Perinatal Human Immunodeficiency Virus-1 Transmission and Intrauterine Growth: A Cohort Study in Butare, Rwanda

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ABSTRACT. *Objective.* **To study the association of perinatal human immunodeficiency virus (HIV)-1 transmission with birth outcomes, including birth weight, gestational age, ponderal index, head circumference, and weight/head ratio.**

Methods. **Data from a prospective cohort study of 627 pregnant women and their infants in Butare, Rwanda, from October 1989 until April 1994 were analyzed. A total of 318 HIV-1-infected and 309 seronegative women were enrolled during pregnancy and gave birth to 590 live singletons. Multiple linear regression modeling was used to assess the association of mother–child HIV status with several birth outcome measures.**

Results. **Unadjusted mean birth weight of HIV-infected infants was 235 g (95% confidence interval [CI] = 94 to 376 g) less than that of HIV-uninfected infants born to HIV-positive mothers (the reference group). After adjustment for gestational age, socioeconomic factors, maternal age, parity, hematocrit, and anthropomorphic measures, mean birth weight of HIV-infected infants was 154 g (95% CI = 38 to 271 g) lower than that of the reference group. When infants born to HIV-seronegative mothers were compared with the reference group, mean birth weights did not differ. Adjusted models resulted in estimates of mean head circumference 0.6 cm smaller (95% CI = 0.2 to 1.1 cm), ponderal index 0.14 lower (95% CI = 0.05 to 0.23), weight/head ratio 3.5 lower (95% CI = 0.5 to 6.4), and gestational age 0.5 weeks shorter (95% CI = 0.1 to 0.9 weeks) for HIV-infected infants than for the reference group.**

Conclusions. **After adjustment for potential confounding variables, this study showed statistically significant differences in birth weight, gestational age, ponderal index, and weight/head ratio when HIV-infected infants were compared with noninfected infants born to HIV-positive mothers.** *Pediatrics* **1998;102(2). URL: http://www.pediatrics.org/cgi/content/full/102/2/e24;** ***HIV-1, mother-to-child transmission, Africa, intrauterine growth, birth weight, gestational age, ponderal index.***

ABBREVIATIONS. HIV, human immunodeficiency virus; PCR, polymerase chain reaction; ECS, European Collaborative Study; IUGR, intrauterine growth retardation; STD, sexually transmitted disease; AIDS, acquired immunodeficiency syndrome; WHO, World Health Organization; MUAC, mid-upper arm circumference; BMI, body mass index; LBW, low birth weight; WB, Western blot; CI, confidence interval.

Birth weight is generally studied because it is an established predictor of infant mortality in developed and developing countries.[1] Perinatal mortality decreases exponentially with birth weight up to the optimum, ~3500 to 3900 g.[2] A substantial increase in mortality is associated with even a modest reduction in birth weight, as in New Delhi, India, where a 22% increase in mortality could be attributed to every 10% reduction in birth weight for infants weighing ≤2700 g.[3] Ponderal index values <2.1 also are associated with an increased risk of perinatal mortality.[4]

As outcomes, birth weight and other body measures may help elucidate the question of when most mother-to-child human immunodeficiency virus (HIV) transmission occurs. Studies providing evidence for the relative contributions of intrauterine, intrapartum, and postnatal HIV transmission have been reviewed.[5–7] On the basis of polymerase chain reaction (PCR) testing and HIV-1 culture, a working definition of in utero compared with intrapartum transmission for nonbreastfeeding infants has been proposed.[8] For breastfeeding infants, the Ghent International Working Group on Mother-to-Child Transmission recommended criteria for distinguishing in utero, intrapartum, and early postnatal mother-to-child transmission.[9] A study of fetuses suggests that early intrauterine HIV infection is rare,[10] and studies based on neonatal PCR[11,12] and/or viral culture[13,14] provide estimates that approximately one third of vertically acquired HIV infection occurs in utero.

Although PCR[10,15] tests and HIV cultures[16] are sensitive and specific for diagnosing HIV infection in infants, they do not provide definitive answers to the question of timing and are not readily available in developing countries. Assumptions must be made about the interval between inoculation and presence of circulating viral markers. Breastfeeding, which may increase the risk of mother-to-child transmis-

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Received for publication Jul 11, 1997; accepted Mar 25, 1998.

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sion by 14%,[17] adds to the difficulty of timing the transmission.

