In utero exposure to antiretroviral therapy: feasibility of long-term follow-up

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Abstract

Most uninfected children born to diagnosed HIV-infected women in the United Kingdom (UK) are exposed to antiretroviral therapy (ART) *in utero* and neonatally, and concerns exist about potential adverse effects of such exposure. We explored the feasibility of using national clinic-based follow-up to investigate the association between ART exposure and adverse health events occurring after the neonatal period.

Active surveillance of obstetric and paediatric HIV infection is conducted through the National Study of HIV in Pregnancy and Childhood (NSHPC). Between 2002 and 2005, health professionals enrolled previously notified uninfected children in a consented follow-up study (the CHART study). Follow-up information was collected opportunistically using a standard questionnaire.

Of 2104 eligible uninfected children born in the UK between 1996 and 2004, 704 (33.5%) were enrolled in CHART; parents of 4.8% (100/2104) declined, 2.8% (59/2104) had gone abroad, 21.6% (455/2104) were not contactable, and the remaining 37.3% (786/2104) were not enrolled mainly because of lack of clinic resources or unwillingness of health professionals to approach the families.

Demographic characteristics and type of ART exposure for enrolled and non-enrolled children were similar. Latest information on enrolled children was available at a median age of 24 months. Minor childhood ailments were reported in the majority of children, febrile seizures in 1.6% (11/704), and major health problems in 3.8% (27/704). It was

reassuring that prevalence of these outcomes was within UK norms, but numbers were small and duration of follow-up was limited.

The difficulties encountered in enrolling and retaining children in this study indicate that comprehensive clinic-based follow-up of ART-exposed uninfected children is not practical. Alternative approaches are required; a robust, secure data linkage protocol would provide a more feasible and sustainable system for long term monitoring of *in utero* ART exposure.

Introduction

Use of antiretroviral therapy (ART), elective caesarean section and avoidance of breast feeding have led to a reduction in mother-to-child HIV transmission (MTCT) rates in resource-rich settings from around 20% to less than 2% (European Collaborative Study, 2005b; Magder et al., 2005; Townsend et al., 2008a). In 2006, over 95% of HIV-infected pregnant women delivering in the UK were diagnosed prior to delivery (The UK Collaborative Group for HIV and STI Surveillance, 2007), and over 95% of these were prescribed ART either to reduce the risk of MTCT or for their own health (Townsend et al., 2008a). These developments, along with the increased prevalence of HIV infection in pregnant women in the UK, which doubled between 2001 (0.11%) and 2006 (0.23%) (The UK Collaborative Group for HIV and STI Surveillance, 2007), contributed to an increase in the number of ART-exposed uninfected infants from about 390 in 2001 to about 1100 in 2006 (NSHPC data).

There are potential short- and long-term risks associated with ART exposure *in utero* and in early life (Thorne & Newell, 2005). The teratogenic nature of some antiretroviral drugs has been demonstrated in animal studies (Public Health Service Task Force, 2007b), though large studies in humans have not found an association between ART exposure and prevalence of congenital abnormalities (Antiretroviral Pregnancy Registry Steering Committee, 2007; European Collaborative Study, 2005a; Thorne & Newell, 2005; Townsend et al., 2006a). Antiretroviral drugs in the nucleoside reverse transcriptase inhibitor (NRTI) class are known to deplete mitochondrial DNA and in 1999 eight ART-exposed uninfected children born in France were reported with persistent mitochondrial dysfunction, two of whom died (Blanche et al., 1999).

However a review of mortality in more than 20,000 children in five US cohorts did not identify any deaths associated with mitochondrial dysfunction (The Perinatal Safety Review Working Group, 2000). The French group also reported that exposure to ART was associated with febrile seizures in children under 18 months of age (Landreau-Mascaro et al., 2002). As NRTIs become incorporated into host DNA, there is potential for long-term carcinogenic effects; tumours have been observed in mice after *in utero* exposure to zidovudine (Olivero et al., 1997; Poirier et al., 2004), but long-term data on humans exposed to zidovudine and other antiretroviral drugs *in utero* are lacking.

While national guidelines recommend that children exposed to antiretroviral drugs are monitored over the long term, practical standard protocols have not been developed (Public Health Service Task Force, 2007a). In order to assess the feasibility of national clinic-based follow-up in the UK, the CHildren exposed to AntiRetroviral Therapy (CHART) study was conducted between 2002 and 2005. Eligible children were identified from reports to the national programme for obstetric and paediatric HIV surveillance, the National Study of HIV in Pregnancy and Childhood (NSHPC) (Townsend et al., 2008b).

