

## Increased Risk of Early Measles in Infants of Human Immunodeficiency Virus Type 1-Seropositive Mothers

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An increase in illness due to measles is one of the potential consequences of the human immunodeficiency virus (HIV) epidemic in Africa. During a study of perinatal HIV transmission conducted in Kenya, the risk of acquiring measles before vaccination (9 months of age) was found to be 3.8 times higher in infants born to HIV-seropositive mothers than in control infants (10 [9%] of 109 vs. 5 [3%] of 194 infants;  $P = .02$ ; odds ratio, 3.8; 95% confidence interval, 1.2–13.2). The majority of infants who developed measles in this study had significant sequelae related to their measles infection. The increased risk of measles appeared to be related to relatively lower anti-measles antibody titers detected in cord blood samples of affected infants born to HIV-seropositive mothers. However, 94% of all infants were susceptible to measles on the basis of ELISA testing at age 6 months regardless of maternal HIV serology. These observations highlight the need for improved measles vaccination strategies in Africa and for studies to delineate the effects of HIV infection on the incidence, presentation, and sequelae of childhood infectious illnesses.

One of the consequences of the heterosexual nature of the human immunodeficiency virus type 1 (HIV-1) epidemic in Africa is that nearly equal numbers of women and men are infected [1]. As women in the childbearing age group are primarily affected, a large number of HIV-1-infected children will be born before the HIV-1 epidemic is controlled. In addition to bearing the direct consequences of HIV-1 infection, these children may be expected to have greater morbidity and mortality from other infectious illnesses.

Measles remains an important cause of infant mortality and morbidity in many developing areas of the world where epidemics continue despite concerted vaccination efforts since the mid-1970s [2–7]. Although measles is generally controlled in North America, major epidemics still occur [8, 9]. During the past 6 years, several cases of measles have been described in individuals who were infected with HIV-1 [10–12]. The clinical course of measles in association with HIV infection was usually severe and often atypical, and the use of intravenous gamma globulin or previous measles im-

munization did not prevent development of life-threatening disease.

Since 1986 we have been engaged in a study of perinatal HIV-1 transmission and of the morbidity and mortality associated with HIV-1 infection in children in Nairobi, Kenya. Infants born to HIV-1-seropositive mothers and seronegative control mothers are enrolled and followed prospectively to determine the frequency of HIV-1 transmission and the presentation and complications of HIV-1-related illness. Two of the objectives of this project are to determine the effect of HIV-1 infection on common childhood diseases and to assess implications for vaccination policies. Measles has been one of the diseases studied in this cohort. This report presents findings concerning the occurrence of measles before age 9 months (the current age at which measles vaccination is given in Kenya) in infants born to HIV-1-seropositive and -seronegative mothers.

### Patients and Methods

This study of perinatal HIV-1 transmission began in January 1986 in Nairobi. Women presenting to a major maternity hospital (>25,000 births/year) between 7:30 A.M. and midnight on work days were invited to participate. Maternal sera were screened for antibodies to HIV-1. Mothers found to be HIV-1-seropositive and randomly selected HIV-seronegative mothers and their infants were enrolled. Within 24 h of delivery, demographic, social, medical, and obstetric histories were obtained from the mothers; the circumstances of labor and delivery were recorded; mothers were examined for signs of HIV-1 infection; and infants were examined for assessment of gestational age and general health. The infant's birth weight, length, and head circumference were recorded.

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All study participants gave informed consent.

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All mothers were initially screened using ELISA (Du Pont de Nemours, Geneva) following the manufacturer's recommended procedures. Positive samples were retested the next working day. Repeatedly ELISA-positive samples were tested by Western blot (Du Pont de Nemours). Criteria for a positive Western blot were the presence of antibody to at least one core protein (p24, p17, or p15) and one envelope protein (gp41, gp120/160) [13]. Mothers with positive EIA but with negative Western blot were considered uninfected, as were those mothers with a negative EIA.

All mother-infant pairs were followed in a similar manner. Infants were seen at monthly intervals for the first 6 months of life and then every 3 months. At each scheduled visit, a history of intercurrent illness was obtained and a physical examination done. Immunizations were given according to the routine schedule of immunizations in Kenya: bacille Calmette-Guérin (BCG) and oral polio within 24–48 h of birth; diphtheria, pertussis, tetanus, and oral polio at ages 6, 10, and 14 weeks; and live measles (Schwartz vaccine strain) at age 9 months. All vaccines except the initial polio and BCG vaccines were administered by the research clinic personnel. Sera were obtained from mothers and cord blood at birth and from mothers and infants at 3-month intervals. Mothers were encouraged to return with their infants at unscheduled times should the infant or the mother become ill.

