Determinants of low birth weight among HIV-infected pregnant women in Tanzania[1–3]

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ABSTRACT

Background: Low birth weight (LBW) increases the risk of infant death, but little is known about its causes among HIV-infected populations in sub-Saharan Africa.

Objective: We assessed sociodemographic, nutritional, immunologic, parasitic, and infant risk factors for birth weight, LBW, and small-for-gestational-age (SGA) status in a cohort of 822 HIV-positive women enrolled in a clinical trial of vitamin supplementation and pregnancy outcomes in Dar es Salaam, Tanzania.

Design: Women were enrolled at prenatal care clinics during their second trimester, at which time blood, stool, urine, and genital specimens were collected, and anthropometric measurements and sociodemographic data were recorded. Birth weight was measured at hospital delivery.

Results: The mean (±SD) birth weight was 3015 ± 508 g, 11.1% of newborns weighed <2500 g (LBW), and 11.5% were SGA. In multivariate analyses, maternal weight at enrollment and a low CD8 cell count were inversely associated with LBW. Advanced-stage HIV disease, previous history of preterm birth, *Plasmodium falciparum* malaria, and any helmintic infection were associated with higher risk of LBW. The intestinal parasites *Entamoeba histolytica* and *Strongyloides stercoralis* were predictors of LBW despite their low prevalence in the cohort. In a multivariate-adjusted linear regression model, BMI, midupper arm circumference, a CD4 cell count $<200 \times 10^6$ cells/L (200 cells/mm^3), primiparity, maternal literacy, and infant HIV infection at birth were significantly associated with birth weight in addition to risk factors included in the LBW model. Determinants of SGA included maternal weight, low serum vitamin E concentration, candidiasis, malaria, and infant HIV infection at birth.

Conclusion: Prevention of HIV disease progression and vertical transmission, improved nutritional status, and better management of malaria and intestinal parasitic infections are likely to reduce the incidence of LBW in Tanzania. *Am J Clin Nutr* 2001;74:814–26.

KEY WORDS HIV infection, pregnancy, low birth weight, small for gestational age, Tanzania, vertical transmission, malaria, parasitic infections

INTRODUCTION

Identifying the determinants of low birth weight (LBW) is important because of the health risks associated with LBW. Infants born with LBW are more likely to die during the neonatal period (1, 2) and during the first year of life (3, 4). LBW is most common in developing countries, where the burden of malnutrition and of infectious diseases is heavy.

Existing research on the determinants of LBW focuses primarily on nutritional determinants in cohorts in industrialized countries. LBW is caused by retarded growth in utero, shortened gestation, or both. Low prepregnancy weight and poor pregnancy weight gain have been identified as the strongest determinants of intrauterine growth retardation leading to LBW (5). Other risk factors for LBW include short maternal stature, low socioeconomic status, nonwhite race, primiparity, smoking, and malaria (5, 6). The role of micronutrient deficiencies, sexually transmitted diseases, compromised immunity, and intestinal parasitic infections is less well known.

The spread of HIV infection worldwide may also add to the burden of LBW, particularly in sub-Saharan Africa where the prevalence of HIV infection is high. An estimated 12.2 million women of childbearing age in sub-Saharan African countries are infected with HIV (7); >25% of women of reproductive age in some urban areas are infected. Numerous studies from the region have reported that HIV-infected pregnant women are at increased risk of delivering LBW infants, of preterm delivery, and of intrauterine growth retardation (8). These poor pregnancy outcomes have also been associated with vertical transmission of HIV (9, 10) and increased mortality among infected children (11).

We enrolled and prospectively followed a cohort of HIV-infected pregnant women in Dar es Salaam, Tanzania, to investigate the determinants of birth weight, LBW, and small-for-gestational-age (SGA) status in this setting. Because women were enrolled as part of their prenatal care and were followed closely throughout their pregnancies, we were able to collect

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extensive data on sociodemographic, nutritional, HIV-related, parasitic, and infant risk factors to better understand their relative contributions to the risk of LBW in this population.

SUBJECTS AND METHODS

Study population

Study subjects were HIV-infected pregnant women living in Dar es Salaam, Tanzania, who were enrolled in an ongoing randomized, double-blind, placebo-controlled clinical trial of supplementation with vitamin A or multivitamins. This trial was designed to test the effects of vitamin supplementation on pregnancy outcomes, vertical HIV transmission, and progression of HIV disease. The trial methods are described in detail elsewhere (12). Briefly, pregnant women between 12 and 27 wk of gestation who were HIV-1 infected and resident in Dar es Salaam were eligible for the clinical trial. This population was representative of women in the general population. Women were recruited from prenatal clinics at 3 district hospitals and 1 maternal and child health clinic in Dar es Salaam. Those who consented to being randomly assigned to a study group were referred to the Muhimbili Medical Centre for study enrollment from April 1995 to July 1997. Women categorized as having HIV disease of clinical stage IV according to the World Health Organization definition (13) were not eligible for enrollment.

Of 1078 women enrolled in the supplementation trial, 1041 (97%) had a known pregnancy outcome. There were 29 spontaneous abortions, 53 stillbirths (4 from twin births), 21 sets of liveborn twins, and 12 singleton live births with no known date of pregnancy outcome. Among the 926 women with live births of singleton infants and a known date of pregnancy outcome, 822 (89% participation) had an eligible infant birth weight measurement and constitute the cohort used for this analysis. One hundred four infants were excluded from this analysis because of missing birth weight data from study hospital deliveries ($n = 6$), missing or unverified birth weight data from other hospital deliveries ($n = 65$), or unavailable birth weight data from deliveries at home ($n = 33$). Women with missing infant birth weight data were younger (23.6 compared with 24.9 y; $P < 0.05$, Wilcoxon's rank-sum test) and were more likely to be infected with intestinal parasites (42.0% compared with 27.9%; $P < 0.01$, chi-square test) than were women included in the present study cohort. However, the 2 groups did not differ by numerous sociodemographic, nutritional, HIV-related, and parasitic risk factors, including parity, income source, weight, height, biochemical indicators of micronutrient status, clinical stage of HIV disease, T lymphocyte cell counts, and malaria prevalence.

The data presented here were collected as part of a vitamin supplementation trial conducted by Muhimbili University College of Health Sciences and the Harvard School of Public Health. 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.

Field methods

Blood, stool, urine, and genital specimens were collected from women at the enrollment visit. Trained nurses interviewed the study subjects to obtain information on age, pregnancy history, socioeconomic status, and history of any illness in the previous month. They also measured the women's height, weight, and midupper arm circumference. The interview about reported history of illness was repeated at each monthly visit during pregnancy.

Infants were weighed to the nearest 10 g on a standard beam balance immediately after birth by research midwives. Infant birth weight measurements were collected for 803 (98%) study subjects who delivered their infants at the Muhimbili Medical Center; for 20 (2%) subjects, infant birth weight measurements were reported from 1 of the 3 recruitment hospitals or another local hospital. Gestational age was evaluated on the basis of reported recall of last menstrual period at enrollment. LBW was defined as birth weight <2500 g and SGA as birth weight <10th percentile for gestational age according to the standards of Brenner et al (14).

