
Bill G. Kapogiannis,1,2,3 Minn M. Soe,4,a Steven R. Nesheim,4,2 Elaine J. Abrams,5,6 Rosalind J. Carter,6,7 John Farley,8,9 Paul Palumbo,10,11 Linda J. Koenig,4 and Marc Bulterys4,a

1Pediatric, Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; Division of Infectious Diseases, Departments of 2Pediatrics and 3Medicine, Emory University School of Medicine, Atlanta, Georgia; 4Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; 5Department of Pediatrics, Harlem Hospital Center and 6ICAP, Mailman School of Public Health, Columbia University, New York, New York; 7Medical and Health Research Association, New York, New York; 8Department of Pediatrics, University of Maryland, Baltimore; 9Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; 10Department of Pediatrics, Dartmouth College, Hanover, New Hampshire; 11Department of Pediatrics, University of Medicine and Dentistry, Newark, New Jersey.

(See the Editorial Commentary by Nachman, on pages 1035–6.)

Background. Highly active antiretroviral therapy (HAART) has improved human immunodeficiency virus (HIV)–associated morbidity and mortality. The bimodal mortality distribution in HIV-infected children makes it important to evaluate temporal effects of HAART among a birth cohort with long-term, prospective follow-up.


Results. Among 364 HIV-infected children, 56% were female and 69% black non-Hispanic. Of 98 deaths, 79 (81%) and 61 (62%) occurred in children ≤3 and ≤2 years old, respectively. The median age at death increased significantly across the eras (P < .0001). The average annual mortality rates were 18 (95% confidence interval [CI], 11.6–26.8), 6.9 (95% CI, 5.4–8.8), and 0.8 (95% CI, 0.4–1.5) events per 100 person-years for the no/monotherapy, mono-/dual-therapy and HAART eras, respectively. The corresponding 6-year survival rates for children born in these eras were 57%, 76%, and 91%, respectively (P < .0001). Among children who received HAART in the first 6 months of age, the probability of 6-year survival was 94%. Ten-year survival rates for HAART and non-HAART recipients were 94% and 45% (P < .05). HAART-associated reductions in mortality remained significant after adjustment for confounders (hazard ratio, 0.3; 95% CI, .08–.76). Opportunistic infections (OIs) caused 31.8%, 16.9%, and 9.1% of deaths across the respective eras (P = .051).

Conclusions. A significant decrease in annual mortality and a prolongation in survival were seen in this US perinatal cohort of HIV-infected children. Temporal decreases in OI-associated mortality resulted in relative proportional increases of non–OI-associated deaths.

Since the introduction of highly active antiretroviral therapy (HAART) during the mid- to late 1990s, there have been substantial improvements in human immunodeficiency virus (HIV)–related morbidity and mortality for HIV-infected adults [1–5] and children [6–10]. Similarly, marked improvement in mortality rates among HIV-infected adults on HAART have been demonstrated within observational cohorts [4, 5, 11–13] and in a large randomized clinical trial [14]. Survival among HIV-infected children has been characterized in international
Methods

The course of perinatal infection.

that this difference is primarily due to deaths occurring early in
before adjustment for morbidity-related confounders, and show
dramatic differences in mortality rates among children not
pediatric HIV has been described elsewhere [52]. We show
the higher mortality risk characteristic of the first 2 years of life
enrollees comprised a birth cohort, allowing observation of
nutrition status [51].

A unique feature of the current prospective long-term study is
that enrollees comprised a birth cohort, allowing observation of
the higher mortality risk characteristic of the first 2 years of life
in HIV-infected children. The bimodal mortality distribution in
pediatric HIV has been described elsewhere [52]. We show
dramatic differences in mortality rates among children not
with HAART compared with HAART recipients, even
before adjustment for morbidity-related confounders, and show
that this difference is primarily due to deaths occurring early
in the course of perinatal infection.

