

# Unexpected Non-HIV Causes of Death in Children Born to HIV-Infected Mothers

Thomas J. Starc, MD, MPH\*; Claire Langston, MD#; Johanna Goldfarb, MD||; Andrew A. Colin, MD‡; Ellen R. Cooper, MDS; Kirk A. Easley, MS¶; Susan Sunkle, BA¶; and Mark D. Schluchter, PhD¶ for the Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group.  
National Heart, Lung, and Blood Institute, Bethesda, Maryland

**ABSTRACT.** *Introduction.* A high incidence of sudden, unexplained deaths in infants born to HIV-infected mothers has been noted in several epidemiologic studies. During the course of a prospective study of heart and lung disease in children born to HIV-infected mothers, we noted that of 5 unexpected non-HIV-related deaths, 4 were attributed to traumatic events.

*Methods.* The Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P<sup>2</sup>C<sup>2</sup>) study is a multicenter, prospective investigation of the incidence of heart and lung disease in HIV-infected children. A total of 805 children were enrolled and followed for 5 to 7 years with serial immunologic, pulmonary and cardiac function studies. During the study, a multidisciplinary committee was formed to review the cause of death for those patients who died. The committee used results of pulmonary, cardiac, and laboratory tests, hospital summaries, as well as autopsy and coroners' reports. The committee formed a consensus about the underlying and contributing causes of death for each subject using the definitions from the 1989 US Standard Certificate of Death.

*Results.* A total of 121 deaths occurred during the course of the P<sup>2</sup>C<sup>2</sup> study. Of the 121 deaths, 5 were traumatic or sudden and unexpected and judged by the Mortality Review Committee to be unrelated to HIV infection. The median age at the time of death was 1.3 months and ranged from 1.2 to 37.8 months. Two infants died of trauma: a skull fracture and subdural hematoma in 1 infant and multiple skeletal fractures consistent with battered child syndrome in the other infant. The third infant died of accidental suffocation at home at 1.2 months of age. The fourth infant died suddenly and unexpectedly at home at 1.3 months of age. The autopsy showed no sign of HIV or other infection and was con-

sistent with sudden unexpected death or SIDS. One non-HIV-related death occurred when a 38-month-old child died together with the mother in an unwitnessed drowning. The cumulative mortality rate attributable to trauma and sudden death at 4 months of age was 0.95% (95% CI: 0.02–1.87%) and the infant mortality rate was 9.5/1000 live births. Three children were born prematurely at 30, 33, and 36 weeks' gestational age, respectively, and 3 mothers admitted using recreational drugs before or during pregnancy.

*Discussion.* These traumatic and sudden non-HIV-related deaths accounted for 4.1% (5/121) of the deaths during the entire P<sup>2</sup>C<sup>2</sup> study period and for 20% (4/20) of the deaths in the first year of life. Four deaths were attributable to accidental and nonaccidental trauma rather than to other common causes of infant death. One death was a sudden unexpected death, similar to SIDS, a leading cause of infant death in the United States. The majority of previously reported non-HIV-related deaths in infants born to HIV-infected mothers have been attributed to SIDS or to unexplained sudden death. In contrast with other reports, 4 of the 5 children in our series died of accidental or nonaccidental trauma and only 1 was a sudden unexplained death. It is unlikely that HIV exposure is related directly to the deaths described in this report; however, maternal HIV infection may be a marker for factors that place the child at risk for sudden or traumatic death.

*Summary.* This report suggests that children born to HIV-infected mothers may be at increased risk for traumatic or sudden, unexplained, non-HIV-related death. These children seem to be at risk regardless of their own HIV infection status. Furthermore, 4 of the deaths in our study occurred within the first few months of life, suggesting that this is a period of increased vulnerability. Studies to identify associated risk factors for non-HIV-related deaths are needed to identify these high-risk infants. Children born to HIV-infected mothers may be more vulnerable than was recognized previously and may be in need of increased social services, especially in early infancy. *Pediatrics* 1999;104(1). URL: <http://www.pediatrics.org/cgi/content/full/104/1/e6>; *human immunodeficiency virus, children, trauma.*

ABBREVIATION. P<sup>2</sup>C<sup>2</sup>, Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection.