Several studies have related HIV status of the mother to birth outcomes. In developing countries, infants born to HIV-1-infected mothers tend to have lower birth weights than do infants of seronegative women.[18–25] Except in a study of 772 women in New York State,[26] these differences were not replicated in developed countries.[27,28] When HIV-infected and -uninfected infants born to HIV-infected mothers were compared, some studies in developing countries[29] and industrialized nations[30–32] showed a reduction in birth weight, whereas others did not.[25,33–36]

In a prospective study of 853 children born to HIV-infected women, the European Collaborative Study (ECS)[37] found a weak association between birth weight and infant HIV infection status after adjustment for other variables, including gestational age, sociodemographic factors, intravenous drug use, and maternal immunologic status. Infants' HIV status was not significantly associated with gestational age. The analysis in the present study follows the ECS approach, using multiple linear regression to analyze data from a prospective cohort study in southern Rwanda. Previous findings from this Rwandan study[24] showed that positive maternal HIV infection status was associated with decreased birth weight and a higher proportion of intrauterine growth retardation (IUGR) in the offspring. Maternal HIV infection was not significantly associated with preterm birth (<37 completed weeks of gestation). The current analysis extends the previous report by investigating differences in birth measures between HIV-infected and uninfected infants, while controlling for possible confounders.

METHODS

Study Population, Cohort Enrollment, and Follow-up

During 28 months from October 31, 1989, to February 29, 1992, 5989 pregnant women attending one of five health centers in a semirural but densely populated area surrounding the town of Butare, Rwanda, were screened for HIV-1 antibody.[38] Overall, HIV-1 seroprevalence was 9.3%. During this period, 441 HIV-1-positive women were randomly selected from all seropositive women. Of these women, 346 met the cohort inclusion criteria: 1) home residence within 25 km of Butare; and 2) alive and still pregnant at the time of enrollment. The methods and enrollment procedures have been documented in detail elsewhere.[24] Of the 346 eligible women, 318 (92%) agreed to participate. A control group of HIV-1-seronegative women meeting the inclusion criteria was enrolled. For each seropositive woman selected, one seronegative woman was randomly chosen among all seronegative women who were screened at the same health center on the same day. Among 335 eligible seronegative women, 309 (92%) agreed to participate.

Women were enrolled in the cohort at the second prenatal visit (median, 32 completed weeks of gestation; range, 12 to 40). Interviewers speaking the native language obtained information about socioeconomic status and medical history with standardized questionnaires. History of sexually transmitted disease (STD) during the past 3 years and weight change from start of pregnancy until cohort enrollment were self-reported. Women were evaluated for signs and symptoms of acquired immunodeficiency syndrome (AIDS) using the World Health Organization (WHO) clinical case definition[39] at enrollment and soon after delivery. Most women were asymptomatic, and none met the WHO clinical definition of adult AIDS. Anthropomorphic measures included mid-upper arm circumference (MUAC), height, weight, and body mass index (BMI).

Women were encouraged to deliver at one of two maternity clinics participating in the study, and neonatal examinations were performed within 48 hours of birth. There were 590 singleton live births (297 among seropositive mothers and 293 among seronegative mothers). Mothers and infants were followed every 6 weeks during the first year after birth and then every 4 months until the study ended in April 1994. All infants were breastfed.

Definition and Selection of Variables

The criteria of the Working Group on Mother-to-Child Transmission of HIV (Ghent, 1992)[40] were used to define each infant's HIV infection status. Infants were classified as positive if they were seropositive at 12 and 16 months of age, whereas those who were negative at both ages were considered uninfected. Seven children who were negative at 12, 16, and 20 months but who became HIV seropositive after 20 months of age were considered to be infected through breastfeeding beyond the first year of life[41] and were classified as HIV-uninfected for the purpose of this perinatal investigation. Infants who died before 12 months of age were considered HIV-infected if severe infection or persistent diarrhea was the probable cause of death and at least one HIV-related sign or symptom was present at the last examination.[40] Twenty-two singletons, who died during the postneonatal period but did not meet the above criteria, were considered indeterminate for HIV-1 infection status. Infants who died before 28 days of age (15 infants with HIV-negative mothers and 10 with HIV-positive mothers) and 11 infants with HIV-positive mothers who were lost to follow-up before 12 months of age were excluded from the analysis. Thus, 43 infants of HIV-positive mothers at enrollment were excluded from the analysis. Two infants were excluded because their mothers, who were HIV-negative at enrollment, seroconverted shortly before or at the time of delivery.

Socioeconomic variables of household income, maternal education and marital status, and nutritional variables of maternal MUAC, BMI, weight change (self-reported weight change from start of pregnancy to enrollment), height, and weight were examined. MUAC was chosen as the main nutritional status variable because this measure did not depend on recall or the timing of enrollment during pregnancy, it correlates well with BMI in well- and undernourished individuals,[42] and the analysis showed similar effects for MUAC and other nutritional variables. Other factors related to maternal health included hematocrit adjusted for weeks of gestation[43] and the presence of malaria parasites in maternal blood cultures at the initial visit.