Measles was diagnosed on clinical grounds based on the history or physical finding of a febrile illness plus cough, coryza, or conjunctivitis and a typical morbilliform rash lasting >3 days that began on the head and shoulders and progressed down the body over the next 48 h. Early measles was defined as measles occurring before age 9 months, the age of scheduled measles vaccination.

Testing for measles antibodies was done using EIA and hemagglutination inhibition (HAI) testing. Measles IgG Enzygnost ELISA plates and all reagents required for ELISA were purchased from Behring Diagnostics (Behringwerke, Marburg, Germany). Test procedures were strictly adhered to as outlined by the manufacturer. HAI was done using the method described by Gershon and Krugman [14] modified by adding 0.4% bovine albumin to the PBS (pH 7.2) diluent. All sera were tested after adsorption with monkey red blood cells and heat inactivation; 4 HAI units of antigen (Whittaker M.A. Bioproducts, Baltimore, MD) were used. End point was read as the highest dilution of serum that completely inhibited agglutination. All assays used in the study have been standardized using international reference sera.

Statistical methods included univariate analysis on selected variables with standard parametric and nonparametric statistical tests. All *P* values reported are two-tailed.

## Results

We enrolled 109 infants born to HIV-1-seropositive mothers (case infants) and 194 infants born to seronegative mothers (controls) and followed them past 9 months of age.

Early measles (in infants < 9 months old) occurred in 10 (9%) of the 109 infants born to seropositive mothers and 5 (3%) of 194 infants born to seronegative mothers (odds ratio,

3.8; 95% confidence interval, 1.2–13.2; *P* = .02). The early measles case fatality rate was 10% among case infants and 20% among controls (*P* = .5, not significant).

All mothers in the study came from similar socioeconomic backgrounds. There was no difference in maternal age (24 vs. 24.6), gravida (3.2 vs. 3.2), or parity (2.2 vs. 1.9) between mothers whose infants developed early measles and those whose infants did not. No HIV-seropositive mother whose infant developed early measles was ill with HIV-related illnesses at the time of her infant's birth. Two of these mothers (20%) had generalized extralingual lymphadenopathy. This is similar to the percentage (28%) of HIV-1-seropositive mothers with lymphadenopathy reported from this study previously [15]. Finally, no HIV-1-seropositive mother whose infant developed early measles developed AIDS within a year of her infant's birth.

All of the infants who developed early measles were born at term, and there was no difference in birth weight (3487 vs. 3220 g) or Apgar score (8.0 vs. 8.3) between infants who did and did not acquire early measles.

Of the 10 infants who developed early measles and who were born to HIV-1-seropositive mothers, only two have confirmed HIV-1 infection. Three are HIV-seronegative at age 18 months and are presumed to be uninfected. The serologic status of the infant who died is unknown, as is that of the four infants who have not yet been tested for antibodies to HIV-1 after age 15 months. All three infants born to HIV-1-seropositive mothers who developed measles after 9 months of age and despite vaccination are uninfected, with negative HIV-1 Western blot tests done after the infants were age 15 months.

The morbidity and mortality of measles in these young infants was considerable (table 1). There was no association between maternal HIV status and increased morbidity; however, the growth disturbances did tend to be more severe in the infants born to HIV-seropositive mothers.

Late measles occurred in some infants after 9 months of age. Six control and three HIV-1-exposed infants acquired measles despite vaccination. The vaccine failure rate was thus 3% (3/99 and 6/187) in both groups followed for a mean of 10 months after vaccination (range, 1 month to 3 years). Two additional unvaccinated control infants became ill with measles at ages 10½ months and 2 years. No child developed an illness resembling measles within 1 month of measles vaccination.

