Papers

Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland

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Abstract

Objective To describe changes in demographic factors, disease progression, hospital admissions, and use of antiretroviral therapy in children with HIV.

Design Active surveillance through the national study of HIV in pregnancy and childhood (NSHPC) and additional data from a subset of children in the collaborative HIV paediatric study (CHIPS).

Setting United Kingdom and Ireland.

Participants 944 children with perinatally acquired HIV-1 under clinical care.

Main outcome measures Changes over time in progression to AIDS and death, hospital admission rates, and use of antiretroviral therapy.

Results 944 children with perinatally acquired HIV were reported in the United Kingdom and Ireland by October 2002; 628 (67%) were black African, 205 (22%) were aged ≥ 10 years at last follow up, 193 (20%) are known to have died. The proportion of children presenting who were born abroad increased from 20% in 1994-5 to 60% during 2000-2. Mortality was stable before 1997 at 9.3 per 100 child years at risk but fell to 2.0 in 2001-2 (trend P < 0.001). Progression to AIDS also declined (P < 0.001). From 1997 onwards the proportion of children on three or four drug antiretroviral therapy increased. Hospital admission rates declined by 80%, but with more children in follow up the absolute number of admissions fell by only 26%.

Conclusion In children with HIV infection, mortality, AIDS, and hospital admission rates have declined substantially since the introduction of three or four drug antiretroviral therapy in 1997. As infected children in the United Kingdom and Ireland are living longer, there is an increasing need to address their medical, social, and psychological needs as they enter adolescence and adult life.

Introduction

Since 1996 antiretroviral therapy with three or four drugs has been increasingly used to treat adults infected with HIV,[1] [2] and its substantial effect on progression of the disease has been well described.[3–5]

Because of difficulties in developing appropriate formulations and the lack of age specific pharmacokinetic data to guide paediatric dosing the introduction of such treatment was delayed in children. Before 1994 only one antiretroviral drug (zidovudine) was available for children. Dual antiretroviral therapy was introduced in 1995, and treatment with three or four drugs followed from mid-1997 and is now standard.[6–8] Reductions in mortality and AIDS during the era of dual therapy were reported,[9] [10] and substantial declines attributed to therapy with three or four drugs were reported in a US paediatric cohort.[11] However, data on changing rates in disease progression since 1997 and their effect on use of medical services remain sparse in children. We investigated changes over time in mortality, morbidity, hospital admission rates, and antiretroviral therapy received in perinatally HIV-1 infected children in the United Kingdom and Ireland.

Methods

Study design

The national study of HIV in pregnancy and childhood (NSHPC) is informed about children who present in the United Kingdom and Ireland with HIV-1 infection and infants born to HIV infected women through two active confidential reporting schemes run in collaboration with the British Paediatric Surveillance Unit and the Royal College of Obstetricians and Gynaecologists.[12] Obstetric data include demographic information, timing of maternal diagnosis, uptake of interventions, and outcome of pregnancy; paediatric data include neonatal details and HIV status. Each year notifying paediatricians subsequently provide minimal clinical information for infected children.

In April 2000, the collaborative HIV paediatric study (CHIPS) was established between the national surveillance study at the Institute of Child Health, London, and the Medical Research Council Clinical Trials Unit, where trials in the Paediatric European Network for Treatment of AIDS (PENTA) are coordinated (www.pentatrials.org). Most perinatally infected children reported to the national surveillance

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study are followed up in 17 paediatric clinics involved in PENTA. The collaborative HIV paediatric study was established to collect more detailed clinical, laboratory, and treatment information on infected children seen at the PENTA centres since 1996. During 2000, retrospective information was collected from clinical records on to standard forms; since then, information has been collected annually by questionnaires and merged with additional data from the national surveillance study and PENTA trials. The merged dataset includes demographic information, data on clinical events, hospital admissions, outpatient visits, antiretroviral therapy, and results of T cell subset and HIV RNA viral load tests. AIDS was defined according to the classification of the Centers for Disease Control (clinical category C disease).[13]

Paediatric HIV surveillance started in 1986, and by October 2002, 944 perinatally infected children had been reported to the national surveillance study. All children were included in analyses of changes in progression to AIDS and death over time. In total 593 children alive in January 1996 were enrolled in the collaborative HIV paediatric study (75% of all children reported to the national surveillance study as alive on this date) and were included in analyses of antiretroviral therapy and hospital admissions.