Outcome variables included birth weight (g), gestational age (weeks of completed gestation), ponderal index (birth weight $\times$ 100/crown-to-heel length^3), head circumference (cm), weight/head ratio (birth weight/head circumference), low birth weight (LBW) (<2500 g), and IUGR (birth weight less than 10th percentile for gestational age). Gestational age was estimated with Ballard maturity scoring at birth, and in those cases in which ultrasonography was performed before 24 weeks of pregnancy, corroborated by the biparietal diameter.[24]

Laboratory Methods

Laboratory tests were performed at the project laboratory in Butare, Rwanda. HIV serology was done by enzyme-linked immunosorbent assay and confirmed by Western blot (WB) analysis. Persistence of HIV-1 antibody using a WB technique (BioRad Laboratories, Hercules, CA) was defined by the presence of at least one reactive band to an HIV-1 core protein (p17, p24, p55), plus at least one reactive band to an HIV-1 envelope protein (gp41, gp120, gp160).[44]

Lymphocyte subsets were determined by standard flow-cytometry procedures using commercial, dual-label monoclonal antibodies (Becton-Dickinson Immunocytometry, San Jose, CA) described previously.[45] Data on CD4 percentage and CD4:CD8 ratio were used because absolute CD4 and CD8 counts vary substantially during the antenatal through postpartum period,[46] and CD4 and CD8 percentages have been shown to remain stable from late pregnancy to 6 weeks' postpartum.[47]

Statistical Methods

Summary statistics for potential explanatory variables and outcome measures were obtained for each of the three mother–infant HIV status groups. Because the distributions of lymphocyte mea-

sures were skewed, natural logarithmic transformations of CD4 percent, CD4:CD8 ratio, or quartiles of these variables were used in models. Proportions were compared with a χ^2 test for homogeneity of proportions or Fisher's exact test. Linear regression was used to assess differences among means. With skewed distributions, the nonparametric Kruskal–Wallis test was used to compare medians. All statistical tests were two-tailed.

Linear regression models were used to assess the association between the set of explanatory variables and the outcome variables, birth weight, ponderal index, gestational age, head circumference, and weight/head ratio. Initial models were based only on observations that had data for all variables. A variety of models were fitted, including simple linear regression, models including interaction terms with HIV status, and models with subsets of related covariates. Variables were included in the full model if they changed the estimate of the coefficient for HIV-infected infants by at least 50 g or significantly affected the precision of this estimate. Other variables were added if they helped predict birth weight (for categorical variables, absolute value of coefficient at least 100 g), were statistically significant ($P < .05$), or were important predictors a priori. The final model was chosen after elimination of variables from the full model. All statistical analyses were performed with SAS software.[48]

RESULTS

Of the 530 singleton infants in the analysis, 48 were in group 1 (HIV-infected infants), 206 were in group 2 (the referent category, HIV-uninfected infants of HIV-positive mothers), and 276 were in group 3 (infants of HIV-negative mothers). The intermediate estimate for the mother-to-child transmission rate was 18.9% (95% confidence interval [CI] = 14.1 to 23.7%) calculated by the direct method outlined by Dabis and associates.[9] Minimum and maximum estimates were 16.1% (95% CI = 11.9 to 20.3%) and 31.1% (95% CI = 25.8 to 36.4%), respectively. Forty-eight percent of group 1 infants had LBW, considerably higher than the 23% of group 2 infants ($P < .001$), whereas the proportion of LBW (23%) in group 3 did not differ significantly from group 2 ($P = .95$). On the other hand, the proportion of infants with IUGR did not differ significantly ($P = .26$) between group 1 (34%) compared with group 2 (26%); however, there was a trend toward significance ($P = .054$) in the difference between group 3 (18% with IUGR) and group 2.

Birth Weight

Groups 1 and 2 differed significantly in mean birth weight, whereas groups 2 and 3 differed on sociodemographic variables such as maternal age, income, and education (Table 1). Proportionately more mothers in group 1 were single and nulliparous than were those in the other groups, whereas more mothers in group 3 were legally married. Group 1 had the highest proportion of mothers who smoked cigarettes or reported a history of any STD; these proportions were successively lower in group 2 and group 3.

Table 2 shows results of linear regression models of birth weight. In the univariate model, there was a significant difference between mean birth weights in group 1 compared with group 2, but not between groups 3 and 2. Infant's gestational age, maternal age <20 years, parity, hematocrit, height, and MUAC were important predictors of mean birth weight in univariate models. Blood smears for malaria parasitemia during pregnancy were available for 273 mothers (Table 1). Maternal malarial parasitemia was associated with decreased birth weight (102 g) in the model adjusted for all three infant HIV groups and gestational age, although this difference was not statistically significant (95% CI = −242 to 38; $P = .15$) (data not shown). Interactions between infant's HIV status and each covariate in Table 2 were examined, but none of these retained statistical significance in the multivariate model (data not shown).