Methods

Subjects and Study Design

The Perinatal AIDS Collaborative Transmission Study (PACTS)
was supported by the CDC from 1986 through 1999. PACTS was
a multicenter, prospective cohort study of HIV-infected preg-
nant women and their newborns conducted in 4 US cities to
monitor the incidence of mother-to-child HIV transmission and
to describe the natural course of pediatric HIV disease pro-
gression. This study was approved by the institutional review
boards at CDC and at the respective centers. Signed parental
informed consent was obtained for each participant. Sites began
enrollment as follows: New York City, 1986; Baltimore, 1989;
Atlanta, 1990; and Newark, 1990. Mother-infant pairs were
followed continuously until September 30, 1999, 1 year after
enrollment terminated. This cohort has been described else-
where [10, 46, 53]. Clinical follow-up of infected children and
a 1:1 control group of HIV-exposed, uninfected children from
PACTS was continued through the PACTS-HIV Follow-up of
Perinatally Exposed Children (PACTS-HOPE) study, conducted
from October 1999 through April 2004 [54]. Hereafter, both
PACTS and PACTS-HOPE enrollees are collectively referred to
as the study cohort or as PACTS/PACTS-HOPE.

Definition of Therapeutic "Eras"

The study cohort was divided into 3 periods: no/monotherapy,
mono-/dual-therapy and triple-therapy (HAART) eras which were
from 1 January 1986 through 31 December 1990; from
1 January 1991 through 31 December 1996; and from 1 January
1997 through 31 December 2004, respectively. The no/mono-
therapy era is defined taking into consideration that the first
antiretroviral, ZDV, did not become available until 1987 and that
its use in children for the treatment of HIV infection increased in
the ensuing years. An analogous rationale applies to the mono-/dual-therapy era definition, because the first use of combination
therapy came after the approval of didanosine in late 1991. These
eras were characterized by a gradual and heterogeneous uptake
of newly approved therapies and approaches to HIV infection, in
contrast to the HAART era in which there was relatively rapid
uptake during 1997, yielding a relatively pure sample of in-
dividuals (additional details described elsewhere) [53].

Use of Antiretroviral Medication

Data were collected at each study visit regarding any anti-
retroviral use since the previous visit. The proportions of all
enrollees receiving nucleoside/nucleotide reverse-transcriptase
inhibitors (NRTIs), protease inhibitors, and non-NRTIs
(NNRTIs) were determined for each calendar year of the
study. Continuous receipt of an antiretroviral medication for
≥3 months was necessary to assign a subject as having received
that agent for treatment of their HIV infection. The trends in
antiretroviral use over the study course were used to contextu-
alize the annual mortality. HAART was defined as the receipt
of combination antiretroviral therapy that consisted ≥ 3 anti-
retrovirals, including 2 NRTIs combined with either a protease
inhibitor or an NNRTI.

Cause of Death

Each mortality event had associated with it up to 3 diagnoses
believed to contribute to the ultimate cause of death. Among
those with >1 associated diagnosis, the database didn’t attribute
a unique cause of death; thus, an algorithm was created to arrive
at a unique cause of death in these subjects. Using all database
diagnoses, 11 broad diagnostic categories were defined and
prioritized by likelihood of their contribution to an ultimate
cause of death. From most to least likely to contribute, these
categories were sepsis, end-stage acquired immune deficiency
syndrome (ES AIDS) [17], opportunistic infection (OI), cardio-
mypathy (CMP), pneumonia, malignancy, hepatic disease, re-
nal disease, central nervous system (CNS) disease, HIV-related
other (HRO), and non-HIV-related other (NHRO). All
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 364)</th>
<th>alive (n = 266)</th>
<th>Deaths (n = 98)</th>
<th>P^a</th>
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<td>1991–1993</td>
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<td>1994–1996</td>
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<td>183 (72.6)</td>
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<td>&gt;=2.5</td>
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<td>168 (78.9)</td>
<td>45 (21.1)</td>
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<td>98 (64.5)</td>
<td>54 (35.5)</td>
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<td>&gt;37</td>
<td>212 (58.2)</td>
<td>168 (79.2)</td>
<td>44 (20.8)</td>
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<td></td>
<td>.01</td>
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<td>Less than –2.4</td>
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<td>42 (63.6)</td>
<td>24 (36.4)</td>
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<td>43 (69.4)</td>
<td>19 (30.6)</td>
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<td>–1.1 to less than –0.06</td>
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<td>49 (80.3)</td>
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<tr>
<td>–0.06 or higher</td>
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<td>54 (87.1)</td>
<td>8 (12.9)</td>
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<td>&lt;.05</td>
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<td>43 (65.2)</td>
<td>23 (34.8)</td>
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</tr>
<tr>
<td>–2.7 to less than –1.7</td>
<td>70 (19.2)</td>
<td>50 (71.4)</td>
<td>20 (28.6)</td>
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<tr>
<td>–1.7 to less than –0.7</td>
<td>65 (17.9)</td>
<td>51 (78.5)</td>
<td>14 (21.5)</td>
<td></td>
</tr>
<tr>
<td>–0.7 or higher</td>
<td>66 (18.1)</td>
<td>56 (84.8)</td>
<td>10 (15.2)</td>
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<td>Thymic dysfunction^d</td>
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</tr>
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<td>42 (11.5)</td>
<td>20 (47.6)</td>
<td>22 (52.4)</td>
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</tr>
<tr>
<td>No</td>
<td>237 (65.1)</td>
<td>188 (79.3)</td>
<td>49 (20.7)</td>
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<td>58 (68.2)</td>
<td>27 (31.8)</td>
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</tr>
<tr>
<td>Timing of infection^e</td>
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<tr>
<td>Intrauterine transmission</td>
<td>65 (17.9)</td>
<td>37 (56.9)</td>
<td>28 (43.1)</td>
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</tr>
<tr>
<td>Intrapartum transmission</td>
<td>88 (24.2)</td>
<td>74 (84.1)</td>
<td>14 (15.9)</td>
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<td>155 (73.5)</td>
<td>56 (26.5)</td>
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</tr>
<tr>
<td>Perinatal ZDV^f prophylaxis</td>
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<td>84 (23.1)</td>
<td>71 (84.5)</td>
<td>13 (15.5)</td>
<td></td>
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<tr>
<td>No</td>
<td>280 (76.9)</td>
<td>195 (69.6)</td>
<td>85 (30.4)</td>
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</tr>
</tbody>
</table>
diagnoses in the database were assigned to one of these diagnostic categories. The diagnostic category with highest priority was assigned as the most likely cause of death. Among those with unique diagnoses, these were directly assigned to the relevant diagnostic category as the cause of death.