Statistical methods

For children whose mothers' HIV-1 status was known before delivery, we considered the date of birth to be the date of the child's first presentation to medical services with HIV-1. For remaining children, we estimated the date of presentation using the earliest date of: first positive results of HIV-1 antibody test, T cell subsets, or viral load tests; HIV related clinical events; clinic visit; or hospital admission. In all analyses, each child began to contribute to follow up from his or her date of presentation.

We censored records at the date children were last known to be alive in the death analysis and at the date of last clinical assessment in the AIDS/death analysis. To reduce presentation bias, we excluded children not identified at birth from analyses of AIDS or death if they first presented within one month of AIDS diagnosis or death, respectively. The effect of calendar period was further examined by using Cox proportional hazards models, adjusted for how the children were identified (at birth or later), ethnicity, sex, and place of birth (United Kingdom and Ireland or abroad). We also carried out separate adjusted analyses by place of birth. Time was measured from birth by using late entry at the age of first presentation.[14] In any calendar period, children were considered at risk only from the first day

Table 1 Characteristics of perinatally HIV-1 infected children in the United Kingdom and Ireland up to October 2002 according to place of birth. Figures are numbers (percentages) of children

	Born in UK or Ireland (n=586)	Born abroad (n=353)	Unknown (n=5)	Total (n=944)
Female	280 (48)	185 (52)	3	468 (50)
Ethnicity:				
White	148 (25)	13 (4)	0	161 (17)
Black	347 (59)	278 (79)	3	628 (67)
Other	88 (15)	61 (17)	1	150 (16)
Unknown	3 (1)	1 (0.3)	1	5 (1)
Region of follow up:				
London	416 (71)	248 (70)	4	668 (71)
Rest of England	92 (16)	73 (20)	0	165 (17)
Scotland	36 (6)	8 (2)	0	44 (5)
Ireland	35 (6)	18 (5)	1	54 (6)
Wales and N Ireland	7 (1)	6 (2)	0	13 (2)
How child was identified:				
Prospectively from birth	121 (21)	11 (3)	0	132 (32)
After birth, asymptomatic	157 (27)	139 (39)	2	98 (14)
After birth, symptomatic	287 (49)	180 (51)	2	469 (50)
Unknown	21 (4)	23 (7)	1	45 (5)
Age at first presentation (years):				
At birth	121 (21)	11 (3)	0	132 (14)
<1	254 (43)	27 (8)	0	281 (30)
1	72 (12)	38 (11)	0	110 (12)
2-4	104 (18)	113 (32)	2	219 (23)
5-9	29 (5)	123 (35)	2	154 (16)
≥10	6 (1)	41 (12)	1	48 (5)
Median (range)	0.46 (0.0-13.4)	4.6 (0.2-15.3)	5.0 (2.7-12.8)	1.6 (0.0-15.3)
Age at last follow up (years):				
<1	104 (18)	11 (3)	0	115 (12)
1-4	203 (35)	99 (28)	2	304 (32)
5-9	198 (34)	121 (34)	1	320 (34)
10-14	67 (11)	97 (27)	2	166 (18)
≥15	14 (2)	25 (7)	0	39 (4)
Median (range)	4.8 (0.0-18.1)	7.3 (0.3-18.6)	8.0 (3.1-14.7)	5.7 (0.0-18.6)
Stage of disease at last follow up*:				
N/A/B	275 (47)	226 (64)	5	506 (54)
C	159 (27)	86 (24)	0	245 (26)
Died	152 (26)	41 (12)	0	193 (20)

*According to classification of Centers for Disease Control.[13]

of the calendar period or the date of presentation, if later. We fitted calendar period as a time varying covariate, with adjustment for an interaction with age.

