Vitamin A Supplements Ameliorate the Adverse Effect of HIV-1, Malaria, and Diarrheal Infections on Child Growth

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ABSTRACT. *Objective.* **Evidence from animal experiments and observational studies in humans suggests that vitamin A plays a fundamental role in physical growth. However, results from vitamin A supplementation trials in children are inconsistent; whereas some did not find an overall effect on growth, others found benefits only among specific groups, including children with low concentrations of serum retinol or short duration of breastfeeding. The apparent lack of an overall effect of vitamin A on growth could be attributed to context-specific distribution of conditions that affect both growth and the response to supplementation, eg, baseline vitamin A status, deficiency of other nutrients (fat, zinc), and the presence of infectious diseases. Human immunodeficiency virus (HIV) infection, malaria, and diarrheal disease adversely affect growth and are associated with increased prevalence of vitamin A deficiency. We hypothesize that vitamin A supplementation could ameliorate the adverse effect of these infections on child growth.**

Methods. **We conducted a randomized, clinical trial among 687 Tanzanian children who were 6 to 60 months of age and admitted to the hospital with pneumonia. Children were assigned to oral doses of 200 000 IU vitamin A (half that dose if <12 months) or placebo on the day of admission, a second dose on the following day, and third and fourth doses at 4 and 8 months after discharge from the hospital, respectively. Anthropometric measurements were obtained at baseline and at monthly visits to the study clinics during 12 months after the initial hospitalization. Surveillance on the incidence and severity of diarrhea and respiratory infections was conducted during biweekly visits, alternately at a study clinic and the child's home, using a pictorial diary that the mothers were trained to use. A blood specimen was drawn at baseline for determination of HIV status, malaria infection, and hemoglobin levels. We used mixed effects models to compare estimated total weight and height increases after 1 year of follow-up between treatment arms, overall and within levels of HIV status, malaria, and other possible baseline effect modifiers. We also assessed the potential modulating effect of vitamin A on the risk of stunting (height-for-age <−2 standard deviations of the gender-specific National Center for Health Statistics median reference) attributable to diarrheal and respiratory infections during follow-up, in the subset of children who were not stunted at baseline. A similar approach was followed for wasting (weight-for-height <−2 standard deviations of the reference median). Cox regression models were used to estimate relative risks and 95% confidence intervals (CI), treating episodes of infection as time-dependent covariates.**

Results. **A total of 554 children had at least 2 follow-up measurements of height or weight and constituted the study base. Baseline characteristics did not differ significantly by treatment arm. Seventy-three percent of the children were <2 years of age, and 37% were <12 months; 31% were stunted at baseline and 9% were wasted. Malaria (*Plasmodium falciparum*) and HIV infection were found in 24% and 9% of the children, respectively. Median duration of follow-up was 351 days, with 10 measurements/child, on average, irrespectively of treatment assignment. Supplementation with vitamin A among children who had HIV infection and were <18 months of age resulted in a significant length increase. Four months after the first dose, infants who were HIV positive in the vitamin A arm had gained, on average, 2.8 cm (95% CI: 1.0–4.6) more than children who received placebo, whereas no effect was observed among infants who were HIV negative (difference at 4 months: −0.2 cm; 95% CI: −0.8–0.5). Children who were <12 months of age and had malaria at enrollment experienced a 747-g (95% CI: 71–1423) higher yearly weight gain attributable to vitamin A; among children without malaria, however, the supplements did not have a significant effect (−57 g; 95% CI: −461–348). These results remained unchanged after controlling for indicators of the socioeconomic and nutritional status at baseline. Linear growth was also improved by vitamin A among children from households with poor water supply (0.8 cm/year; 95% CI: 0–1.5) but not in children with tap water in the house or compound (−1.0 cm/year; 95% CI: −1.9–0). Weight gain was greater among children with mid-upper arm circumference below the 25th percentile of the age-specific distribution at baseline (458 g/year; 95% CI: 1–905), but no benefit was evident among children with higher mid-upper arm circumference. The risk of stunting associated with episodes of persistent diarrhea (lasting 14 or more days) during follow-up was virtually eliminated by vitamin A supplements. Among children in the placebo group, the average risk of stunting associated with 1 or more episodes of persistent diarrhea between 2 consecutive visits was 5.2 times higher (95% CI: 2.4–11.2) than that of children without diarrhea or with acute episodes. In contrast, among children who received vitamin A, there was virtually no risk of stunting associated with persistent diarrhea (relative risk: 1.0; 95% CI: 0.3–1.3). This effect was**

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slightly attenuated after controlling for the number of household possessions, gender, baseline low arm circumference, HIV infection, and presence of malaria parasites in blood. Vitamin A supplements did not modify the associations between respiratory infections and the risk of stunting or wasting.

Conclusions. **Vitamin A supplementation improves linear and ponderal growth in infants who are infected with HIV and malaria, respectively, and decreases the risk of stunting associated with persistent diarrhea. Supplementation could constitute a low-cost, effective intervention to decrease the burden of growth retardation in settings where infectious diseases are highly prevalent.** *Pediatrics* **2002;109(1). URL: http://www.pediatrics.org/cgi/content/full/109/1/e6;** ***vitamin A, growth, HIV infection, malaria, diarrhea, Tanzania.***

ABBREVIATIONS. HIV, human immunodeficiency virus; MUAC, mid-upper arm circumference; CI, confidence interval; RR, relative risk.

Growth retardation and vitamin A deficiency among infants and preschool children are still major public health problems in developing countries.[1] Evidence from animal experiments[2] and observational studies in humans[3–5] indicates an association between vitamin A status and linear and ponderal growth. However, a causal relationship has not been clearly demonstrated in randomized, masked clinical trials conducted among preschool children during the past decade.[6–10] Recent data suggest that the apparent lack of effect of vitamin A on growth could be attributed to context-specific distribution of conditions that affect both growth and the response to supplementation,[11] eg, vitamin A deficiency, breastfeeding practices, and infections. Positive effects of vitamin A on growth have been found in children with low serum retinol levels[11,12] and among nonbreastfed infants,[10,11] but the effect of supplements on growth among children who have infectious diseases is primarily unknown.

