HIV-infected pregnant women and vertical transmission in Europe since 1986

European Collaborative Study

Objective: To describe changes over a 15-year period in characteristics and management of HIV-infected pregnant women in Europe.

Design: Prospective study.

Methods: Analysis of prospective data on 2876 pregnant HIV-infected women and their 3076 infants. Factors examined included maternal socio-demographic, immunological and virological characteristics, antiretroviral therapy and pregnancy outcome.

Results: Among women enrolled, the proportion with heterosexual acquisition of infection has increased significantly from 59% (201/342) in 1985–1987 to 69% (327/471) after 1997 while the proportion acquiring HIV through injecting drug use has declined. Overall median CD4 cell count was 440×10^6/l and 41% of women had undetectable viral load at delivery. In 1995 28% (72/256) of mother–child pairs received the full 076 regimen to reduce risk of vertical transmission, rising significantly to 89% (116/130) by 1999. Use of triple therapy started in pregnancy has increased significantly from $< 1\%$ (1/153) in 1997 to 44% (47/107) in 1999. Exposure to antiretroviral therapy was not associated with prevalence or pattern of congenital abnormalities ($P = 0.88$) but was associated with reversible anaemia in the infant ($P < 0.002$). The elective cesarean section rate has increased from 10% in 1992 to 71% in 1999/2000. The vertical transmission rate declined from 15.5% by 1994 to 2.6% after 1998. In multivariate analysis, adjusting for maternal CD4 cell count, risk of vertical transmission was reduced by 66% (95% confidence interval, 37–82%) with the full 076 regimen and by 60% (95% confidence interval, 33–73%) with elective cesarean section delivery.

Conclusions: Changes in treatment of adult HIV disease have affected the management of infected pregnant women. Despite therapeutic and surgical interventions, vertical transmission still occurs.

AIDS 2001, **15**:761–770

Keywords: AIDS, antiretroviral therapy, pregnancy, vertical transmission, epidemiology

Introduction

In the 6 years since zidovudine was first shown to be effective in reducing the risk of mother-to-child transmission of HIV [1], information has become available on risk factors for, and mechanisms of, vertical transmission and on the effectiveness of other prophylactic interventions. The protective effects of avoiding breastfeeding and vaginal delivery (each of which approximately halve the risk), have been confirmed in randomized controlled trials [2,3], while observational studies have shown an additive effect of the three interventions, potentially reducing vertical transmission to less than 1% [4–6]. The use of interventions to reduce mother-to-child transmission on a population basis has been shown to have resulted in a decline in the number of new paediatric HIV infections [7,8].

The same period has also seen changes in the therapeutic management of HIV disease, in particular an in-

From the European Collaborative Study and prepared by Claire Thorne, Marie-Louise Newell, Linsay Gray, Simona Fiore and Catherine S. Peckham, Department of Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College, London, UK.

Requests for reprints to: M.-L. Newell, Department of Paediatric Epidemiology and Biostatistics, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK.

Received: 1 November 2000; revised: 1 February 2001; accepted: 6 February 2001.

creasing use of combinations of at least three antiretroviral drugs, usually including a protease inhibitor, initiated at an early stage [9,10]. This has resulted in a significant improvement in AIDS-free survival [11,12], with increasing numbers of women becoming pregnant while on combination therapy [13–16]. However, the safety of foetal and neonatal exposure to antiretroviral therapy, especially in combination, is unknown and the short- and longer-term outcome of pregnancies with exposure to potent combinations of antiretroviral drugs needs to be established [17–19].

The situation for HIV-infected women who are pregnant or considering pregnancy is different today than it was in the first decade of the epidemic. In this paper we describe the changes over time in the characteristics of HIV-infected pregnant women and their infants enrolling in the European Collaborative Study.

Methods

The European Collaborative Study (ECS) is a cohort study. HIV-infected women are identified during pregnancy and their infants prospectively followed according to standard clinical and laboratory protocols. In ECS centres, pregnant women are screened for HIV infection and those found to be infected are invited to participate in the study; pregnant women already known to be HIV infected as the result of earlier testing are also invited to take part. The ECS was set up in 1986 and includes 26 centres in nine European countries [6,20]. Informed consent is obtained before enrolment, according to local guidelines and local ethics approval has been granted.

Information collected at enrolment and during pregnancy includes current anti-retroviral treatment, maternal CD4 cell count and viral load [21], maternal injecting drug use (IDU) history and other socio-demographic characteristics. Maternal IDU use was classified into never use, history of IDU and current IDU on the basis of self-report, clinical observation and the presence of drug withdrawal symptoms in the neonate. Information on maternal CD4 cell count was collected from 1992 onwards. Delivery and neonatal characteristics are recorded including mode of delivery, presence of congenital abnormalities and mode of infant feeding. Laboratory tests including HIV RNA PCR, serology and CD4 cell counts, were carried out locally, with assays used recorded. Maternal CD4 cell count and HIV RNA copy number nearest the time of delivery were used in the analyses here. Assay types used were Roche (Amplicor Monitor, versions 1.0 and 1.5, Roche Diagnostic Systems, Basel, Switzerland), NASBA and Nuclisens (Organon Teknika, Oss, The Netherlands); in one centre the branched DNA assay (Chiron Diagnostics, Emeryville, California, USA) was also used. Tests were usually carried out on plasma samples, but occasionally on stored serum samples [6].

A child was classified as infected after the onset of AIDS, or detection of virus or antigen in at least two blood samples (taken on separate occasions) or persistence of antibody beyond 18 months of age; a child was presumed uninfected if at least two blood samples were antibody-negative and if no virus or antigen was ever identified. Neonatal anaemia was defined on the basis of the PACTG toxicity tables, which take into account the age of the infant at the time of the haemoglobin quantification.

Statistical analyses

Univariate comparisons for categorized variables were tested with the Chi-square test and Chi-square test for trends. Univariate and multivariate logistic regression analysis was used to obtain odds ratios (OR) and 95% confidence intervals (CI). All probability values were two-tailed. All analyses of HIV RNA copy number were performed using a logarithmic scale. Data entry and management were carried out using MS Access 97 and analyses were performed using SAS statistical software (version 6.12, SAS Institute, Cary, North Carolina, USA).