Variables included in the final model for birth weight (Table 2) were mother–child HIV status and potential confounding variables: gestational age, parity, maternal age, cigarette smoking, height, hematocrit, MUAC, and family income. After adjustment for these variables, a significant difference in mean birth weight between groups 1 and 2 persisted, but not between groups 2 and 3. The final model excluded self-reported history of STD, maternal syphilis serology, malarial parasitemia, weight gain during pregnancy, and infant's gender, because these variables neither affected the coefficient of positive infant HIV status nor improved its precision. Because <1% of the women had systolic blood pressure at least 140 mm Hg or diastolic blood pressure at least 90 mm Hg, these measures were omitted.

Data on maternal CD4 percent, CD8 percent, and CD4:CD8 ratios were available for 273 mothers who were tested prenatally or within 100 days postpartum. Mean CD4 percent and CD4:CD8 ratio were significant predictors of infant's HIV status; these measures were lower in group 1 than in group 2 (Table 1). To assess the effect of maternal CD4:CD8 ratio and malarial parasitemia on birth weight among infants born to HIV-positive mothers, the full model in Table 2 was used to perform another regression analysis on the subset of 122 mother–infant pairs with complete data on all relevant variables (Table 3). Again group 1 had lower mean birth weight than did group 2 in this multivariate model. Although this difference was statistically significant in the univariate model, significance was lost in the full model adjusted for infant's HIV status, gestational age, maternal parity, age, cigarette smoking, MUAC, height, hematocrit, logarithm of mother's CD4:CD8 ratio, malarial parasitemia, and family income (Table 3). With the variability observed in the final model, the estimated coefficient for the difference in mean birth weight between groups 1 and 2 would need to have been −140 or more extreme to achieve statistical significance. Malarial parasitemia was associated with a significant decrease in birth weight in this model.

Gestational Age

There was a statistically significant difference between groups 1 and 2, but not between groups 2 and 3 (Table 1). Adjustment for possible confounders did not change the association appreciably. The distribution of gestational age for each HIV group was skewed to lower ages. Comparison of gestational ages across the three HIV groups with the Kruskal–Wallis test did not indicate a statistically significant difference ($P = .13$).

TABLE 1. Medical and Sociodemographic Characteristics of 530 Mother–Infant Pairs in Butare, Rwanda, 1989–1994[a]

Variable	Group 1: Mother Positive/ Infant Positive; Mean ± SD or % of Group (n = 48)	Group 2: Mother Positive/ Infant Negative; Mean ± SD or % of Group (n = 206)	Group 3: Mother Negative/ Infant Negative; Mean ± SD or % of Group (n = 276)
Infant			
Birth weight (g) ± SD	2539 ± 431‡	2772 ± 429	2824 ± 408
Gender			
Male	50%	45%	56%
Female	50%	55%	44%
Gestational age (wk)			
<38	11%	6%	6%
38–39	29%	27%	26%
40	51%	50%	48%
≥41	9%	17%	20%
Mean ± SD	39.1 ± 1.6*	39.6 ± 1.2	39.6 ± 1.3
Maternal sociodemographics			
Age (y)†			
15–19	8%	7%	4%
20–24	42%	44%	35%
25–29	42%	42%	42%
≥30	8%	7%	18%
Mean ± SD	26.0 ± 5.5	25.9 ± 5.0	28.2 ± 6.1‡
Parity‡			
0	40%	34%	24%
1–2	42%	45%	32%
≥3	19%	21%	44%
Marital status‡			
Single	27%	15%	5%
Married, legal	10%	19%	43%
Married, common law	54%	62%	50%
Divorced/widowed	8%	4%	2%
Income (monthly, RwF‖)†			
0–499	23%	32%	37%
500–2499	49%	36%	45%
≥2500	28%	32%	18%
Education (y)‡			
0	26%	16%	27%
1–4	21%	25%	31%
5–8	38%	48%	37%
≥9	15%	12%	4%
Maternal health			
Cigarettes (number/d)			
0	83%	89%	93%
≥1	17%	11%	7%
Syphilis serology (RPR)			
Negative	8%	11%	6%
Positive	92%	89%	94%
Self-reported history of STD‡			
None	44%	65%	85%
At least one	56%	35%	15%
Arm circumference (cm)			
<22	38%	27%	25%
22–23	42%	39%	35%
≥24	21%	35%	40%
Malaria parasitemia			
Number with data	27	128	118
Detected	11.1%	16.4%	7.6%
Not detected	88.9%	83.6%	92.4%
Height (cm) ± SD	158.9 ± 6.0	159.2 ± 6.1	158.7 ± 5.7
Hematocrit ± SD	33.1 ± 5.9	33.5 ± 6.0	34.5 ± 5.5
Lymphocyte measures ± SD			
Number with data	29	131	113
CD4 percent	0.28 ± 0.12*	0.35 ± 0.10	0.47 ± 0.08‡
CD4/CD8 ratio	0.63 ± 0.48*	0.88 ± 0.45	1.72 ± 0.60‡
Natural logarithm of CD4:CD8 ratio	−0.70 ± 0.70‡	−0.26 ± 0.55	0.48 ± 0.36‡

* $P \leq .05$; † $P \leq .01$; ‡ $P \leq .001$ using a χ^2 test for homogeneity for categorical variables. For continuous variables, group 1 and group 3 were compared with group 2, using the same linear regression model for both t tests.

