

Morbidity, Mortality, and Response to Treatment by Children in the United Kingdom and Ireland with Perinatally Acquired HIV Infection during 1996–2006: Planning for Teenage and Adult Care

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Background. Recent evidence suggests that decreases in morbidity and mortality in cohorts of adults infected with human immunodeficiency virus (HIV) are showing signs of reversal. We describe changes over time in these characteristics and in the response to treatment among children in the United Kingdom and Ireland with perinatally acquired HIV infection, many of whom are now adolescents.

Methods. We analyzed prospective cohort data reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) and the Collaborative HIV Paediatric Study.

Results. By mid 2006, 1441 HIV-infected children were reported to NSHPC; 40% were ≥ 10 years old at their most recent follow-up visit, and 34% were receiving care outside London. The proportion of children born abroad increased from 24% during 1994–1996 to 64% during 2003–2006. The percentage of total child time during which children received highly active antiretroviral therapy (HAART) increased from 36% during 1997–1999 to 61% during 2000–2002 and 63% during 2003–2006. Of children who were naive to antiretroviral therapy at the start of HAART, the percentage with an HIV-1 RNA load of < 400 copies/mL after 12 months increased from 52% during 1997–1999 to 79% during 2003–2006. In multivariate analysis, only calendar time predicted virological response, whereas both younger age and lower CD4 cell percentage at HAART initiation predicted increases of $> 10\%$ in the CD4 cell percentage. A total of 31% of children aged 5–14 years and 38% aged ≥ 15 years at their most recent follow-up visit had been exposed to drugs from each of the 3 main HAART classes. The rate of AIDS and mortality combined decreased from 13.3 cases per 100 person-years before 1997 to 3.1 and 2.5 cases per 100 person-years, respectively, during 2000–2002 and 2003–2006; rates of hospital admission also declined during this interval. Of 18 children known to have died since 2003, 9 died within 1 month after presentation.

Conclusions. Morbidity and mortality rates among HIV-infected children continue to decrease over time. Because these children are increasingly dispersed outside London, specialist care is now provided in national clinical networks. Transition pathways to adolescent and adult services and long-term observation to monitor the effects of prolonged exposure to both HIV and HAART are required.

Despite a substantial increase in the prevalence of HIV infection among pregnant women in the United King-

dom (UK) and Ireland in recent years, the number of infants born with HIV infection has stabilized as a result of effective interventions to reduce mother-to-child transmission [1, 2]. In addition, the prognosis for HIV-infected children has improved markedly since the introduction of HAART in mid-1997 [3].

Elsewhere, we reported that morbidity, mortality, and hospital admission rates decreased between 1996 and 2002 among children in the UK and Ireland with perinatally acquired HIV infection [4]. Virological re-

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sponse has also improved since the introduction of HAART in both adults and children [5, 6]. However, recent evidence from adult cohorts in Europe and North America suggests that this improvement has not translated into a concomitant decrease in mortality and morbidity, because of a combination of changing demographic characteristics, a high incidence of tuberculosis, and coinfection with hepatitis C virus (HCV) [6–9]. Here, we determine whether rates of mortality and morbidity have continued to decrease to June 2006, describe changing demographic characteristics and responses to HAART to this date, and discuss the implications of these findings for service provision, using data from a cohort of children in the UK and Ireland with perinatally acquired HIV infection.

PATIENTS AND METHODS

Study design. Study methods have been described elsewhere [4]. In brief, the National Study of HIV in Pregnancy and Childhood (NSHPC) receives reports on all infants born in the UK to HIV-infected women and on all children, regardless of birthplace, presenting in the UK and Ireland with HIV-1 infection. Subsequent follow-up information on HIV-infected patients is collected by the Collaborative HIV Paediatric Study (CHIPS). Both studies have been approved by the London Multicenter Research Ethics Committee.

By June 2006, a total of 1441 infants with HIV acquired through mother-to-child transmission (i.e., vertical infection) had been reported to the NSHPC; all are included in the analyses of changes in rates of progression to AIDS and death over calendar time. A total of 1133 of these children, who constitute 87% of perinatally infected children reported to the NSHPC since 1996 and 92% of those receiving care in the UK and Ireland during 2005–2006, were enrolled in the CHIPS cohort and are included in the analyses of HAART responses and rates of hospital admission. Data from 2006 are incomplete and subject to reporting delay.