We used Kaplan-Meier curves to compare survival after initial diagnosis of AIDS by first indicator disease, grouped in hierarchical order: *Pneumocystis carinii* pneumonia, other opportunistic infection, HIV encephalopathy, failure to thrive, severe recurrent bacterial infections. We excluded six children in whom cancer was the first indicator disease. Hospital admission rates were compared with Poisson regression.

Results

Half of the 944 children reported were girls and 628 (67%) were black African (table 1). The proportion of children born abroad increased from 20% in 1994-5 to 60% in 2000-2. In total 132 (14%) children were identified at birth, 281 (30%) during the first year, and 202 (21%) at ≥ 5 years. Whereas the median age at presentation among children born in the United Kingdom and Ireland has remained constant at around 6 months, among children born abroad it increased from 2.5 years before 1991 to 5.2 years in 1994-5 and remained constant thereafter. At last follow up, 205 (22%) children were aged ≥ 10 years and 39 (4%) ≥ 15 years (table 1). A total of 193 children are known to have died (including 54 since 1997); and 41 left the country or were otherwise lost to follow up before 1996. Among 593 children in the collaborative HIV paediatric study, 534 (90%) were in follow up in 2001-2, 30 (5%) in 2000, and 29 (5%) were last seen in 1999 or earlier.

Mortality and progression to AIDS
While the number of perinatally infected children in follow up has increased steadily over time, the annual number of deaths declined markedly after 1996 (table 2). Among 734 children identified at birth, or who survived at least a month after presentation, the crude mortality was stable before 1997 at 9.3 per 100 child years at risk but declined thereafter to 3.3, 2.7, 1.2, 1.3, and 2.0 in 1997, 1998, 1999, 2000, and 2001-2, respectively (log rank test for trend, $P < 0.001$). Figure 1 shows

Table 2 Deaths and children with AIDS by calendar time

Year	No in follow up	No who died	No developing first AIDS indicator disease*
-1989	69	17	30
1990	80	4	12
1991	108	9	17
1992	158	15	27
1993	207	24	38
1994	252	18	46
1995	283	23	35
1996	326	29	37
1997	356	12	42
1998	427	14	40
1999	465	6	24
2000	524	6	38
2001-2	606	16	53
Total	944	193	438

*Includes 13 children who died of HIV-related causes without diagnosis of AIDS. 217 (50%) children developed AIDS or died within one month after presentation with HIV infection; a further eight children born abroad first experienced an AIDS indicator disease at least one month before arrival in UK or Ireland.
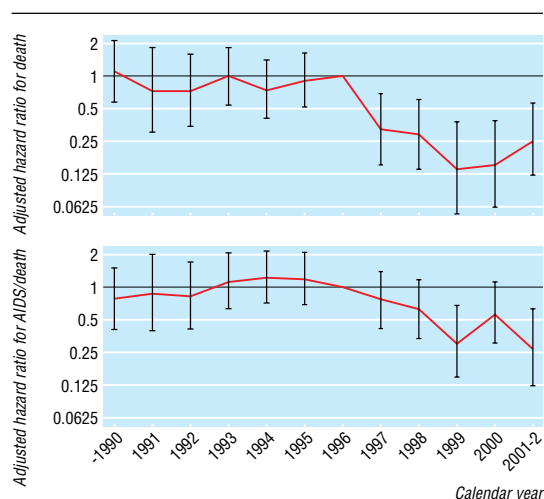
Fig 1 Risk of death or AIDS/death by calendar year relative to 1996, adjusted for age, sex, ethnicity, place of birth, and whether the child was identified prospectively from birth or later (y axis on log scale)

the change in risk relative to 1996, adjusted for place of birth, ethnicity, sex, and whether the child was identified at birth or later. However, improvement in survival since 1997 was more marked in children aged > 1 year (adjusted hazard ratio 0.19, 95% confidence interval 0.12 to 0.30) than in those aged < 1 year (0.72, 0.35 to 1.48; $P = 0.003$, heterogeneity for age) (table 3). Adjusted hazard ratios were similar when we carried out separate analyses for children aged > 1 year born in the United Kingdom and Ireland (0.18, 0.11 to 0.31) and born abroad (0.20, 0.08 to 0.46).