From the Department of \*Pediatrics, Division of Pediatric Cardiology, Babies and Children's Hospital, Columbia-Presbyterian Medical Center, Columbia University, College of Physicians and Surgeons, New York, New York; Department of †Pediatrics, Division of Pulmonology, Children's Hospital, Harvard Medical School, Boston, Massachusetts; Department of ‡Pediatrics, Division of Infectious Disease, Boston Medical Center/Boston University School of Medicine, Boston, Massachusetts; Departments of §Biostatistics and Epidemiology and ||Pediatrics, The Cleveland Clinic Foundation, Cleveland Ohio; and the Department of #Pathology, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas. This study was presented in part at the Ambulatory Pediatric Society Meeting; May 2, 1997; Washington, DC.

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Reprint requests to (T.J.S.) Columbia-Presbyterian Medical Center, Department of Pediatrics, Babies Hospital Rm 255 N, 3959 Broadway, New York, NY 10032. E-mail: [tjs1@columbia.edu](mailto:tjs1@columbia.edu)  
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Infants born to HIV-infected mothers are at risk of acquiring HIV during fetal life or perinatally.<sup>1</sup> If they become HIV-infected, these children can develop acquired immunodeficiency syndrome early in

life and can have an estimated mortality rate of 8% to 12% per year.<sup>2</sup> Although complications of HIV infection are the major health hazards for these children, they also are at risk for other, non-HIV-related events. Three recent reports have described a high incidence of unexplained sudden death in separate cohorts of children born to HIV-infected mothers.<sup>1,3,4</sup> During the course of a prospective study of heart and lung disease in children born to HIV-infected mothers, we noted that of 5 unexpected non-HIV-related deaths, 4 were attributed to traumatic events. We call attention to trauma as a major cause of death in this group of children with the hope that in the future it may be possible to identify and take preventive measures to protect these high-risk children.

## METHODS

### Study Subjects

The Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P<sup>2</sup>C<sup>2</sup>) study is a multicenter, prospective investigation of the incidence of heart and lung disease in HIV-infected children. Children were enrolled at five centers: Baylor College of Medicine/Texas Children's Hospital, Houston, Texas; Columbia-Presbyterian Medical Center/Babies and Children's Hospital, New York, New York; Children's Hospital/Harvard Medical School, and Boston Medical Center/Boston University School of Medicine, Boston, Massachusetts; Mount Sinai School of Medicine, New York, New York; and the University of California at Los Angeles, Los Angeles, California.

Two groups of children born to HIV-infected mothers entered the study between 1990 and 1994 and were followed until 1997. Group 1 (older cohort) consisted of 205 children with known HIV infection with a median age at enrollment of 23 months (range 0.1–14 years). Group 2 subjects (neonatal cohort) were enrolled either prenatally ( $n = 432$  live births; 72%), or after delivery but before 28 days of age ( $n = 168$ ; 28%). Group 2 consisted of 600 live-born infants whose HIV status was unknown at enrollment. For the purposes of this study, infant mortality rates were calculated based on the 432 live-born infants from the group 2 cohort who were enrolled prenatally. Details of recruitment and testing have been published.<sup>5</sup> All data collection and processing were centralized at the coordinating center at the Cleveland Clinic. The study was approved by the institutional review board at each center. Informed consent was obtained from the subject's parent or guardian before enrollment.

### Study Methods

Children underwent serial cardiac, pulmonary, and immunologic testing according to specific protocols. At the time of enrollment, information concerning maternal age, race, smoking, and drug use were obtained as part of the P<sup>2</sup>C<sup>2</sup> study. In 1994, the Mortality Review Committee was formed to study the causes of death of children in the P<sup>2</sup>C<sup>2</sup> study. This multidisciplinary committee was composed of specialists in pediatric pathology, pulmonology, cardiology, and infectious disease. The committee reviewed hospital and clinic summaries and results of pulmonary, cardiac, and laboratory tests, as well as autopsy and coroners' reports. The committee formed a consensus as to the underlying and contributing causes of death for each subject using the definitions from the 1989 US Standard Certificate of Death.<sup>6</sup> The underlying cause of death was defined as "the single disease or injury that initiated the events resulting in death," and the contributing causes of death were defined as "the conditions, if any, leading to the immediate cause of death, but not constituting the single identified underlying cause defined above."<sup>6</sup>

In group 1, HIV status was determined by the presence of a positive HIV antibody test result (enzyme-linked immunosorbent assay with Western blot analysis) and/or a positive HIV culture in peripheral blood mononuclear cells. In group 2, the presence of an HIV infection was defined as two positive HIV blood culture results. Infants with two negative blood culture results, with one after 5 months of age were classified as HIV uninfected. The infants who died or who were lost to follow-up before the status

of HIV infection could be determined were classified as indeterminate.