Laboratory methods

Absolute T lymphocyte counts of CD3, CD4, and CD8 cells were made from blood specimens with use of the FACScount system (Becton Dickinson, San Jose, CA). Hemoglobin was measured with either a CBC5 Coulter Counter (Coulter Corporation, Miami) or by the cyanmethemoglobin method with use of a colorimeter (Corning Inc, Corning, NY). Serum retinol concentrations were measured by HPLC. Sera were also tested for the presence of syphilis antibodies by using the VDRL (Murex Diagnostic, Dartford, United Kingdom) and Treponema Pallidum Hemagglutination (TPHA; Fujirebio, Tokyo) tests. Syphilis was diagnosed as active if the results of both tests were positive. Genital swabs were collected to identify sexually transmitted diseases and candidiasis. Specimens were cultured to detect *Neisseria gonorrhoeae* and *Candida albicans*, and wet mounts were prepared to identify *Trichomonas vaginalis*. Malaria parasites were identified in thick-smear blood films stained with giemsa. The number of malaria parasites per 200 leukocytes was counted to calculate parasite density per liter based on a leukocyte count of 8000×10^6/L ($8000/mm^3$) blood (15). Stool specimens were examined by Kato's concentration technique to identify various intestinal helminths (hookworm, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Schistosoma mansoni*) and pathogenic protozoan (*Giardia lamblia*, *Entamoeba histolytica,* and *Cryptosporidium parvum*) parasitic infections. A urine sample was examined for the presence of *Schistosoma haematobium*. Infant HIV status was determined by polymerase chain reaction analysis of blood specimens; infants who tested positive at birth were likely to have been infected during the intrauterine period.

Statistical analysis

Sociodemographic factors considered in the analysis included age, literacy, education, and occupation of women; source of income support; average household income; marital status; pregnancy history; and season of birth. Maternal weight, height, and midupper arm circumference were examined as continuous variables and also categorically by quartiles. Body mass index (BMI) was calculated as weight in kg divided by height in m^2, and was categorized according to World Health Organization standards (16). For biochemical indicators of nutritional status during pregnancy, anemia was defined as hemoglobin < 110 g/L (17) and severe anemia as hemoglobin < 85 g/L. Serum retinol concentration was categorized as <0.35, 0.35–0.69, and ≥0.70 μmol/L. Low serum vitamin E concentration was defined as the lowest quartile (<8.0 mg/L). CD4 counts were categorized as <200, 200–499, or ≥500 $\times 10^6$ cells/L (<200, 200–499, and ≥500 cells/μL) (18),

and CD8 and CD3 counts were classified by tertiles. Low T lymphocyte cell counts were defined as $<200 \times 10^6$ cells/L for CD4 cells and as the lowest tertile for CD8 and CD3 cells. Reported symptoms related to sexually transmitted diseases included genital ulcers; pain during sexual intercourse; pain, itching, or a foul smell from the genitalia; and watery or abnormal vaginal discharge. Clinical progression of HIV disease was categorized as stages I–III (13). Infant HIV status at birth was classified by testing a sample collected within 21 d of birth (89% within 3 d). We reanalyzed the data by using a cutoff of 10 d and the results were essentially the same for all endpoints. Malaria parasitemia was categorized as light (1–999 $\times$ 10^6/L), moderate (1000–9999 $\times$ 10^6/L), or heavy ($\geq$10 000 $\times$ 10^6/L) (1–999, 1000–9999, and $\geq$10 000/mm^3, respectively). Intestinal parasites were categorized by the presence or absence of ova or larvae in a stool specimen. Sexually transmitted diseases, malaria, and intestinal parasitic infections were treated at the time of diagnosis according to the Tanzanian Ministry of Health standards of prenatal care.

All associations between risk factors and endpoints were first examined in the placebo group before analyses were done in the full cohort. For univariate analysis, the chi-square test was used to test differences in the incidence of LBW and SGA, and Wilcoxon's rank-sum test was used to test differences in birth weight across categories of each risk factor. For risk factors with multiple ordered categories, simple linear regression with an ordinal variable was used to test for a linear trend in birth weight. P values <0.05 were considered to be significant.

Logistic regression models were constructed to estimate the relative odds of LBW and of SGA, and linear regression models were constructed to estimate birth weight differences for each risk factor after adjustment for potential confounding factors (SAS/STAT, version 6.12; SAS Institute, Cary, NC). We calculated 95% CIs for odds ratios in logistic models and for birth weight differences in linear models to measure the strength of the associations. To calculate unadjusted odds ratios and birth weight differences, variables for each risk factor were entered into the model alone. However, for risk factors that varied significantly by stage of pregnancy at which they were measured, including maternal weight, BMI, serum retinol, serum vitamin E, and hemoglobin, gestational age at baseline was also included in the model. Those variables with a univariate regression coefficient that had a P value <0.10 were tested in the multivariate regression models, but only those variables with a P value <0.05 after adjustment were retained. All multivariate regression analyses included adjustment for multivitamin treatment group because a significant effect on birth weight and SGA was found in earlier analyses of the treatment effect (19). To estimate multivariate-adjusted regression coefficients of the association between maternal anthropometric measurements and birth outcomes, each anthropometric variable was entered into a separate model to avoid colinearity. This approach was used for intestinal parasitic infections also. When more than one species was significantly associated with an outcome, variables for these species were put in the model together to verify that there was no confounding or interaction. To test whether the relation of malaria to low birth weight and birth weight differed between primiparous and multiparous women, stratified univariate analyses were conducted and multivariate regression models with interaction terms were estimated. Interaction terms were retained in the models if their P value was <0.15.

RESULTS

The mean (±SD) age of the study participants was 25 ± 5 y (range: 15–45 y; **Table 1**). More than 90% of the women were literate and 75% received full income support from their spouse or partner. Primiparous women made up 33% of the study cohort.

Women were at an average of 20 ± 3 wk of gestation at enrollment (Table 1). The mean weight and height of study participants were 57.3 ± 9.2 kg and 156.6 ± 5.7 cm, respectively, and only 2.9% had a BMI < 18.5. Anemia and vitamin A deficiency were common. Thirty-three percent of women had serum retinol concentrations <0.70 μmol/L, and 82.8% were anemic. More than 80% of women were classified as having stage I HIV disease, and 12.6% had a CD4 cell count $<200 \times 10^6$ cells/L. The prevalence of *P. falciparum* malaria parasitemia was 19% at enrollment and varied significantly by parity (24.0% in primiparas compared with 16.4% in multiparas; $P < 0.05$). Helmintic infections were found in 22.4% of stool specimens; the most common species were hookworm (11.3%), *A. lumbricoides* (5.8%), *S. haematobium* (3.6%), and *S. stercoralis* (1.8%). Pathogenic protozoa were present in 6.6% of the stool specimens; the most common were *C. parvum* (4.1%) and *E. histolytica* (2.2%).