Methods

The core surveillance mechanisms of the NSHPC include two active reporting schemes. Pregnancies in HIV-infected women are reported to the NSHPC in association with the Royal College of Obstetricians and Gynaecologists. Children with HIV infection and infants born to HIV-infected women are reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health (Nicoll et al., 2000) or directly to the NSHPC. Respondents provide information on demographic characteristics, HIV-related laboratory investigations, ART use and perinatal outcomes. Live births reported through the obstetric scheme are linked with paediatric reports using demographic information, as names are not collected. Paediatric cases are followed up to establish HIV infection status and once a child is confirmed uninfected, routine surveillance ceases. Individual patient consent is not required for case notification to the NSHPC and surveillance staff contact is exclusively with health care respondents not patients.

Uninfected children born in the UK and reported to the NSHPC were eligible for enrolment in CHART. The notifying paediatric respondent was asked to approach the child's family to explain the study and seek consent. If the paediatric respondent thought it more appropriate, an alternative health professional aware of the mother's HIV infection, such as a genitourinary (GU) physician or general practitioner (GP), was contacted to do this.

Enrolment of children born between 1996 and 2000 commenced in April 2002 in 11 hospitals (seven in London, one each in Birmingham, Leicester, Oxford, Sheffield)

selected on the basis of the number of UK-born uninfected children reported to the NSHPC (>40% of all reports between 1996 and 2000 were from these 11 hospitals). From January 2003 the study was extended beyond the pilot phase to include all uninfected children born between January 2001 and April 2004 in the UK. Enrolment ceased in June 2005 and data collection in August 2005.

A study information sheet was provided for health professionals and families. Prospectively collected surveillance data, including demographic and perinatal details and information on ART exposure and laboratory investigations was available through the NSHPC. Health professionals completed a short annual CHART questionnaire for each enrolled child, in consultation with parents or carers. This questionnaire was designed to identify children with serious health or developmental problems: data collected included height and weight, perceived problems with movement, speech, hearing, sight or behaviour, and details of hospital admissions, specialist referrals or ongoing medication. We worked closely with the health professionals and they provided feedback on the process of study enrolment, follow-up, and the difficulties they encountered.

Data were managed using Microsoft Access 2002 and analysed using SAS (version 9.1, SAS Institute, Cary, NC, USA). Univariable comparisons were tested with χ^2 tests and *t* tests.

Both the NSHPC and CHART were approved by the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee at

commencement, and subsequently by the London Multi-centre Research Ethics Committee in 2004 (MREC/04/2/009 and 04/MRE02/47 respectively).

Results

Enrolment in CHART

The 2104 eligible children were reported from 168 hospitals. By the end of the study period 33.5% (704/2104) of children had been enrolled (Figure 1). Of those enrolled, 23.6% (166/704) were subsequently lost to follow-up during the study period and the parents of another 1.8% (13/704) withdrew from the study.

[insert Figure 1]

Parents of 4.8% (100/2104) of eligible children declined enrolment because of concerns about confidentiality, difficulty in accepting their own HIV diagnosis, or the inconvenience of participating. Another 2.8% (59/2104) of children had left the UK and two children had died: one with congenital tuberculosis and one sudden infant death (drug withdrawal symptoms at birth, exposed to zidovudine *in utero*). Two percent (44/2104) were excluded because health professionals considered it inappropriate to contact the family (for example because the mother had died, or because of conflict within the family) or could not identify the child from the available information. A further 21.6% (455/2104) were lost to follow-up because the family had moved or no longer attended the clinic, and health professionals were still trying to contact the families of 11.1% (233/2104) when the study ended. Seven paediatric respondents, responsible for 10.9% (230/2104) of eligible children, declined to participate in the study, mainly citing lack of clinic resources. The paediatric contacts who had notified the remaining 13.2% (277/2104) of children made no response, despite reminders.

Families were generally approached about CHART when the child attended clinic for their confirmatory negative antibody test at 12 to 18 months of age. In some cases the approach was by telephone, home visit or letter.

In feedback some health professionals reported that they needed to offer more clinic appointments or spend more time with parents discussing ART exposure because of CHART. Patient loss to follow-up and a lack of resources were frequently mentioned as factors that made involvement in the study difficult; a selection of health professionals' comments is shown in Table 1.