In sub-Saharan Africa, human immunodeficiency virus (HIV)-1 infection, malaria, diarrhea, and respiratory infections are highly prevalent, and their interaction with poor nutritional status accounts for a large proportion of deaths in children and infants.[1] The protective role of vitamin A supplements against morbidity and mortality from infectious diseases including measles, diarrhea, and possibly HIV[13,14] suggests that supplementation could also ameliorate the adverse consequences of such conditions on infant growth.

We examined the effect of vitamin A supplements on growth, and the interactions among vitamin A, infections, and other potential effect modifiers in the context of a double-blind, randomized, clinical trial conducted among children who were 6 to 60 months of age.

METHODS

Study Population and Randomization Process

The Tanzania Vitamin A Study was a randomized, double-blind, placebo-controlled trial conducted between April 1993 and March 1997 in Dar es Salaam among 687 children who were 6 to 60 months of age and admitted to the hospital with pneumonia. The study was designed to test the effect of supplements on the severity of pneumonia during hospital stay and to examine the efficacy of vitamin A on morbidity, mortality, and growth endpoints after discharge. The trial design and characteristics of the study population have been described previously.[15–17] Briefly, children from consenting mothers were enrolled if pneumonia was diagnosed on the basis of clinical criteria. Ineligibility criteria included having eye signs and symptoms of vitamin A deficiency; weight-for-age <60% of the reference median; presence of measles, pulmonary tuberculosis, diphtheria, or whooping cough; and intake of vitamin A supplements in the preceding 4 months. Study personnel asked caregivers about the child's immunization history and feeding practices and obtained sociodemographic information including parental age, literacy, level of education, occupation, quality of housing and water supply, and number and type of household possessions. Anthropometric measurements were obtained by trained personnel using standardized procedures.[18] We measured height and recumbent length (if <24 months) to the nearest 0.1 cm using stadiometers or infant length boards. Weight was measured on calibrated beam balance scales to the nearest 0.1 kg. Mid-upper arm circumference (MUAC) was measured with a nonstretchable tape to the nearest 0.1 cm.

Children were randomized to receive 200 000 IU of vitamin A (60 mg of retinol as retinyl palmitate) or placebo on the day of admission, a second dose on the following day, and third and fourth doses at 4 and 8 months after discharge from the hospital, respectively. Half the dose was given to children <12 months. Vitamin A in corn oil and placebo (only corn oil) were administered by a single research supervisor using droppers from identical opaque bottles labeled with batch numbers. Both solutions contained a small amount of vitamin E (0.24 mg/mL) to increase the stability of the product over time. Assays of the vitamin A solution yielded 95% potency after 2 years of field storage. Compliance with the first 2 doses was virtually 100%, because they were administered in the hospital to all children. The 2 remaining doses were given at a study clinic at 4 and 8 months of follow-up. Seventy-five percent of the children received the third dose, and 74% were given the fourth dose.

Follow-Up Procedures

Anthropometric measurements were obtained at monthly visits to the study clinics during 12 months after the initial hospitalization. Morbidity surveillance was conducted during biweekly visits, alternately at a study clinic and the child's home. At each visit, mothers were asked about the occurrence of signs of diarrhea and respiratory infections on each day during the previous 2 weeks, aided by a pictorial diary that they were trained to use during the child's initial hospitalization and subsequent visits to the clinic. The child's respiratory rate was measured at each visit with a stopwatch. Outpatient visits or admissions to the hospital for 24 hours or longer were also recorded. Diarrhea was defined according to the mother's perception of the number and characteristics of motions. An episode was considered finished when at least 3 days had elapsed without diarrhea. Acute diarrhea included all episodes that lasted <14 days; episodes that lasted 14 days or more were categorized as persistent diarrhea. Dysentery included all episodes with mucus or blood, and all others were defined as watery diarrhea. Respiratory infection was defined as the occurrence of cough and fever or the occurrence of cough alone during the period and rapid respiratory rate on the biweekly visit day.

Laboratory Procedures

A blood specimen was drawn from all children at baseline and from a subsample at 4 and 8 months, concurrent with the administration of the third and fourth doses. Hemoglobin, packed cell volume, and red cell counts were determined by standard techniques.[19] Malaria infection was assessed by thick and thin blood smear. The latest blood specimen available for each child was tested for HIV antibodies using enzyme-linked immunosorbent assay (Murex Biotech Ltd, Dartford, United Kingdom) and confirmed by Western blot (Biorad Laboratories, Ltd, Hertfordshire, United Kingdom). HIV status of children who were younger than 15 months and had positive or indeterminate results was also tested using heat-denatured HIV-p24 antigen assays with confirmatory neutralization assays (DuPont, Wilmington, DE).[20]

Data Analyses

We conducted intent-to-treat analyses of the effect of vitamin A supplementation on both continuous and categorical growth outcomes among children with at least 2 anthropometric measurements after 14 days of discharge from the hospital.