The mean birth weight of live, singleton infants was 3015 ± 508 g, with 11.1% having LBW. The incidence of preterm birth was 23.5%, and 11.5% of infants were SGA (Table 1). Eight percent of infants were HIV-positive at birth.

Risk factors for low birth weight

Sociodemographic factors

The incidence of LBW and the crude and adjusted odds ratios (AORs) are listed by risk factor categories in **Table 2**. Among sociodemographic factors, maternal age, full income support, occupation, season at birth, and a previous history of a preterm birth were significantly associated with the risk of LBW. However, after adjustment for all significant covariates in a logistic regression model, only a previous history of preterm birth was associated with higher odds of LBW (AOR: 2.66; 95% CI: 1.26, 5.81).

Nutritional factors

Maternal weight, height, and midupper arm circumference were significantly associated with lower relative odds of LBW in univariate analyses, but only weight remained a significant factor after adjustment for other covariates (AOR: 0.96; 95% CI: 0.93, 0.99). Risk of LBW did not vary by BMI category. Incidence of LBW tended to be higher in women with lower serum retinol concentrations, but the trend was not significant. Hemoglobin concentration was not associated with LBW (data not shown).

HIV-related factors

Compared with women in stage I of HIV disease, the AOR of LBW appeared to be higher in women with stage II (AOR: 1.64; 95% CI: 0.87, 3.07) and stage III (AOR: 6.12; 95% CI: 1.08, 34.64) disease. A CD4 count $<200 \times 10^6$ cells/L was not significantly related to LBW. However, a CD8 cell count in the lowest tertile was associated with lower risk of LBW after multivariate adjustment (AOR: 0.52; 95% CI: 0.29, 0.93). Presence of active syphilis, *T. vaginalis*, and *C. albicans* did not change the risk of LBW (data not shown). Self-reported abnormal vaginal discharge during pregnancy was associated with significantly higher relative odds of LBW in univariate analyses, but the association was weakened by multivariate adjustment (AOR: 1.77; 95% CI: 0.91, 3.43) and was not retained in the final model.

TABLE 1
Characteristics of HIV-infected pregnant women and their infants in Tanzania (n = 822)

Characteristic	Value
Maternal characteristics	
Age (%)	
<20 y	12.0
20–24 y	40.3
25–29 y	30.3
≥30 y	17.4
Literacy (%)	92.3
Marital status (%)	
Married	64.4
Single, divorced, or widowed	10.7
Cohabiting	24.9
Income source (%)	
Own income or partial support	25.1
Fully supported by partner	74.9
Occupation (%)	
No outside employment	72.9
Professional	2.6
Small business or other	24.6
Season at birth (%)	
Dry (Jan–Feb)	16.3
Long rains (Mar–Jun)	42.5
Dry (July–Oct)	31.5
Short rains (Nov–Dec)	9.7
Parity (%)	
0	32.9
1–2	48.4
≥3	18.7
Previous low-birth-weight infant (%)[1]	11.3
Previous preterm infant (%)[1]	11.0
Gestational age at enrollment (wk)	20.4 ± 3.3[2]
Weight (kg)	57.3 ± 9.2
Height (cm)	156.6 ± 5.7
Midupper arm circumference (cm)	25.6 ± 3.0
BMI (kg/m^2)	23.4 ± 3.3
Serum retinol (%)[3]	
<0.35 μmol/L	4.1
0.35–0.69 μmol/L	29.2
0.70–1.04 μmol/L	41.4
≥1.05 μmol/L	25.3
Hemoglobin (%)	
<85 g/L	27.4
85–109 g/L	55.5
≥110 g/L	17.2
HIV stage (%)	
I	84.3
II	14.6
III	1.1
CD4 count (× 10^6 cells/L)[4]	417 ± 202
CD8 count (× 10^6 cells/L)[4]	742 ± 313
CD3 count (× 10^6 cells/L)[4]	1216 ± 435
Syphilis infection (%)	5.7
Trichomonas vaginalis infection (%)	24.8
Malaria parasitemia (%)	
None	81.1
1–999 × 10^6/L	5.3
1000–9999 × 10^6/L	11.3
≥10 000 × 10^6/L	2.3
Any helminth infection (%)[5]	22.4
Any pathogenic protozoan infection (%)[5]	6.6
Infant characteristics	
Birth weight (g)	3015 ± 508
Low birth weight (%)[6]	11.1
Small for gestational age (%)[7]	11.5
Preterm birth (%)[8]	23.5
Infant sex (% female)	48.0
Infant HIV status at birth (% positive)[9]	8.1

[1] Among multiparous women only, n = 565 for low birth weight, n = 566 for preterm birth.
[2] $\bar{x}$ ± SD.
[3] n = 637.
[4] For CD4 and CD8, n = 772; for CD3, n = 771.
[5] n = 684.
[6] Birth weight < 2500 g.
[7] Birth weight < 10th percentile for gestational age by the standards of Brenner et al (14).
[8] Gestational age < 37 wk.
[9] n = 708.

Parasitic factors

Malaria was associated with a significantly higher risk of LBW after multivariate adjustment (AOR: 1.81; 95% CI: 1.04, 3.16). The association appeared to be density dependent, with significantly higher risk among women with moderate to heavy parasitemia, but the CI for heavy infection included 1 (≥10 000 × 10^6/L compared with no parasitemia: AOR: 2.36; 95% CI: 0.71, 7.81). The risk of LBW associated with malaria did not differ significantly between primiparous and multiparous women (data not shown). Among intestinal parasite species, *E. histolytica* and *S. stercoralis* were associated with 4.68 (95% CI: 1.46, 14.94) and 5.97 (95% CI: 1.23, 28.98) times the adjusted relative odds of LBW, respectively. The occurrence of any helmintic infection was also associated with higher risk of LBW (AOR: 1.85; 95% CI: 1.02, 3.35).

Infant factors

Male sex was significantly associated with lower relative odds of LBW in univariate analyses, but the strength of this association was reduced after adjustment for other risk factors. The incidence of LBW was higher among infants infected with HIV at birth than among uninfected infants, but the association was not significant.

Risk factors for birth weight

Sociodemographic factors

Mean birth weight and unadjusted and adjusted birth weight differences by risk factor categories are presented in **Table 3**. Birth weight after adjustment for other factors varied significantly with primiparity and literacy only.