Results

Maternal socio-demographic and HIV-related characteristics

By June 2000, 2876 HIV-infected women had enrolled in the ECS, with 3076 infants. Approximately half the women had been diagnosed as HIV-infected prior to pregnancy (1382, 48%), with the remaining 52% (2876) being diagnosed antenatally. Average maternal age at the time of delivery was 27 years, increasing from 24 years in 1985 to 30 years in 1999. The main socio-demographic characteristics and mode of acquisition of HIV infection of the mothers at enrolment are summarized in Table 1. Heterosexual acquisition increased from 59% (201/342) in 1985–1987, to 69% (327/471) after 1997, with a significant overall trend (χ^2_{trend}, 7.92; $P = 0.005$). Over the same time period, the prevalence of IDU risk factors declined from 82% (266/323) in 1985–1987 to 33% (149/456) after 1997, a significant decline over the whole 15 year period (χ^2_{trend}, 270.2; $P < 0.0001$). The proportion of women known to be injecting drug users (mainly heroin) during pregnancy also declined significantly over the course of the study (χ^2_{trend}, 15.95; $P = 0.0001$), from 32% (12/38) in 1985 to 25% (42/166) in 1990, 19% (42/216) in 1995 and 8% (9/114) in 1999/2000.

Information on CD4 cell count was available for 1558

Table 1. Maternal socio-demographic characteristics at the time of enrolment.

	n	%
Country of residence (n = 2876)		
Italy	1229	43
Spain	788	27
Belgium	221	8
Germany	171	6
Sweden	159	6
UK	108	4
Netherlands	96	3
Denmark	20	1
Poland	84	3
Area of birth (n = 2733)		
Europe	2285	84
Sub-Saharan Africa	349	13
North Africa and Middle East	26	1
The Americas	47	2
Asia	26	1
Ethnicity (n = 2657)		
Asian	44	2
Black	391	14
White	2303	82
Other	64	2
Parity (n = 2649)		
0	1604	61
1	656	25
2	236	9
3 or more	153	6
Marital status (n = 1144)		
Single	305	27
Married	479	42
Cohabiting	287	25
Divorced, separated, widowed	73	6
Mode of acquisition (n = 2660)		
Injecting drug use only	902	34
Heterosexual contact only	996	37
Injecting drug use or heterosexual contact	720	27
Blood transfusion	39	1.5
Occupational exposure	3	0.1

(54%) mothers, with a median of 440×10^6/l (range, $0-2350 \times 10^6$/l). In 208 participants (13%) the CD4 cell count was $< 200 \times 10^6$/l, in 703 (45%) it was between 200 and 499×10^6/l and in 647 (42%) it was $\geqslant 500 \times 10^6$/l. The proportion of women with serious immunosuppression ($< 200 \times 10^6$ CD4 cells/l) increased from 4% (2/51) in 1985–1987 to 17% (80/461) in 1994–1996, but decreased to 12% (29/242) after 1997. Median CD4 cell count declined from 550×10^6/l in 1985–1987 to 425×10^6/l in 1994–1996, and was unchanged, with a median of 420×10^6/l, in 1997–2000.

Severe immunodeficiency was associated with ethnicity: 20% (47/235) of black women had CD4 cell counts $< 200 \times 10^6$/l, 13% (153/1179) of white women and 14% (7/49) women from other ethnic groups (χ^2, 7.95; $P = 0.019$). In a multivariate analysis involving 1446 women, adjusting for ethnicity, year of delivery and history of IDU, black women were more than twice as likely to be severely immunosuppressed than white women (OR, 2.30; 95% CI, 1.45–3.62; $P = 0.0004$). Although women delivering in 1994–1996 were nearly six times (OR, 5.89; 95% CI, 1.39–24.9; $P = 0.0158$) more likely to be immunosuppressed than those delivering in 1985–1987, women delivering between 1997 and June 2000 were only 3.5 times (OR, 3.48; 95% CI, 0.79–15.3; $P = 0.0981$) more likely to have CD4 cell counts $< 200 \times 10^6$/l than those in the earliest period. In a subanalysis involving 531 women delivering since the start of 1995, receipt of antiretroviral therapy in pregnancy was also included in the multivariate analysis: the increased risk of immunosuppression among black women remained after adjusting for therapy (OR, 2.19; 95% CI, 0.48–4.98; $P = 0.0205$), although no time trends in immunosuppression during the time period were apparent. Receipt of antiretroviral therapy was not a significant predictor of immunosuppression in the model (OR, 1.66; 95% CI, 0.84–3.28; $P = 0.149$), but most women had started therapy only relatively recently (in most cases, during the pregnancy).

Information on HIV RNA copy number was available for a total of 418 women, of whom 171 (41%) had undetectable levels of virus. Among the remaining 247 women with detectable viral load, the geometric mean HIV RNA level was 6039 copies/ml (range, 104–2 600 000 copies/ml). Trends over time in maternal viral load are shown in Table 2. Results for mean viral load for each time period are presented separately by assay type, as results obtained from Roche assays were substantially lower than those obtained with NASBA or Nuclisens assays. To investigate whether the trend towards a lower mean viral load in the later years of the study was a real finding, or a reflection of the improved sensitivity of these assays in more recent years of the study, we limited the analysis to test results within the original limit of detectability of each assay. This showed that there was decline in mean viral load, particularly evident in the last 3 years of the study, although less marked than that shown in Table 2, with a decline from 10 591 copies/ml to 7880 copies/ml for Roche and from 15 533 copies/ml to 7425 copies/ml for NASBA/Nuclisens for the period 1994–1996 to 1997–2000.