Statistical methods. Crude rates of progression to AIDS, death, and hospital admissions per 100 child-years at risk were calculated by grouped calendar year. AIDS and mortality rates exclude children whose infection progressed to AIDS ≤ 1 month after presentation or birth.

The effect of calendar period (categorized as 1996 and earlier [i.e., before the introduction of HAART], 1997–1999, 2000–2002, and 2003–2006) on mortality and AIDS rates was examined using Cox proportional hazards models. Time was measured from birth, using late entry at the age of first presentation [10]. Calendar period was then fitted as a time-varying covariate, allowing for different time trends according to current age (< 1 year vs. ≥ 1 year), and models were adjusted for how children were identified (prospectively from birth vs. after birth), ethnicity, sex and place of birth (UK or Ireland vs. abroad).

Twelve-month response to HAART in previously untreated children was calculated using published methods [11]. Briefly, initiation of HAART was defined as the first time ≥ 3 antiretroviral drugs from at least 2 drug classes or a triple nucleoside reverse-transcriptase inhibitor containing abacavir [4, 12] were administered within 2 weeks of each other. The 12-month virological response to HAART was assessed on the basis of the HIV-1 RNA load measured closest to 1 year (± 3 months) after HAART initiation. The 12-month immunological response was assessed by comparing the baseline CD4 cell percentage (measured ≤ 3 months before or ≤ 1 month after the start of HAART) with the CD4 cell percentage measured closest to 1 year (± 3 months) after HAART initiation. Logistic regression analysis was used to identify the association between HAART response and the following variables: age, CD4 cell percentage, HIV-1 RNA load, and Centers for Disease Control and Prevention disease stage at HAART initiation; sex; year of HAART initiation; number of drugs in the initial regimen; and the times at which the HIV-1 RNA load and CD4 cell percentage were measured ~ 1 year after HAART initiation.

RESULTS

Cohort characteristics. Demographic characteristics were similar to those reported previously [4]: one-half of the children were female, 73% were black African, and 13% were prospectively identified at birth (table 1). The number of new children in whom perinatally acquired HIV infection was diagnosed increased each year, from 212 during 1994–1996 to 366 during 2003–2006; the percentage of those who were born abroad also increased, from 24% during 1994–1996 to 64% during 2003–2006. A total of 52% of children who first presented during 2003–2006 were receiving care at a London hospital, compared with 81% during 1994–1996.

The median age of children at the most recent follow-up visit was 7.2 years (interquartile range, 2.8–11.2 years) for those born in the UK or Ireland and 9.8 years (interquartile range, 6.6–13.5 years) for those born abroad. The median age at presentation for children born abroad increased annually, from 2.4 years before 1992 to 7.6 years during 2004–2006; for children born in the UK or Ireland, the median age at presentation was ~ 0.4 years each year through 2002, increasing to ~ 0.8 years during 2003–2006. The percentage of children in the cohort aged 10–14 years increased from 11% in 1996 to 22% in 2000 and 35% in 2005; the percentage aged ≥ 15 years increased from 0% in 1996 to 5% in 2000 and 9% in 2005. For the 1133 children in CHIPS, 87% had their most recent office visit during 2004–2006, and 4% had their most recent visit during 2002–2003; 9% last visited before 2002.

History of and response to HAART. Of the 1133 children followed up in CHIPS, 24% had never received antiretroviral

Table 1. Characteristics of children with perinatally acquired HIV-1 infection in the United Kingdom and Ireland reported to mid-2006, according to birthplace.

