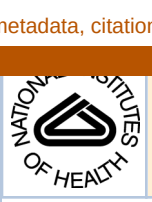

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Lipid-soluble vitamins A, D, and E in HIV-infected pregnant women in Tanzania

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Abstract

Background/Objectives—There is limited published research examining lipid-soluble vitamins in human immunodeficiency virus (HIV)-infected pregnant women, particularly in resource-limited settings.

Subjects/Methods—This is an observational analysis of 1078 HIV-infected pregnant women enrolled in a trial of vitamin supplementation in Tanzania. Baseline data on sociodemographic and anthropometric characteristics, clinical signs and symptoms, and laboratory parameters were used to identify correlates of low plasma vitamin A (<0.7 μmol/l), vitamin D (<80 nmol/l) and vitamin E (<9.7 μmol/l) status. Binomial regression was used to estimate risk ratios and 95% confidence intervals.

Results—Approximately 35, 39 and 51% of the women had low levels of vitamins A, D and E, respectively. Severe anemia (hemoglobin <85 g/l; $P<0.01$), plasma vitamin E ($P=0.02$), selenium ($P=0.01$) and vitamin D ($P=0.02$) concentrations were significant correlates of low vitamin A status in multivariate models. Erythrocyte Sedimentation Rate (ESR) was independently related to low vitamin A status in a nonlinear manner ($P=0.01$). The correlates of low vitamin D status were CD8 cell count ($P=0.01$), high ESR (ESR >81 mm/h; $P<0.01$), gestational age at enrollment (nonlinear; $P=0.03$) and plasma vitamins A ($P=0.02$) and E ($P=0.01$). For low vitamin E status,

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The authors declare no conflict of interest.

the correlates were money spent on food per household per day ($P<0.01$), plasma vitamin A concentration (nonlinear; $P<0.01$) and a gestational age <16 weeks at enrollment ($P<0.01$).

Conclusions—Low concentrations of lipid-soluble vitamins are widely prevalent among HIV-infected women in Tanzania and are correlated with other nutritional insufficiencies. Identifying HIV-infected persons at greater risk of poor nutritional status and infections may help inform design and implementation of appropriate interventions.

Keywords

HIV; AIDS; pregnancy; Africa; vitamins

Introduction

There is limited evidence on the status of lipid-soluble vitamins (A, D and E) in human immunodeficiency virus (HIV)-infected pregnant women, particularly in resource-limited settings. In HIV-uninfected pregnant women, vitamin deficiencies have been shown to lead to intrauterine growth retardation and adverse pregnancy outcomes such as preeclampsia, premature rupture of membranes, preterm delivery and low birth weight (Chappell *et al.*, 1999; Stoltzfus and Humphrey, 2002). Moreover, maternal deficiencies in these nutrients are likely to affect breast milk composition and infant growth and development (Stoltzfus and Humphrey, 2002). Nutrient requirements are much higher during pregnancy to support maternal metabolism, infant growth and development, and physiological and hormonal adaptations (Picciano, 2003). Further, HIV-infected pregnant women are more likely to have several nutritional deficiencies and are at increased risk of adverse pregnancy outcomes (Fawzi, 2003).

Vitamin A deficiency during pregnancy is widely prevalent in developing countries, particularly in sub-Saharan Africa, and among HIV-infected women (Ahmed *et al.*, 2003; Keverenge-Ettyang *et al.*, 2006; Zvandasara *et al.*, 2006); it may affect fetal development and risk of maternal morbidity and mortality (Stoltzfus and Humphrey, 2002). Further, infants depend on breast milk to obtain adequate vitamin A (Allen, 2006); vitamin A deficiency during childhood is associated with severe morbidity and mortality (Fawzi *et al.*, 1993).

Vitamin D is essential for calcium metabolism and fetal skeletal development, with 25–30 g of calcium transferred to the fetus during pregnancy (Specker, 2004). Vitamin D also may be involved in development of the fetal immune system (Reichrath and Querings, 2005; Evans *et al.*, 2006) and may protect against Type I diabetes mellitus (Stene *et al.*, 2000).

As an antioxidant, vitamin E may minimize oxidative stress in the syncytiotrophoblast and prevent early pregnancy failure and preeclampsia (Di Renzo *et al.*, 2005). Vitamin E also may have a role in the prevention of birth defects (Loeken, 2004) by reduction of oxygen free radicals. Maternal vitamin E concentrations have also been correlated with increased fetal growth and decreased risk of small-for-gestational-age births (Scholl *et al.*, 2006).