Fifty four children are known to have died from 1997 onwards, 48 (89%) of whom were born to mothers whose HIV status was not known during pregnancy. Eighteen of 22 children who died aged < 1 year had *P carinii* pneumonia or cytomegalovirus disease, or both. Information on antiretroviral therapy was available for 36 children who died; 14 (including six infants) had not received three or four drug therapy, six died within two months of starting it, and 16 died a median of 10 (range 2-53) months after starting it.

A total of 438 children developed an AIDS indicator disease, but 13 of these died before AIDS was diagnosed. Two hundred and seventeen children (50%) developed AIDS within one month of presentation (table 2). Of the children with AIDS, 119 (28%)had more than one indicator disease for AIDS at diagnosis. The proportion of children with opportunistic infections was higher in 1997-2002 than previously (37% versus 29% for *P carinii* pneumonia; 37% versus 22% for other opportunistic infections), but the distribution of other indicator diseases was similar in the two periods. Prognosis from initial AIDS diagnosis varied: mortality was higher in children with *P carinii* pneumonia or HIV encephalopathy compared with mortality in children with other opportunistic infections, failure to thrive, or severe recurrent bacterial infection (fig 2).

Among 587 children who had not progressed to AIDS within one month of presentation after birth, crude progression rates declined from 15.4 per 100 child years before 1997 to 3.0 per 100 child years at
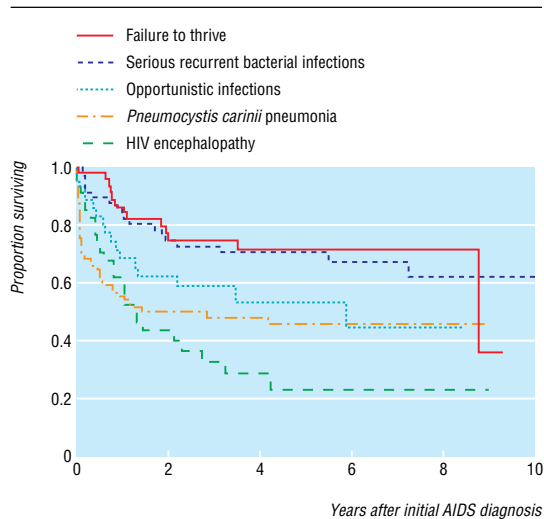
Fig 2 Survival after initial AIDS diagnosis, by presenting indicator disease. Six cancer cases are excluded. Only one indicator disease is shown for children presenting with more than one according to hierarchy: *P carinii* pneumonia, other opportunistic infection, HIV encephalopathy, failure to thrive, serious bacterial infections

risk in 2001-2 (test for trend P < 0.001). Figure 1 shows the adjusted risks relative to 1996. As with mortality, this decline was more marked in children aged >1 year (hazard ratio 0.37, 95% confidence interval 0.25 to 0.53, for before 1997 compared with 1997 onwards, table 3), while progression rates were similar in both periods for children aged <1 (1.03, 0.60 to 1.77, P = 0.002, heterogeneity for age).

Antiretroviral therapy

Of 593 children followed since 1996 in the collaborative HIV paediatric study, 137 (23%) had not started antiretroviral therapy at last report (121) or by the time of death (16). The percentage of child time spent on three or four drug antiretroviral therapy increased from 1% in 1996 to 56% in 1999 and 69% in 2001-2 (fig 3). There was no evidence that this differed in children aged <1. There was a shift over time from

Table 3 Adjusted hazard ratios (95% confidence intervals) for factors associated with progression to death and AIDS/death

