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Effect of periodic vitamin A supplementation on mortality and morbidity of human immunodeficiency virus–infected children in Uganda: a controlled clinical trial

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Abstract

Objective: We investigated whether vitamin A supplementation would decrease mortality and morbidity rates in children infected with the human immunodeficiency virus (HIV).

Methods: We conducted a randomized, double-blind, placebo-controlled clinical trial at Mulago Hospital, a large hospital that serves the urban and semiurban populations of Kampala, Uganda. One hundred eighty-one HIV-infected children were enrolled at 6 mo and randomized to receive vitamin A supplementation, 60 mg retinol equivalent, or placebo every 3 mo from ages 15 to 36 mo. Morbidity was assessed through a 7-d morbidity history every 3 mo, and vital events were measured. Children received daily trimethoprim-sulfamethoxazole prophylactic therapy.

Results: After age 15 mo, children were followed for a median of 17.8 mo (interquartile range = 11.1 to 21.0 mo). The trial was stopped when there was a new policy to implement a program of mass supplementation of vitamin A in the country. Mortality rates among 87 children in the vitamin A group and 94 children in the control group were 20.6% and 32.9%, respectively, yielding a relative risk of 0.54 (95% confidence interval, 0.30 to 0.98; $P = 0.044$) after adjusting for baseline weight-for-height Z score. Children who received vitamin A had lower modified point prevalences of persistent cough (odds ratio, 0.47; 95% confidence interval, 0.23 to 0.96; $P = 0.038$) and chronic diarrhea (odds ratio, 0.48; 95% confidence interval, 0.19 to 1.18; $P = 0.11$) and a shorter duration of ear discharge ($P = 0.03$). Vitamin A supplementation had no significant effect on modified point prevalences of fever, ear discharge, bloody stools, or hospitalizations.

Conclusions: Vitamin A supplementation decreases mortality rate in HIV-infected children and should be considered in the care for these children in developing countries.

Keywords: Children; Human immunodeficiency virus; Morbidity; Mortality; Retinol; Vitamin A deficiency

Introduction

About 700,000 infants are infected with human immunodeficiency virus (HIV) each year through transmission from mother to child, and most of these infants are found in sub-Saharan Africa [1,2]. Currently it is estimated that there are 2.5 million children living with HIV worldwide [2]. In developing countries, vitamin A deficiency may be common in areas with a high prevalence of HIV infection [3]. Vitamin A is essential for normal immune function [4], and vitamin A deficiency has been associated with increased progression to acquired immunodeficiency syndrome and increased mortality rates in HIV infection [3]. Since the

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1920s, vitamin A was known as the "anti-infective" vitamin, and vitamin A supplementation was recognized for its ability to decrease morbidity and mortality rates from some infectious diseases [5]. Recent trials have shown that vitamin A supplementation decreases morbidity and mortality rates from diarrheal disease [6] and decreases morbidity from malaria [7] among preschool children. Vitamin A supplementation has been shown to decrease the mortality rate from acute, complicated measles among infants and young children by about 50% to 75% [6]. Appropriate, low-cost interventions are needed that will improve the health and survival of HIV-infected children in developing countries, and it is unclear whether vitamin A supplementation, an inexpensive therapy, could decrease the mortality rate of HIV-infected children. We hypothesized that large-dose vitamin A supplementation every 3 mo would increase survival rates in HIV-infected children. To address this hypothesis, we conducted a randomized, double-blind, controlled clinical trial in Kampala, Uganda.

Materials and methods

The study population consisted of 181 15-mo-old HIV-infected children seen at Mulago Hospital in Kampala, Uganda. The population served by Mulago Hospital is primarily from the urban and semiurban regions of Kampala (population 1.2 million). Clinical vitamin A deficiency, as manifested by night blindness, Bitot's spots, corneal xerosis, or more severe ocular findings, is relatively uncommon in Kampala. There have been no cases of clinical vitamin A deficiency among infants and children reported in the past decade among the hundreds of child visits in the maternal and child health study clinic by pediatricians who are familiar with the signs and symptoms of clinical vitamin A deficiency. The typical diet of preschool children in the Kampala area includes dried fish, eggs, beans, *matoke*, cooked plantain, groundnuts, greens, cassava, yams, sweet potatoes, maize meal, and tomatoes. To our knowledge, there have been no published reports in peer-reviewed journals on the seasonality of vitamin A deficiency in the Kampala region.