Antiretroviral therapy started before pregnancy

Ninety-four women who delivered after the start of 1994 were known to be taking antiretroviral therapy for their own health at the time they became pregnant. These women had a lower median CD4 cell count than that of the cohort as a whole, at 360×10^6/l (range, $80-800 \times 10^6$/l). These 94 women represent 12% of the 783 mothers delivering since 1994 who received antiretroviral therapy in pregnancy. Of the 94 women, all those who delivered in 1994 and 1995 were on monotherapy, but of the 25 delivering in 1999, 16 (64%) were on triple or quadruple therapy and the other nine were on double therapy, reflecting

Table 2. Trends in viral load closest to delivery, over time.

	Tested (n)	With undetectable viral load [n (%)]	With detectable viral load [n (%)]	Mean viral load in those with detectable virus (copies/ml)		Mean CD4 cell count [$\times 10^6$/l (n)]	On ART prophylaxis in pregnancy [n (%)]	On combination ART in pregnancy [n (%)]
				Roche (n)	NASBA/Nuclisens (n)			
1985–1990	23	3 (13)	20	6607 (4)	16 361 (16)	479 (18)	0	0
1991–1993	198	95 (48)	103	5030 (76)	11 847 (27)	517 (88)	0	0
1994–1996	53	19 (36)	34	6570 (20)	12 203 (14)	399 (19)	14 (41)	0
1997–2000	144	54 (38)	90	3697 (48)	4872 (42)	385 (60)	84 (93)	41 (49)

trends in the management of adult HIV disease. In three-quarters (70/94, 74%) of cases, the regimen contained zidovudine. Zidovudine monotherapy was used predominantly as intra-partum and neonatal prophylaxis to reduce vertical transmission for these 94 infants, although there were five cases of nevirapine received intrapartum, two cases of nevirapine received neonatally and five cases of neonatal combination therapy.

Antiretroviral therapy started during pregnancy

There has been a significant increase in the use of prophylactic zidovudine to reduce vertical transmission. In 1995 the full 076 regimen [1] was applied to 28% (72/256) of pregnant women and children, increasing to 62% (123/199) in 1997 and 89% (116/130) in 1999 (χ^2_{trend}, 125.6; $P < 0.0001$). Although the 076 regimen was followed in most centres, a modified regimen was used in Berlin, with the neonatal component administered as a 10 day course of intravenous zidovudine [22]. Women who injected drugs in pregnancy were significantly less likely to receive prophylactic antiretroviral therapy in pregnancy than women who had never been injecting drug users, although a previous history of IDU had no effect on receipt of therapy (Table 3). In multivariate logistic regression analysis adjusting for ethnicity, year of delivery and centre and including 859 mothers, active injecting drug users were three-quarters less likely to receive prophylaxis than other women. Similarly, black women (who were largely of sub-Saharan African origin) were only half as likely to receive prophylaxis in pregnancy as white women, adjusting for IDU (Table 3).

Of the 693 women who started antiretroviral therapy during pregnancy, 518 (75%) received zidovudine monotherapy, 106 (15%) double therapy and 69 (10%) triple therapy. Use of three-drug regimens initiated in pregnancy has increased from 1 out of 153 (0.7%) women in 1997, to 26 out of 136 (19%) in 1998 and 47 out of 107 (44%) in 1999 (χ^2_{trend}, 76.8; $P < 0.0001$). Information on CD4 cell count and viral load was available for 57 (83%) of the 69 women who started triple therapy regimens during pregnancy: 32 (56%) had plasma HIV RNA levels $> 30\,000$ copies and/or CD4 cell counts $< 350 \times 10^6$/l, which are the levels at which commencement of therapy is recommended. Thus, although the key purpose of initiation of antiretroviral therapy in pregnancy was to prevent vertical transmission, the type of treatment received reflects the woman's own health needs. A total of 30 three- and four-drug combinations were used, with four combinations accounting for most regimens: zidovudine + lamivudine + nelfinavir (24 cases), zidovudine + lamivudine + nevirapine (16 cases), zidovudine + lamivudine + indinavir (12 cases) and zidovudine + didanosine + lamivudine (11 cases). Most infants of the 69 women starting triple or quadruple therapy in

Table 3. Receipt of prophylactic antiretroviral therapy (ART) in pregnancy to reduce vertical transmission 1995–1999: results from univariate and multivariate analyses.

	Prophylactic ART in pregnancy							
	No [n (%)]	Yes [n (%)]	Odds ratio	95% CI	*P*	Adjusted odds ratio	95% CI	*P*
Injecting drug use								
None	118 (22)	418 (78)	1.00			1.00		
Past	52 (25)	152 (75)	0.82	0.57–1.19	0.305	1.10	0.70–1.73	0.685
Current	63 (53)	56 (47)	0.25	0.16–0.37	0.0001	0.23	0.13–0.39	0.0001
	$\chi^2 = 47.4$, $P = 0.001$							
Ethnicity								
White	185 (31)	414 (69)	1.00			1.00		
Black	40 (18)	184 (82)	2.06	1.40–3.02	0.0002	0.51	0.27–0.94	0.0317
Other	11 (23)	36 (77)	1.46	0.72–2.94	0.285	0.66	0.29–1.48	0.315
	$\chi^2 = 14.3$, $P = 0.001$							

*Adjusted for the other variable in the model, plus year of delivery and centre.

pregnancy received zidovudine monotherapy as neonatal prophylaxis, with 24 (22%) receiving combination therapy (mainly zidovudine + lamivudine).

Mode of delivery

In the mid-1980s, most women enrolling in the ECS delivered vaginally. Following early reports from the ECS that vaginal delivery was associated with an increased vertical transmission risk [23,24] and the subsequent results of the mode of delivery trial [2], the elective cesarean section rate doubled between 1992 and 1993 from 10% (26/266) to 19% (52/276) and reached 71% (101/143) in 1999/2000 (Fig. 1). However, there were marked differences between centres, with a range of 14–88% in 1995–2000. The emergency cesarean section rate has remained relatively stable during the latter half of the 1990s, at around 14%, although this represents an increase since the late 1980s and early 1990s; this is probably the result of women who are booked to have an elective cesarean section delivery starting labour prematurely: there has been a significant increase in the prevalence of premature deliveries (before 37 weeks) amongst women having emergency cesarean sections, from 28% (15/54) in 1992–1993 to 35% (17/48) in 1996–1997 and 54% (22/41) in 1998–1999 (χ^2_{trend}, 9.03, $P = 0.00265$).