IgG antibody to measles was determined in available samples of peripartum maternal or cord sera (or both) for 8 of the 15 infants who developed early measles (table 2). Although all five mothers tested had protective levels of measles antibodies, three of eight cord blood samples were found to have borderline antibody titers to measles, with relatively low HAI titers. Peripartum measles immune status was also determined from a subgroup of the study mothers for whom sera were available for testing and whose infants were fol-

**Table 1.** Characteristics of measles illness in infants.

Maternal HIV status, sample no.	Infant HIV status*	Age at measles (months)	Hospitalization	Acute complications	Sequelae†
Positive					
1421	—	8.5	Yes	Pneumonia	FTT
1436	—	8	Yes	None	Decreased growth
2001	+	8	No	None	Decreased growth
2060	?	8	Yes	Pneumonia	Died
2886	—	8	No	Pneumonia, otitis media, croup	Decreased growth
4004	?	7.5	No	Diarrhea	FTT
5649	?	5.5	No	None	Decreased growth
6467	—	8	No	Pneumonia	None
6671	?	6	Yes	Pneumonia, diarrhea	FTT
6744	?	6	No	Pneumonia	?
Negative					
1602	—	8	Yes	Pneumonia	Died
9-2607	—	8.5	No	None	None
6158	—	8	Yes	Diarrhea, pneumonia	FTT
6527	—	6	Yes	Pneumonia	FTT
6969	—	7	No	Pneumonia	?

NOTE. HIV, human immunodeficiency virus; ?, unknown.

\* Based on Western blot serologic testing after age 15 months.

† FTT, failure to thrive: no increase in weight for  $\geq 3$  months; decreased growth: slowing of growth velocity that recovered before development of FTT; died: cause was pneumonia associated with acute measles illness.

lowed for 9 months but who did not develop measles. All 19 HIV-1-positive mothers were immune to measles at the time their infants were delivered, as were 18 of 19 HIV-seronegative mothers. Maternal median peripartum measles titers were similar whether the infant acquired early measles or not. However, the median measles titer of the cord blood sera from HIV-1-positive pregnancies was significantly less than that of the maternal samples (1:5 vs. 1:20,  $P < .05$ ).

The possibility that decreased passive transfer of maternal measles antibody by HIV-1-infected mothers at the time of delivery results in infants becoming susceptible to measles at an earlier age was explored by testing available infant serum samples for measles antibody at age 6 months. Of 24 case infants, none was found to be fully immune to measles at this age, but 1 had borderline immunity. Of 27 control infants, 1 was immune and 2 had borderline immunity. Thus, 47 (94%) of 51 infants in the clinic were found to be susceptible to measles by ELISA antibody testing at age 6 months.

## Discussion

These results demonstrated that infants born to HIV-1-seropositive mothers are at increased risk of acquiring

measles before 9 months of age compared with infants born to HIV-1-seronegative mothers. This has significant public health implications, as 9 months is the age at which measles vaccination is currently recommended in many countries in addition to Kenya, where measles remains a serious health problem.

A high incidence of measles before the age of immunization is common in many developing countries and predates the AIDS epidemic. Thus, this finding needs to be confirmed in other areas and the reasons for increased susceptibility delineated. In a similar study conducted in Zaire, a trend toward an increase in the incidence of measles before age 9 months was also observed, although not as clearly as in this study (unpublished data). The significantly higher infant mortality rate in infants born to HIV-seropositive mothers due to other causes (21% vs. 4%) in the Zaire study may have accounted for the relative decrease in the significance of measles illness in that cohort [16]. The difference in the infant mortality among the cohorts in this study was considerably less (unpublished data).

The morbidity and mortality of early measles in the children in the present study was considerable, although in keep-

**Table 2.** Infants developing early measles: peripartum measles antibody status.

Maternal HIV status, sample no.	Cord blood		Measles antibody in maternal sera	
	EIA*	HAI	EIA	HAI
Positive				
1421	+	1:10	+	1:40
1436	B	1:5	-	-
2001	B	<1:5	+	1:10
2060	B	<1:5	-	-
2886	+	1:160	+	1:80
4004	+	1:20	+	1:20
5649	+	1:5	-	-
Negative				
1602	+	1:10	+	1:10

NOTE. HIV, human immunodeficiency virus; HAI, hemagglutination inhibition assay.

\* B, borderline susceptible: ELISA reading  $\leq 1.5$  times calculated cutoff point for test run.

ing with reports of the adverse consequences of measles in very young children in developing countries [5, 17-21]. In both the perinatal transmission study and a survey of children admitted to hospital with measles conducted in Zaire, the severity of measles illness was believed to be increased among HIV-seropositive children [22] (unpublished data). Growth disturbances are known to occur frequently after measles in children in developing countries with borderline nutritional status or with vitamin A deficiency [6, 17, 18, 21]. Before their measles illness, the infants in this study were well, with adequate growth parameters, although most had growth disturbances subsequently.

