

Vitamin supplementation of HIV-infected women improves postnatal child growth¹⁻³

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ABSTRACT

Background: Linear growth retardation and wasting are common in children born to HIV-infected women. Inexpensive interventions that could improve the postnatal growth pattern of such children are needed.

Objective: The objective was to examine the effect of supplementing HIV-infected women with multivitamins or vitamin A and β -carotene, during and after pregnancy, on the growth of their children during the first 2 y of life.

Design: We conducted a randomized placebo-controlled trial in 886 mother-infant pairs in Tanzania. At the first prenatal visit, HIV-infected women were randomly assigned to 1 of 4 daily oral regimens in a 2×2 factorial fashion: multivitamins (MV: thiamine, riboflavin, vitamin B-6, niacin, vitamin B-12, vitamin C, vitamin E, and folic acid), preformed vitamin A + β -carotene (VA/BC), MV including VA/BC, or placebo. Supplementation continued during the first 2 y postpartum and thereafter. Children were weighed and measured monthly, and all received vitamin A supplements after 6 mo of age per the standard of care.

Results: Multivitamins had a significant positive effect on attained weight (459 g; 95% CI: 35, 882; $P = 0.03$) and on weight-for-age (0.42; 95% CI: 0.07, 0.77; $P = 0.02$) and weight-for-length (0.38; 95% CI: 0.07, 0.68; $P = 0.01$) z scores at 24 mo. VA/BC seemed to reduce the benefits of MV on these outcomes. No significant effects were observed on length, midupper arm circumference, or head circumference.

Conclusion: Supplementation of HIV-infected women with multivitamins (vitamin B complex, vitamin C, and vitamin E) during pregnancy and lactation is an effective intervention for improving ponderal growth in children. *Am J Clin Nutr* 2005;81:880-8.

KEY WORDS Children, HIV infection, multivitamins, vitamin A, growth, length, weight, wasting, underweight, Tanzania

INTRODUCTION

The growth pattern of children born to HIV-infected women is often compromised, particularly in sub-Saharan Africa and other regions of the world where the epidemic is taking the highest toll and where access to antiretroviral medications is limited (1-3). Linear and ponderal growth retardation is especially severe in children who become infected (4-6) and may be evident at birth (7) or as early as 3 mo after birth (2, 3). The mechanisms leading to growth delay are therefore likely to start operating in utero and to continue after birth, possibly in combination with other postnatal insults.

Growth failure, especially in weight, is a strong predictor of mortality among children born to HIV-infected women. Low weight-for-age during the first year of life was associated with a 5-fold increased risk of death by 25 mo in a study from Uganda (5). In Malawi, wasting was one of the major causes of mortality among HIV-infected children (8).

Although the causes of HIV-associated growth retardation are not completely understood, a role for micronutrient deficiencies of the mother or child has been suggested in observational (9, 10) and intervention (11) studies. Among HIV-infected infants aged 6 to 18 mo, vitamin A supplementation resulted in rapid catch-up linear growth (11). We previously reported that supplementation of HIV-infected pregnant women with multivitamins (vitamin B complex, vitamin C, and vitamin E) decreased the risk of intrauterine growth retardation (12). However, the potential role of these or other micronutrients on postnatal growth is unknown.

Inexpensive public health interventions that could reduce the burden and consequences of child growth retardation in the context of HIV infection are urgently needed. We hypothesized that providing vitamin supplements to HIV-infected women during pregnancy and lactation improves the growth pattern of their children during the first 2 y of life. This hypothesis was examined in the context of a randomized clinical trial conducted in Dar es Salaam, Tanzania.

SUBJECTS AND METHODS

Study design and population

We conducted a randomized clinical trial, beginning in April 1995, among pregnant women who attended 4 prenatal care clinics in Dar es Salaam, Tanzania, and who tested positive for

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² Supported by the National Institute of Child Health and Human Development (NICHD R01 32257) and the Fogarty International Center (NIH D43 TW00004).

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Received August 11, 2004.

Accepted for publication November 19, 2004.

HIV. The study was designed to examine the effect of vitamin supplements on pregnancy outcomes, vertical transmission of HIV, and other health and survival endpoints during several years after delivery from the index pregnancy. Detailed descriptions of the trial design were published previously (12, 13). In summary, the women were between 12 and 27 wk of gestational age at enrollment, according to the date of the last menstrual period, and resided in Dar es Salaam. As part of prenatal screening, consent was sought for HIV-1 testing and pre- and posttest counseling were provided. We tested HIV-1 serostatus by enzyme-linked immunosorbent assay (Wellcozyme; Murex Biotech Ltd, Dartford, United Kingdom) and confirmed positive results by Western blot (Bio-Rad Laboratories Ltd, Hertfordshire, United Kingdom). Women who tested positive for HIV-1 and who consented to participate in the trial were randomized in a two-by-two factorial design to 1 of 4 groups to receive, from the time of enrollment and after delivery, a daily oral dose of 1) multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg vitamin B-6, 100 mg niacin, 50 μ g vitamin B-12, 500 ng vitamin C, 30 mg vitamin E, and 0.8 mg folic acid), 2) vitamin A (5000 IU preformed) plus β -carotene (30 mg), 3) multivitamins including vitamin A and β -carotene, or 4) placebo. At delivery, women in groups 2 and 3 received an additional single dose of 200 000 IU vitamin A and those in groups 1 and 4 received placebo. The active treatment and placebo tablets were indistinguishable (Hoffmann-La Roche, Nutley, NJ, and Tishcon Corp, Westbury, NY). Additionally, all women received 120 mg ferrous iron and 5 mg folate daily during pregnancy and malaria prophylaxis weekly in accordance with the standard of prenatal care in Tanzania. After recruitment, the women were invited to attend the antenatal clinic at Muhimbili National Hospital, where all subsequent pre- and postnatal visits, child birth, and study procedures took place.