Nutritional factors

In univariate analyses, maternal weight, height, and midupper arm circumference at baseline were positively associated with birth weight, but only weight and midupper arm circumference remained significant determinants of birth weight in multivariate models. Women with a very low serum retinol concentration (<0.35 μmol/L) delivered infants with significantly lower birth weights than did those with a higher serum retinol concentration (≥0.70 μmol/L), but this difference was attenuated after multivariate adjustment for supple-

TABLE 2
Incidence of low birth weight and odds ratios by risk factor among HIV-infected pregnant women in Tanzania

Risk factor	Birth weight < 2500 g	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[1]
	n (%)		
Sociodemographic factors			
Maternal age (y)			
<20 (*n* = 99)	18 (18.2)	1.00	
20–24 (*n* = 331)	37 (11.2)	0.57 (0.31, 1.05)	
25–29 (*n* = 249)	23 (9.2)	0.46 (0.24, 0.89)	
≥30 (*n* = 143)	13 (9.1)[2]	0.45 (0.21, 0.97)	
Maternal literacy			
No (*n* = 63)	11 (17.5)	1.00	
Yes (*n* = 756)	80 (10.6)	0.56 (0.28, 1.12)	
Marital status			
Married (*n* = 529)	54 (10.2)	1.00	
Single (*n* = 88)	11 (12.5)	1.26 (0.63, 2.51)	
Cohabiting (*n* = 205)	26 (12.7)	1.28 (0.78, 2.10)	
Income source			
Own income or partial support (*n* = 206)	14 (6.8)	1.00	
Fully supported by partner (*n* = 615)	77 (12.5)[2]	1.96 (1.08, 3.55)	
Occupation			
No outside employment (*n* = 599)	76 (12.7)	1.00	
Professional (*n* = 21)	1 (4.8)	0.34 (0.05, 2.60)	
Small business or other (*n* = 202)	14 (6.9)[3]	0.51 (0.28, 0.93)	
Season at birth			
Dry (Jan–Feb) (*n* = 134)	22 (16.4)	1.00	
Long rains (Mar–Jun) (*n* = 349)	37 (10.6)	0.60 (0.34, 1.07)	
Dry (July–Oct) (*n* = 259)	28 (10.8)	0.62 (0.34, 1.13)	
Short rains (Nov–Dec) (*n* = 80)	4 (5.0)[2]	0.27 (0.09, 0.81)	
Primiparous			
No (*n* = 549)	55 (10.0)	1.00	
Yes (*n* = 269)	35 (13.0)	1.34 (0.86, 2.11)	
Previous preterm infant			
No (multiparas) (*n* = 485)	44 (9.1)	1.00	1.00
Yes (multiparas) (*n* = 62)	11 (17.7)[4]	2.16 (1.05, 4.45)	2.66 (1.26, 5.81)
Primiparas (*n* = 269)	35 (13.0)	1.50 (0.94, 2.40)	1.41 (0.83, 2.39)
Nutritional factors			
Weight: 1-kg increment	—	0.96 (0.94, 0.99)[5]	0.96 (0.93, 0.99)
Height: 1-cm increment	—	0.94 (0.91, 0.98)	0.96 (0.92, 1.01)[6]
Midupper arm circumference: 1-cm increment	—	0.91 (0.84, 0.99)	0.92 (0.84, 1.00)[7]
BMI (kg/m^2)			
<18.5 (*n* = 24)	4 (16.7)	1.81 (0.58, 5.68)	2.05 (0.61, 6.90)
18.5–19.9 (*n* = 97)	11 (11.3)	1.14 (0.55, 2.37)	1.01 (0.61, 2.37)
20.0–21.9 (*n* = 184)	23 (12.5)	1.27 (0.72, 2.26)	1.36 (0.73, 2.54)
22.0–24.9 (*n* = 306)	31 (10.1)	1.00	1.00
≥25 (*n* = 210)	21 (10.0)	0.98 (0.55, 1.76)[5]	1.06 (0.55, 2.04)[8]
Serum retinol (μmol/L)			
<0.35 (*n* = 26)	5 (19.2)	2.11 (0.77, 5.78)	
0.35-0.69 (*n* = 186)	24 (12.9)	1.31 (0.79, 2.17)[5]	
≥0.70 (*n* = 425)	40 (9.4)	1.00	
Vitamin E (mg/L)			
<8.0 (*n* = 163)	19 (11.7)	0.99 (0.92, 1.07)[5]	
≥8.0 (*n* = 475)	51 (10.7)	1.00	
HIV-related factors			
Stage of HIV disease			
I (*n* = 693)	68 (9.8)	1.00	1.00
II (*n* = 120)	19 (15.8)	1.73 (1.00, 3.00)	1.64 (0.87, 3.07)
III (*n* = 9)	4 (44.4)[9]	7.35 (1.93, 28.04)	6.12 (1.08, 34.64)
CD4 count (× 10^6 cells/L)			
<200 (*n* = 97)	13 (13.4)	1.36 (0.72, 2.56)	
≥200 (*n* = 675)	69 (10.2)	1.00	
CD8 count (× 10^6 cells/L)			
<563 (*n* = 254)	19 (7.5)	0.58 (0.34, 1.00)	0.52 (0.29, 0.93)
≥563 (*n* = 518)	63 (12.2)[2]	1.00	1.00

(Continued)

TABLE 2 (*Continued*)

Risk factor	Birth weight < 2500 g	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[1]
CD3 count ($\times 10^6$ cells/L)			
<1012 (n = 253)	20 (7.9)	0.63 (0.37, 1.07)	
≥1012 (n = 518)	62 (12.0)	1.00	
Reported vaginal discharge			
No (n = 733)	75 (10.2)	1.00	
Yes (n = 89)	16 (18.0)[2]	1.92 (1.06, 3.47)	
Candidiasis			
No (n = 472)	49 (10.4)	1.00	
Yes (n = 330)	42 (12.7)	1.26 (0.81, 1.95)	
Parasitic factors			
Malaria parasitemia ($\times 10^6$ cells/L)			
None (n = 657)	60 (9.1)	1.00	1.00
1–999 (n = 43)	6 (14.0)	1.61 (0.65, 3.98)	0.80 (0.22, 2.84)
1000–9999 (n = 91)	17 (18.7)	2.29 (1.27, 4.12)	2.20 (1.15, 4.20)
≥10000 (n = 19)	5 (26.3)[9]	3.55 (1.24, 10.21)	2.36 (0.71, 7.81)
Hookworm infection			
No (n = 605)	67 (11.1)	1.00	
Yes (n = 77)	8 (10.4)	0.93 (0.43, 2.02)	
Ascaris lumbricoides infection			
No (n = 644)	68 (10.6)	1.00	
Yes (n = 40)	7 (17.5)	1.80 (0.77, 4.22)	
Strongyloides stercoralis infection			
No (n = 672)	71 (10.6)	1.00	1.00
Yes (n = 12)	4 (33.3)[2]	4.23 (1.24, 14.41)	5.97 (1.23, 28.98)[10]
Entamoeba histolytica infection			
No (n = 669)	69 (10.3)	1.00	1.00
Yes (n = 15)	6 (40.0)[11]	5.80 (2.00, 16.78)	4.68 (1.46, 14.94)[10]
Cryptosporidium parvum infection			
No (n = 656)	75 (11.4)		
Yes (n = 28)	0 (0)	—	—
Any helminth infection			
No (n = 531)	51 (9.6)	1.00	1.00
Yes (n = 153)	24 (15.7)[2]	1.75 (1.04, 2.95)	1.85 (1.02, 3.35)[10]
Any intestinal parasitic infection			
No (n = 493)	47 (9.5)	1.00	1.00
Yes (n = 191)	28 (14.7)[3]	1.63 (0.99, 2.69)	1.65 (0.94, 2.90)[10]
Infant factors			
Infant sex			
Female (n = 394)	53 (13.4)	1.00	
Male (n = 426)	38 (8.9)[2]	0.63 (0.41, 0.98)	
Infant HIV status at birth			
Negative (n = 651)	60 (9.2)	1.00	
Positive (n = 57)	9 (15.8)	1.85 (0.86, 3.95)	

[1] Multivariate-adjusted odds ratio from a logistic regression model controlling for multivitamin and vitamin A supplement group, gestational age at baseline, maternal weight, CD8 count < 563 $\times 10^6$ cells/L, stage of HIV disease, previous history of preterm birth, primiparity, and malaria parasite density.