## RESULTS

### Demographics

Of the 805 children followed in the P<sup>2</sup>C<sup>2</sup> study, 49.4% ( $n = 398$ ) were black, 32.8% ( $n = 264$ ) were Hispanic, 12.4% ( $n = 100$ ) were white/non-Hispanic and 5.3% ( $n = 43$ ) were classified as other. In the group 2 cohort, 93 of the 600 life-born infants (15.5%) were diagnosed with HIV infection, 463 were uninfected, and 44 were of indeterminate HIV infection status.

A total of 121 deaths occurred during the course of the P<sup>2</sup>C<sup>2</sup> study. The Mortality Review Committee reviewed all deaths. A detailed analysis of the underlying and contributory causes of death in the P<sup>2</sup>C<sup>2</sup> study is the subject of another report. A preliminary description of the causes of death in the first 71 patients reviewed has been published in abstract form.<sup>7</sup> Of the 121 deaths, 5 were traumatic or sudden and unexpected and were judged by the Mortality Review Committee to be unrelated to HIV infection or its treatment and are the subject of this report.

### Non-HIV-related Causes of Death

Of the 5 children who died unexpectedly of causes not related directly to HIV infection, the median age at the time of death was 1.3 months and ranged from 1.2 to 37.8 months (Table). Each of the 4 infants had an autopsy examination performed at the office of the medical examiner with jurisdiction for the event. Two infants died of trauma; a skull fracture and subdural hematoma were reported in 1 infant and multiple skeletal fractures consistent with battered child syndrome were reported in the other. The third infant died of accidental suffocation at home at 1.2 months of age. The fourth infant died suddenly and unexpectedly at home at 1.3 months of age. The autopsy showed no sign of HIV or other infection and was consistent with sudden infant death or SIDS. One non-HIV-related death occurred after the infancy period. This death occurred when a 38-month-old child died together with the mother in an unwitnessed drowning. All the traumatic and sudden deaths occurred in group 2 infants who were enrolled in the P<sup>2</sup>C<sup>2</sup> study before birth. Because all these deaths occurred after 1 month of age, the non-HIV related infant and postneonatal infant mortality rates were equal. The cumulative mortality rate attributable to trauma and sudden death at 4 months of age was 0.95% (95% CI: 0.02–1.87%) and the infant mortality rate was 9.5/1000 live births.

The 4 infants who died of non-HIV-related causes were uninfected based on at least one negative HIV peripheral mononuclear cell culture result, and none of the infants had signs of HIV or other infection at autopsy. The 38-month-old child was HIV-negative based on blood culture results and HIV antibody test results after 18 months of age. These children, whose deaths were unrelated to HIV, all had factors that have been associated with an increased risk for child abuse or SIDS (Table 1).<sup>8</sup> Three infants were born prematurely at 30, 33, and 36 weeks' gestational age, respectively. Three mothers admitted using recreational drugs and smoking cigarettes before or during pregnancy. One additional mother reported a history of smoking without drug abuse.

## DISCUSSION

This study describes a high incidence of traumatic and unexpected, noninfectious deaths in children born to HIV-infected mothers. These traumatic and sudden non-HIV-related deaths accounted for 4.1% (5/121) of the deaths during the entire P<sup>2</sup>C<sup>2</sup> study period and for 20% (4/20) of the deaths that occurred in the first year of life. Four deaths were attributable to accidental and nonaccidental trauma, rather than to other common causes of infant death, such as, respiratory illness and congenital anomalies. One death in our series was a sudden unexpected death, similar to SIDS, which is a leading cause of infant death in the United States.<sup>9,10</sup>

The infant mortality rate secondary to the combination of trauma and sudden unexpected death in

