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Human Immunodeficiency Virus-Related Mortality in Infants and Children: Data From the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV (P²C²) Study

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Abstract

Objectives—To identify the causes of mortality in children with vertically transmitted human immunodeficiency virus (HIV) infection and to study age-related mortality trends.

Methods—In the multicenter P²C² HIV Study, 816 children born to HIV-infected mothers were followed for a median of 3.6 years. Two hundred five study participants with HIV infection were enrolled at a median age of 23 months; 611 were enrolled either prenatally or in the neonatal period before their HIV infection status was known. There were 121 deaths in study patients. The cause of death for all patients, its relationship to HIV infection, and pulmonary or cardiac involvement were determined. Age trends in disease-specific mortality were summarized for the HIV-related deaths.

Results—Ninety-three children died of HIV-related conditions. Infection was the most prevalent cause of death for children under 6 years of age with 32.3% caused by pulmonary infection and

another 16.9% caused by nonpulmonary infection. The frequency of pulmonary disease as the underlying cause of death decreased significantly with increasing age: 5/9 (55.6%) by age 1, 1/12 (8.3%) after age 10 years. The frequency of chronic cardiac disease as the underlying cause increased with age—0% by age 1 year, 3/12 (25.0%) after age 10 years, as did the frequency of wasting syndrome with disseminated *Mycobacterium avium* complex—0% by age 1 year, 6/12 (50.0%) after age 10 years.

Conclusions—Children with HIV who survive longer are less likely to die of pulmonary disease or infection and more likely to die of cardiac causes or with wasting syndrome. pediatric acquired immunodeficiency syndrome, mortality, human immunodeficiency virus.

Infection with human immunodeficiency virus (HIV) is an important cause of death among children worldwide and in the United States. Nevertheless, specific causes of death in HIV-infected children have not been studied in detail. Death certificate data are nonspecific, and epidemiologic and prospective studies have focused on age-specific mortality or morbidity by Centers for Disease Control and Prevention (CDC) symptom class.¹ More detailed information of causes of death could help direct HIV therapeutic and research efforts and permit projections of future needs of the at-risk population of HIV-infected children.

We have collected a detailed database about causes of HIV-related death as part of the P²C² HIV Study, a multicenter natural history study sponsored by the National Heart, Lung, and Blood Institute. Infants and children were enrolled in the study at 5 clinical centers. Clinical endpoints included cardiac, pulmonary, immunologic, and growth characteristics as well as mortality. This report summarizes all deaths but focuses on the underlying cause of death and contributing factors for those who died of HIV-related conditions. Linear age trends in mortality for specific infections and age trends related to cardiac and pulmonary disease are summarized.

Methods

The full methodology of the study has been previously reported.² In brief, children born to known HIV-seropositive mothers were enrolled into 2 groups: group I included children with documented vertically transmitted HIV infection enrolled at any time after 28 days of age and born after April 1, 1985, or earlier where vertical transmission of HIV infection could be documented with reasonable certainty. Children with known malignancy or a history of sexual abuse were not eligible for enrollment. Group II participants were enrolled in utero or as newborns (<28 days of age). Their HIV infection status was unknown at enrollment.

Enrollment began in May 1990 and continued through January 1994 with follow-up through January 1997. Of the 816 patients enrolled, 205 were group I; of these, 183 (89.3%) had CDC class P2 symptoms at the time of enrollment. There were 611 group II patients; 443 (72.5%) were enrolled prenatally and the remaining 168 postnatally. The Group II patients were subsequently divided into 96 IIa (15.7%), those with vertically transmitted HIV infection, and 464 IIb (75.9%), those uninfected with HIV. At the conclusion of the study, 51 group II patients (8.3%) remained without a final HIV status determination because of

death or loss to follow-up before HIV infection status could be determined; these subjects are denoted as Ili (indeterminate).

Each patient death and its immediate cause was reported by the clinical centers. A mortality review committee (MRC) was established to conduct a centralized review to ascertain a standardized underlying cause for each death. The members of the MRC were a pediatric pathologist, 2 pediatric infectious diseases specialists, a pediatric pulmonologist, a pediatric cardiologist, and a member of the data coordinating center (DCC).

Clinical centers completed a cause of death case report form and submitted any pertinent available information (Fig 1), including death certificate data, autopsy reports, progress notes and hospital discharge summaries from the hospitalization nearest to or at the time of death, coroner's investigation reports, delivery records, and placenta examination reports. A patient summary from a physician or nurse familiar with the patient was generated at the individual centers. Serial study data extracted from the computerized database including laboratory data, physical examination findings, chest radiograph findings, echocardiogram findings, biopsy results, and therapies used were compiled and distributed in table format by the DCC. Review of the data, discussion, and debate led to consensus in all cases on the immediate and underlying cause of death and any contributing conditions.