At the first visit, trained research assistants obtained information on age, education, socioeconomic and marital status, and obstetric history and measured the women's height, weight, and midupper arm circumference (MUAC). Study physicians performed a complete medical examination and collected blood, urine, stool, and vaginal specimens that were later used for laboratory analyses; these included complete blood cell and T lymphocyte subset counts, serum concentrations of vitamins A and E, malaria parasites in peripheral blood, and evidence of intestinal parasitoses or sexually transmitted diseases. Follow-up was conducted monthly at the study clinic. At delivery, a research midwife weighed infants to the nearest 10 g on a standard beam balance, measured length with an infant length board, and measured head circumference with a nonstretchable tape. Information on the risks and benefits of infant feeding options among HIV-infected women was provided according to World Health Organization (WHO) and Tanzanian Ministry of Health guidelines, and the decision of whether to breastfeed was made by the mothers. Virtually all of the women (>99%) chose to breastfeed. Supplementation with the assigned treatment regimens continued after delivery throughout the 2 y considered in the present study.

Growth monitoring was carried out during the monthly follow-up clinic visits scheduled for the mothers and their infants. At each monthly postnatal visit, physical examinations were conducted by a study physician, and trained research nurses measured recumbent length to the nearest 0.1 cm with an infant

length board (locally manufactured according to WHO recommendations) and weight to the nearest 0.1 kg on calibrated balance-beam scales (model 725; Seca, Hamburg, Germany). MUAC and head circumference were measured with a nonstretchable tape to the nearest 0.1 cm with standard techniques (14). Information on the child's breastfeeding status was also obtained monthly. Details on the assessment of HIV status among children were published elsewhere (13, 15). We planned to collect blood samples at birth, 6 wk, and every 3 mo thereafter. HIV infection was defined as a positive result from a polymerase chain reaction test at any age or a positive enzyme-linked immunosorbent assay result, confirmed by a Western blot test, in children aged \geq 18 mo. The time of transmission was estimated as the midpoint between the last negative and the first positive samples. Antiretroviral medications were unavailable in this setting at the time of the study. At 6 mo of age and every 6 mo thereafter, all children received an oral dose of vitamin A (200 000 IU, or 100 000 IU if <1 y of age) as per the standard of pediatric care in Tanzania.

Compliance with the study regimen after 2 y, defined as the number of tablets absent from the returned bottles at monthly visits divided by the total number of tablets the individual should have taken, was 83% on average. The study protocol was approved by the Research and Publications Committee of Muhimbili University College of Health Sciences, the Ethical Committee of the National AIDS Control Program of the Tanzanian Ministry of Health, and the Institutional Review Board of the Harvard School of Public Health.

Data analyses

We examined the effect of vitamin supplements on child growth during the first 2 y of life. Of 1085 women initially randomly assigned, 7 were later found not to be infected with HIV and were excluded from the analyses. Of the 1078 women who were HIV-1 infected, 3 were nonpregnant, 6 died before delivery, and 42 had a date of delivery or outcome of pregnancy that was unknown (**Figure 1**). For the analyses of growth endpoints, we included 886 singletons born alive who had at least one set of anthropometric measurements taken at or after delivery and at \leq 24 mo of age. Baseline characteristics or treatment assignment in this subset did not differ significantly from the original group of randomly assigned women. To further verify the randomization assumption in the group included for growth analyses, we compared the distribution of baseline characteristics across treatment groups using Kruskal-Wallis tests for continuous variables and chi-square tests for proportions. In September 2000, the data safety and monitoring board recommended that the vitamin A plus β -carotene regimen be terminated because of its adverse effects on mother-to-child transmission of HIV. However, all of the anthropometric measurements included in the present analyses had been obtained before this date. Intent-to-treat analyses were carried out to assess treatment effects on both continuous and binary growth endpoints.

Continuous outcomes

Continuous outcomes included weight, length, head circumference, MUAC, and weight-for-age, weight-for-length, and length-for-age z scores, which were calculated from the WHO/National Center for Health Statistics reference (16) with the use of EPIINFO 6.0 software (Centers for Disease Control and Prevention, Atlanta, GA). We estimated average growth curves for



