

Pregnancy-related changes in the longer-term management of HIV-infected women in Europe

European Collaborative Study^{*,1}

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Abstract

Objectives: To clarify policies regarding management of HIV-infected women, relating to pregnancy, in view of current European consensus guidelines. **Study design:** Postal questionnaire survey in 36 hospitals in 11 European countries. **Results:** Responses were received from 22 (61%) centres, representing all 11 countries. In principle, antiretroviral therapy (ART) would be reviewed in treated women wanting to become pregnant in nearly all centres. Multidisciplinary management of infected pregnant women was routine in 17 (77%) centres, facilitating continuity of care. Approximately half the clinicians would use zidovudine monotherapy for pregnant women without indications for ART, while the remainder prescribed combination therapy. In 1998–2000, pre-eclampsia was the most prominent adverse event (22 centres) in women receiving ART, with congenital abnormalities (13 abnormalities in 6 centres) and stillbirth (5 centres) also reported. **Conclusions:** Policies varied, particularly regarding prophylactic ART for women without indications for treatment and did not always follow current European guidelines.

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1. Introduction

With widespread use of highly active antiretroviral therapy (HAART) to delay disease progression, HIV infection has become a chronic, manageable disease in developed country settings [1,2]. In western Europe, heterosexually acquired infections increased by nearly 50% between 1995 and 2000 [3] and this, combined with improved survival, has resulted in an increasing number of women living with HIV. In the UK, HIV prevalence in pregnant women in 2000 was 1 out of 350 in London (that is, approximately 300 infected women delivered in London in 2000), 0.03% in the rest of England and 0.05% in Scotland [4], and is the highest observed since unlinked anonymous seroprevalence monitoring began.

It has been suggested that HIV-infected women in Europe are now more likely to want to become pregnant, which may be both due to the low rates of vertical transmission achievable [5–7] and improved prognosis [1,2]. Indeed, an increasing number of infected women are becoming pregnant whilst taking potent antiretroviral combinations [5,8,9].

Considerable uncertainties remain regarding the safety of antiretrovirals and prophylactic drugs in pregnancy, both for the woman herself and the developing fetus. Little is known about how clinicians respond to these uncertainties and how the possibility of pregnancy affects the management of infected women. Previously, considerable variation in clinical practice across Europe has been documented [10,11].

We present the results of a survey which aimed to explore the management of HIV-infected women before pregnancy until after delivery in a variety of health care settings and to compare practices and policies with current European consensus guidelines [12]. We wanted to gain an understanding of the “management infrastructure”, in particular, to clarify how management of infected pregnant women, or those who wish to become pregnant, is shared between the appropriate specialists. This survey also provided a first impression of the extent and type of adverse events possibly related to ART experienced in this population in the ante- and peri-natal periods.

2. Methods

A postal questionnaire was sent to one or more named clinicians (obstetrician and/or infectious diseases specialist)

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in 36 centres in 11 European countries. The clinicians were selected as working in areas of relatively high prevalence of HIV infection in women [13], usually in reference centres with a substantial number of HIV-infected pregnant women on their case-load. They were identified through their involvement in HIV research, including the European Collaborative Study, the Swiss mother + child HIV cohort study, the French cohorts and the European arm of the PACTG 316 [5,6,8].

The questionnaire was semi-structured and focused on policies and practices regarding the organisation of care (obstetric and HIV-related) for HIV-infected women of child-bearing ages and the possible pregnancy-related changes, in addition to general information on the clinic setting. The clinicians were also asked whether they had seen any adverse events in pregnant HIV-infected women and their children in the previous three years, within specific categories (obstetric complications, congenital abnormalities, maternal death, neonatal complications) with details requested if appropriate. Questionnaires were sent out in June 2001, with reminders in the autumn 2001. Data management and descriptive analyses were carried out in MS Access.

3. Results

Responses were received from at least one centre in all 11 countries approached. Questionnaires were returned from 22 (61%) centres in Italy (3/6), Spain (2/6), Germany (1/3), the UK (4/4), France (5/7), Poland (1/1), Switzerland (2/4), Belgium (1/1), Denmark (1/1), Sweden (1/1) and The Netherlands (1/2). From the 22 centres, 11 questionnaires were completed by the obstetrician, 7 by the infectious diseases/genitourinary medicine specialist and 4 jointly by the obstetrician and infectious diseases specialist. In the countries with only one response, this was from the centre with the foremost experience. In the 22 centres, there were between 2 and 40 deliveries to identified HIV-infected women in 2000,

with a mean of 16.9 (± 10.6). The number of HIV-infected women giving birth had increased between 1998 and 2000 in 17/20 (85%) centres, and had more than doubled during this time in 10 of these 17 centres; of the remaining 3 centres the number of deliveries had decreased slightly in 2 centres and remained constant in 1. A total of 20 infected infants had been born to 809 women identified as HIV-infected before or at delivery between 1998 and 2000 in the 21 centres with this information available, including 6 infected children out of a total of 338 born in 2000 of whom 2 were born to women who presented for the first time at delivery.