Continuous Outcomes

Increments in height and weight from baseline to 12 months of follow-up constituted the primary endpoints. These were estimated from the interaction term between treatment and time since enrollment, from mixed effects regression models for repeated measurements (Proc Mixed; SAS Institute, Inc, Cary, NC) in which height or weight were dependent variables. Random effects were introduced for the intercept and slope of every individual's set of measurements. In this study population, height followed a linear trend over time in children ≥12 months. A quadratic term for time was highly significant and required to account for nonlinearity in models of length among children 6 to 11 months of age at enrollment and in weight models independent of baseline age. Robust estimates of the variance[21] were used to compute 95% confidence intervals (CI) for treatment effects. The impact of vitamin A supplementation on height and weight increments was also ascertained by comparing the median difference between the last and baseline measurements across treatment arms using the Wilcoxon rank-sum test. Because results were similar, we present only those from the modeling approach, which allows us to make use of all available measurements for each child. We examined the effect of supplements within levels of potential effect modifiers at baseline, including gender, age (6–11 months, 12–23 months, and 24+ months), maternal literacy, quality of water supply, length of exclusive breastfeeding (≤3 months or 4–6 months), HIV infection, malaria parasites in peripheral blood, severe anemia (hemoglobin <70 g/L), MUAC (above or below the 25th percentile of the age-specific distribution in the study population), and season at randomization. The likelihood ratio test was used to ascertain the significance of supplement effects within strata of baseline covariates. Cubic splines[22] were fitted to describe nonlinear effects of the supplements by levels of modifiers.

Categorical Outcomes

Categorical outcomes were stunting and wasting. Gender-specific height or length-for-age and weight-for-height *z* scores were computed from the Centers for Disease Control and Prevention/World Health Organization growth reference data.[23] Children with a height-for-age *z* score below −2 were considered stunted; those with weight-for-height *z* score below −2 were categorized as wasted. Among children who were free from stunting or wasting at baseline, we used Cox proportional hazards models[24] to estimate the hazard ratios for vitamin A supplements in relation to age to the first episode during follow-up, overall, and by levels of potential modifiers, stratified by age at randomization. Independent predictors included treatment, potential modifiers, and indicator variables for the interaction between treatment and potential modifiers. The number of episodes of diarrhea or respiratory infections between visits, and the season at the beginning of the period between visits were introduced as time-dependent covariates. The significance of the interactions between vitamin A supplementation and baseline or time-dependent covariates was tested with the likelihood ratio test. Multivariate models were fitted to adjust for maternal literacy, number of household possessions, malaria and HIV infections, and low MUAC at baseline. Data analyses were conducted with the Statistical Analyses System (SAS Institute).

The protocol was approved by the Research and Publications Committee of Muhimbili University College of Health Sciences, the Research and Ethics Committee of Tanzania Food and Nutrition Center, and the Human Subjects Committee of the Harvard School of Public Health.

RESULTS

Of 687 children randomized, 37 died in the hospital or within 14 days after discharge from the clinic (22 in the vitamin A and 15 in the placebo arms, respectively; $P = .26$) and were excluded from growth analyses. Follow-up anthropometric data were unavailable in children whose caregivers discharged them from the hospital and could not be traced ($n = 18$), moved out of the study area ($n = 25$), or moved within the city to an unknown address ($n = 33$). A total of 554 children had at least 2 follow-up measurements of height or weight and constituted the study base. The median duration of follow-up and median number of measurements per child were virtually identical in the 2 treatment arms: 351 days and 10 measurements/child, respectively.

The distribution of baseline characteristics did not differ significantly by regimen (Table 1). Seventy-three percent of the children were <2 years of age, and 37% were <12 months. The prevalence of stunting and wasting at baseline was 30.7% and 8.6%, respectively. Malaria infection was documented in 115 children (24%); virtually all cases were infection with *Plasmodium falciparum*. Forty-seven children (9%) had HIV infection.

Overall Effect of Supplements

Vitamin A supplements did not have an overall significant effect on height or weight increase after 1 year of follow-up, estimated from a mixed effects model (Table 2). Similar results were obtained by comparing the median difference between the last and first measurements across treatment arms. These results remained unchanged after controlling for baseline malaria and HIV infections, severe anemia, low arm circumference, quality of water supply, number of household possessions, and season at randomization.

Among the 372 children who were not stunted at baseline, vitamin A supplementation was associated with a borderline significant 23% (95% CI: −4%–44%; $P = .09$) reduction in the risk of stunting during the year after randomization. A similar effect was observed after controlling for age, HIV status, malaria, arm circumference, and household number of possessions. Among the 491 children who were not wasted at baseline, the unadjusted and adjusted effects of vitamin A on the risk of wasting during follow-up were similar and not significant (unadjusted relative risk[RR]: 0.88; 95% CI: 0.52–1.50).

Effect of Supplements on Height and Weight Within Levels of Potential Effect Modifiers

Vitamin A had a positive effect on linear growth in children from households of low socioeconomic status, as indicated by inadequate water supply and maternal illiteracy. Among children with poor water supply, the supplements were associated with an extra increase in height of 0.8 cm (95% CI: 0–1.5) after 12 months, whereas among children with tap water in the house or compound, supplementation was related to lower gain in height (−1.0 cm; 95% CI: −1.9–0; $P = .005$, test for interaction). Children with illiterate mothers experienced an average 1.3 cm (95% CI: −0.2–2.8) greater increase in height associated with vitamin A supplementation, whereas no effect was observed in children with literate mothers (−0.3 cm; 95% CI: −0.9–0.4; $P = .06$, test for interaction).

Supplementation with vitamin A to children with

TABLE 1. Characteristics of the Study Population at Baseline in Vitamin A and Placebo Arms*