Mortality Incidence Assessment and Statistical Methods
Clinical charts were reviewed at each study visit, and mortality events were identified by date of occurrence and cause. The linear trend for median age at death was evaluated over the study period [55]. The crude annual mortality rate was calculated by calendar year. The crude average annual mortality was calculated for the no/monotherapy, mono-/dual-therapy, and HAART eras. Kaplan-Meier plots and associated log-rank statistics were used to compare survival distributions among cohorts born during these eras and with different ages at HAART initiation. Overall mortality and OI-associated mortality trends over the therapeutic eras were evaluated using Poisson regression after adjustment for birth year, receipt of ZDV prophylaxis, maternal viral load, and maternal CD4% values were all significant at \( \alpha = 0.05 \).

First available measure within 3 months of age.

First available measure within 6 months of age; the diagnosis of thymic dysfunction based on first available CD4 and CD8 counts, both \(<5\text{th}\) percentile.

Based on positive human immunodeficiency virus (HIV) peripheral blood mononuclear cell culture or HIV DNA polymerase chain reaction results obtained at \(<7\) days of age.

Maternal and/or infant zidovudine (ZDV) received within 24 hours before and/or after delivery, respectively.

Table 1 continued.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 364)</th>
<th>Participants, no. (%) alive (n = 266)</th>
<th>Deaths (n = 98)</th>
<th>( P^{a} )</th>
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<td>Pneumocystis prophylaxis at ( \leq ) 6 mo of age</td>
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</tr>
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<td>Yes</td>
<td>221 (60.7)</td>
<td>168 (76.0)</td>
<td>53 (24.0)</td>
<td>.12</td>
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<tr>
<td>No</td>
<td>143 (39.3)</td>
<td>98 (68.5)</td>
<td>45 (31.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>364 (100.0)</td>
<td>266 (73.1)</td>
<td>98 (26.9)</td>
<td>...</td>
</tr>
</tbody>
</table>

\( ^a \) \( \chi^2 \) test. The bold face indicates significant difference at \( P < 0.05 \).

\( ^b \) Cochran-Armitage trend test for birth years. Differences in height-for-age Z score (HAZ), weight-for-age Z score (WAZ), maternal viral load, and maternal CD4 values were all significant at \( \alpha = 0.05 \).

\( ^c \) First available measure within 3 months of age.

\( ^d \) First available measure within 6 months of age; the diagnosis of thymic dysfunction based on first available CD4 and CD8 counts, both \(<5\text{th}\) percentile.

\( ^e \) Based on positive human immunodeficiency virus (HIV) peripheral blood mononuclear cell culture or HIV DNA polymerase chain reaction results obtained at \(<7\) days of age.