3.1. Before pregnancy

In principle, non-pregnant HIV-infected women in infectious diseases/HIV clinics would be asked about their child-bearing plans by their infectious diseases specialist in two-thirds of centres (Fig. 1). Although such plans would usually be discussed at regular intervals or at any treatment change, in 36% (5/14) centres there was just a one-off discussion at the initial referral to the clinic. There was near unanimous agreement among the responding clinicians that it was now more likely for an HIV-infected woman to plan a pregnancy than in the past (Fig. 1). The main reasons mentioned were the improved clinical prognosis for the woman with the use of HAART (13 responses) and/or the very low rates of vertical transmission achievable with current interventions (12 responses). If a woman indicated contemplating a pregnancy she would be referred to an obstetrician as soon as possible in most (16, 73%) centres, while in 4 (18%) centres such a referral would only routinely take place once she had become pregnant (2 centres, no response). Infertility problems in HIV-infected women were mentioned by 17 (81%) respondents.

If a woman told her physician that she was trying to become pregnant, clinicians would review her antiretroviral therapy (ART) to avoid potentially teratogenic drugs or those associated with an adverse pregnancy outcome (Fig. 1).

Are childbearing plans routinely discussed with non-pregnant infected women in follow-up at the ID clinic?

Has it become more likely than in the past that an HIV-infected woman plans a pregnancy?

If an HIV-infected woman in follow-up says she is trying to become pregnant, would this impact on her therapeutic management?

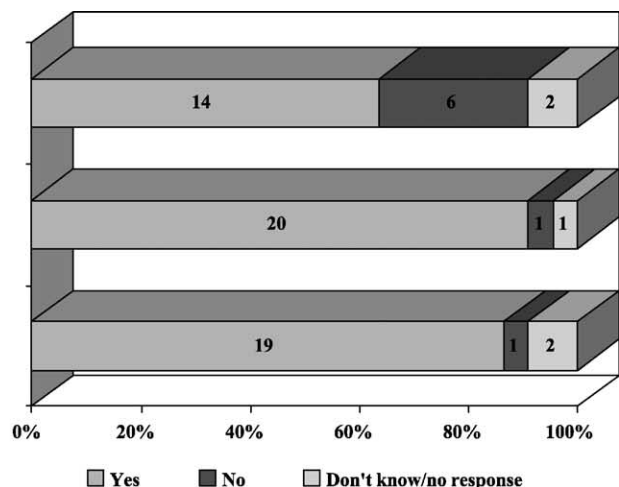


Fig. 1. Child-bearing plans.

Nine clinicians specified antiretroviral agents or combinations they would avoid in pregnancy or in women planning a pregnancy: efavirenz (9 centres), ddC (3 centres), ddi + d4t (1 centre) and indinavir (1 centre). Three (14%) respondents reported that they would consider cessation of all ART for the first trimester of pregnancy.

3.2. Pregnancy

In 20 (91%) centres there was a policy to test all pregnant women for HIV, while in the remaining two (in Poland and Switzerland) there was no policy in place. For women identified as HIV infected for the first time in pregnancy, post-test counselling was usually provided by the obstetrician and/or the infectious diseases specialist, sometimes with additional support from the midwives; in only one centre a counsellor or specialist HIV nurse had the main responsibility for post-test counselling. Sixteen of the 20 centres with universal testing policies provided statistics which showed that on average 40% of 251 infected women having live births in 2000 had been first identified as infected through antenatal screening during the current pregnancy (range 20–92%).

In 17 (77%) centres there was a shared, multidisciplinary approach to the management of pregnant HIV-infected women, regardless of when the woman was identified as infected. The multidisciplinary team usually consisted of obstetricians, infectious diseases/genitourinary medicine specialists and paediatricians with some teams also including HIV counsellors (two centres), HIV health advisors (1), specialist midwives (4), health visitors (1), social workers (7) and psychologists (3). Management of the HIV-infected caseload was usually facilitated by regular meetings, held weekly to monthly depending on the caseload. In four of the five centres without a multidisciplinary approach, infected pregnant women were primarily managed by the infectious diseases specialist, with involvement of the obstetrician only for routine obstetric aspects, and in the remaining centre, the overall management of infected pregnant women (including initiation and modification of ART, monitoring of infection) was in the hands of the obstetrician, who had a special interest and expertise in HIV management.