Given the importance of these vitamins in pregnancy, identification of correlates of vitamin status may help inform appropriate targeted interventions. In this paper, we examined correlates of low vitamins A, D and E status at baseline (12–27 weeks gestation) assessment in a randomized trial of vitamin supplementation in HIV-infected pregnant women in Tanzania.

Methods

Study population

Study participants were HIV-infected pregnant women enrolled between 12 and 27 weeks of gestation in a randomized trial of vitamin supplementation, which has previously been described in detail (Fawzi *et al.*, 1999). The study protocol was approved by the research and publications committee of the 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.

Assessment of baseline covariates

Structured interviews were conducted during the baseline visit to collect information on obstetric history and demographic characteristics, including age, educational level and money spent on food daily. Data were also collected on history of morbidities, symptoms and hospitalizations during the current pregnancy. Gestational age was based on self-reported date of last menstrual period. Study physicians conducted a complete medical examination and collected blood, urine, stool and vaginal swab specimens. HIV disease stage was classified in accordance with the World Health Organization (WHO) guidelines (WHO, 1993). Anthropometric measurements, including weight, height and mid-upper arm circumference, were obtained by trained research assistants using standardized procedures and calibrated instruments.

Laboratory methods

Total leukocyte counts were performed with a CBC5 Coulter Counter (Coulter Corporation, Miami, FL, USA); differential white cell counts were evaluated manually. Absolute CD3, CD4 and CD8 T-cell counts were determined with the FACSCount system (Becton Dickinson, San Jose, CA, USA). Hemoglobin levels were assessed using a CBC5 Coulter Counter (Coulter Corporation) or the cyanmethemoglobin method with colorimeter (Corning Inc., Corning, NY, USA). HIV-1 serostatus was determined by the Enzygnost anti-HIV-1/2 Plus (Dade Behring, Marburg, Germany) followed by the Wellcozyme HIV-1 recombinant test (Murex Biotech Ltd, Dartford, UK) and the discordant results were resolved through western blot analysis (Bio-Rad Laboratories Ltd, Hertfordshire, UK) (Urassa *et al.*, 1994). Selenium concentration was measured in plasma using neutron activation analysis and was adjusted for the sodium concentration of the sample, which is tightly regulated physiologically, to account for the degree of concentration or dilution of the sample (Kupka *et al.*, 2005).

Sera and genital swabs were collected to identify sexually transmitted infections and malaria parasites were identified in thick smear blood films stained with giemsa. Stool specimens were examined to identify intestinal helminths (hookworm, Trichuris trichiura, Ascaris lumbricoides, Strongyloides stercoralis, Schistosoma mansoni) and pathogenic protozoan (Giardia lamblia, Entamoeba histolytica and Cryptosporidium parvum) infections. Urine samples were examined for presence of *S. haematobium*. Sexually transmitted infections, intestinal parasitic infections and malaria were treated at the time of diagnosis according to the Tanzanian Ministry of Health standards of care.

Assessment of outcome and outcome definitions

Blood samples were obtained at baseline, and plasma was stored at or below −70 °C. Measurements of baseline plasma vitamins A and E concentrations were carried out using reversed-phase high-performance liquid chromatography in a modification of the method of Zaman *et al.* (1993). Maternal vitamin D status was assessed using serum levels of 25-hydroxyvitamin D (25(OH)D). Serum 25(OH)D levels were measured by the fully

automated chemiluminescence ADVANTAGE 25(OH)D assay system obtained from Nichols Institute Diagnostics (San Juan Capistrano, CA, USA). Vitamin A deficiency was defined as <0.7 μmol/l, as per conventional criteria (de Pee and Dary, 2002); low vitamin E status was defined according to the study population median (<9.7 μmol/l), as consistent with previous publications from this trial. The cutoff for low vitamin D status was serum 25(OH)D <80 nmol/l, which is considered optimal for calcium homeostasis (Holick, 2004).

Statistical analyses

Sociodemographic factors considered in the analysis included age, literacy level and occupation of women; source of income support; average household income; marital status and pregnancy history. Maternal weight, height and mid-upper arm circumference were examined as continuous variables. Conventional cutoffs were used to categorize predictors where available; otherwise, median values were used to classify variables, as consistent with previous publications from this trial (Antelman *et al.*, 2001). Body mass index (kg/m^2) was categorized according to WHO standards (WHO, 1995). Anemia was defined as hemoglobin <110 g/l and severe anemia as hemoglobin <85 g/l. CD4 counts were categorized as <200, 200–499 or ≥500 cells per μl; and CD8 and CD3 counts were classified according to their median values. Malaria parasitemia was categorized as light (1–999 per μl), moderate (1000–9999 per μl) or heavy (≥10 000 per μl), respectively.