Characteristic	Placebo	Vitamin A
Number randomized (%)	276 (49.8)	278 (50.2)
Girls (*n* [%])	126 (45.8)	126 (45.5)
Age (mo; mean [range])	18.5 (4.5–61.1)	18.9 (5.3–61.1)
Child's anthropometry		
Height (cm; mean [SD])	75.8 (9.5)	76.1 (8.5)
Weight (cm; mean [SD])	9.3 (2.4)	9.4 (2.2)
MUAC (cm; mean [SD])	14.2 (1.4)	14.3 (1.3)
Stunted† (*n* [%])	76 (28.7)	89 (32.7)
Wasted‡ (*n* [%])	25 (9.4)	21 (7.7)
Underweight§ (*n* [%])	76 (27.6)	79 (28.4)
Duration of exclusive breast feeding (*n* [%])		
3 mo or less	154 (73.3)	143 (65.9)
4 to 6 mo	56 (26.7)	74 (34.1)
Hemoglobin (g/L; mean [SD])	86 (22)	86 (23)
Malaria‖ (*n* [%])	54 (23.2)	61 (25.0)
HIV positive (*n* [%])	23 (8.9)	24 (9.1)
Mean mother's age (y; mean [SD])	26.2 (5.2)	25.6 (5.2)
Mother is literate¶ (*n* [%])	235 (85.5)	250 (89.9)
Mother's occupation (*n* [%])		
Housewife	202 (73.5)	199 (71.6)
Petty trader	54 (19.6)	57 (20.5)
Employed	12 (4.4)	11 (4.0)
Professional	7 (2.6)	11 (4.0)
Mother lives with partner (*n* [%])	230 (83.6)	222 (79.9)
Mother's parity (*n* [%])		
No previous births	75 (27.3)	87 (31.5)
1 or 2	120 (43.6)	118 (42.8)
3 or 4	54 (19.6)	48 (17.4)
5 or more	26 (9.5)	23 (8.3)
Household possessions# (*n* [%])		
None	37 (13.5)	36 (13.0)
1	173 (62.9)	172 (61.9)
2 or more	65 (23.6)	70 (25.2)
Water supply (*n* [%])		
Tap in house	49 (17.8)	45 (16.2)
Tap in compound	78 (28.4)	84 (30.2)
Tap outside compound	129 (46.9)	137 (49.3)
Public well	19 (6.9)	12 (4.3)
Season at recruitment (*n* [%])		
January–February (dry)	57 (20.7)	55 (19.8)
March–May (long rains)	84 (30.4)	86 (30.9)
June–October (dry)	104 (37.7)	108 (38.9)
November–December (short rains)	31 (11.2)	29 (10.4)

* Sums may not add up to the total because of missing values.
† Below 2 SD of the height-for-age NCHS/WHO reference.
‡ Below 2 SD of the weight-for-height NCHS/WHO reference.
§ Below 2 SD of the weight-for-age NCHS/WHO reference.
‖ Malaria is defined as the presence of parasites in peripheral blood.
¶ Literacy is defined as the ability to read a sentence during the baseline interview.
# From a list of 5 items including car, bike, refrigerator, radio, and television.

HIV infection resulted in a significant increase in height. This effect was particularly large among children between 6 and 18 months of age at baseline (P = .003, test for interaction; Fig 1). Four months after the first dose, infants who were HIV-positive in the vitamin A arm had gained, on average, 2.8 cm (95% CI: 1.0–4.6) more than children who received placebo. This difference remained constant thereafter. Among infants who were HIV-negative, the supplements had virtually no effect (difference at 4 months: −0.2 cm; 95% CI: −0.8–0.5). Similar results were obtained after adjusting for the number of household possessions and baseline age, stunting, and anemia.

Vitamin A supplements increased weight gain in children with baseline arm circumference below the 25th percentile of the age-specific distribution (P = .02, test for interaction). The average difference in weight gain after 1 year of follow-up between the vitamin A and placebo arms was 458 g (95% CI: 1–905). The supplements did not have a significant effect in children with arm circumference at or above the 25th percentile (difference: −146 g; 95% CI: −347–54).

A positive effect of the supplements on weight gain was also documented among children with malaria, particularly in those <1 year of age (P = .05, test for interaction; Fig 2). Infants who had malaria (<12 months) and received vitamin A experienced a 747 g (95% CI: 71–1423) greater average increase in weight after 1 year, as compared with those in the placebo arm. In contrast, among infants without malaria, the effect was not significant (−57 g; 95% CI: −461–348).

Effect of Supplements on the Risk of Stunting and Wasting Within Levels of Potential Effect Modifiers

Supplementation was associated with a 36% (95% CI: 3%–58%) reduction in the risk of stunting among children with poor water supply, whereas no effect was observed among children with water in the house or compound (RR: 1.00; 95% CI: 0.63–1.61; P = .16, test for interaction; Table 3). A borderline significant interaction on the risk of stunting was also found between vitamin A supplements and the duration of exclusive breastfeeding (P = .08, test for interaction). Supplementation was associated with a 50% (95% CI: 2%–74%) risk reduction among children who were exclusively breastfed for 4 to 6 months, but no effect was found in children with duration of exclusive breastfeeding <4 months (RR: 0.99; 95% CI: 0.67–1.46). These findings remained unchanged when controlling for age, malaria and HIV infections, number of household possessions, and low arm circumference.

Vitamin A reduced the risk of wasting in children who had malaria (RR: 0.28; 95% CI: 0.07–1.02; P = .04, test for interaction) and among those with low arm circumference at enrollment (RR: 0.55; 95% CI: 0.27–1.10; P = .06, test for interaction). A not significant, protective effect was also suggested among the small group of children who were infected with HIV. The association between the supplements and stunting or wasting was not modified by the child's gender, age, baseline hemoglobin, maternal literacy, season at randomization, or season at the occurrence of the outcome.

Vitamin A supplements seemed to modulate the association between episodes of persistent diarrhea during follow-up and subsequent risk of stunting (P = .015, test for interaction; Table 4). Among children in the placebo group, the average risk of stunting associated with 1 or more episodes of persistent diarrhea between 2 consecutive visits was 5.23 times

TABLE 2. Effect of Vitamin A Supplements on Height and Weight Gains at 12 Months of Follow-Up