Characteristic	Born in UK or Ireland (n = 772)	Born elsewhere (n = 664)	Unknown birthplace (n = 5)	Total (n = 1441)
Female sex	384 (49.7)	326 (49.1)	3 (60)	713 (49.5)
Ethnicity				
White	159 (21)	14 (2)	0	173 (12)
Black African	485 (63)	564 (85)	3 (60)	1052 (73)
Other	120 (16)	84 (13)	1 (20)	205 (14)
Unknown	8 (1)	2 (0)	1 (20)	11 (1)
Region of follow-up				
England				
London	525 (68)	405 (61)	4 (80)	934 (65)
Other	151 (20)	198 (30)	0	349 (24)
Scotland	42 (5)	20 (3)	0	62 (4)
Wales	9 (1)	6 (1)	0	15 (1)
Northern Ireland	0 (0)	5 (1)	0	5 (0)
Ireland	45 (6)	30 (5)	1 (20)	76 (5)
Time of identification				
Prospectively from birth	160 (21)	22 (3)	0	182 (13)
After birth				
Asymptomatic	192 (25)	276 (42)	2 (40)	470 (33)
Symptomatic	408 (53)	348 (52)	2 (40)	758 (53)
Unknown	12 (2)	18 (3)	1 (20)	31 (2)
Age at first presentation				
Birth	160 (21)	20 (3)	0	180 (12)
<1 year	324 (42)	39 (6)	0	363 (25)
1 year	89 (12)	52 (8)	0	141 (10)
2–4 years	133 (17)	176 (27)	2 (40)	311 (22)
5–9 years	49 (6)	254 (38)	2 (40)	305 (21)
≥10 years	17 (2)	123 (19)	1 (20)	141 (10)
Median (IQR)	0.5 (0.0–2.1)	5.7 (3.1–8.8)	...	2.4 (0.4–6.1)
Range	0–14	0–15	...	0–15
Year of first presentation, no. of patients/no. with data available (%)				
Through 1993	195/291 (67)	95/291 (33)	1 (0.3)	291 (20)
1994–1996	162/212 (76)	51/212 (24)	0	212 (15)
1997–1999	154/244 (63)	87/244 (36)	3 (1.2)	244 (17)
2000–2002	131/327 (40)	195/327 (60)	1 (0.3)	327 (23)
2003–2006	130/366 (36)	236/366 (64)	0	366 (25)
Age at most recent follow-up visit, years				
<1	100 (13)	7 (1)	0	107 (7)
1–4	188 (24)	90 (14)	1 (20)	279 (19)
5–9	243 (31)	244 (37)	1 (20)	488 (34)
10–14	176 (23)	220 (33)	2 (40)	398 (28)
≥15	65 (8)	103 (16)	1 (20)	169 (12)
Median (IQR)	7.2 (2.8–11.2)	9.8 (6.6–13.5)	...	8.5 (4.7–12.4)
Range	0–20	0–22	...	0–22
Disease stage at most recent follow-up visit				
Not applicable	199 (33)	260 (49)	4 (80)	463 (41)
B	148 (25)	143 (27)	0	291 (26)
C	195 (33)	103 (19)	0	298 (26)
Died	55 (9)	26 (5)	0	81 (7)

Note. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

therapy (ART), and 4% had received only monodrug therapy or dual-drug therapy with antiretroviral drugs. The remaining 72% had received HAART at some time, of whom 655 were

naive to ART at the start of HAART. Of these 655, a total of 548 were observed for at least 9 months after HAART initiation and were eligible for inclusion in the multivariable analysis.

Only 11% of children born abroad reported having ever received ART before they presented in the UK or Ireland. The percentage of their life during which children received HAART increased from 36% during 1997–1999 to 61% during 2000–2002 and 63% during 2003–2006, whereas the percentage of children who did not receive any ART after previously receiving it increased from 3% during 1997–1999 to 5% during 2000–2002 and 9% during 2003–2006. At their most recent follow-up visit, 61% of 664 children receiving HAART were still using first-line treatment, and 31% of those aged 5–14 years and 38% of those aged ≥ 15 years and receiving HAART had been exposed to drugs from all 3 main ART classes.

A total of 475 of 548 children who started HAART for the first time and were followed up for at least 9 months after HAART initiation had their viral load measured 12 months later, at which time the HIV-1 RNA load had decreased to ≤ 400 copies/mL in 67% and to ≤ 50 copies/mL in 39% (table 2). In an adjusted analysis, suppression of the HIV-1 RNA level to ≤ 400 copies/mL improved over calendar time (adjusted OR, 2.06 for 2000–2002 and 3.45 for 2003–2006, compared with 1997–1999) (table 3), and children whose HAART consisted of 4 drugs rather than 3 drugs had twice the odds of suppression ($P = .062$).