[insert Table 1]

Characteristics of children eligible for CHART

Of the eligible children, 75.7% (1566/2069) had mothers born in sub-Saharan Africa and 17.3% (358/2069) in Europe (Table 2). Injecting drug use was the probable HIV risk factor for the mothers of 2.7% (53/1998) of children, while 85.7% (1713/1998) probably acquired infection in countries with generalised HIV epidemics. Median maternal age at delivery was 30 years (range 15-53). Altogether 95.0% (1981/2085) of children were exposed to ART *in utero*, 74.4% (1473/1981) of these to highly active antiretroviral therapy (HAART).

Enrolled and non-enrolled children were similar in terms of maternal region of birth (χ^2=1.89, p=0.389), maternal HIV risk factor (χ^2=2.79, p=0.248) and *in utero* ART exposure (χ^2=8.70, p=0.069) (Table 2). Enrolled children were born to slightly older

mothers (mean maternal age 30.5 vs 29.5 years, t=-3.79, p<0.001). Congenital abnormalities were reported in 3.0% (63/2104) of eligible children and there was no significant difference in prevalence between enrolled (3.3%, 23/704) and non-enrolled children (2.9%, 40/1400) (χ^2=0.27, p=0.603). Information on gestational age was available for 1661 infants, of whom 16.6% (275/1661) were born prematurely (<37 weeks gestation); the prematurity rate did not differ by enrolment status (χ^2=0.58, p=0.448). Median age at last reported contact for non-enrolled children (reported on NSHPC paediatric forms) was 6 months (range 1-45), and for enrolled children, median age at last contact in CHART was 24 months (range 5-106).

[insert Table 2]

Enrolled children

Of the 704 enrolled children, 76.7% (540/704) had one CHART questionnaire completed, 21.0% (148/704) two and 2.3% (16/704) three. Most of the 884 questionnaires were completed by paediatric nurses (58.1%, 514/884) or paediatricians (34.3%, 303/884) and the remainder by GU physicians, GU nurses, GPs or midwives. Three-quarters were completed in clinic (76.1%, 673/884) and in most cases the child was present (82.0%, 552/673).

No health or developmental problems were reported for 37.5% (264/704) of children. Childhood infections and other common conditions were reported for 57.1% (402/704); these included chest infections and colds (201), gastroenteritis (28), wheezing/asthma, eczema or other allergies (93), speech problems or speech delay (50) and other minor

developmental or behavioural problems (63). Some children had more than one minor condition reported.

Febrile seizures were reported in 1.6% (11/704) of children and a variety of other significant health problems or conditions (details shown in Table 3) in another 3.8% (27/704). Seventy-four percent (28/38) of these children were exposed to HAART *in utero*, similar to the exposure rate in all enrolled children (72.0%, 503/704). Altogether, 60 (8.5%) of the 704 enrolled children were reported to have been admitted to hospital on at least one occasion.

[insert Table 3]

Discussion

Despite substantial input from paediatricians, clinical nurse specialists and other health professionals looking after HIV-affected families, we experienced considerable difficulty enrolling and retaining children in this study. Only a third of about 2100 eligible children were enrolled, of whom about a quarter were subsequently lost to follow-up within the three-year study period. Because we had no direct contact with families we relied on local clinic staff, but in many cases they had lost touch with families, lacked the time and resources to participate fully in the study, or because of staff turnover were unfamiliar with the families and reluctant to make contact.

Similar difficulties in recruiting HIV-exposed uninfected children have been reported from the Perinatal AIDS Collaborative Transmission Study – HIV Follow-up Of Perinatally Exposed Children (PACTS-HOPE). In this US study only 22% (180/819) of eligible uninfected children were recruited over a two-year period, despite direct contact with families and relatively low turn over of health care staff (Freedman et al., 2006). Comparable attrition rates to those experienced in CHART were reported from the Pediatric AIDS Clinical Trials Group (PACTG) 219 study, a long-term observational study of children enrolled in the 076 trial, where about 10% were lost to follow-up each year (Culnane et al., 1999).

The number of uninfected ART-exposed infants born each year substantially increased over the study period due to the increasing prevalence of HIV infection in pregnant women from 2000 onwards (The UK Collaborative Group for HIV and STI Surveillance, 2007) together with the successful implementation of routine antenatal

HIV testing and high uptake of interventions, including ART (Townsend et al., 2006b). Early in the HIV epidemic, most affected families in the UK lived in or close to London, but this situation has changed in recent years with the proportion of pregnancies reported to the NSHPC from outside London increasing from 13% in 1997/9 to 43% in 2004/6 (Townsend et al., 2008b). Consequently there has been an increase both in the number of HIV-exposed uninfected children reported per unit, and the number of units reporting cases over time. Many out-of-London units caring for eligible children had no nominated paediatric HIV staff or integrated "family clinic" (Sharland et al., 2003). This is likely to have contributed to the lower rates of enrolment when the study was extended from the initial 11 units (births 1996-2000) to include all UK births (2001-2004); lack of clinic resources was a common problem cited by respondents (see Table 1).