**TABLE 1.** Age, Cause of Death, and Associated Risk Factors in Children of HIV-Infected Mothers

Age at Death (Month)	Cause	Birth Weight (g)	Gestational Age (Week)	Maternal Age (Year)	Maternal Smoking	Maternal Drug Use
1.2	Head trauma	1825	33	21	–	None
1.2	Asphyxia	2615	37	26	+	None
1.3	SUD	1825	36	34	+	C
3.7	Battering	2040	30	26	+	C, M, H
37.8	Drowning	3101	40	33	+	C, M, H, S

Abbreviations: C, cocaine; H, heroin; M, methadone; S, speed; SUD, sudden unexpected death.

our cohort was 9.5/1000 live births and is similar to the 1994 United States infant mortality rate attributable to all causes (8/1000).<sup>9</sup> When compared with the 1994 postneonatal infant mortality rate attributable to all causes of 2.9/1000 live births reported by Guyer et al,<sup>9</sup> the rate in our study is not statistically significantly greater than was expected (standardized mortality ratio: 3.3; 95% CI: 0.89–8.4). However, infant mortality rates for specific causes of death per 100 000 live births in the United States in 1994 were 103 for SIDS, 22.5 for accidents, and 7.9 for homicide and child battering.<sup>11</sup> The higher combined rate for these three categories seen in our study suggests that children born to HIV-infected mothers are at increased risk for traumatic and accidental deaths (standardized mortality ratio: 7.3; 95% CI: 2.0–18.7). Furthermore, 4 of the 5 unexpected non-HIV-related deaths in our study occurred between 1 and 4 months of age, suggesting that this population may be at high risk especially during the first few months of life.

The majority of previously reported non-HIV-related deaths in infants born to HIV-infected mothers have been attributed to SIDS or to unexplained sudden death. In the European Collaborative Study of infants born to HIV-infected women, 3 of 600 infants died of SIDS.<sup>3</sup> Similarly, the French Pediatric HIV Cohort study noted that 6 of 994 infants born to HIV-infected women died of unexplained sudden death between 1 and 4 months of age.<sup>1</sup> A Swiss prospective study of children born to HIV-infected mothers reported 4 of 286 infants who died of SIDS without clinical or autopsy evidence of HIV infection.<sup>4</sup> The mothers of the 4 children who died suddenly in the Swiss study reported intravenous drug use during pregnancy. In contrast to the Swiss,<sup>4</sup> European,<sup>3</sup> and French<sup>1</sup> reports, 4 of the 5 children in our series died of accidental or nonaccidental trauma and only 1 death was a sudden unexplained death. One death from child abuse has been reported in a group of 323 children of HIV-infected mothers in New York City.<sup>12</sup>

Although it is unlikely that HIV exposure is related directly to the deaths described in this report, maternal HIV infection may serve as a marker for factors that place the child at risk for traumatic or sudden death. We noted that 3 infants were born prematurely and that maternal drug abuse and smoking were common. Maternal drug abuse has been associated with an increased risk for SIDS.<sup>8</sup> Similarly, a recent population-based study suggests that neglect and physical abuse are more common among alcohol- and drug-abusing parents than among nonsubstance-abusing parents.<sup>13</sup>

The number of deaths in our study is small and limits our ability to generalize estimates of risk to other populations. Furthermore, our study may not represent the risk for other infants born to HIV-infected mothers. The mothers of the children in our study were HIV-infected and volunteered to be followed in our longitudinal study. Women without prenatal care or those who delivered in other settings may not have been as likely to enroll in the study and their infants may be at different risk. Additionally, infants whose mothers acquire HIV infection secondary to drug abuse may be at different risk for abuse or SIDS than are those infants whose mothers acquire HIV through other means.

## CONCLUSION

In summary, this report indicates that children born to HIV-infected mothers may be at increased risk for traumatic or sudden unexplained, non-HIV-related death. These children seem to be at risk regardless of their own HIV infection status. Furthermore, 4 of the deaths in our study occurred within the first few months of life, suggesting that this is a period of increased vulnerability. Studies to identify associated risk factors for non-HIV-related deaths are needed to enable us to identify these high-risk infants. Children born to HIV-infected mothers may be more vulnerable than was recognized previously and may be in need of increased social services, particularly during early infancy.

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