The effect of multivitamin supplements on motor scores was variable across subgroups. Children who were born to women with a proxy for advanced disease, ie, high ESR, benefited significantly from multivitamin supplements with respect to psychomotor function. Another marker of maternal advanced disease, CD4 count, was not a significant modifier of the multivitamin supplementation effect, although a trend of an effect primarily in the women with advanced disease, CD4 <200, was observed. These were secondary analyses, as were all analyses of effect modifiers, and could be attributable to chance or the result of small sample sizes. However, the observation that multivitamin supplements are protective for psychomotor development in the subgroup of children who are born to women with advanced disease is consistent with the associations reported for multivitamin supplementation with other outcomes in this same population.[24] These secondary analyses do suggest that additional investigation of these modifiers is needed.

Vitamin A supplementation was associated with beneficial effects on motor scores at 6 months. Vitamin A supplements may improve the child's immune function and reduce oxidative stress. These effects may lead to reduced infections and improved integrity of the epithelial lining of the child's gastrointestinal tract.[38] In turn, absorption of nutrients by the infant may be improved, and the child may be more interactive, able to learn, and achieve higher mental and psychomotor development scores.

Within the original study, every attempt was made to minimize loss to follow-up, through scheduled appointments at the study clinic; reimbursement for transport; free access to physicians, nurses, and counselors; and free medicine for those who could not afford it. Even so, loss to follow-up might be associated with higher morbidity/mortality, thus preferentially excluding children

of lower nutritional and socioeconomic status. The population of children who provided at least 1 BSID-II assessment have previously been compared with the larger population of singletons who were born to HIV-1–infected mothers and were found to be at lower risk for LBW and had a smaller hazard of dying in the first 18 months.[39] At the very least, this loss to follow-up reduces the study's power to detect a significant treatment effect. In particular, this study had low power to consider effect modification. It is possible that other factors considered in this article are indeed effect modifiers but were unable to reach statistical significance in this study.

The BSID-II provides us only with an overall cognitive score (MDI) and motor score (PDI) and does not allow us to investigate the effect of supplementation on components of mental and psychomotor development. The BSID-II test was developed and validated in the United States, and there are no normative data for the BSID-II in Kiswahili-speaking societies; thus, there could be significant cultural biases that at least partly explain the overall decrease in neurodevelopmental scores among children in this study over time. Despite this, the tasks that are required by the test battery for a child up to 2 years of age can be more readily applied globally than later items might be, so the issue of language may be less relevant to this particular study given the age range of the children being assessed. The design of the BSID-II also does not fully capture the significant interactions between child and caregiver that would contribute to the total score. Such data were not collected in this study.

To our knowledge, this is the first study to examine the effect of maternal multivitamin supplementation on infant mental and psychomotor development. This study strengthens the current recommendation to give multivitamin supplements (including vitamins B, C, and E) to HIV-1–infected pregnant women in developing country settings, not only to delay HIV disease progression and to reduce the risk for LBW, prematurity, and small for gestational age but also to support infant psychomotor development. However, it is important to underscore that the multivitamin supplements should not be considered as an alternative to antiretroviral therapy but as a complementary intervention that is part of a comprehensive care package. Individuals who are advanced enough in their disease to warrant antiretroviral therapy as per national guidelines should be provided with antiretroviral drugs.

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