Between January 1995 and June 1998, after written informed consent was obtained during an antenatal visit at Mulago Hospital, women were offered counseling and education concerning acquired immunodeficiency syndrome before and after testing for HIV. Infants of HIV-positive women were tested for HIV-1 infection by using a p24 antigen assay (Coulter Diagnostics, Hialeah, FL, USA) until June 1996, after which time infants were tested for HIV-1 by using a qualitative assay for HIV-1 DNA polymerase chain reaction (PCR; HIV-1 Amplicor, Roche Diagnostics, Indianapolis, IN, USA) or a quantitative assay for HIV-1 RNA PCR (Roche Amplicor Monitor, Roche Diagnostics, Branchburg, NJ, USA) with an additional set of primers (SK151-145) to allow detection of all HIV-1 subtypes. Changes in the diagnostic assay were made because of the improvements in diagnostic testing of HIV for infants that were occurring during that period. All results were confirmed by serologic testing at ages 15 to 18 mo and by quantitative HIV-1 RNA PCR at age 15 mo (Roche Amplicor Monitor). Infants received standard titer Schwarz measles vaccine at ages 6 and 12 mo. As per guidelines of the Ministry of Health of Uganda, all infants received large-dose vitamin A (30 and 60 mg of retinol equivalent at ages 6 and 12 mo, respectively) at the same time as the measles immunization.

The study was a randomized, double-blind, placebo-controlled trial that assessed the benefits of giving large-dose vitamin A supplements every 3 mo to HIV-infected children between ages 15 and 36 mo. The primary outcome was mortality rate, and the secondary outcome was infectious disease morbidity as assessed by a standardized morbidity history. Analyses were based on intent to treat. Interim analyses were conducted three times after commencement of the trial for a data and safety monitoring committee, with agreement to stop the study if interim analyses showed risks or benefits of vitamin A supplementation compared with placebo.

Children were eligible for the trial if they 1) were infected with HIV, 2) had no evidence of clinical vitamin A deficiency, i.e., Bitot's spots, night blindness, corneal xerosis, corneal ulceration, or keratomalacia, 3) were resident within 15 km of Mulago Hospital and not planning to move from the area, and 4) had written informed consent given by parent or guardian before 6 mo of age. Children were enrolled at age 6 mo and randomized to receive vitamin A or placebo from ages 15 to 36 mo. The intended duration of treatment was 21 mo. After enrollment in the trial, mothers and children were allowed to enroll in one additional study, the "migration study," that consisted of a structured interview regarding underlying reasons for local mobility, i.e., change in residence in the Kampala area. A measles epidemic began in the study population during the commencement of the trial. To provide better measles vaccine coverage for infants, there was a change in clinical practice to a two-vaccine measles immunization schedule, and all infants received measles vaccine with high-dose vitamin A at ages 6 and 12 mo.

The original sample size and power calculations were based on a placebo-controlled intervention from ages 6 to 36 mo; however, with the administration of vitamin A to all infants at ages 6 and 12 mo concurrent with measles vaccine, children received vitamin A or placebo capsules from ages 15 to 36 mo. The original sample of 300 children provided 80% power to detect a 30% decrease in mortality rate with a two-sided test ($\alpha = 0.05$) and a background mortality rate of 50% between ages 15 and 36 mo. The revised sample of 181 children produced about 80% power to detect a 50% decrease in mortality rate with a two-sided test ($\alpha = 0.05$) and a background mortality rate of 34% between ages 15 and 36 mo. Previous clinical trials of

vitamin A as targeted therapy showed decreases in mortality rate of 50% to 75% for measles [6] and 63% for HIV infection [8].