None of the infants had any other significant illnesses before the development of early measles. There was no indication of increased susceptibility to severe illness due to measles in this group that might have led to a detection bias. Only 2 (20%) of 10 infants have been determined to be HIV-1-infected, and at the time they developed measles, they were asymptomatic for their HIV-1 infection. However, since the appearance of the rash was the major finding leading to measles diagnosis, cases may have been missed in HIV-infected infants with related T cell immunodeficiency. The development of the classic measles rash is dependent on intact T cell immune function, and the absence of rash has been reported in cases of measles in HIV-infected children in the United States [10, 11, 23]. We cannot rule out an increased exposure to measles in the group of HIV-1-exposed infants, but evidence for such risk was not suggested by the socioeconomic status or family characteristics (in particular, number of children) of the cohorts. However, we have shown that there are other subtle differences, primarily related to sexual behavior, between mothers who are HIV-1-seropositive and those who are not, and these potentially may have

resulted in an increased risk of measles exposure to the infants [15]. Study and control infants were enrolled concurrently. Measles in Nairobi occurs as a series of small epidemics, and infants may be at higher risk during some time periods than at others. However, examination of the birth dates of both cohorts did not reveal a relationship with enrollment dates that could be a source of bias. There was no known common source for these children to acquire measles infection. The only common factor among the children was attendance at the research clinic. Measles has been associated with airborne transmission in a doctor's office [24]. However, review of the clinic records showed that none of the children could have been exposed to other study children with measles at the clinic. Only two children had been seen at the research or other clinics during the 2 weeks before their illnesses.

Three of the seven HIV-1-exposed infants had low levels of passively acquired measles antibody as evidenced by the antibody studies in the cord blood sera. The number of samples tested was too small to determine whether the mothers themselves had reduced levels of circulating antibodies. Low maternal antibody titers have been correlated with increased risk of early measles in a study from Haiti [25]. This has also been of theoretical concern in the United States, where young mothers who have been immunized against measles have lower demonstrable antibody titers than older women who have had natural disease [26, 27]. The mothers in the present study were not themselves immunized and presumably had natural measles infection. Previous studies have demonstrated that in areas where measles remains prevalent, almost all adults are immune [2]. Symptomatic HIV-1-infected individuals have a reduced anamnestic response when revaccinated with bacterial toxoids [28]. This decreased anamnestic response may possibly also occur in otherwise well HIV-1-seropositive individuals who are reexposed to measles.

An alternative explanation of the low titers of measles antibodies in the cord blood samples is that there may be a defect in placental transfer of antibodies when the mother has HIV-1 infection. Active transfer of antibodies via the placenta occurs after week 32 of gestation in normal pregnancies, resulting in a cord blood concentration of measles antibodies 1.5-1.7 times that in maternal blood, with preterm infants having relatively lower concentrations of passively acquired antibodies [29]. In contrast, the titers were lower in the cord blood samples in this study. Since all the infants who acquired measles were born at term, length of gestation would not appear to explain this finding.

The finding that 94% of infants were nonimmune to measles at 6 months of age, on the basis of ELISA antibody testing, would support the proposed recommendation of the World Health Organization to change the age of measles immunization to age 6 months in some areas. Other studies

have found that loss of passively transferred immunity to measles occurs in a substantial proportion of infants aged 7–9 months [28–32]. However, the percentage of those non-immune at age 6 months in this study population is somewhat higher than that of studies done elsewhere and those done previously in Kenya [30–32].

New vaccination strategies are being investigated to attempt to control measles illness in young infants [3, 7]. For example, preliminary studies using the high-dose Edmonston-Zagreb vaccine show that this vaccine may be efficacious in the prevention of measles in healthy populations when given at  $\leq 6$  months of age [33–37]. Our results reinforce the importance of this goal for both HIV-infected and -uninfected children born to HIV-1-seropositive mothers as well as for those born to HIV-1-seronegative mothers. HIV is going to impose enormous problems on public health policies of both the developing and developed world and will undoubtedly hamper attempts to control infectious diseases such as measles. New measles vaccination strategies should be tested in infants born to HIV-1-seropositive mothers and infants infected with HIV-1 before such practices are adopted in populations where HIV-1 is prevalent.

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