	Death		AIDS/death	
	Ratio	P value	Ratio	Pvalue
Calendar year:				
Before 1997	1		1	
1997-2002	0.26 (0.17 to 0.38)	P<0.001	0.49 (0.36 to 0.67)	P<0.001
1997-2002, age <1 year	0.72 (0.35 to 1.48)	P=0.003*	1.03 (0.60 to 1.77)	P=0.002*
1997-2002, age ≥1 year	0.19 (0.12 to 0.30)		0.37 (0.25 to 0.53)	
Sex:				
Male	1		1	
Female	0.84 (0.61 to 1.15)	P=0.3	1.06 (0.81 to 1.40)	P=0.7
Ethnicity:				
White	1		1	
Black	0.87 (0.58 to 1.27)		0.77 (0.55 to 1.08)	
Other or not known	1.42 (0.85 to 2.37)	P=0.1	1.09 (0.69 to 1.72)	P=0.1
How child was identified:				
Prospectively from birth	1		1	
After birth	0.49 (0.31 to 0.78)	P=0.001	0.44 (0.30 to 0.64)	P<0.001
Place of birth:				
UK or Ireland	1		1	
Abroad	0.96 (0.62 to 1.48)	P=0.9	1.06 (0.73 to 1.53)	P=0.8

*Test of heterogeneity for age.

Table 4 Change in % composition of initial three or four drug antiretroviral therapy in treatment of children with HIV before 1999 compared with 1999 onwards

Antiretroviral drug combinations including:	Before 1999 (%)	1999 onwards (%)
Protease inhibitor	67	30
Non-nucleoside reverse transcriptase inhibitor	22	54
Both drug types	5	1
Triple nucleoside reverse transcriptase inhibitors	6	15

initial drug regimens containing a protease inhibitor to those containing a non-nucleoside reverse transcriptase inhibitor (table 4). The proportion of children who had previously been on therapy but had currently stopped remained constant after 1996 at around 5% of child time (fig 3).

Among 371 children on antiretroviral therapy when they were last seen in 2000 or later, 48 (13%) were taking four drugs, 301 (81%) three, and 22 (6%) two. Overall 91 different drug combinations were used.

Hospital admissions

The number of children seen in collaborative HIV paediatric study centres increased from 299 during 1996 to 493 in 2001-2, while the number of hospital admissions fell by 26% from 350 to 258. Admission rates declined by 80% from 4.4 per 100 child years of follow up in 1996 to 0.9 in 2001-2 (test for trend P < 0.001). As expected, the rates were lower in children born to mothers whose HIV status was known in pregnancy compared with those in whom it was not (relative risk 0.49, 0.42 to 0.57, P < 0.001). Among those presenting after birth, rates of admission were higher in the first six months after presentation than later (4.21, 3.79 to 4.69, P < 0.001).

Discussion

Mortality

From 1997 onwards we have seen reductions of around 80% in mortality and 50% in progression to AIDS among children perinatally infected with HIV-1 in the United Kingdom and Ireland. In the collaborative HIV paediatric study, hospital admission rates fell substantially. The introduction and increased
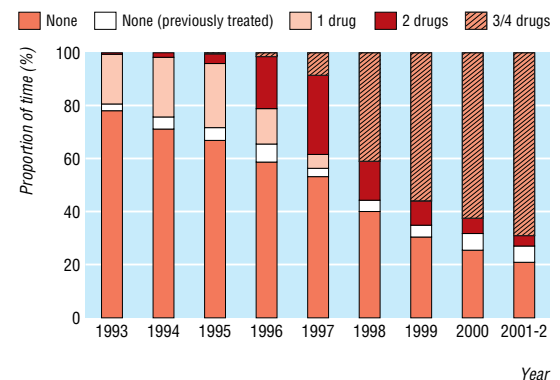

Fig 3 Proportion of time children with HIV spent having never received any drug treatment and while receiving none (previously treated), one, two, or three/four drugs, by calendar year

uptake of three or four drug antiretroviral therapy accompanied these changes and is likely to be the major contributing factor.[15] Similar findings, concurrent with the widespread uptake of antiretroviral therapy, have been reported from cohorts of children in the United States[11] and Italy.[10] Follow up in these studies was only to 1999, but we observed that survival stabilised during 2000-2 after dramatic reductions during 1997-9. A similar pattern has been observed in adult cohorts.[16]