3.3. Antiretroviral therapy in pregnancy

In 19 (86%) centres there was a preferred initial regimen for pregnant women starting on ART for the first time to prevent vertical transmission (i.e. with no indications for ART for their own health): approximately half the centres used the PACTG 076 zidovudine regimen [14], and half prescribed triple therapy regimens (Table 1). There was no difference between these two groups in terms of caseload (mean: 15.3 deliveries in 2000 versus 15.9). There was a preferred initial therapy for previously untreated pregnant women with clinical, immunological or virological indications for ART in nine centres: all specified regimens included

Table 1

Preferred initial antiretroviral regimen for pregnant HIV-infected women with no indications for treatment for their own health (19 centres)

	Centres (n)
Monotherapy with zidovudine	
From 14 weeks	1
From 26 to 32 weeks	7
Double therapy	
ZDV from 14 weeks + nevirapine	1
ZDV + 3TC from 14 weeks	1
Triple therapy	
ZDV + 3TC + PI from 14 to 20 weeks	3
ZDV + 3TC + PI from 28 to 32 weeks	2
ZDV + 3TC + PI, timing not specified	1
Unspecified triple combination from 28 weeks	1
ZDV + 3TC + nevirapine, timing not specified	1
ZDV + 3TC + nevirapine from 36 weeks	1

two nucleoside analogues (ZDV in all nine centres, with 3TC in eight and ddi in one centre) and either nevirapine (three centres) or nelfinavir (six centres). In the remaining 13 centres, decisions regarding initial ART regimen for untreated pregnant women with signs of disease progression would be made on an individual basis.

For women already on ART prior to pregnancy, some modifications to their therapy (mainly to avoid certain potentially dangerous agents) may be made before conception if the pregnancy was planned and they had informed their physician. Regarding changes to therapy during pregnancy in women treated from before pregnancy, decisions were made by the multidisciplinary team in 17 (77%) centres, by the infectious diseases specialist in 4 centres and the obstetrician in 1 centre. Respondents specified participation of the infected woman herself in decisions relating to ART in 9 (41%) centres.

3.4. Mode of delivery

The planned mode of delivery was largely a multidisciplinary decision, although decided solely by the obstetrician in nine (41%) centres. Fourteen respondents indicated specifically that the woman herself would be involved in deciding mode of delivery; in the remaining seven centres the woman was not reported to participate in such decisions. An increasing rate of premature deliveries to infected treated women had resulted in bringing forward the scheduled timing of elective caesarean sections from 38 to 37 weeks gestation in three centres.

3.5. Post-natal management

Continuity of care post-partum was ensured in most centres (17, 77%) by the multi-disciplinary approach taken during pregnancy. Three centres (all in the UK) had family clinics for the follow-up of infected women and their infants. ART was stopped routinely after delivery as a matter of

Table 2

Clinicians reporting adverse events in HIV-infected pregnant women and their infants, 1998–2000

	Number (%) of centres
Obstetric complications	
Stillbirth	5 (22)
Gestational diabetes	7 (32)
Pre-eclampsia	5 (22)
Eclampsia	1 (4)
HELLP ^a syndrome	2 (9)
Congenital abnormalities	6 (26)
Neonatal death	1 (4)
Maternal death	1 (4)

^a Haemolysis, elevated liver enzymes, low platelets.

policy for women without indications for treatment in 11 (50%) centres and decisions regarding continuation of ART for such women were made on an individual basis by the infectious diseases specialist in 10 (45%) centres and by the obstetrician in 1 centre. For women continuing with ART after delivery, extra support with adherence was provided in the post-natal period in eight (36%) centres (for example more frequent follow-up appointments, written information, counselling from adherence nurses).

As with maternal ART, decisions regarding type and duration of neonatal prophylaxis were usually made by the multidisciplinary team (in 17 (77%) centres), but were made by the paediatrician alone in the remaining five centres. A wide range of health care professionals provided support in pregnancy and post-partum regarding neonatal prophylaxis and avoidance of breastfeeding in different centres including obstetricians, paediatricians, neonatologists, infectious diseases specialists, paediatric specialist nurses, midwives, HIV counsellors and social workers.

3.6. Adverse events

Table 2 shows the range of obstetric and neonatal adverse events reported to have occurred in infected women and their infants in several centres in the period 1998–2000. Thirteen congenital abnormalities were reported from six centres (right hydronephrosis, exomphalos, digital anomalies, talipes equinovarus, hypospadias, cleft lip, ventricular septum defect [2], spina bifida/hydrocephalus, hemivertebrae, open foramen ovale, cryptorchidism, anomaly of external ear). Data on total deliveries in this time period were provided for all but two centres (including one of the six centres above, with two congenital abnormalities reported): the overall prevalence of congenital abnormalities was 1.42% (11/772) in these 19 centres.