The proportion of children whose HIV-1 RNA load decreased to ≤ 50 copies/mL after 12 months also improved with calendar time, to 60% during 2003–2006 (table 2). However, this increase could be attributed, in part, to an increasing use in recent years of an assay with a lower limit of detection of

≤ 50 copies/mL. After 12 months of HAART, the CD4 cell percentage in 62% of children had increased by $>10\%$, and in multivariate analysis, this improvement was independently associated with younger age at HAART initiation (adjusted OR, 0.85 per year of age; $P < .001$) and with a lower CD4 cell percentage at HAART initiation (adjusted OR, 0.56 per 5% increase in CD4 cell percentage; $P < .001$) but not with calendar year (table 3).

Rates of hospital admission, progression to AIDS, and mortality. The overall crude mortality rate decreased from 8.2 deaths per 100 person-years before 1997 to 0.9 and 0.6 deaths per 100 person-years, respectively, during 2000–2002 and 2003–2006, and the rate of progression to AIDS and mortality combined decreased from 13.3 cases per 100 person-years before 1997 to 3.1 and 2.5 cases per 100 person-years, respectively, during 2000–2002 and 2003–2006 (figure 1). These decreases were particularly striking for children aged ≥ 1 year: the adjusted HRs for death were 0.2 (95% CI, 0.1–0.3) during 1997–1999, 0.1 (95% CI, 0.05–0.2) during 2000–2002, and 0.05 (95% CI, 0.03–0.1) during 2003–2006, and the adjusted HRs for progression to AIDS during these periods were 0.4 (95% CI, 0.3–0.7), 0.3 (95% CI, 0.3–0.7), and 0.2 (95% CI, 0.2–0.4), respectively. Although the overall mortality rate decreased among infants aged <1 year after 1997 (adjusted HR, 0.6; 95% CI, 0.3–1.1), there was no statistically significant difference in the risk of progression to AIDS between the periods. Ethnicity, sex, and place of birth had no significant effect on rates of mortality or progression to AIDS. Previously reported decreases

Table 2. HIV-1 RNA levels and CD4 cell percentages 12 months after initiation of HAART for children with HIV infection reported to mid-2006, according to year of and age at HAART initiation.

Variable	HIV-1 RNA level			CD4 cell percentage	
	No. for whom data are available	Percentage for whom the level decreased to ≤ 400 copies/mL	Percentage for whom the level decreased to ≤ 50 copies/mL ^a	No. for whom data are available	Percentage for whom the absolute increase was $>10\%$
Year of HAART initiation					
1997–1999	153	52	25	130	61
2000–2002	166	69	33	148	59
2003–2006	156	79	60	149	64
Age at HAART initiation					
<2 years	138	60	27	129	63
2–4 years	121	64	35	106	74
5–9 years	141	76	52	131	56
≥ 10 years	75	65	45	61	51
Overall ^b	475	67	39	427	62

NOTE. Because data were recorded up to the end June 2006, data from 2006 are incomplete and subject to reporting delay.

^a Children with an HIV-1 RNA level of ≤ 400 copies/mL are conservatively assumed not to have a level of ≤ 50 copies/mL. Because children examined at hospitals where the cutoff is ≤ 400 copies/mL could have viral suppression to ≤ 50 copies/mL, the percentages of children whose HIV-1 RNA level decreased to ≤ 50 copies/mL are considered minimum estimates.

^b Of the 655 children naive to antiretroviral drugs at HAART initiation, 548 were observed for at least 9 months after HAART initiation. A total of 475 of 548 had their HIV-1 RNA level measured 12 months after HAART initiation, and 427 had their CD4 cell percentage measured at baseline and 12 months after HAART initiation.

Table 3. Predictors of HIV-1 RNA level and CD4 cell percentage 12 months after HAART initiation.