The statistician in Baltimore generated an allocation schedule, with individuals as the unit of randomization, from computer-generated, randomly permutated codes. Children were given a unique study identification number, and the number was assigned to the next sequentially numbered pill card that contained vitamin A or placebo capsules. The pill cards were identical in appearance and were labeled only by study identification number. Supplements and placebos were provided by Task Force Sight and Life (Basel, Switzerland) and consisted of vitamin A, 60 mg of retinol equivalent, in 200 μL of peanut oil with 10 μg of vitamin E as a preservative, or identical capsules containing peanut oil with only 10 μg vitamin E. Pediatricians and clinic staff were blinded to treatment allocation until termination of the trial. Capsules were directly administered every 3 mo by a trained pediatric nurse or by the study pediatrician. The nipple of the capsule was cut with clean scissors, and the contents of the capsules were directly administered into the mouth of the child. The dose and schedule of large-dose vitamin A supplementation for this trial were based on guidelines from the World Health Organization, United Nations Children's Fund, and the International Vitamin A Consultative Group for the use of vitamin A supplements in this age group [9]. Children received trimethoprim-sulfamethoxazole as prophylactic therapy against *Pneumocystis carinii* pneumonia from ages 6 to 36 mo in a daily dose of 5 mg/kg. No infants received antiretroviral medications during the trial, and other micronutrient preparations were not used in the trial.

Children were seen every 3 mo in an outpatient clinic for a medical history and physical examination by study pediatricians, and a standardized morbidity history [10,11] was obtained by the study pediatrician or study nurse. The mother was asked about a history of fever, cough, rapid breathing, loose watery stools, bloody stools, and ear discharge within the previous 7 d and about any hospitalizations in the previous 30 d. If the child had any of these signs or symptoms, the mother was asked about the duration of the episode in days. A child's length and weight were measured according to standard anthropometric techniques by trained study nurses [12]. Pediatricians examined children at each visit for ocular signs of vitamin A deficiency because clinical vitamin A deficiency (night blindness, Bitot's spots, corneal xerosis, or ulceration) was an exclusion criterion for entry into the trial and a criterion for withdrawal from the trial. Screening for intestinal parasites was not done on a routine basis in this study. Vital events were determined by follow-up with the mother, father, or guardian, and a death report was completed by the health visitors of the study that included questions about signs and symptoms and other information regarding circumstances of death.

At age 15 mo, a blood sample was obtained by venipuncture. Hemoglobin concentrations were measured by an automated T540 hematology analyzer (Coulter Diagnostics). Blood samples were centrifuged, and plasma was immediately aliquoted and stored at −70°C until subsequent laboratory analyses. Plasma HIV load at age 15 mo was measured with quantitative HIV-1 RNA PCR (Roche Amplicor Monitor 1.5) with a sensitivity limit of approximately 400 HIV RNA copies per milliliter. Plasma retinol concentrations were determined by high-performance liquid chromatography [13], and within-assay and between-assay coefficients of variation were 3% and 12%, respectively. Quality control was assessed by repeat analysis of standard reference material (SRMb, National Institute of Standards and Technology, Gaithersburg, MD, USA). The study protocol was conducted in accordance with the Helsinki Declaration and was approved by the Joint Committee on Clinical Investigation at Johns Hopkins University and the Uganda National Council for Science and Technology through its Subcommittee on Acquired Immunodeficiency Syndrome, with final approval by the Office for Protection from Research Risk of the National Institutes of Health (Bethesda, MD, USA).

Growth standards from the National Center for Health Statistics were used as reference [14]. Comparisons between continuous variables were made with Student's *t* test. Appropriate variable transformations were made for skewed data, such as $\log_{10}$ transformation for plasma HIV load. Comparisons of categorical data were made with chi-square or exact tests. Multiple morbidity events per infant were expressed as prevalence per child-month. These were calculated by taking the total number of episodes of a given outcome and dividing that number by the child-months of observation and then adjusting for extra-Poisson variability in log-link regression analysis [15,16]. Comparison of morbidity rates between treatment groups was conducted by generating odds ratios and standard errors using repeated measures regression models that used generalized estimating equations (PROC GENMOD, SAS, Cary, NC, USA). Comparisons between treatment groups were calculated by performing individual contrast analyses. Differences in mortality rate between treatment groups were analyzed with Cox's proportional hazards models after adjusting for baseline weight-for-height *Z* score. Kaplan-Meier analysis was used to compare survival rates between groups. SAS 8.1 was used for all analyses.