Definitions for immediate, contributing, and underlying cause of death were taken from the 1989 US Standard Certificate of Death³ as adopted by most states: Immediate Cause of Death, the single final disease, injury, or complication directly causing the death; Contributing Causes of Death, the conditions if any leading to the immediate cause of death but not constituting the single identified underlying cause; Underlying Cause of Death, the single disease or injury that initiated the events resulting in death. Thus, only one underlying cause and one immediate cause could be assigned for each case; more than one contributing cause could be identified. The MRC agreed that HIV infection, although clearly the initiating disease state for the HIV-related deaths, was not a sufficient cause and the underlying cause must be that complication of HIV infection that led to patient death.

Definitions for specific diagnoses, such as HIV-related encephalopathy, wasting, and failure to thrive were taken from the CDC Guidelines.¹ Disseminated *Mycobacterium avium* complex (MAC) was diagnosed by positive blood culture or by positive culture from a site other than the respiratory tract, skin, or cervical or hilar lymph node in a chronically ill child with fever. Chronic lung disease and chronic cardiac disease were considered present if included in the submitted clinical outline and supported by specific data previously submitted from the clinical center. In addition, chronic lung disease was also considered present if chest radiograph reports were noted to be repeatedly and continuously abnormal for 6 months or more with no resolution at the time of death. Chronic cardiac disease was also established by evidence of chronic cardiac disease on autopsy examination, chronic cardiac dysfunction on echocardiogram, or there was chronic use of cardiac medications.

After the immediate, underlying, and contributing causes of death were determined, they were grouped into broader categories for analysis. Immediate cause of death was not addressed further because it was often nonspecific or represented a common mechanism of

dying and thus did not further illuminate the factors contributing to morbidity in the children who died. The underlying cause of death was considered to best represent the process leading to patient death. In the data tabulation, a hierarchy was used so that a patient with more than one finding in a defined category would not be included in the tabulation twice. For example, if cardiomyopathy was identified as the underlying cause of death, a contributing cause of death of cardiomegaly was not included.

The data were tabulated by HIV infection status, age at death, cytomegalovirus (CMV) infection status, and the presence of chronic cardiac disease, chronic pulmonary disease, or both. The cumulative HIV-related mortality rate for each group was estimated by the Kaplan-Meier method. Confidence intervals (95%) were provided over 5 years of follow-up for group I and by age for group IIa. The Cochran-Armitage test for linear trend was used to determine whether the frequency of selected underlying causes of death increased or decreased following a linear pattern with increasing age. χ^2 tests were used to test for association between completeness of data with location of death and resuscitation status.

Results

The 816 study patients enrolled from the 5 clinical centers were followed a median of 3.6 (range: 0-6.5) years. There were 121 deaths in study patients (14.8%); 71 group I (late enrollment), 32 group IIa (early enrollment, HIV-infected), 2 group IIb (early enrollment, HIV-uninfected), 16 group IIi (early enrollment, HIV infection status undetermined). Most children were black ($n = 50$; 41.3%) or Hispanic ($n = 47$; 38.8%), and 46.3% were male. Race and gender did not differ by HIV infection. The cumulative 5-year mortality for HIV-related deaths was similar in both groups, 34.3% (95% confidence limit: 27.2-41.4) in group I and 29.6% (95% confidence limit: 19.4-39.7) in group IIa (Fig 2). Median age at death was older in the group I patients (59 months; range: 4 months to 15 years) than in the group II patients (19 months; range: 5.7-61 months); median age at enrollment for group I patients was 23 months. The impact of antiretroviral therapy was not specifically assessed in this study. Most of the patients who died had received antiretroviral therapy (Table 1), although a few group IIa patients who died in infancy did not. The patients who died received similar therapies to those who did not. Many study patients were coenrolled in a number of other studies related to the efficacy of specific therapeutic interventions.

Forty-five autopsies (37.2% of deaths) were reported to the DCC (19 group I, 18 group IIa, 1 group IIb, 7 group IIi). Six of the 11 fetal demises (54.6%) had autopsies. Nine of the 45 autopsies were performed at medical examiner offices, and one coroner investigation without autopsy was also performed. The frequency of autopsy declined with age from 65.0% (13/20) at 0 to 1 year to 40.0% (22/55) at 1 to 5 years to 11.4% (4/35) at or above 5 years of age.