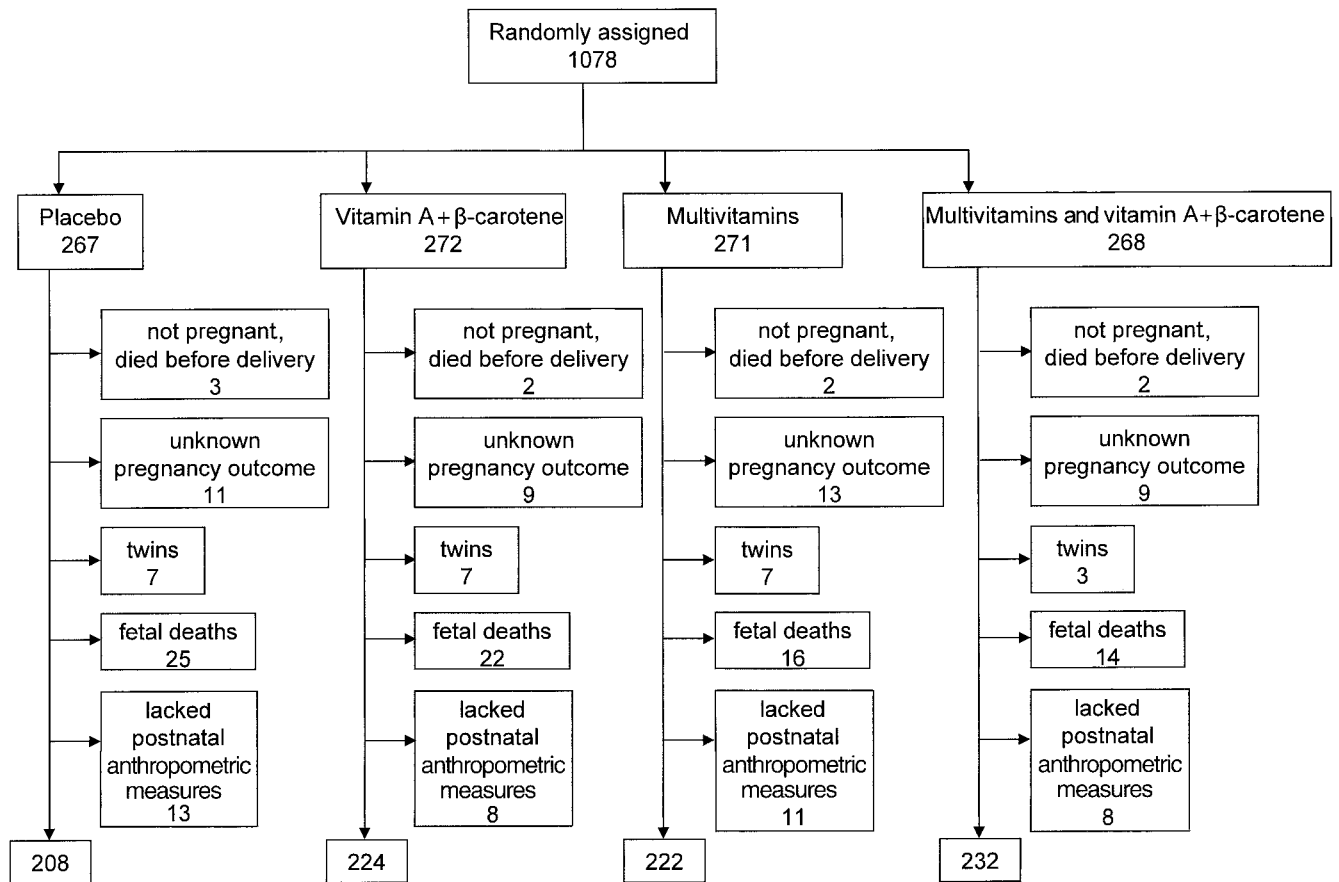


FIGURE 1. Study profile.

each of these outcomes by using mixed-effects models (PROC MIXED; SAS Institute Inc, Cary, NC) with restricted cubic splines (17); knots were placed at ages 1, 2, 3, 6, 9, 12, 15, 18, and 22 mo. The outcome in each model was one of the anthropometric variables, whereas predictors included linear and spline terms for age in months. These mixed models used random effects for the intercept and the linear term for age (slope), which account for the within-person correlation of measurements in the estimation of the variance (18). These methods do not require the same number of observations on each subject or that the measurements be conducted at exactly the same time intervals between or within individuals (18); therefore, all available anthropometric measurements for every child were included in the models.

For each of the 4 treatment arms, we estimated the average attained values of the dependent anthropometric variable at ages 0, 6, 12, 18, and 24 mo from the spline model. Treatment effects at these time points were estimated as the difference in attained growth between each of the 3 active treatment arms and the placebo group, from the interaction terms between the treatment variables and the linear and spline variables for age. CIs around the treatment effects were constructed by using robust estimates of the variance (19).

We examined the interaction between multivitamins and vitamin A plus β -carotene on each continuous growth outcome by assessing the statistical significance of cross-product terms between multivitamins, vitamin A plus β -carotene, and the time (age) splines. For each outcome, a model with these 3-way cross-product terms was compared against a main-effects model with

multivitamins \times time and vitamin A plus β -carotene \times time only, with the use of the likelihood ratio test.

We also used the likelihood ratio test to assess whether treatment effects were modified by the child's HIV status by comparing a main-effects model against one with additional interaction terms between treatment, age splines, and HIV status as a time-varying covariate that was updated at the time of each anthropometric measurement.

Binary outcomes

Wasting, underweight, and stunting were defined as < -2 of the respective weight-for-length, weight-for-age, and length-for-age z scores. We examined treatment effects on the incidence of each of these outcomes during follow-up among children who were free from the outcome at birth. Children who did not develop the outcome were censored at their last clinic visit. Hazard ratios for each of the 3 active treatment arms compared with placebo were obtained from Cox proportional hazards models, with time to first episode as the outcome and age as the time metamer. In supplemental analyses, we assessed modification of treatment effects by baseline characteristics and by the HIV and breastfeeding status of the child as time-varying covariates. We compared Cox models with and without interaction terms between treatment and each of the potential modifiers by using partial likelihood ratio tests. We also formally tested a statistical interaction between multivitamins and vitamin A plus β -carotene by assessing the significance of a cross-product term between the 2 treatment arms.