Results

From January 1995 to June 1998, 23,439 pregnant women were screened for HIV-1 antibody at Mulago Hospital, and 3751 (16%) were found to be positive for HIV. At ages 3 to 5 mo, 1677 infants were screened for HIV infection. Three hundred infants considered to be infected with HIV were enrolled at age 6 mo, but 29 infants who were originally diagnosed as having HIV on the basis of the p24

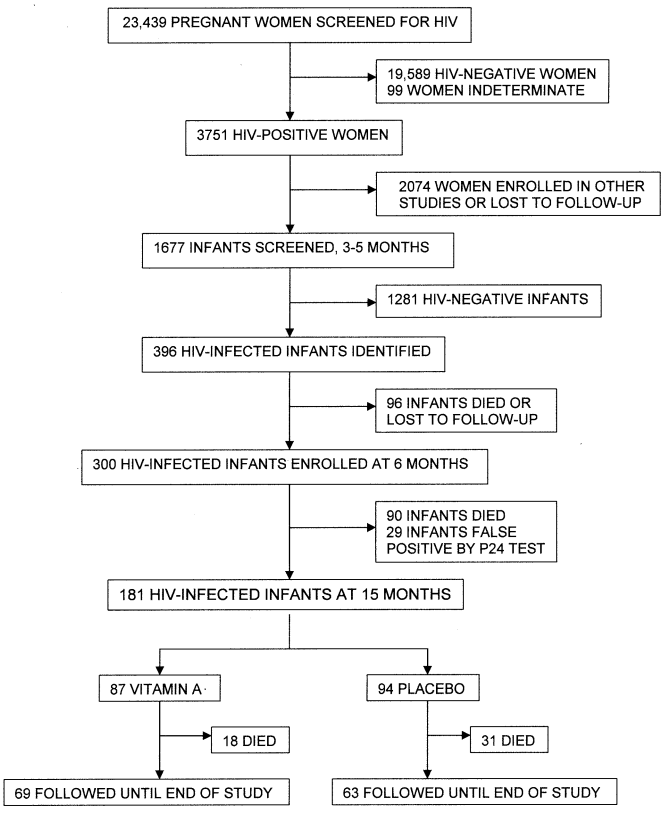

Fig. 1. Clinical trial profile. HIV, human immunodeficiency virus.

antigen assay were found to be negative by the HIV-1 RNA PCR assay. Thus, 271 HIV-infected infants were enrolled and followed from age 6 mo every 3 mo until age 15 mo. Ninety infants died or were lost to follow-up before commencement of the treatment period at age 15 mo. The clinical trial profile is shown in Figure 1. Between ages 6 and 15 mo, 90 infants died. One hundred eighty-one 15-mo-old children were randomized to treatment in the trial, and characteristics of the two treatment groups are presented in Table 1. No children developed any signs of clinical vitamin A deficiency during the study. Forty and 36 children in the vitamin A and placebo groups, respectively, completed the study protocol period to 36 mo. There were no significant differences in sex, anthropometry, hemoglobin [17], $CD4^+$ lymphocyte count, plasma HIV load, or plasma vitamin A concentrations between treatment groups, except for a difference suggesting that children in the placebo group had lower weight-for-height *Z* scores and that a larger proportion of children in the placebo group had diarrhea longer than 7 d.