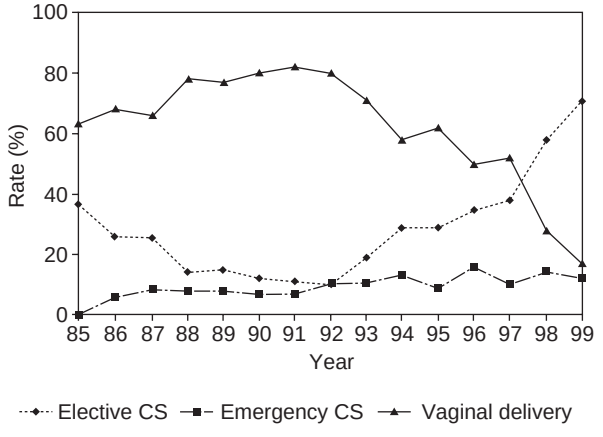

Fig. 1. Trends in mode of delivery over time.

Breastfeeding

Fifty-four (2%) women breastfed their infants, with duration of breastfeeding ranging from 6 h to 38 weeks. These cases were concentrated in the early years of the study, with only four women breastfeeding since the start of 1996. Three of these women were African and were diagnosed with HIV infection at the time of delivery; two stopped breastfeeding as soon as the positive test result became available (within 24 h), while the remaining woman continued to breastfeed her infant for 1 week after she received the test result. The fourth woman who breastfed her infant was an active IDU and had been diagnosed as HIV-positive 8 years previously; no information was available regarding duration of breastfeeding in this case.

Neonatal anaemia

Information on haemoglobin levels in the first 2 months of life was available for 332 infants. Among the 202 infants exposed to prophylactic antiretroviral therapy, mean haemoglobin level was 11.7 g/dl (range, 8.3–20.0 g/dl) for the 126 exposed to monotherapy and 13.3 g/dl (range, 7.9–19.9 g/dl) for the 76 exposed to combination therapy, significantly lower than that among the 130 infants not exposed to antiretroviral prophylaxis (mean, 14.7g/dl; range, 8.2–21.8 g/dl; $P < 0.002$). There was a strong association between exposure in foetal or early neonatal life to antiretroviral therapy and a reversible anaemia, with 46 (37%) of the 126 monotherapy-exposed and 39 (51%) of the 76 combination therapy-exposed infants having anaemia compared with 19 (15%) of the non-exposed infants (χ^2_{trend}, 32.02; $P < 0.0001$).

Congenital abnormalities

There were 37 children with congenital abnormalities, with a similar prevalence and pattern among the infants

exposed to antiretroviral therapy *in utero* (1.25%, 10/800) compared with those not exposed (1.40%, 27/2283). Of the 10 exposed children with congenital abnormalities, two had Down's Syndrome, four had ventricular septal defects and the remaining four had cataract, hydrocephalus, polycystic kidney and an unspecified familial anomaly. There was a similar pattern of abnormalities in the 27 unexposed children.

Longer-term paediatric follow-up of uninfected children

Of the 1345 uninfected children in the 11 paediatric centres followed up regularly, with clinical information reported, 381 (28%) had been exposed to antiretroviral therapy *in utero*. Two children exposed to zidovudine monotherapy and nine unexposed children had severe neurological abnormalities associated with other recognized chronic conditions. A total of 201 uninfected children were reported to have moderate clinical symptoms on at least one follow-up visit, 35 of whom had been exposed to antiretroviral therapy *in utero*. Most of these reports of moderate symptoms related to infections, such as gastro-enteritis and *Candida*, and were concentrated in the first few months of life. There were no reports suggestive of mitochondrial abnormalities, although specific investigations for this condition were not carried out routinely.

Vertical transmission

The overall rate of vertical transmission declined from 15.5% (251/1620) up to the end of 1994 to 2.6% (4/156) after 1998. Overall, the transmission rate was 5.7% (35/612) for mother–child pairs receiving an incomplete 076 regimen, 4.0% (20/494) for those receiving all three components and 1.7% (2/118) for those taking combination therapy in pregnancy (excluding those who were on combination therapy for their own health). The vertical transmission rate was 2.2% (6/268) where there was no breastfeeding, a complete 076 regimen and an elective cesarean section delivery. Neither of the two infected infants whose mothers received combination therapy in pregnancy were delivered by elective cesarean section; in one case, the mother started therapy (zidovudine and lamivudine) only 2 weeks before delivery and in the other the mother was on triple therapy throughout pregnancy and had a detectable viraemia.

Results from a multivariate analysis of risk of vertical transmission allowing for treatment, mode of delivery and maternal CD4 cell count including 1539 mother–child pairs are presented in Table 4. Use of prophylactic zidovudine during pregnancy, during labour/at delivery and to the neonate was associated with a two-thirds reduction in risk of vertical transmission; elective cesarean section delivery was associated with a more than halved risk.

Discussion

The characteristics of the HIV-infected women enrolling in the ECS have changed since we last described them 5 years ago [25,26]. HIV-infected women enrolling in recent years were more likely to have acquired their infection heterosexually than through IDU [25], reflecting patterns in Europe generally [27]. They are also having their children at increasingly older ages and are more likely to know that they are HIV-infected when they become pregnant. In recent years there have been more women who acquired their infection heterosexually and these women tend to be older when they have their babies than IDU; the older average maternal age also reflects the general trend in Western Europe. The decline in average maternal CD4 cell count over time reported previously [26] has levelled out in the last few years, which may be due to the increased use of antiretroviral therapy before pregnancy: for example, the use of triple combination

Table 4. Maternal and obstetric risk of vertical transmission. Multivariate analysis involving 1539 mother–child pairs, adjusting for antiretroviral therapy, mode of delivery and maternal CD4 cell count.