\( ^f \) Maternal and/or infant zidovudine (ZDV) received within 24 hours before and/or after delivery, respectively.

RESULTS
Among 364 HIV-infected children in the study cohort, there were 98 deaths (Table 1). Of those, 79 (81%) and 61 (62%) were younger than 3 and 2 years old, respectively, at the time of death (Figure 1), and 82 (84%) were born before 1994, at least 3 years before widespread HAART availability. Significantly more children died who were born in the late 1980s or early 1990s (\( P < .01 \)), had a birth weight \(<2.5\) kg (\( P < .01 \)), were born prematurely (<37 weeks) (\( P < .01 \)), or were in lower quartiles for HAZ (\( P = .01 \)) or WAZ scores (\( P < .05 \)) by 3 months of age. There were also more deaths among those who had evidence of thymic dysfunction (\( P < .01 \)) or intrauterine infection (\( P < .01 \)) and in those who had not received perinatal ZDV prophylaxis (\( P < .01 \)). The distribution of mortality did not vary significantly by clinical site of care, sex, race, or receipt of Pneumocystis pneumonia prophylaxis. Among those who died, the median age at death increased significantly across the eras and was 0.6, 1.6, and 5.5 years in the no/monotherapy, mono-/dual-therapy, and HAART eras, respectively (trend test \( P < .0001 \)) (Figure 1).

The cohort’s annual mortality rate experienced stepwise declining trends that corresponded to the sequential milestones in antiretroviral advancement (Figure 2). There were statistically significant declines in the average annual mortality rate between
the 3 therapeutic eras, with a >60% reduction from the no/monotherapy to the mono-/dual-therapy era and another almost 90% reduction in the HAART era compared with the mono-/dual-therapy era (Figure 2).

The 6-year survival rates of children born in the no/monotherapy (1986–1990), mono-/dual-therapy (1991–1996), and HAART eras (1997–2004) were 57%, 76%, and 91%, respectively (P < .0001; log-rank test) (Figure 3). To facilitate comparisons with data from other groups, we also determined that the 6-year survival rates for children born in 1986–1989, 1990–1994, and 1995–1999 were 55%, 71%, and 89%, respectively. Kaplan-Meier survival analysis showed a significant prolongation in 10-year survival among those who received HAART at any age during the study compared with those who never received HAART (94% and 45%, respectively; P < .05) (Figure 3). Survival did not differ among subgroups with differing ages at HAART initiation. Among 21 children who received HAART within 6 months of birth (the first of whom began therapy in late 1996), the probability of 6-year survival was 94.4%.

After adjustment for covariates using multivariable Poisson regression modeling, the declining linear trend in overall mortality was highly significant (trend test, P = .002), and the adjusted mortality rates in the no/mono- and mono-/dual-therapy eras were ~6-fold (P = .001) and ~2-fold (P = .068), respectively, the rates in the HAART era (Table 2). Cox regression modeling showed that HAART-associated reductions in mortality remained
significant after adjustment for covariates (hazard ratio, 0.3; 95% confidence interval [CI], .08–.76) (Table 3).

Among the 98 deaths, the 3 most common causes were end-stage AIDS, OI, and pneumonia, accounting for 23 (23.5%), 19 (19.4%), and 15 (15.3%) of all events, respectively. The cause of death varied across the 3 eras, with no significant differences for individual causes (Table 4). When all 13 categorical causes of death were combined into either OI- or non–OI-associated causes, the proportions of deaths caused by OIs showed stepwise declines from 31.8% in 1986–1990 to 16.9% in 1991–1996 to 9.1% in 1997–2004 (P = .051), a trend that remained after adjustment by Poisson regression (P = .056).

When the contribution of the timing of HIV transmission to mortality was evaluated among a subset of evaluable patients (n = 153), intrauterine transmission was associated with higher mortality than intrapartum transmission (P < .001; Fisher’s exact test) and remained a significant predictor of mortality after adjustment for covariates with Cox regression; however, the effect was only significant until 2 years of age (hazard ratio, 2.8; 95% CI, 1.52–5.02).

**DISCUSSION**

Multiple natural history studies of perinatally acquired HIV infection have demonstrated benefits associated with the use of HAART. Ours is the longest prospective birth cohort study to show dramatic declines in mortality associated with HAART use among HIV-infected children. Furthermore, because of its design in capturing the important mortality peak in the first years of life among HIV-infected children (Figure 1), the benefits associated with HAART were readily apparent even before specific adjustment for confounders inherent to disease severity and treatment bias that others have shown to be important [22].