4. Discussion

Although prevention of mother-to-child transmission of HIV is a success in developed country settings, with

vertical transmission rates of less than 2% reported [5–7], programmes need a coherent approach to include the identification and monitoring of infected women from before pregnancy, as well as antenatal and post-natal management. As many European centres only see a few pregnant-infected women annually, and given the rapidly changing field of HIV therapy, consensus expert guidelines are important in guiding practice at a local level. The recent European consensus on the management of pregnancy and HIV infection [12], stressed the need not only to offer, but to recommend, antenatal HIV testing as an integral component of antenatal care. The first step to effective prevention of mother-to-child transmission is identification of infected women and it is therefore surprising that two centres here lacked antenatal HIV screening policies.

Overall management of pregnant HIV-infected women, or those wishing to become pregnant, in the centres surveyed was predominantly multidisciplinary in approach. This allows for sharing of expertise so that the woman receives optimum care, regarding her own HIV disease, reducing vertical transmission risk and the pregnancy and delivery per se. Furthermore, the early involvement of paediatricians is important in discussing neonatal prophylaxis, avoidance of breastfeeding and the follow-up of the infant. The organisation of care for pregnant HIV-infected women here contrasts with that seen earlier in the epidemic, when only 17% of 54 obstetric centres surveyed in 1994 had multidisciplinary teams [11].

Increasing numbers of infected women are becoming pregnant whilst taking potent combinations of antiretroviral drugs [5,8,9]. European consensus guidelines [12] recommend that in such cases, women should continue with the same therapy unless there are problems of intolerance, or the drugs have teratogenic potential, such as efavirenz [15]. Most clinicians here reported that they would review and if necessary modify the ART of an infected woman trying to conceive. Three clinicians here indicated that they would consider discontinuation of HAART in the first trimester despite the lack of evidence about the risks and benefits of discontinuation. However, by the time most women realise they are pregnant and visit their physicians, the period of organogenesis is likely to be completed.

There was a lack of consensus among the clinicians surveyed regarding type of antiretroviral prophylaxis in women not requiring treatment for their own health. Use of HAART for women with low viral loads and no clinical or immunological indications for treatment is not evidence-based; in the European consensus guidelines [12], it is recommended that such women should be started on the three-part 076 zidovudine monotherapy regimen at 28–32 weeks, with an elective caesarean section at 38 weeks, unless they have a viral load above 10,000 copies/ml, in which case HAART should be considered from the second trimester. These recommendations reflect the desire to limit exposure of the fetus to multiple antiretroviral agents, to

avoid unnecessary treatment and to maximise future therapy options for the woman.

The need to involve women themselves in decisions regarding interventions to reduce vertical transmission, particularly elective caesarean section and ART, is highlighted in current guidelines and recommendations [12,16]. This is especially important for aspects of management where there remain uncertainties. However, fewer than half the respondents here reported routine participation of the women themselves in decisions regarding ART, with only a slightly higher proportion involved in mode of delivery decisions.

Little is known about ART adherence rates in pregnancy in non-trial populations, although it has been reported that women treated from before pregnancy have better adherence than those treated for the first time in pregnancy [17]. Good maternal adherence to neonatal prophylaxis is associated with her own adherence during pregnancy and the presence of an effective support network [18]. Although little specific post-natal support with adherence was provided here, the multidisciplinary management of infected women and their infants is likely to facilitate general support of mother and child, particularly in the initial period of uncertainty regarding the infection status of the infant.

Limited information is available regarding adverse events in pregnancy in HIV-infected women taking ART [8]. An objective of this survey was to obtain an impression of the extent and type of adverse events experienced in this population although the methods used precluded estimation of prevalence. Several clinicians here reported cases of HELLP syndrome and eclampsia. Recent cases of lactic acidosis in pregnant women receiving ddi + d4t-containing ART [19] indicate the need for clinicians to be aware that elevated liver enzymes and lactate levels, combined with clinical symptoms such as nausea, may actually be drug toxicity-related. The reports of congenital abnormalities here are consistent with results from a large European cohort study [5]. Recent reports of malformations in fetuses/infants of women receiving a combination of ART and PCP prophylaxis in the first trimester [9,20] require further investigation, and interruption of the use of folate antagonists in the first trimester is recommended [12].

Although there are limitations to the conclusions that can be drawn from this descriptive study in terms of generalisability, it is unlikely that the findings are strongly biased by non-response as questionnaires were received from at least one centre in all 11 countries surveyed. Our results support the view that, in the light of low rates of vertical transmission and the impact of HAART on quality and length of life, HIV-infected women in Europe are increasingly planning to have children and that access to assisted reproductive technologies for HIV-infected couples now needs further attention [21]. Within Europe there continues to be considerable variation in practice although the multidisciplinary approach, which seems most appropriate for this rapidly changing field, is increasingly being adopted.

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