Fetal Deaths

Eleven of the 121 deaths were fetal demises at gestational ages from 8 to 33 weeks and occurred in the 443 prenatal enrollments, a 2.5% fetal loss rate. Three were shown to be HIV-infected and 1 HIV-uninfected by in situ hybridization. Tissues from the other 7 were not available for these studies, and their HIV status remains indeterminate. A determination

of underlying cause of death could be made for only 2 fetuses; parvovirus fetopathy and intrauterine hypoxia and ischemia in the setting of maternal cocaine use. In only 3 of the 9 was any other condition identified; for 2, there was a history of maternal cocaine use, not directly linked to fetal death, and a third showed placental abnormalities of ischemia not judged sufficient to result in death.

Liveborn Patient Deaths

Of the 805 liveborn study patients, 110 (13.7%) died during the study. The majority of these (93/110, 84.5%) died of HIV-related disease; a small number died of non-HIV-related causes, and for a few, death could not be categorized.

Non-HIV-Related Deaths

Twelve of the 110 liveborn patients (10.9%) died of non-HIV-related causes. One belonged to group I, 2 to IIa, 1 to IIb, and 8 to Iii. Five of these 12 deaths are the basis of a separate report of unexpected death in this patient population.⁴ Of the 7 not included in that report, 3 died in the neonatal period, 2 with extreme prematurity, and 1 of multiorgan failure related to perinatal asphyxia. The fourth, a 3-month-old group Iii male infant, died unexpectedly during hospitalization for otitis media complicated by periorbital cellulitis; sepsis was the cause of death. The fifth, a 6-month-old group IIa male infant, died of lipid overload syndrome caused by malfunction of a parenteral nutrition pump during his initial hospitalization for HIV-related disease. The group I infant, enrolled at 10 months of age, had many HIV-related contributing conditions but died of bronchopulmonary dysplasia, a complication of extreme prematurity, at 30 months of age. The seventh, a 44-month-old group IIa boy, died at home unobserved. Although neither autopsy nor medical examiner investigation was performed, emergency department data, obtained during unsuccessful resuscitation attempts, suggested concealed hemorrhage.

Noncategorized Deaths

Despite the review procedure and an intensive search, information was insufficient to categorize 5 deaths (4.5%). These include 1 group Iii infant who died in a foreign country at 3 months of age and 4 older children, 10 months to 10 years of age (3 group I, 1 group IIa) all of whom were lost to follow-up before death. They were reported to the DCC at death, but with insufficient information to reconstruct the circumstances surrounding their deaths. None had autopsy examination.

HIV-Related Deaths

Ninety-three of the 110 liveborn children who died in the study died of HIV-related disease. The youngest was a 4-month-old group I female infant who died of *Pneumocystis carinii* pneumonia (PCP); the oldest, a 15-year-old group I girl, died of wasting syndrome. The HIV-related deaths include 67 group I and 26 group IIa children. The youngest group IIa death was a 5.7-month-old female infant who died of disseminated CMV, and the oldest a 61-month-old girl who died of cardiomyopathy. The HIV-related deaths were equally distributed across age categories (Fig 2) with similar cumulative mortality across the 5 years of follow-up. However, the causes of death (Table 2), contributing factors (Table 3), and

noncontributing conditions present (Table 4) differed by age group. Younger children were more likely to die of infection (non-MAC), both pulmonary ($P = .02$) and nonpulmonary ($P = .02$; Fig 3B). The most prevalent underlying cause of death for children under 6 years of age was infection (32/65 deaths; 49.2%), with 21 of these deaths caused by pulmonary infection (32.3% of deaths <6 years of age, 65.6% of infectious disease deaths <6 years of age). Older children had more diverse underlying causes of death, with wasting in combination with MAC infection and/or HIV encephalopathy being far more frequent than in younger children ($P = .01$; Fig 3C). The underlying cause of death of wasting with encephalopathy did not change linearly with age, but the frequency increased from birth to age 3 years, followed by a decline in frequency after age 3 (Fig 3C).