At the time the study commenced, there was no general vitamin A capsule distribution program in Uganda for preschool children, but there were guidelines for administration of vitamin A capsules with measles immunizations and for children with measles. The clinical trial was stopped February 1, 2001 after the Ugandan Ministry of Health changed their guidelines to recommend that all preschool children in the country should receive high-dose vitamin A supplementation, 60 mg of retinol equivalent, every 6 mo. The date of censoring for the trial was February 1, 2001. After the policy change, children in the trial received high-dose vitamin A supplementation according to the new ministry guidelines. The median follow-up after age 15 mo for children in the trial was 17.8 mo (range = 0.1 to 21 mo; interquartile range = 11.1 to 21.0 mo). Exclusive of mortality rate, there were no losses to follow-up or later refusals to participate in either treatment group from age 15 mo until termination of the study. During follow-up, 18 children in the vitamin A group (20.6%) died and 31 in the placebo group (32.9%) died. Of the 18 deaths in the vitamin A group, eight occurred in the hospital, seven occurred at home, one occurred in the village, and two occurred in another location. Of the 31 deaths in the placebo group, 16 occurred at the hospital, 14 occurred at home, and one occurred in another location. The major reported causes of death among children in the vitamin A group were diarrheal disease ($n = 8$), pneumonia ($n = 4$), tuberculosis ($n = 4$), failure to thrive ($n = 1$), and severe anemia ($n = 1$). The

Table 1
Baseline characteristics of children at 15 mo of age*

Characteristic	Vitamin A ($n = 87$)	Placebo ($n = 94$)
Maternal age (y)	25.6 ± 3.9	25.9 ± 4.7
Maternal education (%)†		
No formal schooling	1.4	1.3
Primary school	56.9	67.9
Secondary school	37.5	28.2
Post-secondary school	4.2	2.6
Breastfeeding terminated (%)‡	29.0	30.7
Female (%)	47.1	53.1
Weight-for-age *Z* score§	−12.07 ± 1.20	−12.20 ± 1.52
Height-for-age *Z* score§	−12.40 ± 1.05	−12.34 ± 1.45
Weight-for-height *Z* score§	−10.76 ± 1.13	−11.00 ± 1.38
$CD4^+$ lymphocyte count (cells/μL)	1200 ± 604	1322 ± 941
Log_{10} plasma HIV load (copies/mL)	5.81 ± 0.59	5.62 ± 0.79
Hemoglobin (g/L)‖	92 ± 14	90 ± 13
Plasma vitamin A (μM/L)#	0.58 ± 0.20	0.56 ± 0.23
Diarrhea last 7 d (%)	27.6	42.5
Chronic diarrhea >30 d (%)	1.2	5.3
Cough last 7 d (%)	73.6	74.5
Persistent cough >30 d (%)	1.2	3.8
Fever last 7 d (%)	25.3	34.0
Fever >30 d (%)	0	1.0
Blood in stool last 7 d (%)	1.1	3.2

HIV, human immunodeficiency virus.

* Values are mean ± standard deviation or percentage $P > 0.05$ except for diarrhea in previous 7 d.

† Missing data for 15 children in the vitamin A group and 16 in the placebo group.

‡ Missing data for one child in the vitamin A group and three children in the placebo group.

§ National Center for Health Statistics reference population [14].

‖ Hemoglobin below 110 g/L is defined as anemic in children of this age [17].

Plasma retinol concentration lower than 0.70 μM/L is considered consistent with vitamin A deficiency [13].

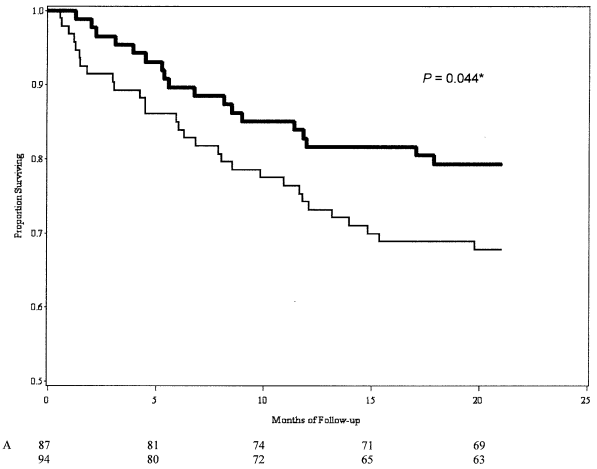

Fig. 2. Survival curves of children infected with the human immunodeficiency virus who received vitamin A (thick line) or placebo (thin line) adjusted for baseline weight-for-height *Z* score. *By Cox proportional hazards model after adjustment for weight for height. No participants were excluded from this Kaplan-Meier survival analysis.