Predictor	Decrease of HIV-1 RNA level to ≤ 400 copies/mL ($n = 375$)		Absolute increase of CD4 cell percentage of $>10\%$ ($n = 374$)	
	Adjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)	<i>P</i>
At HAART initiation				
Age, per year increase	1.04 (0.97–1.12)	.250	0.85 (0.79–0.92)	$<.001$
CD4 cell percentage, per 5% increase	1.03 (0.91–1.17)	.648	0.56 (0.48–0.65)	$<.001$
HIV-1 RNA level, per 1 \log_{10} copies/mL	0.93 (0.67–1.31)	.682	1.28 (0.90–1.82)	.167
Sex				
Male	1.00		1.00	
Female	1.19 (0.75–1.90)	.464	1.47 (0.91–2.39)	.115
B and/or C disease-stage events before HAART initiation ^a				
None	1.00		1.00	
B or C event	0.88 (0.54–1.41)	.589	0.96 (0.59–1.56)	.867
No. of drugs in initial HAART regimen				
3	1.00		1.00	
4	2.14 (0.93–4.92)	.062	1.23 (0.54–2.81)	.624
Year of HAART initiation				
1997–1999	1.00		1.00	
2000–2002	2.06 (1.19–3.57)		0.98 (0.53–1.80)	
2003–2006	3.45 (1.91–6.25)	$<.001$	1.16 (0.63–2.13)	.821
Timing of response	1.00 (1.00–1.01)	.423	1.00 (0.99–1.00)	.566

NOTE. All results from multivariable models have been adjusted for all variables. A total of 375 of 475 children with 12-month data on their HIV-1 RNA level and 374 of 427 with 12-month data on their CD4 cell percentage have complete covariable data for the analyses.

^a Includes events that occurred ≤ 90 days after HAART initiation.

in hospital admission rates also continued over time, from 4.3 admissions per 100 person-years during 1996 to 1.0 and 0.7 admissions per 100 person-years during 2000–2002 and 2003–2006, respectively ($P < .001$, by the χ^2 test for trend) (figure 1).

Deaths since 2003. Eighteen children are known to have died since 2003. Seven died in infancy, all of whom were born in the UK or Ireland, including 6 whose mothers' HIV status was not known during pregnancy; 5 infants presented with AIDS and/or died within 1 month after presentation. Primary causes of death among these infants were cytomegalovirus infection (2 infants), *Pneumocystis jirovecii* pneumonia (i.e., *Pneumocystis pneumonia*) (2), bacterial pneumonia (1), and septicemia (1); 1 child died of an unknown cause while on vacation in Africa. Five infants received HAART during their acute illness; 1 received no ART, and 1 was exposed to ART only in utero, to reduce the risk of mother-to-child transmission.

Eight of 11 children who died >12 months after birth were born abroad. Four children presented with AIDS and/or died within 1 month after presentation, and 5 others presented with HIV-related symptoms. Primary causes of death were *Pneumocystis pneumonia* (1 child), sepsis (1), non-Hodgkin lymphoma (2), complicated chicken pox (2), chronic lung disease (1), suspected yellow fever (1, while on holiday), subdural hem-

orrhage (1), neurocysticercosis (1), and gastrointestinal bleeding (1). Seven had received HAART: 1 child died 1 month after presentation, 4 died 11–14 months after presentation, and 2 were followed up for >6 years.

Only 20 of 553 AIDS-defining events were characterized as extrapulmonary *Mycobacterium tuberculosis* infection. Detection of HCV was relatively rare, with HCV antibody detected in only 6 of 147 children for whom results of tests for detection of HCV were reported; 4 of the 6 also tested positive for HCV RNA.