Outcome	*n*	Placebo	Vitamin A	Difference (95% CI)	*P* Value
Height gain (cm)* (mean [SE])					
Overall	554	7.8 (0.22)	7.8 (0.21)	0.0 (−0.6, 0.6)	.89
Age group at baseline					
6–11 mo	231	8.4 (0.33)	8.5 (0.36)	0.2 (−0.8, 1.1)	.75
12–23 mo	184	7.6 (0.40)	7.2 (0.37)	−0.4 (−1.4, 0.7)	.53
24–60 mo	139	7.0 (0.38)	7.5 (0.33)	0.5 (−0.5, 1.5)	.34
Weight gain (kg)* (mean [SE])					
Overall	554	2.24 (0.07)	2.27 (0.07)	0.03 (−0.16, 0.23)	.75
Age group at baseline					
6–11 mo	231	2.25 (0.11)	2.35 (0.13)	0.10 (−0.23, 0.44)	.55
12–23 mo	184	2.28 (0.14)	2.23 (0.09)	−0.04 (−0.38, 0.29)	.78
24–60 mo	139	2.14 (0.12)	2.20 (0.13)	0.06 (−0.29, 0.40)	.75

Outcome	*n*	Placebo	Vitamin A	Hazard Ratio (95% CI)	*P* Value
Risk of stunting† (number of events/total at risk)					
Unadjusted		92/189	75/183	0.77 (0.56, 1.04)	.09
Adjusted				0.78 (0.57, 1.06)	.11
Risk of wasting† (number of events/total at risk)					
Unadjusted		29/240	27/251	0.88 (0.52, 1.50)	.65
Adjusted				0.89 (0.52, 1.51)	.66

* From individual mixed effects regression models for repeated measurements in which height or weight is the dependent variable and the predictors include time since enrollment, treatment, and their interaction term.
† From individual Cox proportional hazard models: outcome variable is "time to first episode" (after hospitalization), and time metameter is age. Stunting is defined as a <-2 *z* score of height (length)-for-age; wasting is defined as <-2 *z* score of weight-for-height. Predictors in the adjusted model for stunting included treatment regimen (vitamin A or placebo), HIV status (positive or negative), baseline malaria infection (present or absent), arm circumference (above or below the 25th percentile of age-specific distribution), and number of possessions in the household (2 indicator variables for 3 categories: none, 1, 2 or more). Adjusted model for wasting included HIV status, arm circumference, and number of possessions in the household. Only children who did not have the outcome at baseline were included in the analyses.

higher (95% CI: 2.44–11.2) than that of children without diarrhea or with acute episodes. In contrast, among children who received vitamin A, there was virtually no risk of stunting associated with persistent diarrhea (RR: 1.04; 95% CI: 0.33–1.32). The effect of vitamin A on the association between persistent diarrhea and stunting was slightly attenuated after controlling for the number of household possessions, gender, baseline low arm circumference, HIV infection, and presence of malaria parasites in blood.

In univariate analysis, the risk of wasting associated with the occurrence of 1 or more episodes of dysentery between visits was also lower in children who received vitamin A ($P = .08$, test for interaction). In the placebo arm, dysentery was associated with nearly 3-fold (95% CI: 1.38–6.12) greater risk of wasting, but no excess risk was observed among children who received the supplements (RR: 1.04; 95% CI: 0.42–2.59). This interaction was not significant after adjusting for potential confounding variables.

The supplements did not modify the associations between respiratory infections and the risk of stunting or wasting.

DISCUSSION

In this randomized, clinical trial among children who were admitted to the hospital with pneumonia, we found that the periodic administration of vitamin A improves the growth pattern of those who have infectious diseases that are highly prevalent in developing countries. A large positive effect on linear growth was evident among infants with HIV infection, whereas weight gain was favored among children with malaria infection at baseline. The risk of stunting associated with persistent diarrhea was strongly attenuated by vitamin A supplements. Children of low socioeconomic status were also likely to benefit from supplementation, as were those with low MUAC at enrollment. These results are not likely to be attributable to confounding, given the randomized study design.

Both child growth and the response to vitamin A supplementation depend on several conditions that vary in prevalence across geographic settings. Inconsistencies in overall estimates of the effect of vitamin A on growth from previous supplementation trials may be attributable to differences in these context-specific modifiers, including the baseline vitamin A status, intake of nutrients (eg, fat, zinc) that affect the bioavailability of supplements, and the burden of infectious diseases.[25] In some trials, the efficacy of vitamin A supplements on growth has been examined by levels of selected modifiers. In Indonesia, a supplementation study similar to the one we implemented resulted in significant height increases at 4-month intervals among nonbreastfed children and children who were older than 2 years of age, and improved both height and weight in children with serum retinol <0.35 μmol/L.[11] Short-term increases in weight, attributable to a single dose of 200 000 IU of vitamin A, were documented in a trial from India among children who were enrolled during the summer season, when subclinical vitamin A deficiency was more likely to be present.[12] In Tanzania, com-