	Risk of vertical transmission					
	Odds ratio	95% CI	*P*	Adjusted odds ratio	95% CI	*P*
Treatment group						
No treatment	1.00			1.00		
Incomplete 076 regimen	0.34	0.24–0.49	0.0001	0.41	0.25–0.67	0.0004
Whole 076 regimen	0.25	0.15–0.40	0.0001	0.34	0.18–0.63	0.0006
Combination therapy	0.10	0.02–0.39	0.001	0.15	0.002–1.13	0.0659
Elective cesarean section						
No	1.00			1.00		
Yes	0.30	0.22–0.42	0.0001	0.42	0.27–0.67	0.0003
Maternal CD4 cell count						
$\geqslant 500 \times 10^6$/l	1.00			1.00		
$200–499 \times 10^6$/l	1.32	0.93–1.87	0.076	1.52	1.06–2.18	0.0223
$< 200 \times 10^6$/l	1.31	0.80–2.14	0.052	1.57	0.95–2.60	0.0781

CI, Confidence interval.

therapy in pregnancy more than doubled between 1998 and 1999.

Viral load was undetectable by the assays available in a large proportion (41%) of mothers, and among those with detectable virus, average viral load has declined over the study period. However, the analysis of trends in maternal viral load highlights the need to take into account changing sensitivities of assays for HIV RNA copy number when making comparisons over time. Although these assay changes have contributed to the decline in maternal viral load over time, there was evidence of a real decline as well, which could be related to the increased use of antiretroviral therapy in pregnancy in the cohort. It was interesting that in the more recent years of the study, women with low viral loads also had quite low CD4 cell counts, which could be related to the timing of initiation of antiretroviral prophylaxis relative to the timing of the tests. Most women in our cohort started therapy in the second or third trimesters of pregnancy, and whereas viral load may decline quite rapidly after initiation of therapy, there may be a delay before there is an increase in CD4 cell count [28]. As CD4 cell counts after delivery are not available in this dataset, we cannot investigate this possibility further.

Prophylactic use of zidovudine to reduce vertical transmission in our cohort has increased significantly since the PACTG 076 trial results were published in 1994 [1]. Although this increase has been slower than reported elsewhere [5,29] by 1999 only 8% of women and 2% of neonates did not receive prophylactic zidovudine to reduce vertical transmission. Active injecting drug users in our cohort were less likely to receive prophylaxis than other women, even allowing for year of enrolment. Lower rates of antiretroviral therapy for clinical indications among injecting drug users compared with other HIV-infected groups have been reported elsewhere [30–33]. The poor adherence of injecting drug users to antiretroviral therapy [34] and their irregular clinic attendance may help to explain why health care providers are reluctant to start known substance abusers on complex antiretroviral regimens. Black women in our study were also less likely to receive prophylaxis during pregnancy, most probably because they tended to be diagnosed at a later stage than white women (data not shown). Furthermore, most black women here were refugees or immigrants from Africa; although we do not have information on the immigration status of these women, a survey carried out in several European centres, including 11 in the ECS, suggests that many do not have permanent residency status, which is likely to be a barrier to accessing health care [35]. The finding that black women in our cohort were more likely to be severely immunosuppressed than white women is consistent with their reduced access to treatment in general [36,37].

In 1999, nearly half of the women starting antiretroviral therapy during pregnancy were taking triple therapy regimens, compared with only 1% in 1997. Furthermore, by 1999 most (64%) women becoming pregnant while taking antiretroviral therapy for their own health were on triple therapy [38,39]. It is unclear whether zidovudine needs to be part of the antenatal regimen for vertical transmission prophylaxis, and whether zidovudine monotherapy for the neonate is appropriate in these circumstances. In the ECS, just under one-quarter of infants exposed to triple therapy *in utero* received neonatal prophylaxis with two or more drugs.

Observational data suggest that combination antiretroviral therapies involving three or more drugs in pregnancy are highly effective in reducing risk of vertical transmission [14,15], although questions remain regarding the long-term safety of these newer combinations of drugs in pregnancy. In the 076 trial, no excess of congenital malformations was found in the infants in the zidovudine monotherapy arm compared with those receiving a placebo; the most common adverse effect in the trial was a transient anaemia [40,41]. A lack of cardiac toxicity related to zidovudine exposure was recently noted [42]. In the Bangkok trial of short-course zidovudine to reduce vertical transmission, no adverse events were identified during 18 months of follow-up [43]. In our cohort, there was no evidence of any serious adverse effects on pregnancy outcome among those exposed to antiretroviral therapy (largely zidovudine monotherapy). There was also no evidence of conditions suggestive of mitochondrial abnormalities among antiretroviral-exposed, uninfected children, although no specific investigations for such abnormalities were carried out. Further investigations of a possible link between exposure to antiretroviral drugs and mitochondrial disease will require a collaborative approach involving follow-up of large numbers of exposed children, but incidence of mitochondrial disease is likely to be very rare [19].

By 1999 nearly three-quarters of infants in the ECS were delivered by elective cesarean section. The trend towards a increased emergency cesarean section rate, associated with a premature delivery in women planning to have an elective cesarean section, has also been observed in the Swiss Mother + Child HIV Cohort (Rudin, Personal Communication, 2000). A significant interaction between zidovudine prophylaxis and elective cesarean section delivery in reducing vertical transmission has been reported elsewhere [4,5]. Here we report a considerably lower vertical transmission rate, of 2%, among mother–child pairs where there was no breastfeeding, an elective cesarean delivery and prophylactic antiretroviral therapy (mainly zidovudine), compared with 4% with no breastfeeding and prophylaxis alone, consistent with earlier reports [6]. Our finding of a 2% vertical transmission risk with zidovu-

dine monotherapy and elective cesarean section may reassure any HIV-infected woman or health care provider who has concerns about starting a potent triple therapy regimen in pregnancy.