[2,3,11] Chi-square test: [2] $P < 0.05$, [3] $P = 0.05$, [11] $P < 0.005$.

[4] Birth weight of multiparas with and without a previous preterm birth significantly different, $P < 0.05$ (chi-square test).

[5] Adjusted for gestational age at enrollment.

[6] Maternal height was added to the multivariate-adjusted model described in footnote 1.

[7] Maternal midupper arm circumference was substituted for weight in the multivariate-adjusted model described in footnote 1.

[8] Maternal BMI was substituted for weight in the multivariate-adjusted model described in footnote 1.

[9] Chi-square test for trend: $P < 0.005$.

[10] Each intestinal parasite species or summary variable was added individually to the multivariate-adjusted model described in footnote 1.

ment group and other significant risk factors. Birth weight was not associated with hemoglobin concentration (data not shown).

HIV-related factors

Infant birth weight did not differ significantly among women in the earlier stages of HIV disease, but was significantly lower in women in stage III than in women in stage I (−463 g; 95% CI: –821, –105 g). Candidiasis and sexually transmitted diseases diagnosed at enrollment, including syphilis and *T. vaginalis,* were not related to birth weight (data not shown). CD4 and CD8 cell counts were associated with birth weight even after multivariate adjustment that included maternal HIV stage of disease.

Parasitic factors

Malaria was associated with a multivariate-adjusted lower birth weight of 133 g (95% CI: –221, –45 g). Birth weight was progressively lower with increasing density of *P. falciparum* malaria ≥1000 $\times$ 10^6/L. Although birth weight decrements by

TABLE 3
Birth weight and birth weight differences by risk factors among HIV-infected pregnant women in Tanzania

Risk factor	Birth weight[1]	Unadjusted birth weight difference (95% CI)	Adjusted birth weight difference (95% CI)[2]
		g	*g*
Sociodemographic factors			
Maternal age (y)			
<20 (*n* = 99)	2878 ± 468		
20–24 (*n* = 331)	3021 ± 504	144 (30, 257)	
25–29 (*n* = 249)	3059 ± 508	181 (63, 299)	
≥30 (*n* = 143)	3022 ± 532[3]	145 (15, 274)	
Maternal literacy			
No (*n* = 63)	2785 ± 435		
Yes (*n* = 756)	3034 ± 509[4]	249 (120, 379)	246 (114, 377)
Marital status			
Married (*n* = 529)	3039 ± 499		
Single (*n* = 88)	3044 ± 539	4 (−110, 119)	
Cohabiting (*n* = 205)	2942 ± 511[5]	−97 (−179, −16)	
Income source			
Own income or partial support (*n* = 206)	3112 ± 547		
Fully supported by partner (*n* = 615)	2984 ± 490[6]	−126 (−206, −46)	
Occupation			
No outside employment (*n* = 599)	2984 ± 491		
Professional (*n* = 21)	3148 ± 431	164 (−56, 384)	
Small business or other (*n* = 202)	3095 ± 552[5]	111 (31, 192)	
Primiparous			
No (*n* = 549)	3056 ± 520		
Yes (*n* = 269)	2930 ± 468[4]	−127 (−200, −53)	−110 (−183, −37)
Previous preterm infant			
No (multiparas) (*n* = 485)	3070 ± 519		
Yes (multiparas) (*n* = 62)	2954 ± 528	−115 (−248, 19)	
Primiparas (*n* = 269)	2930 ± 467	−139 (−214, −64)	
Nutritional factors			
Weight: 1-kg increment	—	12 (8, 16)[7]	9 (6, 13)
Height: 1-cm increment	—	12 (6, 18)	4 (−3, 10)[8]
Midupper arm circumference: 1-cm increment	—	23 (12, 35)	17 (5, 29)[9]
BMI (kg/m^2)			
<18.5 (*n* = 24)	2954 ± 482	−98 (−308, 112)	−25 (−236, 186)
18.5–19.9 (*n* = 97)	2887 ± 476	−156 (−271, −41)	−167 (−284, −50)
20.0–21.9 (*n* = 184)	2950 ± 500	−93 (−185, −1)	−88 (−179, 3)
22.0–24.9 (*n* = 306)	3039 ± 503		
≥25 (*n* = 210)	3108 ± 520[10]	71 (−18, 159)[7]	48 (−41, 137)[11]
Serum retinol (μmol/L)			
<0.35 (*n* = 26)	2790 ± 531	−261 (−461, −60)	
0.35–0.69 (*n* = 186)	2986 ± 492	−64 (−151, 24)[7]	
≥0.70 (*n* = 425)	3052 ± 505[10]		
Vitamin E (mg/L)			
<8.0 (*n* = 163)	3013 ± 503	27 (−64, 117)	
≥8.0 (*n* = 475)	3040 ± 516		
HIV-related factors			
Stage of HIV disease			
I (*n* = 693)	3027 ± 504		
II (*n* = 120)	2988 ± 511	−39 (−137, 59)	−13 (−110, 84)
III (*n* = 9)	2454 ± 435[3]	−573 (−905, −241)	−463 (−821, −105)
CD4 count (× 10^6 cells/L)			
<200 (*n* = 97)	2901 ± 563	−135 (−243, −28)	−145 (−251, −40)
≥200 (*n* = 675)	3036 ± 496[5]		
CD8 count (× 10^6 cells/L)			
<563 (*n* = 254)	3101 ± 480	122 (46, 198)	141 (67, 215)
≥563 (*n* = 518)	2979 ± 514[5]		
CD3 count (× 10^6 cells/L)			
<1012 (*n* = 253)	3044 ± 509	39 (−37, 115)	
≥1012 (*n* = 518)	3005 ± 503		
Reported vaginal discharge			
No (*n* = 733)	3025 ± 505		
Yes (*n* = 89)	2936 ± 522	−89 (−201, 22)	

(Continued)

TABLE 3 (*Continued*)