TABLE 1
Maternal characteristics according to treatment assignment¹

Characteristic	Placebo (n = 208)	Vitamin A + β -carotene alone (n = 224)	Multivitamins (n = 222)	Multivitamins and vitamin A + β -carotene (n = 232)
Gestational age at recruitment (wk)	20.2 \pm 3.6 ²	20.2 \pm 3.5	20.6 \pm 3.1	20.3 \pm 3.2
Age (y)	24.9 \pm 4.8	24.7 \pm 5.0	24.7 \pm 4.7	24.9 \pm 4.5
Completed primary school (%)	85.6 (178)	87.9 (197)	84.7 (188)	90.1 (209)
Lives with partner (%)	90.4 (188)	87.1 (195)	90.5 (201)	87.9 (204)
Nulliparous (%)	30.0 (62)	34.7 (77)	34.2 (76)	30.9 (71)
Height (cm)	156.6 \pm 6.0	156.9 \pm 6.2	156.5 \pm 5.3	156.4 \pm 5.8
Weight (kg)	56.4 \pm 8.6	57.5 \pm 9.8	58.1 \pm 9.4	57.0 \pm 8.4
Midupper arm circumference (cm)	25.4 \pm 2.9	25.7 \pm 3.1	25.9 \pm 2.9	25.6 \pm 2.8
Serum retinol (μ mol/L)	0.92 \pm 0.42	0.86 \pm 0.34	0.84 \pm 0.33	0.86 \pm 0.30
Serum vitamin E (μ mol/L)	9.8 \pm 2.9	9.9 \pm 3.1	9.7 \pm 3.0	10.4 \pm 2.9
Hemoglobin (g/L)	97 \pm 17	95 \pm 18	94 \pm 16	94 \pm 17
CD4 cell count (/mm ³)	451 \pm 268	440 \pm 272	453 \pm 259	428 \pm 235
HIV disease symptomatic (%) ³	23.6 (49)	28.1 (63)	20.7 (46)	24.1 (56)
Infections (%)				
Malaria	16.8 (35)	19.3 (43)	17.7 (39)	22.8 (53)
Ascariis	4.3 (8)	4.7 (9)	5.6 (11)	7.8 (16)
Hookworm	10.8 (20)	7.9 (15)	12.7 (25)	13.7 (28)
Syphilis	5.5 (11)	5.1 (11)	7.1 (15)	4.4 (10)
<i>Trichomonas vaginalis</i>	25.2 (52)	20.3 (45)	25.8 (57)	26.7 (62)

¹ n values in parentheses. There were no significant differences between groups, $P > 0.05$.

² $\bar{x} \pm$ SD (all such values).

³ Symptomatic women were in stages 2 or 3 at recruitment according to the WHO staging system of HIV disease.

RESULTS

Study population

At baseline, maternal characteristics did not differ significantly by treatment arm (Table 1). On average, the women attended their first prenatal care visit at a mean (\pm SD) of 20.3 \pm 3.3 wk (at the age of 24.8 \pm 4.8 y), had completed primary school (90%), did not contribute to the household income (75%), and lived with a partner (89%). One-third (33%) of the population had serum retinol concentrations $<0.70 \mu$ mol/L, and 82% had hemoglobin concentrations <110 g/L at enrollment. A minority of women (24%) were HIV-symptomatic (above stage 1 of the WHO classification) (20) or had CD4 cell counts $<200/\text{mm}^3$ (12%). Forty-nine percent of newborns were female, irrespective of treatment assignment. We previously reported that multivitamin supplements resulted in a significantly greater birth weight and a lower incidence of small-for-gestational-age births (12).

The total duration of follow-up during the first 2 y of life comprising the present study was 13 434 child-months, with a median 21.0 mo per child ($\bar{x} \pm$ SD: 15.2 \pm 9.7 mo). Two hundred eight (24%) children died at or before 24 mo of age. The number of children with measurements at ages 6, 12, 18, and 24 mo (\pm 1 mo) was 525, 495, 476, and 392, respectively. These numbers did not differ significantly by treatment arm at each time point. Breastfeeding was adopted virtually by all mothers ($>99\%$). At age 12 mo, 94% of children were still breastfeeding. The proportion of children breastfeeding decreased during the second year, to 74% at 18 mo and 22% at 24 mo. In this cohort of 886 children, information on HIV status was available for 852; of these children, 29% were HIV-infected during the first 2 y of life. HIV infection was significantly more frequent among children born to mothers who received vitamin A plus β -carotene (33%) than among those who did not receive vitamin A plus β -carotene (25%; $P =$

0.01); this finding was consistent with our previous report (13). Multivitamins were not associated with transmission.

Effect of vitamins on postnatal average growth curves

Compared with women who received placebo, multivitamins resulted in a significantly greater attained child weight; the effect at birth that we reported previously (12) was sustained postnatally and increased during the second year, with a treatment effect at 24 mo that averaged 459 g ($P = 0.03$) (Table 2). This effect was attenuated when mothers also received vitamin A plus β -carotene (215 g; 95% CI: $-229, 659$ g; $P = 0.34$; P for interaction = 0.004). The effect of multivitamins alone on attained weight at 24 mo was stronger for children who became HIV-positive (1332 g; 95% CI: 323, 2340 g; $P = 0.01$; P for interaction < 0.001). We estimated the multivitamin effect on postnatal ponderal growth, independent of the previously reported effect on birth weight (ie, with control for weight differences at birth), by comparing the total weight change from birth to 24 mo between treatment arms. Average total postnatal weight gains (\pm SE) were 7248 \pm 135 and 6983 \pm 170 g in the multivitamins and placebo arms, respectively; the difference (treatment effect) was 265 g (95% CI: $-160, 691$ g; $P = 0.22$).

Children whose mothers received multivitamins had significantly greater weight-for-length and weight-for-age z scores at 24 mo of age than did the placebo group (Table 3). Vitamin A plus β -carotene significantly attenuated the effect of multivitamins on both weight-for-age (P for interaction = 0.03) and weight-for-length (P for interaction = 0.02) z scores. Multivitamin supplements had no effect on length, length-for-age z scores, head circumference, or MUAC growth, and there were no significant interactions between multivitamins and vitamin A plus β -carotene on these outcomes (P for interaction = 0.91, 0.73,

TABLE 2

Effect of vitamin supplementation of HIV-infected women on infant growth in weight, length, head circumference, and arm circumference between 0 and 24 mo of age in Tanzania¹