Location of Death, Resuscitation Status, and Completeness of Data—Most of the HIV-related deaths occurred in the hospital (60; 64.5%), but 22 children (23.7%) died at home, 7 (7.5%) died in hospice care and 4 (4.3%) died at other locations. For 5 patients no information on do not resuscitate (DNR) orders was available. Of the remaining 88, 64 (72.7%) had DNR orders at the time of death. An autopsy was performed in 32 of the 93 children who died of HIV-related disease (34.4%). Sixty-two of the 93 HIV-related deaths (66.7%) were judged to have sufficient information to determine the immediate and underlying causes of death. For the remaining 31 (33.3%), there were sufficient data to implicate a number of specific disease processes in the terminal course, but not to identify the immediate, or less frequently, the underlying causes of death. For these children, the immediate and, less often, the underlying cause of death was listed as unknown.

Resuscitation status was not associated with completeness of data, but dying in the hospital ($P = .006$) and having an autopsy performed ($P = .002$) were associated with data completeness. Death in the hospital was more common among cases with complete data (46/62; 74.2%) than among cases with incomplete data (14/31; 45.2%). Of the 62 cases with complete data, 43.5% (27/62) had an autopsy performed, but only 16.1% (5/31) of those with incomplete data had an autopsy. More than 70% of both groups had DNR orders at the time of death (72.9%; 43/59 for those with complete data; 72.4%; 21/29 for those with incomplete data). Absence of DNR status and the presence of autopsy data were related but the relationship was not dependent on completeness of data. The autopsy rate was 25.0% (16/64) for DNR cases, but >50% (13/24; 54.2%) for patients who did not have DNR orders ($P = .01$).

Infant Deaths—The tendency for younger children to die of infection is particularly exemplified in the infant deaths. Of the 9 infant deaths (range: 4–12 months) that were HIV-related, infection, both pulmonary and nonpulmonary, was the most common underlying cause (6/9; 66.7%). For 3, PCP was the underlying cause of death, the other 3 infectious deaths included pulmonary infection, sepsis syndrome without organism identification, and disseminated CMV infection. The 3 noninfectious infant deaths included 2 hemorrhagic deaths and 1 death from liver failure because of hepatitis of undetermined cause.

Four of the 9 infants had failure to thrive. Five had encephalopathy, of which only 1 was HIV-related. Encephalopathy was not thought to have contributed to death in these 5 infants. Two of the 9 infants had chronic cardiac disease; for 1 of the 2, cardiac disease contributed

to death as congestive heart failure developing in the course of prolonged PCP. The other infant with chronic cardiac disease had cardiomyopathy in the setting of impaired brain growth, failure to thrive, and loss of developmental milestones. Two of the 9 had chronic pulmonary disease, both in the setting of previous PCP infection.

PCP—Five children had PCP as the underlying cause of death. Their ages ranged from 4 to 25 months, and 3 were <1 year old. Of these 3, the youngest also had failure to thrive, hepatosplenomegaly, anemia, and congestive heart failure with PCP as the acquired immunodeficiency syndrome (AIDS)-defining illness at 3 months of age. The other 2 infants died at 6 and 8 months of age with PCP as their AIDS-defining illness without other conditions present. None had received PCP prophylaxis, because the use of PCP prophylaxis in children without a diagnosis of AIDS was not standard practice at the time. The 2 children >1 year old with PCP as their underlying cause of death both had wasting syndromes and 1 had disseminated CMV identified at autopsy.

MAC—Of the 93 children who died of HIV-related disease, 39 (41.9%) met the definition for disseminated MAC and 7 of these also had documented MAC pulmonary infection. In 22 patients, MAC was considered the underlying cause of death (Table 2), in 15 others it was considered to be a contributing condition (Table 3), and in 2 it was present but not thought to contribute to mortality (Table 4). Wasting and encephalopathy were both associated with MAC in those who died, with 12 also manifesting wasting and 10 both wasting and encephalopathy. The combination of wasting and MAC was not seen as an underlying cause of death in children under 2 years of age (Table 2). MAC disease as a contributor to mortality became more important with increasing age. It increased significantly in frequency ($P = .01$) with increasing age (Fig 3C) becoming the underlying cause of 50% of deaths in children >10 years old.

CMV—CMV infection was the underlying or contributing cause of death in 12 children, ages 5.7 to 183 months. Nine were diagnosed clinically and an additional 3 were identified at autopsy. CMV was known to be present but not implicated in mortality for an additional 4 children. Of the children with CMV infection as a contributing or underlying cause of death, 12 had severe immunosuppression with CD4% <15 on the last testing before death, and most had other debilitating conditions such as disseminated MAC with congestive heart failure and wasting or severe encephalopathy and wasting.