Risk factor	Birth weight[1]	Unadjusted birth weight difference (95% CI)	Adjusted birth weight difference (95% CI)[2]
Candidiasis			
No (n = 472)	3012 ± 507		
Yes (n = 330)	3008 ± 516	−4 (−76, 68)	
Parasitic factors			
Malaria parasitemia (× 10^6 cells/L)			
None (n = 657)	3051 ± 492		
1–999 (n = 43)	3022 ± 544	−29 (−183, 126)	−26 (−182, 131)
1000–9999 (n = 91)	2874 ± 517	−176 (−286, −67)	−140 (−249, −31)
≥10 000 (n = 19)	2650 ± 638[12]	−401 (−629, −172)	−337 (−561, −112)
Hookworm infection			
No (n = 605)	3027 ± 514		
Yes (n = 77)	2925 ± 486	−102 (−223, 19)	−93 (−211, 25)[13]
Ascaris lumbricoides infection			
No (n = 644)	3017 ± 508		
Yes (n = 40)	2972 ± 562	−44 (−208, 119)	
Strongyloides stercoralis infection			
No (n = 672)	3014 ± 509		
Yes (n = 12)	3033 ± 638	20 (−273, 312)	
Entamoeba histolytica infection			
No (n = 669)	3022 ± 506		
Yes (n = 15)	2680 ± 677[5]	−342 (−603, −81)	−252 (−496, −7)[13]
Cryptosporidium parvum infection			
No (n = 656)	3004 ± 511		
Yes (n = 28)	3241 ± 472[5]	237 (44, 429)	222 (30, 413)[13]
Any helminth infection			
No (n = 531)	3032 ± 509		
Yes (n = 153)	2951 ± 516	−81 (−173, 11)	−92 (−183, −2)[13]
Any intestinal parasitic infection			
No (n = 493)	3030 ± 504		
Yes (n = 191)	2974 ± 529	−56 (−142, 29)	−53 (−136, 31)[13]
Infant factors			
Infant sex			
Female (n = 394)	2973 ± 515		
Male (n = 426)	3055 ± 499[5]	83 (13, 152)	68 (−1, 136)
Infant HIV status at birth			
Negative (n = 651)	3042 ± 483		
Positive (n = 57)	2846 ± 529[6]	−195 (−327, −63)	−178 (−316, −40)

[1] $\bar{x}$ ± SD.

[2] Multivariate-adjusted birth weight difference from a linear regression model controlling for multivitamin and vitamin A supplement group, gestational age at baseline, maternal weight, CD4 count <200 × 10^6 cells/L, CD8 count <563 × 10^6 cells/L, literacy, stage of HIV disease, primiparity, malaria parasite density, infant sex, and infant HIV status.

[3,10,12] Test for trend: [3] $P < 0.05$, [10] $P < 0.01$, [12] $P < 0.0005$.

[4–6] Wilcoxon rank-sum test: [4] $P < 0.0005$, [5] $P < 0.05$, [6] $P < 0.005$.

[7] Adjusted for gestational age at enrollment.

[8] Maternal height was added to the multivariate-adjusted model described in footnote 2.

[9] Maternal midupper arm circumference was substituted for weight in the multivariate-adjusted model described in footnote 2.

[11] Maternal BMI was substituted for weight in the multivariate-adjusted model described in footnote 2.

[13] Each intestinal parasite species or summary variable was added individually to the multivariate-adjusted model described in footnote 2.

parasite density were smaller in primiparous than in multiparous women, there was no significant interaction between primiparity and malaria parasitemia (data not shown). Among helminths, hookworm infection was associated with a marginally significantly lower birth weight. However, infection with the protozoa *E. histolytica* was associated with a large birth weight difference of −252 g (95% CI: −496, −7). Birth weight among women infected with *C. parvum* was significantly higher than in uninfected women even after multivariate adjustment (222 g; 95% CI: 30, 413 g). Infection with any helminth species was associated with a significantly lower birth weight, but, because of the positive association of *C. parvum* with birth weight, infection with any intestinal parasite species was not.

Infant factors

Infant HIV infection at birth was associated with a significant difference in birth weight of −178 g after multivariate adjustment (95% CI: −316, −40 g). In a multivariate-adjusted model, male infants were heavier than females by 68 g (95% CI: −1, 136 g).

Risk factors for small-for-gestational age status

Incidence rates and odds ratios for risk factors for SGA are presented in **Table 4**. Similar to the regression models for LBW and birth weight, anthropometric indicators of maternal nutritional status, particularly weight, were important risk factors for SGA. By contrast, a low vitamin E concentration (<8.0 mg/L) was asso-

TABLE 4
Incidence of small-for-gestational-age status and odds ratios by risk factor among HIV-infected pregnant women in Tanzania

Risk factor	Small for gestational age	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[1]
	n (%)		
Sociodemographic factors			
Maternal age (y)			
<20 (*n* = 99)	14 (14.1)	1.00	
20–24 (*n* = 331)	35 (10.6)	0.72 (0.37, 1.40)	
25–29 (*n* = 249)	27 (10.8)	0.74 (0.37, 1.48)	
≥30 (*n* = 143)	19 (13.3)	0.93 (0.44, 1.96)	
Maternal literacy			
No (*n* = 63)	5 (7.9)	1.00	
Yes (*n* = 756)	89 (11.8)	1.55 (0.60, 3.96)	
Marital status			
Married (*n* = 529)	58 (11.0)	1.00	
Single (*n* = 88)	9 (10.2)	0.93 (0.44, 1.94)	
Cohabiting (*n* = 205)	28 (13.7)	1.28 (0.79, 2.08)	
Income source			
Own income or partial support (*n* = 206)	21 (10.2)	1.00	
Fully supported by partner (*n* = 615)	74 (12.0)	1.21 (0.72, 2.01)	
Occupation			
No outside employment (*n* = 599)	72 (12.0)	1.00	
Professional (*n* = 21)	0 (0.0)	0	
Small business or other (*n* = 202)	23 (11.4)	0.94 (0.57, 1.55)	
Season at birth			
Dry (Jan–Feb) (*n* = 134)	15 (11.2)	1.00	
Long rains (Mar–Jun) (*n* = 349)	47 (13.5)	1.23 (0.66, 2.29)	
Dry (July–Oct) (*n* = 259)	27 (10.4)	0.92 (0.47, 1.80)	
Short rains (Nov–Dec) (*n* = 80)	6 (7.5)	0.64 (0.24, 1.73)	
Primiparous			
No (*n* = 549)	61 (11.1)	1.00	
Yes (*n* = 269)	34 (12.6)	1.16 (0.74, 1.81)	
Previous preterm infant			
No (multiparas) (*n* = 485)	54 (11.1)	1.00	
Yes (multiparas) (*n* = 62)	7 (11.3)	1.02 (0.44, 2.34)	
Primiparas (*n* = 269)	34 (12.6)	1.15 (0.73, 1.82)	
Nutritional factors			
Weight: 1-kg increment	—	0.94 (0.92, 0.97)[2]	0.95 (0.92, 0.98)
Height: 1-cm increment	—	0.94 (0.91, 0.98)	0.97 (0.93, 1.02)[3]
Midupper arm circumference: 1-cm increment	—	0.93 (0.86, 1.00)	0.93 (0.86, 1.01)[4]
BMI (kg/m^2)			
<18.5 (*n* = 24)	7 (29.2)	3.67 (1.40, 9.60)	2.56 (0.88, 7.47)
18.5–19.9 (*n* = 97)	17 (17.5)	1.80 (0.95, 3.41)	1.76 (0.91, 3.42)
20.0–21.9 (*n* = 184)	21 (11.4)	1.09 (0.61, 1.95)	1.17 (0.64, 2.13)
22.0–24.9 (*n* = 306)	33 (10.8)	1.00	1.00
≥25 (*n* = 210)	17 (8.1)[5]	0.72 (0.39, 1.33)[2]	0.77 (0.40, 1.46)[6,7]
Serum retinol (μmol/L)			
<0.35 (*n* = 26)	3 (11.5)	0.95 (0.28, 3.23)	
0.35–0.69 (*n* = 186)	18 (9.7)	0.77 (0.45, 1.32)[2]	
≥0.70 (*n* = 425)	51 (12.0)	1.00	
Vitamin E (mg/L)			
<8.0 (*n* = 163)	27 (16.6)	1.92 (1.15, 3.22)[2]	1.89 (1.10, 3.27)
≥8.0 (*n* = 475)	45 (9.5)[8]	1.00	1.00
HIV-related factors			
Stage of HIV disease			
I (*n* = 693)	84 (12.1)	1.00	
II (*n* = 120)	10 (8.3)	0.66 (0.33, 1.31)	
III (*n* = 9)	1 (11.1)	0.91 (0.11, 7.34)	
CD4 count (× 10^6 cells/L)			
<200 (*n* = 97)	15 (15.5)	1.58 (0.86, 2.89)	
≥200 (*n* = 675)	70 (10.4)	1.00	
CD8 count (× 10^6 cells/L)			
<563 (*n* = 254)	25 (9.8)	0.83 (0.51, 1.36)	
≥563 (*n* = 518)	60 (11.6)	1.00	