Endpoint	Placebo (n = 208)	Vitamin A + β -carotene alone (n = 224)		Multivitamins (n = 222)		Multivitamins and vitamin A + β -carotene (n = 232)	
		Value	Difference (95% CI)	Value	Difference (95% CI)	Value	Difference (95% CI)
Weight (g)							
0 mo (birth)	2916 \pm 46 ²	2992 \pm 37	76 (-40, 193)	3109 \pm 34	194 (81, 306)	3019 \pm 40	104 (-16, 223)
6 mo	7014 \pm 97	7107 \pm 79	92 (-153, 338)	7105 \pm 79	90 (-155, 336)	7186 \pm 78	171 (-73, 415)
12 mo	8173 \pm 108	8227 \pm 102	54 (-238, 346)	8364 \pm 87	191 (-81, 463)	8327 \pm 92	155 (-124, 433)
18 mo	9167 \pm 131	9055 \pm 123	-112 (-464, 240)	9335 \pm 109	168 (-165, 501)	9317 \pm 117	150 (-193, 494)
24 mo	9898 \pm 168	9907 \pm 153	9 (-436, 453)	10357 \pm 137	459 (35, 882)	10113 \pm 153	215 (-229, 659)
Length (cm)							
0 mo (birth)	49.0 \pm 0.2	49.0 \pm 0.2	0.02 (-0.55, 0.60)	49.4 \pm 0.2	0.41 (-0.16, 0.98)	49.0 \pm 0.2	0.05 (-0.51, 0.60)
6 mo	64.3 \pm 0.2	64.4 \pm 0.2	0.14 (-0.52, 0.80)	64.6 \pm 0.2	0.28 (-0.36, 0.93)	64.6 \pm 0.2	0.33 (-0.30, 0.96)
12 mo	71.1 \pm 0.3	71.2 \pm 0.2	0.11 (-0.62, 0.84)	71.2 \pm 0.3	0.13 (-0.61, 0.87)	71.2 \pm 0.2	0.10 (-0.61, 0.82)
18 mo	76.4 \pm 0.3	76.5 \pm 0.3	0.08 (-0.77, 0.92)	76.7 \pm 0.3	0.24 (-0.60, 1.07)	76.6 \pm 0.3	0.15 (-0.67, 0.98)
24 mo	80.6 \pm 0.4	80.2 \pm 0.3	-0.40 (-1.40, 0.60)	81.0 \pm 0.3	0.36 (-0.61, 1.34)	80.5 \pm 0.3	-0.12 (-1.13, 0.89)
Head circumference (cm)							
0 mo (birth)	34.3 \pm 0.1	34.5 \pm 0.1	0.20 (-0.11, 0.51)	34.7 \pm 0.1	0.36 (0.08, 0.65)	34.5 \pm 0.1	0.19 (-0.11, 0.48)
6 mo	42.7 \pm 0.1	42.8 \pm 0.1	0.14 (-0.22, 0.49)	42.7 \pm 0.1	0.03 (-0.32, 0.38)	42.9 \pm 0.1	0.25 (-0.11, 0.61)
12 mo	45.1 \pm 0.1	45.2 \pm 0.1	0.09 (-0.25, 0.43)	45.3 \pm 0.1	0.14 (-0.17, 0.45)	45.3 \pm 0.1	0.20 (-0.12, 0.52)
18 mo	46.4 \pm 0.1	46.5 \pm 0.1	0.07 (-0.29, 0.42)	46.4 \pm 0.1	0.03 (-0.31, 0.37)	46.6 \pm 0.1	0.17 (-0.17, 0.50)
24 mo	47.1 \pm 0.1	47.3 \pm 0.2	0.15 (-0.27, 0.57)	47.3 \pm 0.1	0.16 (-0.24, 0.56)	47.2 \pm 0.1	0.11 (-0.28, 0.51)
Midupper arm circumference (cm)							
1 mo	11.7 \pm 0.1	11.6 \pm 0.1	-0.16 (-0.51, 0.20)	12.0 \pm 0.1	0.26 (-0.08, 0.61)	11.8 \pm 0.1	0.10 (-0.25, 0.45)
6 mo	13.7 \pm 0.1	13.8 \pm 0.1	0.05 (-0.25, 0.36)	13.8 \pm 0.1	0.10 (-0.20, 0.41)	13.8 \pm 0.1	0.02 (-0.29, 0.33)
12 mo	13.9 \pm 0.1	14.0 \pm 0.1	0.04 (-0.28, 0.36)	14.1 \pm 0.1	0.22 (-0.07, 0.51)	14.1 \pm 0.1	0.21 (-0.09, 0.51)
18 mo	14.1 \pm 0.1	14.0 \pm 0.1	-0.17 (-0.49, 0.15)	14.1 \pm 0.1	-0.05 (-0.35, 0.25)	14.2 \pm 0.1	0.04 (-0.27, 0.35)
24 mo	14.1 \pm 0.1	14.1 \pm 0.1	-0.03 (-0.41, 0.34)	14.4 \pm 0.1	0.27 (-0.08, 0.62)	14.2 \pm 0.1	0.05 (-0.33, 0.43)

¹ Mean values were estimated from cubic spline models with each anthropometric variable as the outcome and predictors that included treatment, spline variables for age, and interaction terms between treatment and the age spline terms. Differences reflect the treatment effect compared with the placebo group at each time point; 95% CIs for the differences were constructed by using robust estimates of the variance. In a main-effects model that compared children whose mothers received multivitamins or multivitamins and vitamin A + β -carotene with children whose mothers did not receive multivitamins (ie, received placebo or vitamin A + β -carotene alone) the average effect of multivitamins on attained weight at 24 mo of age was 331 g (95% CI: 42, 619 g; $P = 0.03$). However, an interaction between multivitamins and vitamin A + β -carotene on weight was statistically significant (P for interaction = 0.004, likelihood ratio test), whereby which vitamin A + β -carotene decreased the effect of multivitamins on attained weight, as shown in this table. The main effects of vitamin A + β -carotene alone were not significant. Neither multivitamins nor vitamin A + β -carotene alone had significant effects on length, head circumference or midupper arm circumference, and there were no significant interactions between the 2 treatment arms on these outcomes.