Similar results to ours have been reported from the Women and Infants Transmission Study (WITS), with prophylactic zidovudine therapy being associated with a two-thirds decrease in risk of transmission in both studies. Our OR of 0.15 for combination therapy is consistent with the WITS OR for combination therapy with and without protease inhibitors (0.05 and 0.18 respectively) [14]. However, although in our study, elective cesarean section was effective in further reducing vertical transmission risk for each treatment group, in WITS the effect of elective cesarean section, although in the same direction, was of borderline significance. In another cohort study from the USA, preliminary results suggest that elective cesarean section may reduce vertical transmission risk among women on combination therapy, with vertical transmission rates of 0% and 2.9% for women having elective cesarean section and vaginal deliveries respectively [44]. Such results are consistent with an earlier finding of the ECS, that elective cesarean section delivery is effective in reducing risk of vertical transmission even in women with low viral loads [6]. An issue frequently raised regarding cesarean section delivery concerns the risk of side-effects. In the mode of delivery trial, although there was a higher rate of postpartum fever in the cesarean section group than in the vaginally delivered group (7% versus 1%), the overall complication rate was low, with no serious or persistent side-effects reported [2].

As the rates of vertical transmission reported here show, there is a higher risk of transmission where an incomplete 076 regimen is used. A recent trial in Thailand has provided more information on the efficacy of maternal and neonatal zidovudine regimens of various lengths, in which transmission rates in the long maternal regimen (starting at 28 weeks) and short neonatal regimen (3 days) arm and in the short maternal regimen (starting at 35 weeks) and long neonatal regimen (6 weeks) arm were equivalent to the 076 regimen [45]. Poor adherence to antiretroviral therapy may also result in an increased risk of vertical transmission. We do not have information on adherence to drug regimens in pregnancy, but a recent study suggested that up to a third of people in trials of highly active antiretroviral therapy are not adherent [46]. However, pregnant women may be more motivated to adhere to therapy than the non-pregnant population.

In our cohort of non-breastfeeding women, a small number of vertical transmissions occurred despite reported use of both elective cesarean section and antiretroviral prophylaxis. Although the situation today in developed countries is such that vertically transmitted infections are increasingly rare, it is important to remember when counselling women with HIV infection who are considering having a baby and those who are already pregnant that there is a risk, in isolated cases, for a woman despite her antiretroviral therapy, having an elective cesarean section and not breastfeeding to still have an infected infant.

ECS Acknowledgments

We thank L. Chieco-Bianchi, F. Zacchello, R. D'Elia, A. M. Laverda, S. Cozzani, C. Cattelan, A. Mazza, B. Grella, A. R. Del Mistro, V. Giacomet, O. Rampon, S. Oletto (Padua); C. Feiterna, R. Weigel (Berlin); S. Burns, N. Hallam, P. L. Yap, J. Whitelaw (Edinburgh); B. Sancho, G. Fontan-Casanego (Madrid); F. Asensi, M. C. Otero, A. Perez Tamarit, A. Gonzalez Molina, M. Gobernado, J. L. Lopez, J. Cordoba (Valencia); G. Mulder, T. Kosten, M. C. A. van Leeuwen, the participants of the Dutch collaborative study of HIV-infected women and their children (Amsterdam); G. Lidin-Jansson, B. Christensson, C. Ottenblad, P. O. Pehrson, K. Gyllensten, K. Elfgren, A. Sönnerborg (Sweden); G. Di Siena, E. Pontali, M. F. Pantarotto, G. Mantero, P. Dignetti (Genoa); A. Hottard, M. Poncin, S. Sprecher, B. Lejeune, G. Zississ, N. Clumeck (Brussels); J. Llorens, M. Iglesias (Hospital del Mar, Barcelona), B. Martinez de Tejada, L. Zamora, R. Vidal (Hospital Clinic, Barcelona), G. Zucotti (Ospedale San Paolo, Milano); M. Carla Re (Bologna); C. Christini, F. Castelli, A. Rodella (Brescia); I. Quinti, A. Pachí (Roma); G. Noia (Roma); P. A. Tovo, C. Gabiano (Turino); A. Maccabruni, (Pavia); G. Ferraris, (Clinica Mangiagalli, Milano); E. Pagliaro, M. T. Melisi (Naples), The Regional Health Office and RePuNaRC (Naples).

Sponsorship: The European Collaborative Study is a concerted action of the European Commission (Biomed II PL 97 2005). The Medical Research Council (UK) provides support to the co-ordinating centre. Collaborating Centres were supported by grants from the Ministero della Sanita - Istituto Superiore di Sanita, progetto AIDS (Padua, Genoa); the Medical Research Council (UK), the AIDS Virus Education Research Trust, the Scottish Office Home and Health Department (Edinburgh); Praeventiefonds number 28-1704 (Amsterdam); Bundesminister fur Gesundheit (Berlin); Fonds Houtman, Office de la Naissance et de L'Enfance, Communaute Francaise de Belgique (Brussels), and the Swedish Medical Research Council (Stockholm).

References

1. Connor EM, Sperling RS, Gelber R, *et al.* **Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment.** *N Eng J Med* 1994, **331**:1173–1180.
2. The European Mode of Delivery Collaboration. **Elective caesar-**