Lung Disease—Pulmonary disease was an important contributor to HIV-related mortality (Table 5). In 39 of the 93 deaths (41.9%), pulmonary disease was either the underlying cause or a contributing factor. Although pulmonary disease was implicated in 6/9 HIV-related deaths (66.7%) in the first year of life and in 17/30 of deaths (56.7%) in children from 1 year to 3 years old, only 11/43 children (25.6%) >4 years of age had pulmonary disease as an underlying or contributing cause of death. The frequency of pulmonary-related deaths decreased with age. This trend was most striking for pulmonary death as the underlying cause of death ($P = .002$; Fig 3A) and was present, but less striking, for infectious pulmonary deaths ($P = .02$; Fig 3B).

Chronic Lung Disease—Fifty-four of the 93 HIV-related deaths (58.1%) were in children who met the definition for chronic lung disease, a subset of those with lung disease. Of these, 29 (53.7%) had a pulmonary death with pulmonary disease being the underlying cause of death in 65.5% (19/29) and a contributory cause in 34.5% (10/29). All pulmonary deaths in patients >4 years old were in children with chronic lung disease (Table 5).

Chronic Cardiac Disease—More than one half of children with HIV-related deaths (51.6%; 48/93) had chronic cardiac disease. Chronic cardiac disease was the underlying cause of death in 11.8% (11/93). None of the 9 infants who died in the first year of life had chronic cardiac disease as the underlying cause of death. The frequency of chronic cardiac disease as the underlying cause of death increased with age ($P = .05$; Fig 3A). The age-related distribution of chronic cardiac disease is exemplified by the finding of chronic cardiac disease in 61.2% of HIV-related deaths (41/67) in group I children, compared with 26.9% of HIV-related deaths (7/26) in group IIa. Among the 67 group I children, 27 (40.3%) had cardiac disease as a contributing or underlying cause of death and it was the underlying cause in 10 (14.9%). Cardiomyopathy was the underlying cause of death in these 10 children. Only 2 group IIa children (7.7%) had cardiac disease as a contributing or underlying cause of death, and in only 1 (3.9%) was chronic cardiac disease with cardiomyopathy the underlying cause of death.

Pancreatitis—Fourteen patients had pancreatitis and in 3 patients it was their underlying cause of death (Table 2); all 3 had received ddI. In 2, drug toxicity was implicated as the cause of the pancreatitis; the third had prolonged pancreatitis and died in the setting of dehydration and shock. In 5 patients, pancreatitis was a contributing cause of death; all had other gastrointestinal disease including persistent diarrhea (3), sclerosing cholangitis (2), and hepatitis (3). In only 1 was drug toxicity directly implicated as the cause of the pancreatitis, but 3 others received didanosine (ddI) or zalcitabine. In 6 other patients, pancreatitis was present but did not contribute to death; 1 of the 6 also had persistent diarrhea.

Neoplasia—Four patients developed neoplastic disease with 3 dying during follow-up. For 2 children, malignancy was the underlying cause of death. One was a primary central nervous system tumor presumed to be lymphoma that developed in the setting of HIV encephalopathy, cardiomyopathy, and wasting with death 3 months after tumor diagnosis at age 4 years. The other, a large cell immunoblastic lymphoma, positive for T cell markers, arose in the mediastinum and eroded into the trachea and esophagus, leading to death at 29 months of age. A third patient, a 40-month-old, had an unclassifiable malignancy that arose in the scapular region and was presumed to be an undifferentiated lymphoma. She died when antineoplastic treatment was withdrawn; however, autopsy showed necrotizing CMV pneumonia as the underlying cause of death. The only other patient with neoplastic disease had a lymphoma diagnosed by lung and tonsillar biopsies; she responded to therapy and remained free of tumor at the completion of follow-up.

Discussion

In the P²C² Study, mortality was assessed in a uniform manner using all available data, analogous to the verbal autopsies used to collect disease-specific information in settings in

which medical information is incomplete.^{5,6} This study is unique in its focus on the causes of mortality in perinatally acquired HIV infection. Cause-specific mortality data are difficult to compile in large collaborative studies, primarily because of incomplete data and variations in reporting standards. In pediatric AIDS, these general difficulties are further compounded when parents and health care providers choose to allow these children to die undisturbed when there is no longer any hope of useful intervention. Because a significant proportion of these patients die outside the hospital (35.5%; $n = 33$, in this study), the record of events leading to death is generally scanty, and reconstruction of the circumstances surrounding death is incomplete. Death certificate data are widely considered to be inadequate for other than the broadest categorization of mortality.^{7,8} In this study, most death certificates listed AIDS as the cause of death. Studies from pediatric AIDS registries may report more specific causes of death, but in a necessarily undefined population.^{9,10} Epidemiologic studies report age-specific mortality, sometimes as it relates to CDC symptom class and presence of PCP. However, prospective collaborative studies have not focused specifically on the causes of mortality, reporting mortality in relation to CDC symptom class and age, without defining specific causes.¹¹⁻¹⁵ Our study was unique because distinct prospectively collected data were available for review to enable us to identify specific causes of death.