² $\bar{x} \pm$ SE (all such values).

0.09, and 0.09, respectively). No effects of vitamin A plus β -carotene alone were noted in any of the continuous outcomes.

Effect of vitamins on postnatal incidence of wasting, underweight, and stunting

Compared with placebo, multivitamins including vitamin A plus β -carotene resulted in a 47% reduction in the risk of wasting among children who were not wasted at birth ($P = 0.01$) and in a 33% decrease in the incidence of underweight ($P = 0.03$) (Table 4). The interactions between multivitamins and vitamin A plus β -carotene on the incidence of wasting or underweight were not statistically significant in a multiplicative scale (P for interaction = 0.36 and 0.14, respectively). None of the treatments had a significant effect on the risk of stunting.

We assessed whether the effects of multivitamins including vitamin A plus β -carotene on postnatal wasting and underweight were modified by time-varying covariates (HIV and breastfeeding) or baseline characteristic, including the mother's CD4 cell

count, stage of HIV disease at the first prenatal visit, the children's sex, and preterm birth status. None of these variables significantly modified the treatment effects.

DISCUSSION

We examined the effects of vitamin supplements provided to HIV-infected women during pregnancy and lactation on the growth pattern of their children during the first 2 y of life. Supplementation with vitamin B complex, vitamin C, and vitamin E resulted in greater weight gain. The treatment effect that we had reported on birth weight (12) was sustained throughout the 2 y and increased after 18 mo of age. Chance or confounding was an unlikely explanation for the results, given the large sample size and the randomized nature of the study.

The specific effect of vitamin B complex, vitamin C, and vitamin E on child growth has not been examined in randomized trials of maternal or child supplementation; nevertheless, a few

TABLE 3

Effect of vitamin supplementation of HIV-infected women on change in infant weight-for-age, weight-for-length, and length-for-age *z* scores between 0 and 24 mo of age in Tanzania¹

Endpoint	Placebo (<i>n</i> = 208)	Vitamin A + β -carotene alone (<i>n</i> = 224)		Multivitamins (<i>n</i> = 222)		Multivitamins and vitamin A + β -carotene (<i>n</i> = 232)	
		Value	Difference (95% CI)	Value	Difference (95% CI)	Value	Difference (95% CI)
Weight-for-age <i>z</i> score							
0 mo (birth)	-0.72 \pm 0.09 ²	-0.55 \pm 0.08	0.17 (-0.06, 0.41)	-0.30 \pm 0.07	0.41 (0.19, 0.64)	-0.49 \pm 0.08	0.22 (-0.02, 0.46)
6 mo	-0.68 \pm 0.10	-0.48 \pm 0.08	0.19 (-0.06, 0.45)	-0.47 \pm 0.08	0.21 (-0.04, 0.47)	-0.45 \pm 0.08	0.23 (-0.03, 0.48)
12 mo	-1.71 \pm 0.11	-1.61 \pm 0.10	0.10 (-0.19, 0.39)	-1.44 \pm 0.09	0.27 (0.00, 0.54)	-1.51 \pm 0.09	0.20 (-0.08, 0.47)
18 mo	-1.80 \pm 0.12	-1.81 \pm 0.11	-0.02 (-0.32, 0.29)	-1.54 \pm 0.09	0.26 (-0.04, 0.55)	-1.59 \pm 0.10	0.21 (-0.09, 0.50)
24 mo	-1.91 \pm 0.15	-1.87 \pm 0.12	0.04 (-0.34, 0.41)	-1.49 \pm 0.10	0.42 (0.07, 0.77)	-1.68 \pm 0.12	0.23 (-0.15, 0.60)
Weight-for-length <i>z</i> score							
0 mo (birth)	-0.88 \pm 0.10	-0.69 \pm 0.10	0.19 (-0.08, 0.46)	-0.58 \pm 0.09	0.30 (0.03, 0.57)	-0.72 \pm 0.09	0.16 (-0.10, 0.42)
6 mo	0.04 \pm 0.09	0.17 \pm 0.07	0.14 (-0.09, 0.37)	0.13 \pm 0.07	0.10 (-0.13, 0.33)	0.21 \pm 0.08	0.18 (-0.06, 0.41)
12 mo	-0.63 \pm 0.10	-0.60 \pm 0.09	0.03 (-0.22, 0.29)	-0.52 \pm 0.07	0.11 (-0.12, 0.34)	-0.48 \pm 0.07	0.15 (-0.09, 0.38)
18 mo	-0.87 \pm 0.10	-1.00 \pm 0.09	-0.13 (-0.39, 0.13)	-0.77 \pm 0.09	0.11 (-0.14, 0.36)	-0.75 \pm 0.08	0.13 (-0.13, 0.38)
24 mo	-0.94 \pm 0.12	-0.83 \pm 0.11	0.11 (-0.21, 0.42)	-0.56 \pm 0.10	0.38 (0.07, 0.68)	-0.69 \pm 0.11	0.25 (-0.06, 0.57)
Length-for-age <i>z</i> score							
0 mo (birth)	-0.52 \pm 0.08	-0.41 \pm 0.08	0.10 (-0.12, 0.33)	-0.27 \pm 0.07	0.25 (0.03, 0.46)	-0.40 \pm 0.07	0.11 (-0.10, 0.33)
6 mo	-1.03 \pm 0.08	-0.92 \pm 0.07	0.11 (-0.09, 0.32)	-0.84 \pm 0.07	0.19 (-0.01, 0.40)	-0.90 \pm 0.07	0.13 (-0.07, 0.33)
12 mo	-1.54 \pm 0.10	-1.43 \pm 0.09	0.10 (-0.16, 0.36)	-1.39 \pm 0.09	0.15 (-0.12, 0.41)	-1.41 \pm 0.09	0.12 (-0.13, 0.38)
18 mo	-1.75 \pm 0.10	-1.70 \pm 0.10	0.05 (-0.23, 0.33)	-1.63 \pm 0.09	0.12 (-0.15, 0.39)	-1.68 \pm 0.09	0.08 (-0.19, 0.35)
24 mo	-1.94 \pm 0.11	-2.04 \pm 0.11	-0.10 (-0.41, 0.22)	-1.80 \pm 0.11	0.14 (-0.17, 0.44)	-1.97 \pm 0.11	-0.03 (-0.34, 0.27)