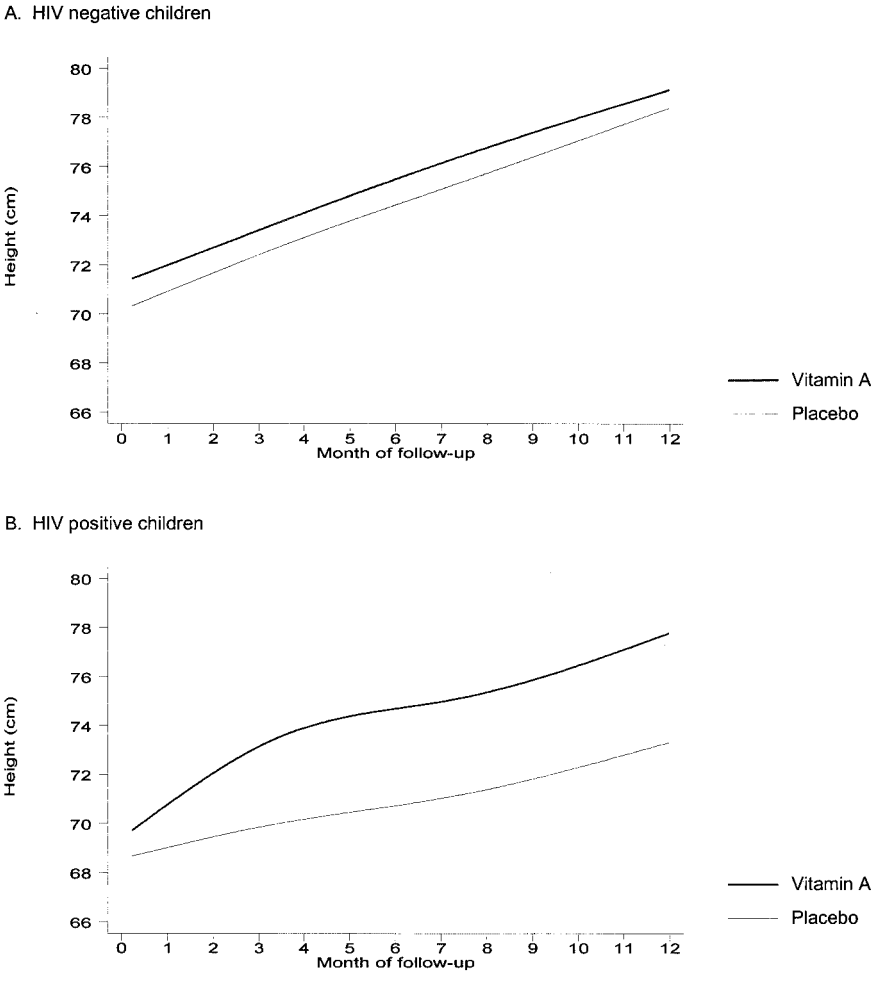

Fig 1. Effect of vitamin A supplementation on length during 1 year of follow-up among children 6 to 18 months of age at recruitment, according to HIV status. A, Children who were HIV negative (vitamin A, $n = 159$; placebo, $n = 154$). B, Children who were HIV positive (vitamin A, $n = 13$; placebo, $n = 17$). Mixed effects models with restricted cubic splines were used to fit the average growth curves. The mean difference in attained height between the vitamin A and placebo arms was 2.8 cm (95% CI: 1.0–4.6) at 4 months of follow-up among children who were HIV positive. No effect was observed among children who were HIV negative. $P = .003$, test for interaction.

bined supplementation with both vitamin A (5000 IU/day) and iron (200 mg of ferrous sulfate/day) 3 days a week over a 3-month period resulted in significantly higher weight and height increases in comparison to supplementation with only iron or only vitamin A, suggesting that vitamin A may improve growth among iron-deficient children.[26] In a study from the Sudan, a significantly greater increase in height after 18 months of enrollment was reported among nonbreastfed children who received vitamin A as compared with those who received placebo, but the magnitude of the effect was small and unlikely to be clinically relevant.[10] Among nonxerophthalmic children from Nepal, the administration of 200 000 IU of vitamin A every 4 months was related to a marginally significant 0.13-cm greater increase in height after 12 months of enrollment, but only in children with arm circumferences >13.5 cm.[27] Finally, in a study from Indonesia, a positive effect of vitamin A on growth was attenuated by respiratory infections but not by diarrhea.[28] None of the previous studies examined the effect of vitamin A supplements on growth among children who had other infectious conditions, such as malaria and HIV, that are highly prevalent in many developing countries.

We found that vitamin A supplementation in children with HIV-1 infection was associated with a large increase in height during the 4 months after randomization, particularly in infants <18 months of age. The growth pattern of children who are HIV positive is often compromised. Among perinatally infected infants, progressive "proportional" stunting seems to be the most frequently observed growth alteration. In studies of Ugandan[29] and Rwandan[30] children followed from birth to 2 and 4 years, respectively, infants with HIV infection exhibited significantly lower height-for-age and weight-for-age curves than their uninfected peers. Multiple factors are likely to be responsible for HIV-related growth alterations. Specific micronutrient deficiencies with the potential to impair growth, including that of vitamin A, have been identified in the course of HIV infection; however, data are inconsistent.[31] Additional mechanisms include infections of the gastrointestinal tract and malabsorption of macronutrients, decreased dietary intake, and neuroendocrine alterations.[32] The large increase in height attributable to vitamin A supplements in our study (2.8 cm increase in 4 months) may indicate that vitamin A could be a limiting factor for growth in children with HIV infection. The correction of subclinical deficiency with the first dose could have triggered short-term catch-up growth, with stabilization of growth velocity after 4 months. Indirect mechanisms that may mediate the beneficial effects of vitamin A on growth during HIV infection include improved humoral[33]