(Continued)

TABLE 4 *(Continued)*

Risk factor	Small for gestational age	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)[1]
CD3 count ($\times 10^6$ cells/L)			
<1012 (n = 253)	30 (11.9)	1.13 (0.71, 1.82)	
≥1012 (n = 518)	55 (10.6)	1.00	
Reported vaginal discharge			
No (n = 733)	82 (11.2)	1.00	
Yes (n = 89)	13 (14.6)	1.36 (0.72, 2.55)	
Candidiasis			
No (n = 472)	66 (14.0)	1.00	1.00
Yes (n = 330)	29 (8.8)[8]	0.59 (0.37, 0.94)	0.59 (0.36, 0.96)
Parasitic factors			
Malaria parasitemia			
No (n = 657)	66 (10.0)	1.00	1.00
Yes (n = 153)	27 (17.6)[9]	1.92 (1.18, 3.12)	1.79 (1.06, 3.02)
Any helminth infection			
No (n = 531)	63 (11.9)	1.00	
Yes (n = 153)	19 (12.4)	1.05 (0.61, 1.82)	
Any pathogenic protozoan infection			
No (n = 639)	77 (12.0)	1.00	
Yes (n = 45)	5 (11.1)	0.91 (0.35, 2.38)	
Any intestinal parasitic infection			
No (n = 493)	58 (11.8)	1.00	
Yes (n = 191)	24 (12.6)	1.08 (0.65, 1.79)	
Infant factors			
Infant sex			
Female (n = 394)	57 (14.5)	1.00	1.00
Male (n = 426)	38 (8.9)[8]	0.58 (0.37, 0.90)	0.60 (0.38, 0.94)
Infant HIV status at birth			
Negative (n = 651)	72 (11.1)	1.00	1.00
Positive (n = 57)	11 (19.3)	1.92 (0.95, 3.88)	2.11 (0.97, 4.59)

[1] Multivariate-adjusted odds ratio from a logistic regression model controlling for multivitamin and vitamin A supplement group, gestational age at baseline, maternal weight, low vitamin E concentration, candidiasis, malaria, infant sex, and HIV status at birth.
[2] Adjusted for gestational age at enrollment.
[3] Maternal height was added to the multivariate-adjusted model described in footnote 1.
[4] Maternal midupper arm circumference was substituted for weight in the multivariate-adjusted model described in footnote 1.
[5] P for trend < 0.005 (chi-square test for trend).
[6] Maternal BMI was substituted for weight in the multivairate-adjusted model described in footnote 1.
[7] P for trend < 0.01 (linear test for trend).
[8,9] Chi-square test: [8] $P < 0.05$, [9] $P < 0.01$.

ciated with higher risk of SGA but was not a determinant of LBW. Clinical stage of HIV disease was not associated with higher risk of SGA nor were T lymphocyte cell counts. Women with candidiasis at baseline were less likely to have an SGA infant than were uninfected women. Malaria was associated with a significantly higher relative odds of SGA after multivariate adjustment (AOR: 1.79; 95% CI: 1.06, 3.02), but this association did not differ by parity or malaria parasite density (data not shown). Intestinal parasitic infections were not associated with SGA. Infant HIV infection at birth appeared to be associated with higher risk of SGA, and when maternal BMI was substituted for maternal weight in the multivariate regression model, the association became statistically significant (AOR: 2.26; 95% CI: 1.04, 4.91).

DISCUSSION

Our study findings suggest that both poor nutritional status and infectious diseases contribute to the burden of LBW among HIV-infected women in urban Tanzania. In our analysis of 822 pregnant women, we identified maternal weight, primiparity, a previous history of preterm birth, advanced-stage HIV disease, intrauterine HIV transmission, CD4 and CD8 cell counts, *P. falciparum* malaria, and various intestinal parasitic infections as significant determinants of LBW. Among these risk factors, only maternal weight, malaria, and intrauterine HIV transmission were also associated with SGA status.

Both immunologic and clinical markers of HIV disease progression were important determinants of birth weight in our study cohort. A study of a cohort of HIV-positive pregnant women in the United States also showed a significant association between low CD4 percentage and LBW (20). However, other cohort studies of HIV-positive and HIV-negative women in the United States (21) and sub-Saharan Africa (22) did not find T lymphocyte counts during pregnancy to be determinants of birth weight. CD4 and CD8 cell counts are often measured as immunologic surrogates of clinical HIV disease progression. However, their association with birth weight independent of clinical disease stage suggests that they are also markers of compromised immune status in general. Immunosuppression in HIV-positive women may contribute to LBW by increasing

women's susceptibility to infections and by compromising their nutritional status. Conversely, poor nutritional status could alter T lymphocyte counts, leading to increased immunosuppression and an effect on birth weight. We reported previously that multivitamin but not vitamin A supplementation during pregnancy resulted in increased CD4, CD8, and CD3 cell counts in our study cohort (19).