[a] For all variables, data were available for >93% of mother–infant pairs, except for lymphocyte measures taken prenatally or within 100 days' postpartum and malaria parasitemia. Percentage totals may not add to 100 because of rounding.

‖ 140 Rwandan francs (RwF) = 1 US dollar in 1992.

TABLE 2. Results of Regression Models of Birth Weight (g) and 95% CI for 434 Infants Who Survived the Neonatal Period in Butare, Rwanda, 1989–1994

	Unadjusted			Adjusted for Gestational Age			Full Model§		
	Coefficient	95% CI		Coefficient	95% CI		Coefficient	95% CI	
		Lower	Upper		Lower	Upper		Lower	Upper
Infant									
HIV status									
Mother positive									
Infant infected (group 1)‖	−235†	−376	−94	−187†	−312	−62	−154†	−271	−38
Infant uninfected (group 2)	0			0			0		
Mother negative	38	−45	121	25	−49	98	−1	−73	70
Gestational age (wk)									
<38	−647‡	−800	−493				−609‡	−751	−468
38–39	−285‡	−369	−200				−243‡	−322	−165
40	0						0		
>40	146†	50	243				106*	16	196
Maternal factors									
Age (y)									
15–19	−229†	−394	−64	−146	−293	0	−23	−162	115
20–24	0			0			0		
25–29	21	−67	108	29	−49	106	−64	−151	22
≥30	78	−50	205	75	−37	187	−47	−185	92
Parity									
0	−162‡	−255	−68	−159‡	−241	−77	−154‡	−239	−69
1–2	0			0			0		
≥3	47	−48	142	29	−55	113	39	−58	137
Cigarettes/d									
0	0	0		0			0		
≥1	−38	−177	101	−9	−131	114	−32	−146	82
Family Income (monthly FRw)									
0–499	−33	−125	59	−23	−103	58	8	−68	84
500–2499	0			0			0		
≥2500	100	0	200	85	−4	173	51	−32	135
MUAC (cm)									
<22	−160‡	−255	−66	−128†	−212	−44	−80	−161	2
22–23	0			0			0		
≥24	149†	59	239	129†	49	209	109†	31	187
Height (per cm increase)	15‡	9	22	12‡	7	18	9†	3	14
Hematocrit (per unit increase)	16‡	9	23	14‡	8	20	12‡	6	18

* $P \leq .05$; † $P \leq .01$; ‡ $P \leq .001$.
§ Model including gestational age, infant's HIV status, maternal age, parity, income, cigarette-smoking, height, hematocrit, and MUAC.
‖ Unadjusted difference between groups 1 and 2 is 233 g in Table 1 because means are based on 513 infants.

Head Circumference and Body Proportionality Measures

Head circumference, ponderal index, and weight/height ratio differed significantly for groups 1 and 2 (Table 4). Results of regression models for head circumference, ponderal index, and weight/head ratio are summarized in Table 5. These measures were significantly lower for group 1 than for group 2 in unadjusted and multivariate models. Groups 2 and 3 did not differ significantly in body proportionality measures.

Excluded Observations

Of the 25 infants excluded from the present study because they died before 28 days of age, 10 mothers were HIV-positive and 15 mothers were HIV-negative. Mean birth weight for the 10 infants born to HIV-positive mothers was 2100 g, and to HIV-negative mothers, 2806 g ($P < .02$). Mean gestational age was 37.4 and 39.4 weeks, respectively, for these two groups ($P = .06$). For the 22 infants with indeterminate HIV status who died between 1 and 12 months of age, mean birth weight was 2581 g. Among the 96 infants who were excluded from the multivariate model for birth weight because of incomplete data, the difference between mean birth weight of groups 1 and 2 was 381 g, greater than the 235 g difference for corresponding groups in the model fitted with 434 observations. Predicted birth weight remained lower for group 1 than for group 2 in sensitivity analyses that added infants excluded previously from either group 1 or group 2 in the multivariate model. The difference between groups 2 and 3 was statistically insignificant in all of the fitted models.