HIV-associated mortality is an important cause of death among children both world-wide and in the United States. US mortality figures for 1997 indicate a decline in HIV infection as a leading cause of death from 6th most common in 1993 through 1995 to 11th most common for children 1 to 4 years of age. HIV infection remains the 7th most common cause of death for black children and the 10th most common for Hispanic children in this age group. In children 5 to 14 years of age it is the ninth most common cause of death overall, seventh in black children and eighth in Hispanic children.¹⁶ In discussions of pediatric HIV infection, it is generally assumed that there is a group of infants, estimated to be ~20%, who become ill early in life with severe immunodeficiency, encephalopathy, and opportunistic infection, progress rapidly, and are likely to die in infancy.^{10,17} This progression has been related to host factors,¹⁸⁻²¹ thymic dysfunction,²² viral phenotype,^{23,24} and timing of transmission,²⁵ and results in increased viral load.²⁶ A larger group of patients, ~80%, become ill later and survive longer with slower disease progression with a proportion remaining asymptomatic beyond age 5 or 6 years.¹⁷ These observations imply differences in age-specific mortality in pediatric HIV-infection.

In the P²C² Study we did not find a change in age-specific mortality across the study period, with relatively equal proportions of study patients dying each year, regardless of original group, or whether analysis is by age or age from enrollment. This results in an almost linear cumulative mortality over the study. There are, however, significant age-related trends in disease-specific mortality. Those dying earlier are more likely to die of pulmonary disease, predominantly infectious, and those dying later are more likely to have wasting syndrome often with MAC, encephalopathy, or both. Cardiac deaths also show an age-related trend, becoming more frequent with increasing age. PCP was not a prominent contributor to mortality; there were only 5 PCP deaths, 3 in infants.

Fetal loss rates vary across gestation, being 10% to 15% for all recognized pregnancies, with most occurring early in the embryonic period. Less than 3% of pregnancies that reach 10 weeks result in fetal loss.²⁷ The fetal loss rate (2.5%) in this study seems to be within this normal range, as all but one occurred after 10 weeks gestation. This study was not designed to evaluate the role of HIV in fetal loss. Other studies suggest that there is an increased fetal loss rate in association with maternal HIV infection, and that this increased fetal loss is associated with HIV transmission.²⁸ This essentially normal fetal loss rate is appropriate for the relatively low HIV transmission rate noted in the P²C² Study.

One of the major aims of the P²C² Study was to assess the impact of chronic cardiac and pulmonary disease on children with vertically transmitted HIV. In this study of mortality in the P²C² cohort, cardiac and pulmonary disease both play important roles as underlying and contributing causes of death. Pulmonary disease, usually infectious, has been considered to be the most prominent manifestation of AIDS in children as well as adults and was once thought to be a universal feature of pediatric AIDS.²⁹⁻³¹ In this study it remains an important cause of HIV-related deaths, being the underlying or contributory cause of 41.9%. The role of pulmonary disease and particularly infectious pulmonary disease in mortality decreased substantially with age. Chronic lung disease was present in 58.1% of all children who died in this study with one third of children under 1 year of age having chronic lung disease, and one half or more at all later times being affected. Although it was not always associated with death from pulmonary causes, all pulmonary deaths after age 4 years were in children with chronic lung disease.

Cardiac disease was a prominent contributor to mortality, being the underlying cause or an important contributing factor in almost one third of patients (29/93; 31.2%). An additional 20.4% (19/93) had evidence of cardiac disease not thought to contribute to death; thus, just more than one half of the children (48/93; 51.6%) had evidence of cardiac disease at death. Cardiac disease as an underlying cause of death shows a significant age-related trend. It is not seen in infancy, is unusual in early childhood, and increases to 25% of deaths in children >10 years old. The mortality related to cardiac disease in HIV-1-infected children has been noted previously,^{32,33} but is generally under-appreciated. The cause of cardiac dysfunction in HIV-1-infected children remains unknown; secondary viral infection³⁴ and antiretroviral drug therapy have been implicated in some cases.