Our findings of a 70% reduction in mortality during the HAART era are consistent with those of Gortmaker and colleagues, who found a step-wise reduction in yearly mortality during 1996–1999 among a PACTG cohort and showed, after adjusted analyses, a very similar reduction (67%) in the risk of death among those beginning combination antiretroviral therapy [18]. Our results are also consistent with a recent comprehensive analysis of a larger PACTG cohort followed up from 1994 to 2004, which showed annual mortality rates of 7.2 and 0.8 events per 100 person-years for 1994 and 2004, respectively [17]. Notably, when the 6-year survival probabilities among 3 birth cohorts in our study were compared with those from the analogous PACTG birth cohorts and from a large Italian study, our results (1986–1989, 55%; 1990–1994, 71%; and 1995–1999, 89%) were in closer agreement with findings in the Italian cohort study (1980–1989, 59%; 1990–1995, 63%; and 1996–1999, 90%), which had enrolled a larger majority of children followed up from birth [24] than had the PACTG study (1985–1989, 90%; 1990–1994, 93%; and 1995–1999, 97%) [17]. Although the median age of death increased across therapeutic eras, a finding consistent with improved survival probabilities over these eras, our results contrast with those of the PACTG study in that the median age at death among children in the HAART era in our cohort was much younger. This probably reflects differences between ages at enrollment among the cohorts as well as some ascertainment bias with more medically complicated or sicker and perhaps older children enrolling into PACTG interventions that made up the larger cohort, although sicker children may not have enrolled in a follow-up study.

Consistent with findings from other studies, we demonstrated that birth year, percentage of CD4 T cells, anthropometrics, timing of HIV transmission, and maternal CDC classification were independent predictors of mortality. Prematurity, receipt...
of perinatal ZDV prophylaxis, maternal HIV viral load, and receipt of *Pneumocystis* pneumonia prophylaxis did not have a significant effect on mortality. Owing to the relative unavailability of HIV viral load testing early in the pediatric epidemic, when the majority of the deaths occurred, we were unable to evaluate viral load as a predictor. Similarly, although there were significantly more deaths among those with thymic dysfunction, the scarcity of evaluable thymic function data precluded further evaluation. Despite the observed difference in mortality between those who had ever received HAART and nonrecipients, evaluation of mortality by age at therapy initiation failed to show an association with earlier treatment, in

![Kaplan-Meier survival analysis](https://academic.oup.com/cid/article-abstract/53/10/1024/333576)

**Figure 3.** Kaplan-Meier survival analysis among enrollees in the Perinatal AIDS Collaborative Transmission Study (PACTS/PACTS-HOPE) (1986–2004) by birth cohort (A) and age at initiation of highly active antiretroviral therapy (HAART) (B) (log-rank test, \( P < .05 \) for no HAART vs HAART initiation in different age groups considered separately and \( P < .01 \) for same comparison with combined age groups).
In contrast to findings from a recent prospective study [16], this lack of association in our study was probably due to the inherent limitations of its retrospective design and the small sample size in the subanalyses.

A recent Thai study found 1- and 5-year survival rates of 84.3% and 76.7% among HIV-infected children who began treatment before 12 months of age, and 95.7% and 94.8% among those whose treatment began after 12 months of age [60]. This is in some contrast to the finding of increased progression to AIDS or death among HIV-infected European children in whom treatment was deferred beyond 3 months of age [26]. Furthermore, neither we nor the investigators in the European study found the persistently elevated mortality risk among our birth cohorts that the Thai investigators identified. Potential explanations for this discrepancy might lie in inherent differences between developing and more industrialized nations [61]. The Thai cohort had more exposure to a period without HAART, as reflected by the fact that 68% of infants <12 months old at the time of treatment were born before 2003, when HAART became available. Moreover, 28 of the 40 evaluable deaths were from infections, indicating that developing countries may pose more infectious disease hazards than more industrialized nations. It is nonetheless noteworthy that the 6-year survival among those 21 children in PACTS/PACTS-HOPE who began HAART in early infancy was 94.4%, a finding not previously demonstrated for this length of time.