Risk ratios and 95% confidence intervals were estimated by binomial regression with the log-link function. When the log-binomial model failed to converge, log-Poisson models—which provide consistent, but not fully efficient, estimates of the risk ratio and its confidence intervals—were used (Spiegelman and Hertzmark, 2005). Variables with univariate *P*-values <0.20 were included in multivariate regression models and retained if their *P*-values were <0.05. Potential nonlinear relationships between covariates and outcomes were examined nonparametrically with stepwise restricted cubic splines (Durrleman and Simon, 1989; Govindarajulu *et al.*, 2007). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. When a nonlinear relationship was found, restricted cubic spline variables were created and entered into the binomial regression model. Observations with missing data for covariates were retained using the missing indicator method for variables missing >1% of observations (Miettinen, 1985). Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the study population are presented in Table 1. The average age (±s.d.) of study participants was 24.7 (±4.8) years. Most (92%) women were literate and over 70% described their occupation as housewife. The averagege stational age at randomization was 20.4 (±3.4) weeks and more than one-third of women were primiparous. 83% of women were anemic (<110 g/l) and 27% were severely anemic (<85 g/l) at baseline. Approximately 85% of women had stage I HIV disease, and 12% had CD4 cell counts <200 cells per μl. *Plasmodium falciparum* malaria parasitemia was prevalent in 19% of participants.

A total of 829, 884 and 830 study participants had baseline measurements of vitamins A, D and E concentrations, respectively. The mean plasma vitamins A, D and E levels at baseline were 0.9 μmol/l (±0.3), 89.2 nmol/l (±31.0) and 9.8 μmol/l (±3.0), respectively. No significant correlations were observed between plasma vitamin D levels and season of blood draw (not shown).

Univariate correlates (P<0.20) of low vitamin A status (<0.7 μmol/l) are presented in Table 2. In the multivariate model (Table 2), risk of low vitamin A status was 36% lower per 10 μmol/l increase in vitamin E levels at baseline and 11% lower for every 25 nmol/l increase in vitamin D levels. Women with severe anemia (Hb <85 g/l) at baseline had a 47% higher risk of having low vitamin A status. Similarly, a 0.1 μg/ml increase in baseline selenium levels was associated with a 51% lower risk of low vitamin A status at baseline. The relationship of erythrocyte sedimentation rate (ESR) with low vitamin A status was nonlinear, with a sharp increase in risk of low vitamin A status at higher levels of ESR, after multivariate adjustment.

Univariate correlates (P<0.20) of low vitamin D status (<80 nmol/l) are presented in Table 3. In multivariate analysis (Table 3), risk of low vitamin D status was 4% higher with each 100 cells per μl increase in CD8 cell counts, and 69% higher with a 10 μmol/l increase in baseline vitamin E levels. Women with elevated ESR at baseline (ESR >81 mm/h) had a 45% higher risk of having low vitamin D status. The risk was 13% lower with each 0.35 μmol/l increase in vitamin A levels. The relationship of low vitamin D status with gestational age at randomization remained nonlinear after multivariate adjustment; the risk of low vitamin D status decreased with increasing gestation until approximately 24 weeks and then increased again.

Univariate (P<0.20) and multivariate-adjusted (P<0.05) correlates of low vitamin E status (<9.7 μmol/l) are presented in Table 4. A 16% lower risk of low vitamin E status was observed with every 1000 additional shillings spent per household on food daily (≈US$2 in 1995). Women who were enrolled earlier in the pregnancy (<16 weeks gestation) had a 23% higher risk of low vitamin E status. The nonlinear relationship of low vitamin E status with vitamin A levels at baseline remained after multivariate adjustment, with a sharp decrease in the risk of low vitamin E status observed once vitamin A levels reached ≈1.23 μmol/l.

Discussion

In this study, we assessed the concentrations of lipid-soluble vitamins (A, D and E) and their correlates in HIV-infected pregnant women in Tanzania. Approximately 35, 39 and 51% of the women in the study had low vitamins A, D and E status, respectively.