¹ *z* Scores were calculated from the World Health Organization/National Center for Health Statistics reference (16). Mean values were estimated from cubic spline models with each anthropometric variable as the outcome and predictors that included treatment, spline variables for age, and interaction terms between treatment and the age spline terms. Differences reflect the treatment effect compared with the placebo group at each time point; 95% CIs for the differences were constructed by using robust estimates of the variance. In a main-effects model that compared children whose mothers received multivitamins or multivitamins and vitamin A + β -carotene with children whose mothers did not receive multivitamins (ie, received placebo or vitamin A + β -carotene alone) the average effects of multivitamins on weight-for-age and weight-for-length *z* scores at 24 mo of age were 0.32 (95% CI: 0.07, 0.56; *P* = 0.01) and 0.26 (95% CI: 0.05, 0.48; *P* = 0.01), respectively. However, there were significant interactions between multivitamins and vitamin A + β -carotene on both outcomes (*P* for interaction = 0.03 and 0.02, respectively), whereby which vitamin A + β -carotene seemed to decrease the benefit of multivitamins on weight-for-age and weight-for length. The main effects of vitamin A + β -carotene alone were not significant. Neither multivitamins nor vitamin A + β -carotene alone had significant effects on length-for-age, and there were no significant interactions between the 2 treatment arms on this outcome.

² $\bar{x} \pm$ SE (all such values).

previous studies assessed the effect of different micronutrient combinations that included some or all of the vitamins that we tested plus minerals. Multimicronutrient-fortified beverages administered to Tanzanian children 6–10 y of age resulted in significantly greater weight and height gains after 6 mo (21) and improved weight-for-height *z* scores after 8 wk in children 5–11 y of age from Botswana (22). Among younger children, multimicronutrient supplementation has had varying effects on growth. Whereas a supplement with 13 vitamins and 6 minerals administered to Mexican children <12 mo of age improved linear growth after 1 y (23), no overall effect was found in a study of Vietnamese children who received a supplement with iron, zinc, retinol, and vitamin C (24). It is not possible to compare our results directly with those from previous studies, given that the composition and manner of administration of the micronutrient supplements were different; supplementation in our study started in utero and the actual dose received by children postnatally would have depended on the excretion of nutrients in breast milk and the frequency and efficiency of breastfeeding.

The vitamin status of infants is strongly dependent on that of the infants' mothers before (25, 26) and after (27) delivery. Women with micronutrient deficiencies are more likely to have children who will become deficient themselves. The risk of micronutrient deficiencies during pregnancy is particularly high

among HIV-infected women (28, 29) because of increased losses and utilization, which may further worsen underlying deficits from low dietary intakes. Previous observational studies suggest that HIV-infected persons need higher dietary intakes of vitamins to achieve normal serum concentrations (30); therefore, vitamin supplementation at several times the recommended dietary allowance to pregnant and lactating HIV-infected women is likely to correct potential underlying deficiencies and increase the substrate available for fetal intrauterine growth through placental transfer, and for postnatal growth through increased concentrations of nutrients in breast milk.

In this study, the effect of multivitamins was larger at 24 mo of age than at birth; in addition, multivitamins decreased the risk of wasting and underweight in children free of these outcomes at birth. These findings suggest that the effects of multivitamins on intrauterine growth and postnatal weight gain could be mediated through different pathways and may depend on the duration of the exposure. The effect in utero may be related to improvements in the immunologic and nutritional status of the mother, as reported previously: multivitamins increased maternal CD4 cell counts during pregnancy (12) and decreased the risk of maternal wasting (weight loss) during the third trimester (31). On the other hand, the effect on postnatal growth could be mediated through direct enhancements of specific aspects of the child's immune

TABLE 4

Effect of vitamin supplementation of HIV-infected women on the postnatal incidence of stunting, wasting, and underweight in their infants in Tanzania

Outcome ¹	Placebo	Vitamin A + β -carotene alone	Multivitamins	Multivitamins and vitamin A + β -carotene	HR (95% CI), main effect of multivitamins ²	HR (95%), main effect of vitamin A + β -carotene ³
Wasting					0.77 (0.56, 1.08) ⁴	0.73 (0.52, 1.00) ⁵
No. at risk ⁶	158	183	172	184		
Child months of follow-up	2014	2558	2423	2573		
No. of events	37	40	40	26		
HR (95% CI) ⁷	1.00	0.83 (0.53, 1.29)	0.88 (0.56, 1.37)	0.53 (0.32, 0.88)		
Underweight					0.77 (0.60, 0.98) ⁸	0.89 (0.90, 1.14) ⁴
No. at risk ⁶	170	193	196	198		
Child months of follow-up	2000	2361	2492	2574		
No. of events	58	76	69	53		
HR (95% CI) ⁷	1.00	1.06 (0.75, 1.49)	0.92 (0.65, 1.31)	0.67 (0.46, 0.97)		
Stunting					0.92 (0.73, 1.16) ⁴	0.88 (0.70, 1.11) ⁴
No. at risk ⁶	165	178	177	180		
Child months of follow-up	1742	2123	2053	2191		
No. of events	68	76	76	70		
Hazard ratio (95% CI) ⁷	1.00	0.90 (0.65, 1.25)	0.94 (0.68, 1.31)	0.81 (0.58, 1.13)		

¹ Wasting, underweight, and stunting were defined from weight-for-length, weight-for-age, and length-for-age *z* scores, respectively, as < -2 . The World Health Organization/National Center for Health Statistics reference (16) was used to calculate the *z* scores. HR, hazard ratio.