ean section versus vaginal delivery in preventing vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999, **353**:1035–1039.
3. Nduati R, John G, Ngacha DA, *et al.* **Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomised clinical trial.** *JAMA* 2000, **283**:1167–1174.
4. Kind C, Rudin C, Siegrist C-A, *et al.* **Prevention of vertical HIV transmission: additive protective effect of elective Cesarean section and zidovudine prophylaxis.** *AIDS* 1998, **12**:205–210.
5. Mandelbrot L, Le Chenadec J, Berrebi A, *et al.* **Perinatal HIV-1 transmission - interaction between zidovudine prophylaxis and mode of delivery in the French Perinatal Cohort.** *JAMA* 1998, **280**:55–60.
6. European Collaborative Study. **Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one.** *AIDS* 1999, **13**:1377–1385.
7. Centers For Disease Control and Prevention. *HIV/AIDS Surveillance General Epidemiology.* 17 July 2000, www.cdc.gov/hiv/graphics/surveill.htm
8. PHLS AIDS and STD Centre - Communicable Diseases Surveillance Centre and SCIEH. Unpublished quarterly surveillance tables. 49, Table 14. 2000. London: PHLS.
9. Spira R, Marimoutou C, Binquet C, Lacoste D, Dabis F. **Rapid change in use of antiretroviral agents and improvement in a population of HIV-infected patients: France, 1995 to 1997.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, **18**:358–364.
10. Kirk O, Mocroft A, Katzenstein TL, *et al.* **Changes in use of antiretroviral therapy in regions of Europe over time.** *AIDS* 1998, **12**:2031–2039.
11. Sendi PP, Bucher HC, Craig BA, Pfluger D, Battegay M, for the Swiss HIV Cohort Study. **Estimating AIDS-free survival in a severely immunosuppressed asymptomatic HIV-infected population in the era of antiretroviral triple combination therapy.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1999, **20**:376–381.
12. Vittinghoff E, Scheer S, O'Malley P, *et al.* **Combination antiretroviral therapy and recent declines in AIDS incidence and mortality.** *J Infect Dis* 1998, **179**:717–720.
13. Lorenzi P, Spicher VM, Laubereau B, *et al.* **Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects.** *AIDS* 1998, **12**:F241–F247.
14. Blattner WA, Cooper E, Charurat M, *et al.* **Effectiveness of potent antiretroviral therapies on reducing perinatal transmission of HIV-1.** *XIII International Conference on AIDS.* Durban, July 2000 [abstracts LbOr4].
15. Zorilla CD, Matos M, Morales A, Bonano JF. **Increasing trend towards HAART use during pregnancy with good perinatal outcome.** *XIII International Conference on AIDS.* Durban, July 2000 [abstract WePpB1303].
16. Thorne C, for the European Collaborative Study. **Antiretroviral therapy and caesarean section to reduce vertical transmission of HIV in Europe.** *XIII International Conference on AIDS.* Durban, July 2000 [abstract MoOrC240].
17. Blanche S, Tardieu M, Rustin P, *et al.* **Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues.** *Lancet* 1999, **354**:1084–1089.
18. European Collaborative Study and the Swiss Mother + Child HIV Cohort Study. **Combination antiretroviral therapy and duration of pregnancy.** *AIDS* 2000 **14**:2913–2920.
19. McIntosh K. **Mitochondrial toxicity of perinatally administered zidovudine**. *Seventh Conference on Retroviruses and Opportunistic Infections.* San Francisco, January–February 2000 [abstracts S14].
20. European Collaborative Study. **Vertical transmission of HIV-1: maternal immune status and obstetric factors.** *AIDS* 1996, **10**:1675–1681.
21. European Collaborative Study, Swiss HIV and Pregnancy Collaborative Study Group. **Immunological markers in HIV infected pregnant women.** *AIDS* 1997, **11**:1859–1865.
22. Grosch-Worner I, Schäfer A, Obladen M, *et al.* **Two to four weeks oral maternal and 10 days intravenous neonatal zidovudine prophylaxis and elective caesarean section: effective and safe in reducing vertical transmission of HIV-1 infection.** *AIDS,* 2000 **14**:2903–2911.
23. European Collaborative Study. **Risk factors for mother-to-child transmission of HIV-1.** *Lancet* 1992, **339**:1007–1012.
24. European Collaborative Study. **Caesarean section and risk of vertical transmission of HIV-1 infection.** *Lancet* 1994, **343**:1464–1467.
25. European Collaborative Study. **Characteristics of pregnant HIV-1 infected women in Europe.** *AIDS Care* 1996, **8**:33–42.
26. European Collaborative Study. **Clinical and immunological characteristics of HIV-1 infected pregnant women.** *Br J Obstet Gynaecol* 1995, **102**:869–875.
27. WHO-EC Collaborating Centre on AIDS. *HIV/AIDS Surveillance in Europe, end year report 1999. no 62.* Paris: European Centre for the Epidemiological Monitoring of AIDS; 2000.
28. Renaud M, Katlama C, Mallet A, *et al.* **Determinants of paradoxical CD4 cell reconstitution after protease-inhibitor-containing antiretroviral regimen.** *AIDS* 1999, **13**:669–676.
29. Mayaux MJ, Teglas JP, Mandelbrot L, *et al.* **Acceptability and impact of zidovudine prevention on mother-to-child HIV-1 transmission in France**. *J Pediatr* 1997, **131**:857–862.
30. Kaplan JE, Parham DL, Soto-Torres L, *et al.* **Adherence to guidelines for antiretroviral therapy and for preventing opportunistic infections in HIV-infected adults and adolescents in Ryan White-funded facilities in the United States.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1999, **21**:228–235.
31. Bassetti S, Battegay M, Furrer H, *et al.* **Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued?** *J Acquir Immune Defic Syndr Hum Retrovirol* **1999, 21:114–119.**
32. Napoli PA, Dorrucci M, Serraino D, *et al.* **Frequency and determinants of use of antiretroviral and prophylactic therapies against Pneumocystis carinii Pneumonia (PCP) before AIDS diagnosis in Italy.** *Eur J Epidemiol* 1998, **14**:41–47.
33. Carrieri MP, Moatti JP, Vlahov D, *et al.* **Access to antiretroviral treatment among French HIV infected injection drug users: the influence of continued drug use.** *J Epidemiol Community Health* 1999, **53**:4–8.
34. Gordillo V, Del Amo J, Soriano V, Gonzalez-Lahoz J. **Sociodemographic and psychological variables influencing adherence to antiretroviral therapy.** *AIDS* 1999, **13**:1763–1769.
35. Thorne C, Newell M-L, Peckham CS. **Clinical and psycho-social service needs of children and families affected by human immunodeficiency virus in Europe.** *Eur J Public Health* 1999, **99**: 8–14.
36. Mercey D, Griffioen A, Woronowski H, Stephenson J. **Uptake of medical interventions in women with HIV infection in Britain and Ireland.** *Genitourin Med* 1996, **72**:281–282.
37. Hankins C, Lapointe N, Walmsley S. **Participation in clinical trials among women living with HIV in Canada.** *Can Med Assoc J* 1998, **159**:1359–1365.
38. Carpenter CCJ, Cooper DA, Fischl MA, *et al.* **Antiretroviral therapy in adults. Updated recommendations of the International AIDS Society - USA Panel.** *JAMA* 2000, **283**:381–390.
39. Taylor GP, Lyall EGH, Mercey D, *et al.* **British HIV Association guidelines for prescribing antiretroviral therapy in pregnancy (1998).** *Sex Trans Infect* 1999, **75**:90–97.
40. Sperling RS, Shapiro DE, McSherry GD, *et al.* **Safety of the maternal-infant zidovudine regimen utilized in the Pediatric AIDS Clinical Trial Group 076 study.** *AIDS* 1998, **12**: 1805–1813.
41. Culnane M, Fowler MG, Lee SS, *et al.* **Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women.** *JAMA* 1999, **13**:151–157.
42. Lipshultz SE, Easley KA, Orav EJ *et al.* **Absence of cardiac toxicity of zidovudine in infants.** *New Engl J Med* 2000, **343**:759–766.
43. Chotpitayasunondh T, Vanprapar N, Simonds RJ, *et al.* **Safety of late in utero exposure to zidovudine in infants born to human immunodeficiency virus-infected mothers: Bangkok.** *Pediatrics* 2000, **107**:1–6.
44. Fiscus S, Adimora A, Schoenbach V, *et al.* **Elective C-section may provide additional benefit in conjunction with maternal combination antiretroviral therapy to reduce perinatal HIV transmission.** *XIII International Conference on AIDS.* Durban, July 2000 [abstract WePpC1388].
45. Lallement M, Jourdain G, Le Coeur S, *et al.* for the Perinatal HIV Prevention Trial (Thailand) Investigators. **A randomized double-blind controlled equivalence trial of shortened zidovudine treatment regimens to prevent mother to child transmission of human immunodeficiency virus type 1 in Thailand.** *New Engl J Med* 2000 **343**:982–991.
46. Chesney MA, Ickovics JR, Chambers DB, *et al.* **Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG Adherence Instruments.** *AIDS Care* 2000, **12**:255–266.