Wasting, encephalopathy, and MAC both alone and in various combinations become important factors in mortality with increasing age in the study patients, becoming the most important underlying cause of mortality in children >10 years old. The higher autopsy rate in younger children suggests that there is no ascertainment bias for MAC disease, because clinically unsuspected disease was not identified in these intensively studied young children. With increasing survival of children with vertically transmitted HIV-1 infection, the devastating effects of these diseases may become much more prevalent.

Changing therapies for AIDS and the use of prophylaxis against opportunistic infection may also impact the manifestations of HIV infection in children. Children in this study received a wide variety of antiretroviral therapies and prophylaxis against opportunistic infection. Although it is not possible to dissect the contribution of these to increasing survival in these

study patients, those who died received similar therapies to those who survived. The children in the study were followed between 1990 and 1997, before the use of protease inhibitors. Therefore, the effect of these new, more effective antiretroviral agents on disease outcome and mortality was not a feature of this study.

An analysis of the causes and contributing factors to mortality in this long-term multicenter study of vertically transmitted HIV infection shows that although the death rate remains fairly constant across the study, the causes of mortality change dramatically with increasing postnatal survival. These changes are likely to be related to differences in host factors, including genetic makeup and immunologic responsiveness, as well as viral burden, and virus-specific factors. Those diseases whose mortality increases with increasing age are likely to become more important clinically as more and more patients survive the early years with their concomitant risk of death from infection and pulmonary disease. Knowledge of specific age-related causes of mortality, as identified in this study, can guide efforts directed at the future needs of the population of HIV-infected children.

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Appendix

The following is an abbreviated list of study participants. A complete list can be found in reference 2.

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Policy, Data, and Safety Monitoring Board

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Abbreviations

HIV	human immunodeficiency virus
CDC	Centers for Disease Control and Prevention
MRC	mortality review committee
DCC	data coordinating center
MAC	<i>Mycobacterium avium</i> complex
CMV	cytomegalovirus
PCP	<i>Pneumocystis carinii</i> pneumonia
DNR	do not resuscitate
AIDS	acquired immunodeficiency syndrome
ddI	didanosine

Fig 1.
Summary of the P²C² HIV mortality review process.

Fig 2.
Cumulative HIV-related mortality (boldface) with 95% confidence intervals (nonboldface) for group I (67 deaths) and group IIa (26 deaths) children.

Fig 3.
Linear age trends for the underlying cause of death in 93 HIV-related deaths.

Table 1

Summary of Medication Use Among HIV-Infected Children

Medication	Older Cohort						Birth Cohort					
	Survivors (n = 134)			Nonsurvivors (n = 71)			Survivors (n = 64)			Nonsurvivors (n = 29)		
	No.	%	Median Duration of Therapy (Months)	No.	%	Median Duration of Therapy (Months)	No.	%	Median Duration of Therapy (Months)	No.	%	Median Duration of Therapy (Months)
AZT (zidovudine)	118	88.1	37.6	70	98.6	20.0	51	79.7	29.1	23	79.3	8.0
ddI	88	65.7	27.2	39	54.9	11.2	44	68.8	18.3	13	44.8	8.1
ddC (zalcitabine)	17	12.7	13.8	11	15.5	2.6	3	4.7	2.8	1	3.4	.7
3TC (lamivudine)	37	27.6	6.6	7	9.9	8.9	19	29.7	5.9	0	.0	—
Interferon	2	1.5	5.9	1	1.4	1.9	1	1.6	5.3	1	3.4	4.1
Nevirapine	9	6.7	20.7	0	.0	—	4	6.3	18.6	0	.0	—
d4T (stavudine)	29	21.6	7.9	11	15.5	7.7	16	25.0	8.2	4	13.8	19.7
Intravenous immune globulin	47	35.1	44.3	41	57.7	18.2	15	23.4	8.4	11	37.9	2.4
Any antiretroviral	130	97.0	69.8	70	98.6	34.3	59	92.2	45.1	26	89.7	19.4
Any protease inhibitor	18	13.4	4.3	3	4.2	2.1	8	12.5	8.4	0	.0	—