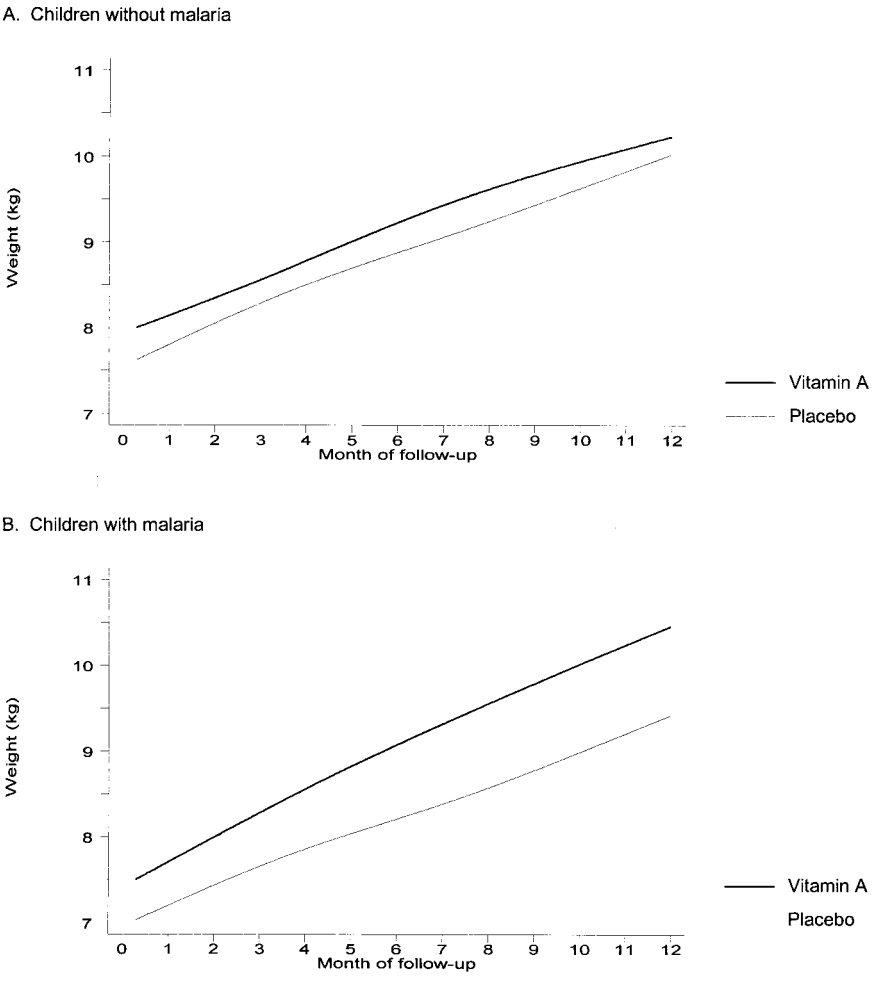

Fig 2. Effect of vitamin A supplementation on weight during 1 year of follow-up among infants <12 months of age with and without malaria at recruitment. A, Children without malaria (vitamin A, $n = 72$; placebo, $n = 83$). B, Children with malaria (vitamin A, $n = 20$; placebo, $n = 24$). The mean difference in weight gain between the vitamin A and placebo arms was 747 g (95% CI: 71–1423) at 12 months of follow-up among infants with malaria at baseline. No significant effect was observed among infants without malaria. $P = .05$, test for interaction.

TABLE 3. Effect of Vitamin A Supplementation on the Risk of Stunting and Wasting by Levels of Potential Baseline Effect Modifiers

	Stunting				Wasting			
	Number of Events/ Total at Risk		Hazard Ratio* (95% CI)	*P* for Interaction†	Number of Events/ Total at Risk		Hazard Ratio* (95% CI)	*P* for Interaction†
	Placebo	Vitamin A			Placebo	Vitamin A		
Water supply				0.16				0.74
Tap in house or compound	32/81	40/89	1.00 (0.63, 1.61)		10/110	11/115	1.00 (0.42, 2.36)	
Outside compound or well	59/107	35/94	0.64 (0.42, 0.97)		19/129	16/136	0.83 (0.43, 1.62)	
Exclusive breastfeeding				0.08				0.85
≤3 mo	53/109	51/100	0.99 (0.67, 1.46)		19/133	20/128	1.08 (0.58, 2.04)	
4–6 mo	20/36	15/49	0.50 (0.26, 0.98)		6/48	7/65	0.96 (0.32, 2.85)	
Malaria				0.53				0.04
No	56/124	46/119	0.76 (0.51, 1.12)		18/149	23/169	1.14 (0.62, 2.12)	
Yes	21/35	24/39	0.95 (0.52, 1.74)		9/48	3/51	0.28 (0.07, 1.02)	
HIV infection				0.55				0.14
No	76/164	67/162	0.83 (0.59, 1.15)		20/207	22/217	1.02 (0.56, 1.87)	
Yes	11/16	6/13	0.60 (0.21, 1.67)		7/19	2/22	0.31 (0.06, 1.52)	
Arm circumference				0.77				0.06
≥ 25th percentile	65/146	51/138	0.77 (0.53, 1.11)		9/181	14/188	1.52 (0.66, 3.51)	
<25th percentile	27/42	24/45	0.70 (0.40, 1.21)		20/59	13/63	0.55 (0.27, 1.10)	

* From individual Cox proportional hazard models: outcome variable is "time to first episode" (after hospitalization), and time metameter is age. Stunted or wasted children at baseline were excluded from the analyses.
† *P* value, test for interaction (likelihood ratio test).

and cellular[34] immunity and enhanced physical integrity and mucosal secretion of immunoglobulins in the gastrointestinal epithelium,[35] which may in turn decrease the incidence and severity of diarrheal infection. Treatment with antiretrovirals and protease inhibitors has been shown to ameliorate the burden of HIV infection on growth.[36–38] In countries where these therapies do not yet constitute the standard of care, vitamin A supplementation could be a useful public health and clinical intervention.

TABLE 4. Risk of Stunting or Wasting Associated With 1 or More Episodes of Infection by Treatment Arm

Infection	Stunting			Wasting		
	Placebo (Hazard Ratio* [95% CI])	Vitamin A (Hazard Ratio* [95% CI])	*P* for Interaction†	Placebo (Hazard Ratio* [95% CI])	Vitamin A (Hazard Ratio* [95% CI])	*P* for Interaction†
Acute diarrhea						
Unadjusted	0.74 (0.47, 1.18)	0.80 (0.49, 1.32)	.83	1.86 (0.88, 3.90)	1.27 (0.58, 2.76)	.48
Adjusted	0.68 (0.43, 1.08)	0.83 (0.50, 1.37)	.57	1.55 (0.72, 3.32)	1.19 (0.55, 2.60)	.63
Persistent diarrhea						
Unadjusted	5.23 (2.44, 11.2)	1.04 (0.33, 1.32)	.02	4.59 (1.36, 15.5)	1.13 (0.15, 8.38)	.21
Adjusted	3.71 (1.65, 8.35)	1.03 (0.32, 3.36)	.07	1.89 (0.52, 6.86)	1.18 (0.16, 8.93)	.69
Watery diarrhea						
Unadjusted	0.87 (0.52, 1.47)	0.83 (0.46, 1.50)	.91	1.43 (0.63, 3.28)	1.26 (0.53, 3.00)	.83
Adjusted	0.83 (0.49, 1.40)	0.86 (0.48, 1.54)	.93	1.22 (0.50, 2.94)	1.13 (0.47, 2.70)	.91
Dysentery						
Unadjusted	1.13 (0.70, 1.84)	0.81 (0.45, 1.48)	.40	2.91 (1.38, 6.12)	1.04 (0.42, 2.59)	.08
Adjusted	0.95 (0.58, 1.56)	0.84 (0.46, 1.55)	.78	2.06 (0.96, 4.42)	1.06 (0.42, 2.69)	.27
Cough with rapid respiration						
Unadjusted	0.67 (0.34, 1.34)	0.85 (0.44, 1.67)	.63	1.60 (0.65, 3.97)	0.98 (0.34, 2.85)	.49
Adjusted	0.72 (0.36, 1.45)	0.87 (0.44, 1.73)	.70	1.11 (0.43, 2.90)	0.95 (0.33, 2.78)	.84
Cough with fever						
Unadjusted	1.02 (0.64, 1.62)	0.75 (0.43, 1.31)	.41	1.80 (0.84, 3.83)	1.00 (0.42, 2.38)	.32
Adjusted	0.83 (0.58, 1.18)	0.78 (0.45, 1.37)	.43	1.54 (0.70, 3.38)	1.04 (0.43, 2.48)	.51