Appendix

The collaborating clinicians in the ECS are C. Giaquinto, E. Ruga, A. De Rossi (Universita degli Studi di Padova, Italy); I. Grosch-Wörner, K. Seel, (Charite Virchow-Klinikum, Berlin, Germany); J. Mok (Royal Hospital for Sick Children, Edinburgh), F. Johnstone (Department of Obstetrics University of Edinburgh, UK); M. C. Garcia-Rodriguez, I. Bates, I. de José, F. Hawkins, C. Ladrón de Gevara, J. Mª Peña, J. Gonzalez Garcia, J. R. Arribas Lopez (Hospital Infantil La Paz, Madrid); F. Asensi-Botet, M. C. Otero, D. Pérez-Tamarit, S. Ridaura, P. Gregori, R. de la Torre (Hospital La Fe, Valencia, Spain); H. Scherpbier, M. Kreyenbroek, K. Boer (Academisch Medisch Centrum, Amsterdam, The Netherlands); A. B. Bohlin, S. Lindgren, A. Ehrnst, B. Anzén, K. Lidman, E. Belfrage, L. Navér (Huddinge and Karolinska Hospitals, Sweden); J. Levy, P. Barlow, M. Hainaut, A. Peltier, S. Wibaut, G. Debruyne (CHU St Pierre, Brussels, Belgium); A. Ferrazin, D. Bassetti, (Department of Infectious Diseases, University of Genoa, Italy); A. De Maria (Department of Internal Medicine, University of Genoa, Italy) C. Gotta (Department of Obstetrics & Gynecology-Neonatology Unit, University of Genoa, Italy); A. Mur, A. Payà, M. Viñolas, M. A. López-Vilchez, P. Martinez-Gómez, R. Carreras (Hospital del Mar, Universidad Autónoma, Barcelona, Spain); J. Jimenez (Hospital 12 De Octubre, Madrid, Spain), O. Coll, C. Fortuny (Hospital Clinic, Barcelona, Spain); J. Boguña (Hospital Sant Joan de Deu, Barcelona, Spain); M. Casellas Caro (Hospital Vall D'Hebron, Barcelona, Spain); Y. Canet (Hospital Parc Tauli de Sabadell, Barcelona, Spain); G. Pardi, M. Ravizza (Ospedale San Paolo, Milano, Italy); B. Guerra, M. Lanari, S. Bianchi, L. Bovicelli (Policlinico S Orsola, Bologna, Italy); E. Prati, M. Duse (Universita di Brescia, Brescia, Italy); G. Scaravelli, M. Stegagno (Universita La Sapienza, Roma, Italy); M. De Santis (Universita Cattolica, Roma, Italy); A. E. Semprini, V. Savasi, A. Viganò (Ospedale L. Sacco, Milan, Italy); F. Ravagni Probizer, A. Maccabruni (Policlinico S Matteo, Pavia, Italy); A. Bucceri, L. Rancilio (Clinica Mangiagalli and Clinica De Marchi, Milano, Italy); G. P. Taylor, E. G. H. Lyall (St Mary's Hospital, London); Z. Penn (Chelsea and Westminster Hospital, London); N. H. Valerius (Hvidovre Hospital, Denmark); W. Buffolano (Pediatric Department, Federico II University, Naples) P. Martinelli, M. Sansone (Obstetric Department, Federico II University, Naples, Italy); C. Tibaldi, N. Ziarati, C. Benedetto (University di Torino, Italy); T. Niemieç, A. Horban (Centrum Diagnostyki I Terapii AIDS, Warsaw, Poland).