DISCUSSION

In this cohort of Rwandan mother–infant pairs from a semirural area, mean birth weight of HIV-infected infants surviving the neonatal period was lower than that of uninfected infants born to infected mothers. Shortened gestation explained only part of the decreased birth weight in HIV-infected infants. Because the difference persisted after controlling for gestational age, maternal age, parity, MUAC, smoking, income, hematocrit, and malaria, the findings suggest that the lower birth weight among HIV-infected infants may be attributable to the effects of intrauterine infection in some infants rather than to confounding socioeconomic factors or chronic maternal ill health. The difference persisted after addition

TABLE 3. Results of Regression Models of Birth Weight for a Subset of 122 Infants With HIV-Positive Mother Having Data for Maternal CD4 Percent, CD8 Percent, and Malarial Parasitemia in Butare, Rwanda, 1989–1994§

	Changes in Birth Weight (g) and 95% CI			
	Unadjusted Model	Trivariate Models Adjusted for Infant's HIV Status, Gestational Age, and		Full Model‖
		ln(CD4:CD8 ratio)	Malaria	
Infant's HIV status				
Infected	−208 (−398, −18)*	−140 (−307, 28)	−140 (−298, 19)	−91 (−231, 49)
Not infected	0	0	0	0
Gestational age (wk)				
≤37	−817 (−1043, −590)‡	−744 (−1009, −480)‡	−777 (−1038, −516)‡	−747 (−968, −527)‡
38–39	−328 (−465, −192)‡	−329 (−480, −178)‡	−324 (−471, −177)‡	−243 (−371, −114)‡
40	0	0	0	0
≥41	221 (55, 389)†	174 (−22, 370)	166 (−26, 358)	157 (−9, 323)
Logarithm of CD4:CD8 ratio	42 (−90, 174)	−15 (−129, 99)		28 (−66, 121)
Malarial parasitemia	−153 (−364, 58)		−197 (−370, −24)*	−189 (−332, −45)*

* $P \leq .05$; † $P \leq .01$; ‡ $P \leq .001$.
§ Lymphocytes were tested prenatally or within 100 days' postpartum. Of the 122 infants having data for all variables in the full model, 24 infants were infected and 98 were uninfected.
‖ Model including logarithm of mother's CD4:CD8 ratio and malarial parasitemia, in addition to infant's HIV status, gestational age, maternal parity, age, cigarette-smoking, MUAC, height, hematocrit, and family income.

of CD4:CD8 ratio to a multivariate model, although it was no longer statistically significant. Because the analysis with lymphocyte measures and malarial parasitemia included less than half of the HIV-infected mothers, these results must be interpreted with caution. The loss of statistical significance could be attributable to loss of power, selecting a subset with different characteristics from the original cohort, or confounding due to maternal immunodeficiency and malarial infection.

The mother-to-child HIV-1 transmission rate in this cohort, calculated using standardized methods,[40] was lower than in most other studies conducted in sub-Saharan Africa, where reported rates average ~30%.[9,49,50] Possible differences in diagnostic criteria, neonatal mortality, or loss to follow-up are unlikely to fully account for this. Our study population lived in a rural or semirural environment, where the quality and distribution of risk factors for vertical HIV transmission may differ from those in urban settings.[45] To our knowledge, no other large prospective cohort study of mother-to-child HIV-1 transmission in sub-Saharan Africa has been conducted in a rural area.

Our results comparing birth weights are consistent with ECS findings,[37] in which mean adjusted birth weight was 96 g lower for infected infants than for uninfected infants of HIV-positive mothers. Our results also support findings from a cohort study in Kigali, Rwanda,[29,51] where birth weight of infected and uninfected infants differed. In the latter study, none of the mothers had clinical AIDS at delivery, and the researchers suggested that the decreased birth weight of infected infants was attributable to intrauterine HIV infection rather than to chronic maternal disease. The Women and Infants Transmission Study in the United States and Puerto Rico[32] reported growth outcomes adjusted for covariates including maternal CD4 percentages and use of illicit drugs, alcohol, and tobacco, and showed a reduction in birth weight only for HIV-infected infants. Methodologic factors may have contributed to discrepancies observed among a number of other studies. Because most analyses have focused on other outcomes, such as infant mortality and HIV vertical transmission rates, authors of these studies have reported only unadjusted birth weights.[21,25,29–31,33–36]

The role of gestational age relative to the association between mother-to-child HIV transmission and birth weight is unclear. Prematurity may be a consequence of intrauterine infection or a cause of increased susceptibility to HIV infection during labor and delivery. The latter explanation is supported by results of sequential PCR testing of neonates, which suggest that infants born preterm and small for gestational age had significantly higher risk of pre-

TABLE 4. Body Measures of Singleton Infants Who Survived the Neonatal Period, by Mother–Child HIV Status in Butare, Rwanda, 1989–1994