There are clearly limitations in using cohort studies to ascribe changes in patterns of disease to particular interventions. As in the Italian study[10] we allowed for late entry at first presentation to reduce bias due to children with a good prognosis surviving longer and being more likely to be enrolled. In addition we repeated analyses separately for children born in the United Kingdom and Ireland or born abroad and observed similar results; this is particularly important in our cohort with the increasing proportion of children born abroad in recent years. As we included all children ever reported in the United Kingdom and Ireland, biases related to referral patterns to specialist centres are not an issue.

AIDS and hospital admissions

Our study is among the first to report reductions in hospital admissions over time in children with HIV, paralleling reductions in mortality and morbidity. The pattern of AIDS diagnoses before and since 1997 were similar, except for a trend towards a higher proportion of opportunistic infections in the later period. Improvements in the uptake of antenatal HIV testing and interventions to prevent transmission from mother to child have substantially increased the proportion of women diagnosed before delivery (from 32% in 1997 to 77% in 2001 in the United Kingdom[17]) and led to a corresponding decrease in the proportion of infected infants. As expected, mortality, progression to AIDS, and hospital admission rates were lower in infected children born to mothers whose diagnosis was known before the child was born. Caution must be exercised in interpreting these results to suggest that antenatal testing has benefits beyond prevention of transmission by improving the outcome of infected children; presentation bias could play a part as asymptomatic infected children born to undiagnosed women will not be identified until they present with symptoms. Despite the marked reduction in hospital admission rates, total admissions have declined by only one quarter since 1996, underlying the need for continued inpatient as well as outpatient services for HIV infected children.

Infants compared with older children

Whereas in children aged over 1 year under clinical care mortality decreased by 81% and progression to AIDS or death decreased by 63%, we saw only modest improvements among infants. This may reflect a decrease in the proportion of infants in the cohort followed from birth, due to the reduction in mother to child transmission rates,[18] although we attempted to control for this. Other explanations include the possibility that three or four drug antiretroviral therapy is not started early enough in infants. Pharmacokinetic issues may also hamper the effectiveness of antiretroviral therapy in this age group.[19] In recent years,

What is already known on this topic

In adults with HIV, rates of death, morbidity, and hospital admission have fallen since the introduction of three or four drug antiretroviral therapy in 1996

In children, treatment has lagged behind because of difficulties in the development of appropriate formulations of antiretroviral drugs and the lack of age specific pharmacokinetic data to guide paediatric dosing

What this study adds

In children perinatally infected with HIV in United Kingdom and Ireland, mortality decreased by 80% between 1997 and 2001-2, paralleling the increased use of three and four drug combination antiretroviral therapy; AIDS progression and hospital admission rates also substantially decreased

Most reductions occurred in 1997-9; rates stabilised between 2000 and 2002

Nearly a quarter of these children were aged over 10 years in 2002, highlighting the need for intensive outpatient care for delivery of antiretroviral therapy and psychosocial support to older children and adolescents

Despite the 80% decrease in hospital admission rates, the absolute number of admissions decreased by only 25%; the increasing number of HIV infected children requiring care has implications for service requirements for HIV infected children and adolescents in the United Kingdom and Ireland

most infants presented with symptoms as they had been born to mothers undiagnosed at delivery. As reported here and previously, some infants die from *P carinii* pneumonia or cytomegalovirus disease, or both, before antiretroviral therapy can be started.[20] The outlook for infants infected despite maternal diagnosis in pregnancy cannot easily be deduced from this study as numbers are small. However, we can speculate that transmission of maternal viruses that are drug resistant or more virulent may be also important. Ethnicity, sex, and place of birth had no significant effect on outcome.

Antiretroviral therapy

We observed a change over time from first use of antiretroviral therapy regimens based on protease inhibitors to those containing a non-nucleoside reverse transcriptase inhibitor. Although an increasing proportion of children receive four drug antiretroviral therapy, nearly all start with triple therapy. Further analyses of changes in prescribing practices for antiretroviral therapy and associated changes in HIV RNA and CD4 cell count responses are planned.