² Comparison of children whose mothers received multivitamins alone or multivitamins and vitamin A + β -carotene with children whose mothers received vitamin A + β -carotene alone or placebo.

³ Comparison of children whose mothers received vitamin A + β -carotene alone or multivitamins and vitamin A + β -carotene with children whose mothers received multivitamins alone or placebo.

⁴ NS (Wald test).

⁵ $P = 0.06$ (Wald test).

⁶ Only subjects without the outcome at baseline were considered to be at risk.

⁷ From Cox proportional hazards models with time-to-event as the outcome and treatment as the predictor. The reference category was the placebo group.

⁸ $P = 0.03$ (Wald test).

function. We previously found that maternal multivitamin supplementation increased the number of circulating CD4 cells in this group of children (32). Although additional evidence from randomized clinical trials on the immunomodulatory effects of vitamins B, C, and E among children is scarce, studies in adults also suggest that these vitamins can positively influence immunity. Vitamin E supplementation can improve the cutaneous delayed-type hypersensitivity response, an indicator of T cell-dependent macrophage activation (33–35), lymphocyte proliferation, interleukin 2 production (33), and antibody concentrations (34). Vitamin C supplements have been related to increased lymphocyte proliferation in the elderly (36), whereas combined vitamin E and C supplements appeared to decrease the HIV viral load among HIV-infected adults (37).

Improved child immunity through micronutrient supplementation of their mothers could decrease the incidence and severity of infections that adversely affect growth. In the current population, maternal supplementation with multivitamins was associated with a decreased incidence of child diarrhea (32), an important risk factor for impaired weight gain in children < 2 y of age (38–42).

The duration of breastfeeding did not appear to modify the effect of maternal supplementation on child growth, even though it could be expected that children with the longest breastfeeding period would have benefited the most. Breastfeeding was very


common at least during the first 18 mo, and only declined thereafter. It is possible that the biological mechanisms that mediate the effect of vitamins on growth, such as the improvement of immunity discussed above, require a lag time to produce a measurable result on length and weight gains. We have found that multivitamin supplementation decreases the risk of HIV disease progression and mortality in adult women (43); it is conceivable that healthier mothers would be able to provide better child-care, which could reflect on physical growth, independent of whether the child is breastfed or not after 18 mo of age.

Vitamin A plus β -carotene alone had no effect on growth outcomes. The effect of maternal vitamin A supplementation on early growth was studied in one randomized clinical trial conducted among presumably HIV-uninfected women from Indonesia (44). In that study, weekly supplementation with ≈ 16 000 IU vitamin A during pregnancy had no significant effects on length or weight gains at 12 mo of age, which agreed with our findings. Several other studies examined the effect of vitamin A supplementation of children, as recently reviewed by Rivera et al (45). Vitamin A supplements appear to have a growth effect only in children with severe infections (11), who are vitamin A-deficient (46–48), or who are not being breastfed (46, 49). In our study, all children received vitamin A supplements at 6 mo of age and every 6 mo thereafter, as part of the standard of care; this may

have obscured any potential benefit of maternal vitamin A plus β -carotene supplementation on child growth.

To our knowledge, the effect of β -carotene alone on child growth has not been studied in randomized clinical trials. One longitudinal study suggested that low serum concentrations of β -carotene among children infected with HIV were associated with lower attained length and weight at 9 mo (9). Independent of its provitamin A potential, β -carotene alone has strong antioxidant properties and its biological effects appear to be dose-related. Animal studies (50) suggest that the adverse effects of high-dose β -carotene supplementation on outcomes such as lung cancer (51) could be partly the result of a transient increase in the production of oxidative metabolites that destroy retinoic acid. This mechanism could have also obscured a potential benefit of vitamin A on child growth, but it was not possible for us to separate the potential effects of vitamin A or β -carotene in this study because they were administered together.

Our study has some limitations. First, measurement error of anthropometric variables, especially length, could have reduced the statistical power to detect potentially significant treatment effects. Because this was a blinded study, measurement error was probably nondifferential with respect to the interventions and, therefore, would have biased any potential associations toward the null value. Second, although the frequency of intake from the treatment regimen was high, any lack of compliance may also affect the comparisons by biasing the estimates toward the absence of effect. Third, although efforts were made to obtain anthropometric data as scheduled, and follow-up was very high, the random presence of missing values could reduce statistical power.

In conclusion, supplementation of HIV-infected women during pregnancy and lactation with multivitamins at several times the recommended dietary allowance is associated with a greater weight gain in their children during the first 2 y of life. Long-term daily multivitamin supplementation has been recommended to HIV-infected persons because of its protective effects against disease progression (43); the benefits on child growth that we presently report further strengthen the rationale for such recommendation. The effect of vitamins B, C, and E on growth endpoints, when administered directly to HIV-infected or -uninfected children, needs to be considered in future research. The effects among HIV-uninfected pregnant women on growth and child health outcomes also deserve evaluation in clinical trials. 

We thank the women and children who participated in this project; the study investigators, coordinator, physicians, and research assistants; and the laboratory technicians, nurses, midwives, and administrative staff who made the study possible.

WWF, DJH, GM, and EV contributed to the study design. ES, KM, AB, and EV participated in the study implementation and field supervision. RJB and EH participated in the statistical data analyses. EV conducted the data analyses, interpreted the results, and wrote the initial draft of the manuscript. All authors participated in the data interpretation and helped write the final draft. None of the authors had a conflict of interest in relation to this article.

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