The mean plasma vitamin A level was 0.9 μmol/l; this is similar to concentrations observed in HIV-infected pregnant women (22–35 weeks gestation) in Zimbabwe (0.87 μmol/l) (Friis *et al.*, 2001). Another study in Zimbabwe also found similar vitamin A levels (0.98 μmol/l) in HIV-infected women, though these were measured postpartum (Zvandasara *et al.*, 2006). HIV-infected individuals are expected to have lower concentrations of plasma vitamin A compared to HIV-uninfected individuals (Friis *et al.*, 2001; Zvandasara *et al.*, 2006). Vitamin A deficiency in pregnancy is also a major public health problem in HIV-uninfected pregnant women; about seven million pregnant women in developing countries are vitamin A deficient (West, 2002). The WHO states that vitamin A deficiency is a severe problem when the percentage of deficient subjects is >20%. In our study, the prevalence of vitamin A deficiency was 35%, which is similar to the prevalence reported in the study in Zimbabwe (Friis *et al.*, 2001). The prevalence among HIV-infected nonpregnant women was 26% in a study in Kenya (Baeten *et al.*, 2004); in contrast, the prevalence of vitamin A deficiency among presumably HIV-uninfected pregnant women was 26% in another study in Tanzania (Mulokozi *et al.*, 2003) and 9% in Bangladesh (Ahmed *et al.*, 2003), suggesting that the magnitude of this problem may be larger in HIV-infected women. Maternal vitamin A deficiency in HIV-uninfected women has been shown to increase risks of maternal morbidity and mortality (Christian *et al.*, 2000) and compromise the vitamin A status of the breastfeeding infant (Fawzi *et al.*, 1993; Allen, 2006).

We found that higher hemoglobin, vitamins D and E, and selenium concentrations were associated with decreased risk of low vitamin A levels. Several studies have observed an association between anemia and vitamin A status in presumably HIV-uninfected pregnant women, notably in Tanzania (Hinderaker *et al.*, 2002) and Nepal (Bondevik *et al.*, 2000). In a randomized trial in Indonesia, 97% of pregnant women supplemented with both vitamin A and iron became non-anemic, compared to 68% of those who received iron alone (Suharno *et al.*, 1993). A possible explanation could be an impaired mobilization of iron from stores seen in vitamin A deficiency (Roodenburg *et al.*, 1994). Vitamins A, D and E are lipid-soluble vitamins, and hence correlate with fat stores in the body; this might explain the relationship of vitamins D and E with risk of low vitamin A status.

ESR was related nonlinearly with greater risk of poor vitamin A status, at very high ESR levels. The nonlinear relationship with ESR and the increase in risk seen at higher ESR levels could indicate two potential mechanisms: first, in women with greater degree of inflammation, the vitamin A levels decline and they may not actually be deficient as the liver stores may be replete; and second, the women with poorer nutritional and vitamin A status are susceptible to greater inflammation and worse disease outcomes, compared to women with normal/high vitamin A status.

The main source of vitamin D is the synthesis in the skin catalyzed by ultraviolet-B solar radiation (Holick, 2004). Vitamin D inadequacy is not classically associated with equatorial regions, due to the abundance of perennial sunlight. Therefore, it was remarkable to observe approximately a 40% prevalence of vitamin D insufficiency (<80 nmol/l) in this cohort in Tanzania, only 6° from the Equator. The mean baseline vitamin D concentration was 89.18 nmol/l. Several studies have examined vitamin D concentrations in pregnant women in developed settings; a recent study in pregnant women in Pittsburgh (40° from the Equator) found that Caucasian women had a mean serum vitamin D concentration of 72.5 nmol/l (4–21 weeks gestation), compared to 40 nmol/l in African-American women (Bodnar *et al.*, 2007). Approximately, 62% of Caucasian women and 96% of African-American women had vitamin D insufficiency. One recent study in the Gambia examined vitamin D levels in pregnant women in presumably HIV-uninfected pregnant women, and found only 20% of the women at insufficient levels at 20 weeks gestation (Prentice *et al.*, 2009). The women included in this study, however, were mostly farmers who work outdoors for most of the day. The women in our study were recruited from a largely urban population in Dar es Salaam. Further, it may be possible that HIV infection itself may be responsible for the lower vitamin D levels observed in our study.

Low vitamin D status was associated with higher CD8 cell counts and ESR. This could suggest a possible role of vitamin D in inflammation. Although, the conventional role of CD8 cells is as cytotoxic cells, they also may be effector cells in inflammation (Babbe *et al.*, 2000). The involvement of vitamin D in modulating CD8 cells is also indicated by the fact that CD8 cells express the highest concentration of vitamin D receptor of the immune cells (Veldman *et al.*, 2000).