Conclusions

Rates of death, progression to AIDS, and hospital admission in children with HIV in the United

Kingdom and Ireland have significantly fallen. As antenatal detection rates improve and fewer children born to infected women are themselves infected, children presenting to paediatric services with HIV are likely to be older and to have been born abroad. This, combined with improved life expectancy, means that the demand for specialist paediatric HIV services will continue to increase.[21] Transitional links with adult services are required to deal with the medical, social, and psychological needs of children entering adolescence and adult life.

1 Guidelines for the use of antiretroviral agents in HIV infected adults and adolescents (accessed 14 July 2003).
2 British HIV Association (BHIVA). Guidelines for the treatment of HIV infected adults with antiretroviral therapy (accessed 18 Aug 2003).
3 Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998;352:1725-30.
4 Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853-60.
5 Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA* 1998;280:1497-503.
6 Sharland M, Castelli Gattinara di Zub G, Ramos JT, Blanche S, Gibb DM on behalf of the PENTA Steering Committee. PENTA (Paediatric European Network for Treatment of AIDS) guidelines for the use of antiretroviral therapy in paediatric HIV infection. *HIV Med* 2002;3:215-26.
7 Working Group on Antiretroviral Therapy, Medical Management of HIV-infected Children convened by National Pediatric and Family HIV Resource Center, Health Resources and Services Administration, and National Institutes of Health. Guidelines for the use of antiretroviral agents in pediatric HIV (accessed 22 Sep 2003).
8 World Health Organization. *Scaling up antiretroviral therapy in resource-limited settings; guidelines for a public health approach.* Geneva: World Health Organization, 2002.
9 Paediatric European Network for Treatment of AIDS (PENTA). Five-year follow-up of vertically HIV-infected children in a randomised double blind controlled trial of immediate versus deferred zidovudine: the PENTA 1 trial. *Arch Dis Child* 2001;84:230-6.
10 De Martino M, Tovo PA, Balducci M, Galli L, Gabiano C, Rezza G, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. *JAMA* 2000;284:190-7.
11 Gortmaker SL, Hughes M, Cervia J, Brady M, Johnson GM, Seage JR 3rd, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med* 2001;345:1522-8.
12 Ades AE, Davison CF, Holland FJ, Gibb DM, Hudson CN, Nicoll A, et al. Vertically transmitted HIV infection in the British Isles. *BMJ* 1993;306:1296-9.
13 Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Recomm Rep* 1994;43(RR-12):1-10.
14 Clayton C, Hills M. *Statistical models in epidemiology.* Oxford: Oxford University Press, 1993.
15 Tarwater PM, Mellors J, Gore ME, Margolick JB, Phair J, Detels R, et al. Methods to assess population effectiveness of therapies in human immunodeficiency virus incident and prevalent cohorts. *Am J Epidemiol* 2001;154:675-81.
16 Cascade Collaboration. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet* 2003;362:1267-74.
17 Unlinked Anonymous Surveys Steering Group. *Prevalence of HIV and hepatitis infections in the United Kingdom 2001.* London: Department of Health, 2002.
18 Cliffe S, Tookey PA, Nicoll A. Antenatal detection of HIV: national surveillance and unlinked anonymous survey. *BMJ* 2001;323:376-7.
19 Litalien C, Faye A, Compagnucci A, Giaquinto C, Harper L, Gibb DM, Jacqz-Aigrain E for PENTA. Pharmacokinetics of Nelfinavir and its active metabolite, M8, in infants perinatally infected with HIV-1. *Pediatr Inf Dis J* 2003;22:48-55.
20 Williams AJ, Duong T, McNally LM, Tookey PA, Masters J, Miller R, et al. Pneumocystis carinii pneumonia and cytomegalovirus infection in children with vertically acquired HIV infection. *AIDS* 2001;15:335-9.
21 Kinghorn G. A sexual health and HIV strategy for England. *BMJ* 2001;323:243-4.

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