* From individual Cox proportional hazard models: outcome variable is "time to first episode" (after hospitalization), and time metameter is age. Independent predictors are the number of episodes of infection (none, 1 or more) at each between-visit interval. The event was evaluated at the end of each between-visits time interval. Adjusted models also included as predictors the number of household possessions (2 indicator variables for 3 categories: none, 1, 2, or more), child's gender, HIV status, malaria infection, and low arm circumference at baseline.

† From the likelihood ratio test comparing the main effects model (episodes of infection and regimen) to the model with interaction terms between episodes of infection and treatment.

We also report that vitamin A supplements substantially increased weight gain among infants <1 year with malaria. Protein-energy malnutrition has been associated with greater malaria morbidity and mortality,[39] and supplementation with vitamin A is related to fewer malarial attacks.[40] In our study population, vitamin A supplements had a protective effect against malaria-related deaths.[17] An improvement in the anthropometric status could be on the causal pathway of this effect. Short-term linear growth is negatively related to the concentration of acute phase proteins in children with malaria, particularly α(1)-acid glycoprotein, and C-reactive protein,[41] and these, in turn, are negatively correlated with serum retinol in the course of malaria infection.[42] In vivo studies suggest that vitamin A downregulates these and other inflammatory responses[43]; this may constitute an explanatory mechanism for the improvement in weight gain during malaria infection and the protective role of supplements against wasting in children with *P falciparum* infection. Retinol has also been found to inhibit parasite growth directly in studies in vitro.[44] All children whose malaria was diagnosed at baseline were given treatment according to the standard of care in Tanzania; however, there is evidence of widespread resistance of *P falciparum* to chloroquine in Tanzania.[45,46] In vitro experiments show that retinol and quinine act synergistically in improving indices of parasite clearance[47]; thus, vitamin A could constitute a low-cost, effective adjuvant of pharmacological treatment against adverse outcomes associated with malaria infection in infants.

In children without severe growth impairment at enrollment, we found that vitamin A significantly decreased the risk of stunting associated with persistent diarrhea, and the risk of wasting related to dysentery, independent of baseline malaria infection, HIV status, and socioeconomic indicators. Children with persistent diarrhea have been found to have markedly lower levels of serum retinol[48,49] and retinol-binding protein[48] than children with acute or no diarrhea. Similarly, secondary severe infections are more likely to occur when persistent diarrhea is accompanied by vitamin A deficiency.[48] Episodes of diarrhea that last 14 days or more seem to have the greatest adverse effect on growth, as compared with other forms of diarrhea.[50] Therefore, a positive effect of vitamin A supplementation on growth is more likely to occur in children with more severe forms of diarrhea, as we have noted. Poor access to water supply and maternal illiteracy are conditions associated with limited hygienic practices and increased incidence of infections.[51] The positive effect of supplements on growth among poorer children could actually represent the observed higher efficacy in the course of more frequent and severe episodes of infection.

Vitamin A supplements boosted the protective effect of prolonged exclusive breastfeeding against the risk of stunting. Mothers in this population are likely to be affected by some degree of vitamin A deficiency, thus having low breast milk concentrations of retinol. Supplementation to postpartum women has been demonstrated to increase significantly the concentration of vitamin A in breast milk as well as serum retinol and vitamin A stores in breastfed children.[52] The benefits of exclusive breastfeeding from 4 to 6 months in regions of the world with high prevalence of vitamin A and other micronutrient deficiencies may be enhanced by micronutrient supplementation to both mother and child.

This study has some limitations. Approximately 75% of the children received the third and fourth doses. Nondifferential lack of compliance with respect to treatment and outcomes could have biased the results toward the null association. Measurement error in height and weight, although minimized by training and standardization of procedures, could have also introduced random variation and slightly reduced the statistical power to detect treatment effects. Some children were lost to follow-up during the first year after enrollment. However, the baseline characteristics of children who were included in the analyses of growth were homogeneously distributed across treatment regimens, suggesting minimal selection bias. Our study base comprises children who were admitted to the hospital with pneumonia. It is possible that children with pneumonia were more likely to experience subclinical vitamin A deficiency, and therefore they could have been more responsive to supplementation than children without a severe infection. Future studies should include an assessment of the baseline vitamin A status of the study population. Finally, we had limited power to detect the effect of supplements on the incidence of wasting.

CONCLUSION

Vitamin A supplementation every 4 months to children <5 years of age is likely to improve the pattern of growth in populations with high incidence of infectious diseases including HIV, malaria, persistent diarrhea, and dysentery. It can constitute a low-cost, efficacious intervention to decrease the burden of linear growth retardation during HIV infection in settings where antiviral therapies are not yet readily available.

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