Infant Body Measure	Group 1: Mother Positive/Infant Positive (n = 48)			Group 2: Mother Positive/Infant Negative (n = 206)			Group 3: Mother Negative/Infant Negative (n = 276)		
	n	Mean ± SD	Range	n	Mean ± SD	Range	n	Mean ± SD	Range
Birth weight (g)	45	2539 ± 431‡	1500–3400	203	2772 ± 429	1700–4000	265	2824 ± 408	1900–4000
Crown-to-heel length (cm)	45	47.2 ± 2.5	41.0–53.0	196	47.7 ± 2.1	40.0–55.0	263	47.9 ± 2.0	43.0–53.0
Head circumference (cm)	44	33.5 ± 1.6†	29.4–36.5	195	34.2 ± 1.5	30.8–38.0	263	34.4 ± 1.4	30.5–38.4
Ponderal index§	44	2.42 ± 0.28†	1.93–3.24	196	2.55 ± 0.28	1.60–3.37	261	2.57 ± 0.29	1.81–3.65
Weight/head ratio‖	43	75.7 ± 10.5†	51.0–97.1	195	80.8 ± 10.5	53.1–109.6	261	81.9 ± 10.0	58.5–111.1

* $P \leq .05$; † $P \leq .01$; ‡ $P \leq .001$. Groups 1 and 3 were compared with group 2, using the same linear regression model for both t tests.
§ Birth weight × 100/crown-heel length^3.
‖ Birth weight/head circumference.

TABLE 5. Results of Regression Models of Head Circumference, Ponderal Index, and Weight/Head Ratio of 530 Mother–Infant Pairs, Showing Data for Pairs With HIV-Positive Mother in Butare, Rwanda, 1989–1994

Outcome	Mother–Child HIV Status	*n*	Changes in Outcome Measure With 95% CI		
			Unadjusted	Adjusted for Gestational Age	Full Model§
Head circumference (cm)		433			
	Infant infected		−0.8 (−1.3, −0.3)†	−0.6 (−1.1, −0.2)†	−0.6 (−1.1, −0.2)†
	Infant not infected		0	0	0
Ponderal index		434			
	Infant infected		−0.16 (−0.25, −0.06)†	−0.15 (−0.24, −0.06)†	−0.14 (−0.23, −0.05)†
	Infant not infected		0	0	0
Weight/head ratio		439			
	Infant infected		−4.8 (−8.3, −1.4)†	−3.8 (−6.9, −0.7)*	−3.5 (−6.4, −0.5)*
	Infant not infected		0	0	0

* $P \leq .05$; † $P \leq .01$.

§ Groups 1 and 3 were compared with group 2, using the same linear regression model for both *t* tests. Coefficients for group 3 compared with group 2 are not shown, because none was statistically significant.

Models included, for head circumference: mother–infant HIV status, gestational age, infant's sex, maternal education, height, and hematocrit; for ponderal index: mother–infant HIV status, gestational age, income, mother's MUAC, and hematocrit; for weight/head ratio: mother–infant HIV status, gestational age, maternal parity, height, marital status, MUAC and hematocrit.

sumed intrapartum infection.[52] If prematurity results from intrauterine HIV infection, controlling for gestational age may diminish the true effect of infant's HIV status on birth weight.[53] However, the 0.6-week difference in mean gestational age between HIV groups could account for only a portion of the birth weight difference between HIV-infected and HIV-uninfected infants.

Differences in body proportionality measures, such as ponderal index and weight/head ratio, have been proposed as an approach to detecting the time of an intrauterine insult. According to this hypothesis, disproportional infants experienced third-trimester intrauterine fetal growth retardation.[54] Because the slope of the fetal weight curve rises sharply after 30 weeks of pregnancy, differences in the ponderal index and weight/head ratio suggest that the adverse impact of HIV-1 infection on fetal growth may have been most severe toward the end of pregnancy, resulting in a lean infant (low ponderal index) with a relatively large head.[24] Because the HIV-infected infants in our cohort had significantly lower mean ponderal index and weight/head ratio than did HIV-uninfected infants of HIV-positive mothers, and the latter group resembled infants of HIV-negative mothers, they may have suffered an insult during the third trimester. Alternatively, these infants may have been more likely to become HIV-infected during labor and delivery because of complications in the delivery process.

One strength of our study was that the analysis included 530 of 590 singleton live births (90%). The primary limitation of this study was the lack of early diagnostic testing for infants and prolonged breastfeeding, which could lead to misclassification of infants' HIV status. In addition, infant mortality from causes other than HIV infection may have contributed to misclassification, because definition of infants' HIV status depended on survival to at least 12 months for most children. As in most other studies of mother-to-child HIV transmission, information about HIV status of spontaneous abortions was unavailable, but this would not have affected conclusions about differences in birth weight among live born infants.