The higher risk of LBW associated with advanced-stage HIV disease was much greater among women with stage III disease. However, only 1% of study subjects were classified as having stage III disease at enrollment. A meta-analysis of studies examining the relation of HIV infection to pregnancy outcomes concluded that HIV-infected women are at higher risk of LBW than are uninfected women (8). The few studies that examined this relation stratified by stage of disease found that symptomatic HIV-positive women tend to have a higher risk of LBW than do asymptomatic women (23–24). Our findings suggest that the relation of HIV infection to birth weight is primarily attributable to women who enter pregnancy in the later stages of HIV disease and are more immunosuppressed, but the mechanism of action for this relation is uncertain. It cannot be explained by increased vertical transmission of HIV because control for this factor in the multivariate models did not change the associations of clinical stage of HIV disease and T lymphocyte counts with birth weight. It is also unlikely that advanced-stage HIV disease contributes to LBW by causing fetal growth retardation because HIV disease stage was not significantly associated with SGA in our analyses.

Positive infant HIV status at birth was associated with higher risk of LBW and SGA and with a significantly lower birth weight by 178 g after adjustment for other risk factors. This relation was not confounded by stage of HIV disease or immunologic disease progression in mothers, nor did it change the associations of these maternal factors with birth weight. This suggests that fetal HIV infection contributed to poor intrauterine growth independent of maternal disease progression. Some studies from industrialized countries reported an inverse association between infant HIV infection and birth weight (10, 25), whereas others reported no association (26–28). However, illicit drug use may have confounded the relation between infant HIV infection and birth weight in these studies. Two studies from Rwanda found significantly lower birth weights in HIV-infected infants than in uninfected ones, but these studies did not examine the effect of immunologic and clinical indicators of maternal disease status (9, 29). These findings suggest that in utero transmission of HIV may lead to fetal growth retardation, or the relation could be reversed, ie, retarded growth in utero increases susceptibility of the fetus to HIV infection. However, in many of the studies reported so far, infants who seroconverted in the first 12–24 mo of life were compared with seronegative infants; thus, these studies could not distinguish between transmission in utero and peri- or postnatal transmission, and their findings may be biased toward the null.

Maternal nutritional status during pregnancy was an important predictor of birth weight and intrauterine growth retardation independent of clinical HIV disease progression and associated immunosuppression in our cohort. Although it is well established that maternal nutritional status before and during pregnancy is an important predictor of poor pregnancy outcomes (6, 16), few studies have examined these relations in the presence of HIV infection. A large malaria prevention trial in Malawi reported that a maternal weight of <50 kg at enrollment was a significant predictor of LBW independent of the effects of maternal HIV status, placental malaria infection, and malaria prophylaxis (30). A cohort study of HIV-positive and HIV-negative pregnant women in Rwanda reported that the last prenatal weight measurement was significantly associated with higher risk of LBW independent of maternal HIV status (22). However, the weight late in pregnancy was lower in infected women than in uninfected women (22). HIV infection is associated with reduced dietary intake, malabsorption of nutrients, and metabolic alterations early in the infection (31). It appears that maternal nutritional status remains an important factor in fetal growth among HIV-positive women, and HIV disease may also affect birth weight indirectly through its negative effect on maternal nutrition during pregnancy.

We found that *P. falciparum* malaria parasitemia during pregnancy was significantly associated with lower birth weight and higher risk of LBW and SGA among both primiparas and multiparas. Other studies in sub-Saharan Africa observed this relation among women in their first and sometimes second pregnancies only (32–35). All of our study subjects were given weekly malaria prophylaxis (chloroquine) according to the Ministry of Health standards of prenatal care in Tanzania and were also given a treatment regimen if malaria was diagnosed during pregnancy. Trials of malaria prophylaxis with chloroquine alone have had limited (36) or no (37) effect on birth weight. Development of drug resistance by the malaria parasite in East Africa (38, 39) has led to reduced effectiveness of chloroquine in preventing or clearing *P. falciparum* malaria (40) and may explain the relation between malaria and birth weight observed in our study. More recent chemoprophylaxis trials found other antimalarial drugs such as proguanil (34, 41), sulfadoxine-pyrimethamine (42), and mefloquine (30) to be more effective than chloroquine for improving birth weight and reducing the risk of LBW.

The presence of HIV infection may also influence the effect of malaria on intrauterine growth by increasing the susceptibility of pregnant women to heavier malaria parasitemia loads and increased placental infection. HIV infection was significantly associated with increased malaria prevalence and parasite density at enrollment and delivery among pregnant women enrolled in 2 studies in Malawi (43, 44). Rates of placental infection and cord blood parasitemia were also higher among HIV-infected women in one of these studies (44). In this latter study population, placental malaria and maternal HIV infection were both independently associated with a significantly higher risk of LBW (30). Parasite density and infection of the placenta have a negative effect on fetal growth, so we would expect to see malaria as an important determinant of LBW in HIV-infected women.

Various intestinal parasitic infections were associated with higher risk of LBW in our study population. Although the prevalence of these infections was low and infections were treated at enrollment, these findings are provocative and may have important implications in rural African communities where these intestinal parasites are more prevalent. Our ability to observe relations between many of these parasitic infections and birth weight may also have been hindered by the absence of a measure of the intensity of infection.

Little is known about the contribution of intestinal parasites to fetal growth. Two studies in Southeast Asian refugee populations found that intestinal parasites were not associated with birth weight

(45, 46), but a large prospective cohort study in Guatemala observed that intestinal parasitic infection was associated with increased risk of SGA, particularly among chronically malnourished women (47). A small study in Ecuador reported that *E. histolytica* parasite burden was associated with significant reductions in indicators of fetal growth (48). In this study, various intestinal parasites were associated with LBW but not with SGA. It remains unclear whether the observed effects of intestinal parasites on birth weight are due to the cumulative burden of multiple infections or the specific action of individual parasite species.

We identified nutritional, immunologic, and parasitic risk factors for LBW in our study population of HIV-infected pregnant women in Tanzania. Poor maternal nutritional status was an important determinant of LBW in this population, as has been found in many other settings, but its contribution in this cohort may have been further exacerbated by the effects of HIV disease on maternal health. Although maternal HIV infection was associated with a higher risk of LBW only among women in an advanced clinical stage of the disease, it may also have contributed indirectly through negative effects on maternal immunity and nutritional status. Vertical HIV transmission in utero appears to contribute to poor intrauterine growth, although the causal relation could also be reversed when poor growth increases susceptibility to transmission of the virus. *P. falciparum* malaria continues to be an important risk factor for LBW in sub-Saharan Africa despite chemoprophylaxis and treatment efforts as part of prenatal care. The interrelations between HIV infection, its associated immunosuppression, and malaria infection during pregnancy are still poorly understood. Finally, the association of intestinal parasitic infections with a higher risk of LBW suggests that these infections could be significant contributors to the burden of LBW in populations in whom the prevalence and severity of these infections is high. Efforts to reduce the burden of LBW in sub-Saharan African populations should focus on improving nutritional status, reducing HIV vertical transmission and disease progression, and implementing case management of malaria and intestinal parasitic infections to reduce the risk of LBW and other adverse pregnancy outcomes.

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