DISCUSSION

Key characteristics of this cohort of children vertically infected with HIV have changed in recent years, with more children presenting at older ages and a large proportion coming from abroad, as observed in other European countries [13, 14]. The numbers of children with new diagnoses and children receiving care continue to increase each year. To date, most new arrivals have not previously received ART, although recently there has been increased availability of ART for children in Africa. In the future, pediatricians may expect to see more children who have been taking simple, fixed-dose combinations of generic first-

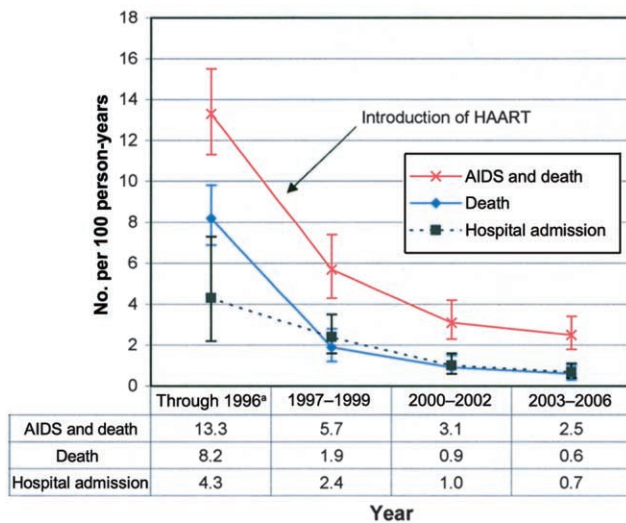


Figure 1. Rates of hospital admission, mortality, and AIDS and mortality combined, by year. *Hospital admission rates are for 1996 only.

line drugs, from which they will have to switch to single-drug formulations. In addition, more children may have resistance to drugs, after having received regimens that failed.

One-quarter of children currently being followed up have never received ART, whereas one-third have been exposed to all 3 drug classes, and nearly 10% (mainly adolescents) were participating in an unstructured treatment-interruption program when last seen. Clinical management of this cohort, which includes both children with highly resistant virus and older children who are naive to treatment, is becoming increasingly complex. Despite this, short-term virological responses improved significantly over calendar time, after adjustment for other factors, and two-thirds of children receiving HAART were still using first-line agents at the time of their most recent follow-up visit [15]. Although we previously reported that older children were more likely than younger children to achieve virus load suppression, this difference was no longer observed. Better understanding of HAART management, together with improved formulations and more-efficacious, simpler regimens might have contributed to this change. Increases of >10% in CD4 cell percentages were more marked among children initiating HAART at a younger age and with a lower CD4 cell percentage at baseline, reflecting better thymus activity in younger children [16] and a possible “ceiling effect” [11].

In contrast to some adult cohorts [6], initial decreases in overall rates of progression to AIDS and death after the introduction of HAART in 1997 have been sustained, with further decreases between 2002 and 2006. The reversal of this trend in adults has been ascribed in part to increased rates of tuberculosis. Extrapulmonary tuberculosis was a rare AIDS-defining event in our cohort, so changes over time could not be assessed,

but they are likely to be small. This is also true for hepatitis C, which is rare in our cohort, in keeping with anonymous data that suggest low rates of hepatitis C among African women giving birth in London [17]. Among infants aged <1 year, although the mortality rate decreased by ~40% from 1997 onwards, the risk of progression to AIDS did not decrease significantly after the introduction of HAART. As discussed in a previous article that focused on the outcome in children who had HIV infection diagnosed during infancy [18], this finding may reflect changes in the social circumstances and natural history of infants with recent diagnoses, who were infected despite antenatal diagnoses for their mothers; continued presentation in some sick infants born to women without a previous diagnosis may also contribute to this finding.

Decreasing hospital admission rates over the 10-year period of HAART availability have resulted in a shift in the clinical care of children infected with HIV from pediatric wards to outpatient departments. There has also been an increase in geographical dispersal within the UK of families from countries where the prevalence of HIV infection is high. These factors have major implications for health care provision and underline the importance of well-supported national clinical networks to ensure quality of care regardless of where a child lives [19, 20]. As the number of children requiring services and the average age of the cohort increase, transitional adolescent clinics aimed at ensuring successful transfer between pediatric and adult services need further development. The majority of children with a diagnosis of HIV infection are now expected to reach adulthood and will require support for a range of psychosocial issues. Minimizing the toxicity of long-term HAART while maintaining the regimen’s efficacy has become a critical issue in the treatment of children. Long-term observation of this cohort of children perinatally infected with HIV is required to increase understanding of the ongoing effects of early and prolonged exposure to both HIV and HAART [21–23].

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