To address concerns about misclassification of infant's HIV status, models were fitted after adding the infants excluded previously. The resulting estimates suggest that mean birth weight for group 1 would have been lower than that for group 2 even if all infants dying before 12 months of age were included. Moreover, the inclusion of some infants who may have acquired HIV through breastfeeding would most likely decrease the observed effect of HIV infection on birth measures. Misclassification of maternal HIV status was highly unlikely, because mothers were followed serologically after birth and HIV-negative mothers who seroconverted at approximately the time of delivery were excluded from the present analysis.

Unlike studies in developed countries, this analysis did not need to control for intravenous drug use, which was absent in our predominantly rural population in sub-Saharan Africa. Greater than 95% of women reported drinking the local beer, and the frequency of beer consumption was similar for seropositive and seronegative women. Cigarette smoking, a well-established risk factor for decreased birth weight,[55] lacked importance because the prevalence of smoking was low in the study population, and smoking mothers consumed no more than four cigarettes per day on average.[38] Maternal occupation in agricultural labor has been associated with decreased birth weight in rural Rwandan women,[56] but in our study, almost all women (96%) engaged in farm labor regularly.[38]

Direct information or proxy measures were available for most of the established factors with direct causal impacts on IUGR in rural developing countries: low maternal caloric intake, short stature, primiparity, hematocrit, and infant's gender.[55] Prepregnant weight was unavailable, but MUAC was likely to provide partial control for this factor.

However, our analysis was limited by lack of information on several measures of maternal health, including HIV viral load, and by incomplete data on

CD4 and CD8 counts and maternal malaria. Although the mothers in our study did not meet the clinical definition for AIDS in adults, milder HIV-related illness may have affected birth measures. Maternal malarial infection is a major determinant of LBW and prematurity in endemic areas.[57–59] Although it does not appear to interact with or be associated with HIV infection in adults, including pregnant women,[60–62] maternal malaria may act as an effect modifier and/or confounder of the association between the mother–infant HIV status and birth weight. There is evidence that maternal HIV infection increases the risk and density of placental malaria infection, but it is not known whether placental malaria increases the risk of mother-to-child HIV transmission.[63] Malaria also might have decreased the accuracy of defining the HIV status of infants by increasing infant mortality, because infants with mothers having both placental malaria and HIV appear to have a higher risk of postneonatal death than do infants whose mothers have either placental malaria or HIV.[64] On the other hand, if maternal malaria infection is not associated with perinatal HIV transmission, as reported from Kinshasa,[64] this infection should not be a confounder in our study. Moreover, inclusion of parity in our analysis may have partially controlled for maternal malaria, because primiparous women are more likely than multiparous women to have this infection during pregnancy.[59,65]

Maternal micronutrient deficiencies may be important confounders for which data were unavailable on the entire cohort. An association between severe maternal vitamin A deficiency and mother-to-child transmission of HIV has been reported in developing[66] and developed areas,[67] even after controlling for CD4 percent. Increasing risk of shedding HIV-1 infected cells in the genital tract of women with decreasing vitamin A levels may be attributable to the multiple roles that this vitamin plays in maintaining epithelial surfaces and normal immune function.[68] In addition, low cord blood vitamin A levels may be associated with IUGR.[69] Ongoing clinical trials in sub-Saharan Africa that provide vitamin A supplementation to HIV-infected pregnant women will elucidate further the possible role of this micronutrient in mother-to-child HIV transmission and in IUGR.

In conclusion, our analysis supports findings in other studies in developing and industrialized societies that mother-to-child transmission of HIV is associated with a decrease in birth weight. The estimated average effect is on the same order of magnitude as other important determinants of birth weight, such as primiparity and infant's gender, and is somewhat lower than the average effect of maternal smoking during pregnancy.[1,55] The magnitude of the difference in birth weight of HIV-infected and uninfected infants, together with relative sparing of other body measures, suggests that HIV infection occurred in a substantial proportion of infants during the late third trimester or during passage through the birth canal. These findings support interventions targeting the third trimester of pregnancy and the intrapartum period to reduce mother-to-child transmission of HIV.

ACKNOWLEDGMENTS

This work was supported by grants from the US National Institute of Child Health and Human Development (HD22496 and HD25785 to A.S.) and from the World AIDS Foundation (WAF 114-96-024 and WAF 140-97-032 to M.B.).

We gratefully acknowledge the Rwandan women whose participation made this study possible; the faculty and staff of the National University of Rwanda School of Medicine; the staff of the Health Centers of Save, Rango, and Matyazo; and all the dedicated staff members of the National University of Rwanda–Johns Hopkins University AIDS Research Project in Butare, Rwanda from 1989 through 1994. Dr Marie-Louise Newell (London, UK) and Dr Scott Grosse (Atlanta, GA) provided helpful comments on an earlier draft of the manuscript.

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DOI: 10.1542/peds.102.2.e24

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