Table 2

Underlying Cause of Death in 93 HIV-Related Deaths

Age at Death (Years)	Number of Patients	Wasting			HIV Encephalopathy		Infection Non-MAC		Chronic Cardiac	Organ Failure	Neoplasn	Hemorrhage	Pancreatitis	Other	Unknown
		Alone	With MAC	With HIV Encephalopathy	Both	Without Wasting	Pulmonary	Nonpulmonary							
0-1	9	0	0	0	0	0	4	2	0	1	0	1	1	0	0
>1-2	13	0	0	1	1	0	3	3	2	1	0	0	1	1	0
>2-3	17	0	1	2	3	1	7	2	0	0	1	0	0	0	0
>3-4	11	0	1	0	2	0	4	2	1	0	0	0	0	0	1
>4-6	15	0	3	1	1	0	3	2	2	0	1	1	1	0	0
>6-10	16	0	2	1	2	0	2	0	3	2	0	2	0	1	1
>10	12	1	5	0	1	0	1	0	3	0	0	0	0	0	1
Total patients	93	1	12	5	10	1	24	11	11	4	2	4	3	2	3

Table 3

CCOD in 93 HIV-Related Deaths*

Age at Death (Years)	Number of CCOD/ Number of Patients	Wasting		No Wasting		MAC Only	Infection Non-MAC	Pulmonary		Renal	Cardiac		GI	Neoplasm	Hemorrhage/ DIC
		Alone	With MAC	With HIV Encephalopathy	With Both	HIV Encephalopathy Without MAC	HIV Encephalopathy With MAC	Acute	Chronic		Acute	Chronic			
0-1	8/9	0	0	0	0	0	0	1	0	1	1	0	4	0	1
>1-2	23/13	5	0	2	0	1	0	4	1	1	1	3	4	0	1
>2-3	18/17	3	0	2	1	0	1	5	2	0	0	2	2	0	0
>3-4	18/11	0	1	1	1	1	0	2	1	2	0	3	2	1	1
>4-6	19/15	3	3	2	0	0	0	3	1	0	0	4	2	0	1
>6-10	18/16	2	5	1	0	0	0	5	0	0	0	1	3	0	0
>10	20/12	3	2	0	0	0	0	5	0	1	0	5	3	0	0
Total	124/93	16	11	8	2	2	1	24	6	3	2	18	20	1	4

CCOD indicates contributing causes of death; GI, gastrointestinal; DIC, disseminated intravascular coagulation.

* Patients may have >1.

Table 4

CP in 93 HIV Related Deaths*

Age at Death	Number of CP/ Number of Patients	Wasting		No Wasting		MAC Only	Pulmonary (Infectious and Noninfectious)		Renal	Cardiac	GI	Failure to Thrive	CMV Disease
		Alone	With HIV-Encephalopathy	HIV Encephalopathy without MAC	HIV Encephalopathy with MAC								
(Years)													
0-1	18/9	0	0	1	0	0	1	2	5	1	1	3	0
>1-2	6/13	2	0	0	0	0	0	0	2	1	1	0	0
>2-3	25/17	0	0	2	0	0	3	3	0	6	6	1	2
>3-4	14/11	0	1	1	1	0	2	2	1	1	3	0	0
>4-6	14/15	0	0	1	0	0	4	0	0	3	5	1	0
>6-10	19/16	1	0	0	0	1	4	3	0	6	4	0	0
>10	6/12	0	0	0	0	0	2	1	0	1	2	0	0
Total	102/93	3	1	5	1	1	16	11	8	19	22	5	2

CP indicates conditions present but not contributing to death; GI, gastrointestinal.

* Patients may have >1.

Table 5

Age	Number of Patients	Chronic Lung Disease		No Chronic Lung Disease		Pulmonary Death			
		Total	Pulmonary Death* Nonpulmonary Death	Total	Pulmonary Death* Nonpulmonary Death	Underlying or Contributing Causes of Death	Underlying Cause of Death Only		
0-1	9	2/9	2 (1)	0	7/9	4 (4)	3	6/9 (67%)	5/9 (56%)
>1-2	13	9/13	5 (4)	4	4/13	2 (1)	2	7/13 (54%)	5/13 (39%)
>2-3	17	10/17	7 (4)	3	7/17	3 (3)	4	10/17 (59%)	7/17 (41%)
>3-4	11	7/11	4 (4)	3	4/11	1 (0)	3	5/11 (45%)	4/11 (36%)
>4-6	15	9/15	6 (3)	3	6/15	0	6	6/15 (40%)	3/15 (20%)
>6-10	16	8/16	2 (2)	6	8/16	0	8	2/16 (13%)	2/16 (13%)
>10	12	9/12	3 (1)	6	3/12	0	3	3/12 (25%)	1/12 (8%)
Total	93	54/93	29 (19)	24	39/93	10 (8)	30	39/93 (42%)	27/93 (29%)

* Number of deaths in which the pulmonary disease was the underlying or contributing cause of death; number in parentheses is the number attributable to underlying cause of death only.