We also observed a nonlinear relationship of gestational age at randomization with risk of low vitamin D status; the study from Pittsburgh cited above conducted repeated analyses of vitamin D levels, at 4–21 and 37–42 weeks of gestation, and found that the vitamin D levels increased with gestational age (Bodnar *et al.*, 2007). Though we did not conduct repeat measurements, the nonlinear relationship with gestational age suggested that women presenting later during pregnancy have higher levels of vitamin D.

The mean plasma vitamin E level in this cohort was 9.8 μmol/l; this is considerably lower compared to levels of 15 and 26 μmol/l in studies in Tanzania (Mulokozi *et al.*, 2003) and

Ethiopia (Wondmikun, 2005) among presumably HIV-uninfected pregnant or postpartum women. We found that risk of low vitamin E status was reduced with greater spending on food; this may be an indication of the fact that vitamin E-rich food sources, such as almonds, spinach and mangoes, are comparatively more expensive.

We also found that risk of low vitamin E status decreases with increasing gestational age. This is consistent with several previous studies (Knight *et al.*, 1994). This increase in plasma vitamin E has been observed to parallel the rise in total lipid levels during pregnancy (Horwitt *et al.*, 1972). The increased plasma vitamin E levels during pregnancy may be a result of the increase in the transport capacity for the vitamin in the plasma; β-lipoprotein is the major transport protein and is elevated as part of the hyperlipidemia associated with pregnancy (Haga *et al.*, 1982). Therefore, this increase may not represent a true increase in the total tocopherol level.

Many of the benefits of the lipid-soluble vitamins are due to their involvement in the immune system. Vitamin A is important at all levels of the immune system (Villamor and Fawzi, 2005), including maintenance of epithelial integrity, acute-phase reactant in response to infection, monocyte differentiation and function, cytotoxicity of natural killer cells, antibody responses to tetanus toxoid (Semba *et al.*, 1992) and measles vaccines (Coutsoudis *et al.*, 1992), and total lymphocyte count (particularly CD4). Vitamin D increases phagocytic capacity of macrophages, number of natural killer cells and cell-mediated immunity, and is involved in the innate immune response (Bar-Shavit *et al.*, 1981; Yang *et al.*, 1993; Liu *et al.*, 2006). Vitamin E is responsible for improving delayed type hypersensitivity skin response, increasing IL-2 production, neutrophil phagocytosis, lymphocyte proliferation and antibody response to T-cell-dependent vaccines, and reducing production of inflammatory cytokines such as TNF-α and IL-6 (Wang *et al.*, 1995; Meydani *et al.*, 1997).

The immunological benefit of these vitamins may assume greater importance in the context of HIV infection. Identification of women at increased risk of micronutrient deficiencies may help inform the design and implementation of targeted interventions for HIV-infected pregnant women in resource-poor settings.

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Table 1

Baseline characteristics of women enrolled in the trial (N = 1077)

Variable	N	*Mean ± s.d./Percentage*
Sociodemographic		
Age (years)	1077	
<20		13.0
20–24		40.4
25–29		30.4
≥30		16.2
Shillings[a] per person per day for food ≤500	965	40.6
HIV-related		
WHO HIV stage	1076	
1		84.5
2		14.1
3		1.4
CD4 category (cells per μl)	1017	421.02±205.60
1 (<200)		12.7
2 (200–500)		56.2
3 (≥500)		31.1
CD3 (cells per μl)	1016	1231.19±455.70
CD8 (cells per μl)	1017	750.52±332.56
Laboratory results		
ESR (mm/h)	973	58.82±36.16
High ESR (>81)		25.8
Hemoglobin (g/l)	1053	94.30±16.80
Severe anemia (<85)		27.5
Vitamin E (μmol/l)	830	9.84±2.99
Low vitamin E (<9.7)		51.3
Vitamin A (μmol/l)	829	0.86±0.35
Vitamin A deficiency (<0.70)		34.7
Selenium adjusted for sodium (μg/ml)	949	0.13±0.03