Despite such dramatic reductions in mortality, our average annual mortality during the HAART era remained 50-fold higher than the background mortality in otherwise healthy populations of children in this age group during the same period in the United States (0.8/100 HIV-infected children vs 0.016/100 children aged 5–14 years during 2005) [62]. Such persistently higher mortality rates despite effective HAART may be due to factors not directly related to plasma viremia but rather related to indirect mechanisms resulting in an increased predisposition to death from other causes, as has been postulated in adult cohorts [14]. Our findings of substantial increases in the relative proportion of non–OI-associated mortality during periods of increasing availability of combination antiretroviral therapy are consistent with this hypothesis and with findings of the PACTG study [17]. The exact mechanisms that underlie this shift in the spectrum of causes of mortality remain to be fully elucidated.

During this 18-year study, standards in pediatric HIV care have spanned the spectrum of prevention, diagnosis, and management (eg, prophylactic antibiotics, intravenous immunoglobulin, immunizations, mother-to-child transmission prophylaxis, antiretroviral medications, and HIV viral load monitoring). In Zambia, cotrimoxazole prophylaxis afforded a 43% reduction in mortality among HIV-infected children [63]. As our cohort aged, subjects with survival advantages could have been selected. The interaction of such trends and variables probably influenced survival. In the early epidemic, prophylaxis against OIs partly led to significant improvement in survival among HIV-infected individuals. Prevention of these OIs has subsequently been further aided by the immune reconstitution HAART provides by diminishing viral replication and thus mitigating CD4 T-cell destruction. However, viral replication accounts for a small proportion of CD4 T-cell loss [64]; furthermore, HAART has been recently associated with restoration of the balance in immune regulation, as reflected by reduction in immune activation markers, which also play a significant role in prognosis [65, 66]. The immunopathogenesis behind such improvements needs further research to hone in on stronger

### Table 2. Adjusted Average Annual Mortality Rate Ratios With Multivariable Poisson Regression Modeling Among Enrollees in the Perinatal AIDS Collaborative Transmission Study (PACTS/PACTS-HOPE) (1986–2004)*

<table>
<thead>
<tr>
<th>Era</th>
<th>Rate ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/monotherapy (1986–1990)</td>
<td>6.6 (2.15–20.00)</td>
<td>.001</td>
</tr>
<tr>
<td>Mono-/dual-therapy (1991–1996)</td>
<td>2.0 (1.00–4.22)</td>
<td>.069</td>
</tr>
<tr>
<td>HAART (1997–2004)</td>
<td>1.0</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy.

* The model was adjusted for birth year, receipt of zidovudine prophylaxis, maternal AIDS classification, maternal history of injection drug use, prematurity, sex, and race.

### Table 3. Final Cox Regression Model for Independent Predictors of Time to Death Among Enrollees in the Perinatal AIDS Collaborative Transmission Study (PACTS/PACTS-HOPE) (1986–2004)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth year&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.9 (0.85–0.99)</td>
<td>.029</td>
</tr>
<tr>
<td><strong>HAART</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.3 (0.08–0.76)</td>
<td>.015</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 T cells, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>2.0 (1.24–3.20)</td>
<td>.004</td>
</tr>
<tr>
<td>15 to &lt;25</td>
<td>0.8 (0.49–1.46)</td>
<td>.546</td>
</tr>
<tr>
<td>≥25</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.9 (0.84–0.96)</td>
<td>.001</td>
</tr>
<tr>
<td>WAZ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.7 (0.66–0.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Maternal AIDS classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class C</td>
<td>1.5 (1.00–2.32)</td>
<td>.05</td>
</tr>
<tr>
<td>Class A or B</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAZ, height-for-age Z score ; HAART, highly active antiretroviral therapy; WAZ, weight-for-age Z score.

* χ² test.

<sup>b</sup> Per 1-year increment.

<sup>c</sup> Per 1–standard deviation increment.
correlates that might someday be useful in better predicting outcomes and tailoring therapy accordingly.

In summary, we have documented a high incidence of mortality in early childhood and dramatically decreasing mortality trends over this 18-year prospective birth cohort study of HIV-infected children; these paralleled increasing use of antiretroviral therapy and HAART. There has also been a notable increase in the proportion of deaths with non–OI-associated causes. Such trends in mortality deserve closer monitoring in ongoing and future studies, which will be of particular relevance to HIV-infected children, because they will bear the burden of the lengthiest exposure to HIV infection, HAART, and any associated complications. These studies would ideally be rigorously designed, prospective, randomized, controlled trials that could more definitively determine the individual contributions of HIV and HAART to disease progression.

Notes

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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