Since confirmatory tests to exclude HIV infection can now be carried out within three months of birth (in the absence of a continuing risk through breastfeeding) (Hawkins et al., 2005), families do not necessarily have an incentive to continue contact with the paediatric clinic. Paediatric respondents not in continuing contact with families were understandably cautious about approaching GPs and health visitors, in case they were not aware of the family's HIV status.

Our ability to draw conclusions from this study about the safety or otherwise of ART exposure is limited. While it was reassuring that enrolled and non-enrolled children were similar in terms of their baseline demographic characteristics and ART exposure, numbers were small and the follow-up period was short. It was not possible to identify

and enrol an appropriate control group with comparable ethnic make-up and maternal chronic disease levels within the scope of this study. Unexposed infants born to diagnosed women were not a suitable control group since diagnosed women who do not take ART antenatally are likely to differ systematically from those who do (for example, having declined treatment, been diagnosed very close to delivery, or delivered very prematurely) (Townsend et al., 2007). In fact only 5% of eligible children, and only 3% of the enrolled group, were not exposed antenatally.

In the absence of a formal control group we compared reported health outcomes in the enrolled children with those of the UK Millennium Cohort Study (MCS), a cohort study of approximately 18,800 babies born in 2000 and 2001, in which children from disadvantaged and ethnic wards were over-sampled. MCS parents reported prevalence rates for chest infections (29%), wheezing or asthma (6%) and hospitalisation (13-15%) among infants by nine months of age (Dezateux et al., 2005); these compare with reported prevalence rates in CHART of 29%, 7% and 9% respectively at a median age of 24 months. In the population of HIV-exposed children born in the UK and Ireland, no association has been detected between ART exposure and congenital abnormalities (Townsend et al., 2006a); the reported prevalence of congenital abnormalities in the CHART children was within UK population parameters of 2-3% for major abnormalities (Boyd et al., 2005), as was that of febrile seizures.

Earlier routine enrolment of families into follow-up could have eased some of the problems encountered in this study; however, the overall increasing number of uninfected children, lack of staff resources, parental concerns about confidentiality, and

the continuing attrition of enrolled children because of family mobility were also substantial barriers to recruitment and retention. Issues of confidentiality and lack of staff resources were also raised in a survey of parents' and health professionals' views on the acceptability of different ways to monitor ART-exposed children over the longer term (Hankin et al., 2007a). Our experience indicates that consented opportunistic clinic-based follow-up is not a practical approach for monitoring ART-exposed uninfected children in the UK over the long term, and alternative strategies need to be developed. Paediatric reports to the NSHPC are now linked to routine cancer and death data collected by the Office for National Statistics for long term monitoring; although this approach is limited to specific outcomes, it demonstrates the feasibility and potential of data linkage (Hankin et al., 2007b).

HIV-infected pregnant women are taking increasingly complex drug regimens at all stages of pregnancy, including at conception, and the number of exposed uninfected children is rising rapidly. A robust, secure data linkage protocol for monitoring their long-term health must be developed within an appropriate ethical framework which acknowledges that they might not be aware, as adults, of their exposure. Concerns about consent, confidentiality and disclosure of maternal HIV status to health professionals and the uninfected child must be considered alongside potential longer term benefits. If unexpected late onset adverse outcomes were identified, for example in relation to growth, aging or reproduction, this could guide changes in HIV treatment guidelines, or inform screening or treatment of ART-exposed individuals. Similar situations have occurred in the past, for example with prenatal exposure to diethylstilboestrol (Royal College of Obstetricians and Gynaecologists, 2007; Troisi et al., 2007). Such a protocol

could potentially be extended or adapted to cover other sensitive prenatal or perinatal exposures, for example assisted reproduction, treatment for ambiguous genitalia, or other drug treatments.

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Competing Interests

Claire Hankin was a research fellow at UCL ICH when this work was carried out. She is currently working for Bristol-Myers Squibb, Global Epidemiology and Outcomes Research, Braine-l'Alleud, Belgium.

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