Variable	N	*Mean ± s.d./Percentage*
Vitamin D (serum 25(OH)D) (nmol/l)	884	89.18±30.95
Vitamin D insufficiency (<80)		39.3
Clinical signs and symptoms including OB/GYN and relevant medical history		
Primipara	972	34.0
Gestational age at randomization	1077	20.37±3.36
Parasitoses and coinfections		
Vaginal candidiasis	1051	40.0
Syphilis (VDRL+)	916	6.3
Malaria parasitemia	1065	
None		81.3
Light (1–999)		5.3
Moderate (1000–9999)		11.0
Heavy (≥10 000)		2.4
Any helminth infection (hookworm, *Trichuris*, *Ascaris*, *Strongyloides*)	1083	15.9
Any intestinal parasite (any helminth, *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*)	1083	20.5
Anthropometric		
BMI at baseline (kg/m^2)	1044	23.30±3.26
<18.5		3.1
18.5 to <25		71.7
≥25 and <30		21.3
≥30		3.9
Mid-upper arm circumference at baseline (cm)	1061	25.60±2.90

Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate HIV, human immunodeficiency virus; 25(OH)D, 25-hydroxyvitamin D; OB/GYN, obstetrics and gynecology; VDRL, Venereal Disease Research Laboratory; WHO, World Health Organization.

[a]US$1 ≈ 500 Tanzanian shillings at the time the trial was conducted.

Table 2

Univariate ($P<0.20$) and multivariate ($P\leq0.05$) correlates of low vitamin A (<0.7 μmol/l) status

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	**p[a]**	**Risk ratio (95% CI)**	**p[a]**
Sociodemographic				
Shilling per person per day for food ≤500	1.19 (0.97, 1.45)	0.10		
Occupation		0.04		
Housewife	1			
Professional	1.32 (0.86, 2.03)			
Business	1.00 (0.76, 1.30)			
Public house	0.20 (0.03, 1.36)			
Employed	0.82 (0.53, 1.26)			
Other	1.61 (1.03, 2.52)			
HIV-related				
WHO HIV stage	1.35 (1.14, 1.60)	<0.01		
WHO stage	0.06			
I	1			
II	1.36 (1.01, 1.82)			
III	1.79 (0.84, 3.80)			
Baseline HIV stage group >1	1.39 (1.13, 1.72)	<0.01		
CD3 ≥1174.5 cells per μl	0.87 (0.72, 1.05)	0.15		
Laboratory results				
ESR (mm/h)	— [b]	<0.01[c]	— [b]	0.01[c]
ESR ≥81 mm/h	1.35 (1.10, 1.65)	<0.01		
Total lymphocytes ≥1340	0.86 (0.70, 1.06)	0.17		
Hemoglobin (per 10 g/l)	0.87 (0.83, 0.92)	<0.01		
Severe anemia (Hb <85 g/l)	1.47 (1.21, 1.77)	<0.01	1.47 (1.15, 1.89)	<0.01
Anemia (Hb <110 g/l)	1.35 (1.01, 1.80)	0.04		
Vitamin E levels (per 10 μmol/l)	0.66 (0.47, 0.93)	0.02	0.62 (0.42, 0.92)	0.02
Low vitamin E (<9.7 μmol/l)	1.13 (0.94, 1.37)	0.19		
Selenium adjusted for sodium (per 0.1 μg/ml)	0.53 (0.35, 0.80)	<0.01	0.49 (0.30, 0.82)	0.01

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	**p[a]**	**Risk ratio (95% CI)**	**p[a]**
Vitamin D levels (per 25 nmol/l)	— [b]	<0.01[c]	0.89 (0.80, 0.98)	0.02
Low vitamin D (<80 nmol/l)	1.26 (1.03, 1.52)	0.02		
Clinical signs and symptoms including OB/GYN and relevant medical history				
Vaginal bleeding (index pregnancy)	0.64 (0.33, 1.24)	0.18		
Gestational age at randomization	1.03 (1.00, 1.06)	0.06		
Gestational age <16 weeks	0.75 (0.58, 0.98)	0.03		
History of low birth weight	0.70 (0.45, 1.10)	0.12		
History of preterm birth	0.74 (0.48, 1.14)	0.17		
Diastolic hypertension	0.57 (0.26, 1.26)	0.16		
Systolic blood pressure	0.99 (0.98, 1.00)	0.03		
Systolic hypertension	0.47 (0.19, 1.17)	0.10		
Parasitoses and coinfections				
Vaginal candidiasis	0.84 (0.69, 1.03)	0.10		
Genital ulcer (index pregnancy)	1.28 (0.94, 1.76)	0.12		
Sexually transmitted diseases	1.24 (1.02, 1.51)	0.03		
Trichomonas	1.27 (1.03, 1.55)	0.02		
Yeast infection	0.79 (0.59, 1.05)	0.11		
No. of malaria parasites (per 1000 parasites per μl)	1.03 (1.01, 1.05)	0.01		
Malaria	1.23 (1.00, 1.52)	0.05		
Cryptosporidium infection	1.40 (0.96, 2.05)	0.08		
Entamoeba histolytica infection	1.64 (0.98, 2.74)	0.06		
Hookworm infection	1.25 (0.94, 1.67)	0.13		
Strongyloides infection	1.52 (0.81, 2.84)	0.20		
Trichomonas in urine	1.24 (1.00, 1.54)	0.05		
Any helminth infection (hookworm, *Trichuris, Ascaris, Strongyloides*)	1.22 (0.95, 1.56)	0.12		
Any intestinal parasite (any helminth, *Giardia, E. histolytica, Cryptosporidium*)	1.26 (1.00, 1.57)	0.05		
Anthropometric				
Weight (kg)	0.99 (0.98, 1.00)	0.14		
BMI (kg/m^2)	0.98 (0.95, 1.01)	0.14		
MUAC (cm)	0.95 (0.91, 0.98)	<0.01		

Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MUAC, mid-upper arm circumference; OB/GYN, obstetrics and gynecology; WHO, World Health Organization.

[a] *P*-values are from binomial regression models.

[b] Nonlinear variables.

[c] *P*-values represent overall significance of the curve between the variable and low vitamin A status using the log-likelihood ratio test.

Table 3

Univariate ($P<0.20$) and multivariate correlates ($P\leq0.05$) of low vitamin D status (<80 nmol/l)

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	p[a]	*Risk ratio (95% CI)*	p[a]
Sociodemographic				
Married	1.14 (0.96, 1.36)	0.13		
Center of recruitment		0.06		
Temeke	1			
Mwananyamala	0.98 (0.81, 1.20)			
Ilala	0.85 (0.68, 1.06)			
MMC	0.48 (0.08, 2.80)			
Mwenge	0.83 (0.58, 1.17)			
Mburahati	2.07 (1.48, 2.87)			
Occupation		0.09		
Housewife	1			
Professional	1.15 (0.73, 1.80)			
Business	0.90 (0.69, 1.16)			
Public house	1.20 (0.66, 2.18)			
Employed	1.48 (1.16, 1.88)			
Other	0.87 (0.42, 1.79)			
HIV-related				
WHO HIV stage	1.23 (1.04, 1.45)	0.01		
Baseline HIV stage group >1	1.22 (1.01, 1.49)	0.04		
CD3 cells (per 100 cells per μl)	1.02 (1.00, 1.04)	0.02		
CD3 ≥1174.5 cells per μl	1.16 (0.98, 1.38)	0.08		
CD8 cells (per 100 cells per μl)	1.04 (1.02, 1.06)	<0.01	1.04 (1.01, 1.07)	0.01
CD8 ≥682 cells per μl	1.24 (1.05, 1.47)	0.01		
Laboratory results				
ESR (per 10 mm/h)	1.06 (1.03, 1.08)	<0.01		
ESR ≥81 mm/h	1.49 (1.25, 1.76)	<0.01	1.45 (1.14, 1.83)	<0.01
Hemoglobin (per 10 g/l)	0.96 (0.92, 1.01)	0.13		

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	p[a]	*Risk ratio (95% CI)*	p[a]
Anemia (Hb <110 g/l)	1.28 (1.00, 1.65)	0.05		
Vitamin A levels (per 0.35 μmol/l)	0.87 (0.79, 0.96)	<0.01	0.87 (0.77, 0.98)	0.02
Low vitamin A (<0.7 μmol/l)	1.24 (1.03, 1.49)	0.02		
Vitamin E levels (per 10 μmol/l)	1.58 (1.19, 2.09)	<0.01	1.69 (1.16, 2.45)	0.01
Low vitamin E (<9.7 μmol/l)	0.88 (0.73, 1.05)	0.16		
Clinical signs and symptoms including OB/GYN and relevant medical history				
Vaginal bleeding (index pregnancy)	1.35 (0.95, 1.91)	0.1		
Parity	0.94 (0.88, 1.00)	0.06		
Total number of pregnancies before the current one	0.96 (0.91, 1.02)	0.17		
Gestational age at randomization	— [b]	0.04[c]	— [b]	0.03[c]
History of low birth weight	0.74 (0.49, 1.11)	0.15		
History of preterm birth	0.77 (0.52, 1.14)	0.2		
Parasitoses and coinfections				
Vaginal candidiasis	0.83 (0.69, 0.98)	0.03		
Sexually transmitted diseases	1.13 (0.95, 1.35)	0.16		
Malaria parasitemia		0.13		
None	1			
Light (1–999)	1.26 (0.91, 1.73)			
Moderate (1000–9999)	1.31 (1.05, 1.64)			
Heavy (≥10 000)	1.28 (0.81, 2.02)			
Malaria	1.29 (1.07, 1.55)	0.01		
Giardia infection	1.90 (1.07, 3.36)	0.03		
Strongyloides infection	1.52 (0.91, 2.54)	0.11		
Anthropometric				
Weight (kg)	0.99 (0.98, 1.00)	0.07		
BMI (kg/m^2)	0.98 (0.95, 1.00)	0.09		
MUAC (cm)	0.98 (0.95, 1.01)	0.13		

Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MUAC, mid-upper arm circumference; OB/GYN, obstetrics and gynecology; WHO, World Health Organization.

[a] *P*-values are from binomial regression models.

[b] Nonlinear variables.

[c] *P*-values represent overall significance of the curve between the variable and low vitamin D status using the log-likelihood ratio test.

Table 4

Univariate ($P<0.20$) and multivariate correlates ($P\leq0.05$) of low vitamin E status (<9.7 μmol/l)

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	p[a]	*Risk ratio (95% CI)*	p[a]
Sociodemographic				
Mother's source of income		0.08		
Self-supported	1.65 (1.07, 2.52)			
Partially supported	1.00			
Totally supported	1.16 (0.98, 1.37)			
Shillings per household per day on food (1000 shillings)	0.83 (0.74, 0.93)	<0.01	0.84 (0.75, 0.94)	<0.01
Occupation		0.08		
Housewife	1.00			
Professional	0.57 (0.32, 1.02)			
Business	0.93 (0.76, 1.13)			
Public house	0.93 (0.55, 1.58)			
Employed	0.76 (0.55, 1.05)			
Other	0.70 (0.37, 1.32)			
Occupation—housewife	1.20 (1.02, 1.41)	0.03		
HIV-related				
CD4 cells (per 100 cells per μl)	0.97 (0.94, 1.01)	0.13		
Laboratory results				
ESR (per 10 mm/h)	0.98 (0.96, 1.00)	0.11		
Severe anemia (Hb <85 g/l)	0.88 (0.75, 1.04)	0.13		
Vitamin A levels (μmol/l)	—[b]	<0.01[c]	—[b]	<0.01[c]
Low vitamin A (<0.7 μmol/l)	1.10 (0.96, 1.26)	0.18		
Selenium adjusted for sodium (per 0.1 μg/ml)	1.36 (1.02, 1.81)	0.03		
Clinical signs and symptoms including OB/GYN and relevant medical history				
Abnormal vaginal discharge (index pregnancy)	0.79 (0.59, 1.06)	0.11		
Abnormal vaginal discharge at baseline (Dx by physician)	0.86 (0.69, 1.06)	0.15		
Primipara	0.90 (0.78, 1.05)	0.19		
Parity	1.03 (0.99, 1.07)	0.15		

Variable	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	p[a]	*Risk ratio (95% CI)*	p[a]
Gestational age at randomization	0.96 (0.94, 0.98)	<0.01		
Gestational age <16 weeks	1.26 (1.09, 1.45)	<0.01	1.23 (1.07, 1.41)	<0.01
History of preterm birth	1.27 (1.04, 1.55)	0.02		
History of hypertension	1.28 (1.00, 1.64)	0.05		
Parasitoses and coinfections				
Ascaris	1.23 (0.95, 1.60)	0.11		
Genital ulcer (index pregnancy)	0.81 (0.60, 1.11)	0.19		
Trichomonas in urine	1.18 (1.01, 1.37)	0.04		
Anthropometric				
Weight (kg)	0.99 (0.98, 0.99)	<0.01		
BMI (kg/m^2)	0.96 (0.94, 0.98)	<0.01		
BMI		0.07		
<18.5	1.31 (0.99, 1.74)			
18.5 to <25	1.00			
≥25 and <30	0.88 (0.74, 1.06)			
≥30	0.67 (0.42, 1.06)			
MUAC (cm)	0.97 (0.95, 0.99)	0.01		

Abbreviations: BMI, body mass index; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MUAC, mid-upper arm circumference; OB/GYN, obstetrics and gynecology.

[a] *P*-values are from binomial regression models.

[b] Nonlinear variables.

[c] *P*-values represent overall significance of the curve between the variable and low vitamin E status using the log-likelihood ratio test.