reported causes of deaths among children in the placebo group were diarrheal disease ($n = 14$), pneumonia ($n = 7$), tuberculosis ($n = 5$), failure to thrive ($n = 1$), sepsis ($n = 1$), malaria ($n = 1$), dehydration ($n = 1$), and unknown ($n = 1$). The survival curves of children ages 15 to 36 mo in the two treatment groups are shown in Figure 2. Mortality rates in the vitamin A and control groups were 20.6% and 32.9%, respectively, yielding a relative risk of 0.54 (95% confidence interval, 0.30 to 0.98; $P = 0.044$) after adjusting for baseline weight-for-height *Z* score in Cox proportional hazards analysis.

The modified point prevalences of the various causes of morbidity are presented in Table 2. Vitamin A supplementation had no significant effect on the modified point prevalences of reported diarrhea, cough, fever, or blood in the stool in the previous 7 d, or reported hospitalizations. Vitamin A supplementation was associated with a decrease in persistent cough longer than 30 d ($P = 0.038$) and a trend toward a decrease in diarrhea longer than 30 d ($P = 0.11$). The reported geometric mean (upper and lower 95% confidence intervals) duration of morbidity in days per episode was compared between treatment groups. In the vitamin A and placebo groups, the geometric mean (upper and lower standard deviations) durations of diarrhea were 3.37 d (3.05 and 3.73) and 3.55 d (3.17 and 3.96), respectively ($P = 0.41$), the geometric mean durations of cough were 5.07 d (4.83 and 5.32) and 5.12 d (4.88 and 5.37), respectively ($P = 0.66$), the geometric mean durations of ear discharge were 4.61 d (4.00 and 5.32) and 5.71 d (4.98 and 6.55), respectively ($P = 0.03$), and geometric mean durations of blood in stools were 3.12 d (1.95 and 4.99) and 2.95 d (1.73 and 5.01), respectively ($P = 0.92$).

Discussion

In this study, high-dose vitamin A supplementation every 3 mo decreased the mortality rate of HIV-infected children by 46%. Three previous studies have suggested that vitamin A supplementation may have promise for HIV-infected children. In Durban, South Africa, periodic, high-dose vitamin A supplementation appeared to decrease diarrheal morbidity among infants born to HIV-infected mothers, but in a stratified analysis of the 28 HIV-positive infants in the trial, the beneficial effect did not reach statistical significance [18]. In Cape Town, South Africa, HIV-infected children who received vitamin A supplementation had significant increases in circulating $CD4^+$ lymphocyte counts and natural killer cells compared with controls [19]. In a controlled clinical trial in Dar es Salaam, Tanzania that was originally designed to determine whether vitamin A supple-

Table 2
Modified point prevalance per child-month follow-up

Outcome	Modified point prevalence/child-month*		OR (95% CI)	*P*
	Vitamin A ($n = 83$)	Placebo ($n = 85$)		
Diarrhea last 7 d	0.061	0.054	1.13 (0.88–1.46)	0.32
Chronic diarrhea >30 d	0.003	0.006	0.48 (0.19–1.18)	0.11
Cough last 7 d	0.139	0.137	1.01 (0.89–1.15)	0.77
Persistent cough >30 d	0.004	0.010	0.47 (0.23–0.96)	0.038
Fever last 7 d	0.061	0.059	1.03 (0.80–1.34)	0.77
Fever >30 d	0.001	0.001	1.29 (0.35–4.65)	0.69
Ear discharge last 7 d	0.026	0.021	1.26 (0.62–2.57)	0.51
Blood in stool last 7 d†	0.004	0.007	0.65 (0.20–2.04)	0.46
Hospitalization	0.011	0.009	1.23 (0.68–2.20)	0.48

CI, confidence interval; OR, odds ratio.

* Modified point prevalence per child-month was defined as the total number of episodes of a given outcome divided by the child-months of observation and then adjusted for extra-Poisson variability in log-link regression analysis [15,16]. Nine children in the placebo group and four children in the vitamin A group did not have at least one follow-up visit because they died before follow-up.

† No blood in stool was reported for longer than 30 d.

mentation could decrease morbidity and mortality rates among children hospitalized with acute lower respiratory infections, there was no effect of vitamin A supplementation on morbidity and mortality rates from acute lower respiratory infections [8]. Archived serum samples were analyzed retrospectively to identify HIV-positive subjects of the 687 children who had participated in the trial, and stratified analysis suggested that two doses of vitamin A, during hospitalization and repeated at 4 and 8 mo after discharge, significantly decrease mortality rate by 63% among a subsample of 58 HIV-positive children in the trial. It was unclear in this stratified analysis whether these two treatment groups were similar at the time of randomization [8].

Previous studies have shown that vitamin A, originally known as the "anti-infective" vitamin in the 1920s [20], decreases morbidity and mortality rates from diarrheal disease and measles [6], and this clinical trial shows that the benefits of high-dose vitamin A supplementation can be extended to HIV infection in children. In the present study, children were carefully examined at each visit for ocular signs of vitamin A deficiency, i.e., Bitot's spots, corneal xerosis, and corneal ulceration, and no clinical vitamin A deficiency was observed. The low plasma concentrations of vitamin A at age 15 mo suggest that the prevalence of subclinical vitamin A deficiency was high. These findings suggest that vitamin A supplementation may have benefit for HIV-infected preschool children who are not on antiretroviral medications and come from populations with similar socioeconomic and nutrition conditions. These findings cannot be extrapolated to HIV-positive children younger than 15 mo or older than 36 mo because the study did not address the effects of vitamin A supplementation in infants and children in these age groups. Vitamin A deficiency affects many aspects of immunity, including generation of an antibody response to certain antigens, functions of T and B cells, neutrophil function, and maintenance of mucosal surfaces of the eye and of the respiratory, gastrointestinal, and genitourinary tracts [4]. Vitamin A deficiency in preschool children has been associated with decreased antibody responses to vaccination [21] and T-cell subset abnormalities [22]. Vitamin A supplementation presumably decreases morbidity and mortality rates through enhancement of immune function [4]. The effect of vitamin A supplementation on immunity was not directly assessed in the present study, but, as noted previously, vitamin A supplementation has been shown to modulate T-cell subsets in HIV-infected children [19]. A recent study conducted in Durban, South Africa has suggested that improvement of vitamin A status of pregnant women may have benefits in decreasing gut permeability among their HIV-infected infants [23]. Vitamin A supplementation has been shown to improve gut integrity among infants in Gambia [24], and this is another potential mechanism by which vitamin A may decrease the morbidity of diarrheal disease.

A limitation of the present study was that the pathogens involved in diarrheal and respiratory disease morbidities, such as *Cryptosporidium* and *Pneumocystis carinii* were not assessed in the local setting, and children were not assessed for intestinal parasites during the study. Another limitation is that the study did not examine other medications and their potential effects on morbidity in the two treatment groups. As with previous vitamin A clinical trials [6], this study showed a clearer effect on mortality rate than on morbidity rate, and this may be partly attributed to the difficulty in measuring infectious disease morbidity in children. This study shows that vitamin A supplementation, 60 mg of retinol equivalent, decreases mortality in HIV-infected children when given every 3 mo, and it cannot be extrapolated from this study that other dosage schedules, such as every 6 mo, will have a similar effect on mortality.

Vitamin A supplementation appeared to decrease mortality and some morbidity among HIV-infected children, and this study suggests that regular vitamin A supplementation should be included as standard care for HIV-infected children in developing countries. In many developing countries, there may not be the facilities and resources for testing infants for HIV infection, and there may be benefit for providing vitamin A supplementation for all children born to HIV-infected mothers. Given the low cost of vitamin A supplements and the known cost effectiveness of vitamin A supplementation programs in general [25], it is likely the cost effectiveness of vitamin A supplementation will be high for HIV-infected children.

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