British HIV Association guidelines for prescribing antiretroviral therapy in pregnancy (1998)

Graham P Taylor, E G Hermione Lyall, Danielle Mercey, Richard Smith, Tracey Chester, Marie-Louise Newell, Gareth Tudor-Williams

The aim of antiretroviral therapy in pregnancy is to deliver a healthy uninfected child to a healthy mother, without prejudicing the future treatment opportunities of the mother. The use of zidovudine monotherapy rapidly became standard practice once it had been shown to reduce by 67% mother to child transmission in women with CD4+ lymphocyte counts above 200 \times 10^6/l. High rates of transmission are seen when maternal disease is advanced (high viral load, low CD4+ lymphocyte counts) despite zidovudine. In these women highly active antiretroviral therapy gives the best prospect for prolonged health and it is anticipated that reducing plasma viral load below the limits of detection will further reduce transmission rates. However, safety data for antiretroviral therapy in pregnancy are limited and each additional treatment exposes a significant proportion of uninfected infants to potential long term hazards. Where maternal therapy is not indicated and the sole objective of treatment is to reduce mother to child transmission, recent data suggest that short course zidovudine (especially in conjunction with prelabour caesarean section) is a reasonable option. This may minimise the emergence of viruses with reduced sensitivity to zidovudine and preserve maternal options for later therapy.

**Introduction**

In inner London as many as one in 200 pregnant women are infected with HIV.\(^1\) Mother to child transmission of HIV can be reduced from 25% to less than 2% by avoidance of breastfeeding, appropriate management of the delivery, and by antiretroviral therapy. Therapy in non-pregnant adults (and children) is advancing rapidly with 14 compounds accessible in the United Kingdom. The current consensus is that therapy should be initiated with three compounds, usually two nucleoside analogues (NARTI) and a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI), to delay treatment failure.\(^2,3\) Treatment of a non-pregnant woman with monotherapy would be deemed poor medical practice. Conversely, the most significant advance in the prevention of mother to child transmission has been zidovudine monotherapy which reduces the number of infected infants by 67%,\(^4\) and remains the only treatment for which substantial safety data in pregnancy exist.\(^5\)

In this paper we summarise the available data and attempt to balance the therapeutic needs of the mother and the possibility of reducing mother to child transmission with the considerations for the fetus and infant. Antenatal screening, breast feeding, mode of delivery, prolonged rupture of membranes, and vaginal cleansing are not discussed.

**Safety data**

None of the currently available antiretroviral agents has been shown to be safe during the first trimester of pregnancy in humans, and women of child bearing age prescribed these drugs should be clearly informed of this lack of safety data. The FDA classification and animal carcinogenicity and teratogenicity studies are summarised in table 1.

**ZIDOVUDINE**

Pharmacokinetic studies indicate that no dose adjustment of zidovudine is required in pregnancy, that zidovudine crosses the placenta reaching therapeutic levels in the cord blood and is present in breast milk.\(^6\) In the AIDS Clinical Trials Group (ACTG) Protocol 076 study zidovudine was well tolerated by mothers and infants.\(^6\) Although children exposed to zidovudine were more likely to be anaemic than those on placebo the anaemia was mild and resolved without treatment following completion of the regimen. Bone marrow toxicity did not cause problems in the mothers. A similar lack of toxicity was found in the PACTG 185 study comparing zidovudine plus intravenous HIV specific IgG with zidovudine and human immunoglobulin even though more mothers had advanced HIV disease than in the ACTG 076 study.\(^7\) No maternal or infant toxicity has been seen with short duration zidovudine monotherapy in HIV infected women in west Africa\(^8\) or in Thailand.\(^9\) To date no long term sequelae have been found in zidovudine exposed children from the ACTG 076 study who are being followed to age 21 years, in the PACTG 219 study.\(^10\) Outside these studies no increase in congenital abnormalities has been observed in a further 300 children exposed to zidovudine during pregnancy including 89 children exposed during the first trimester.\(^5\)

In carcinogenicity studies mice exposed to high dose zidovudine in utero and for a prolonged postnatal period (but not if only exposed in utero) developed vaginal tumours.
in late adult life. In mice, but not in humans, zidovudine is predominantly excreted unmetabolised in urine. Reflux of urine into the vagina is common in mice and the tumours may be a consequence of chronic chemical irritation. An increased incidence of solid tissue tumours has also been reported in adult CD-1 mice exposed to high dose zidovudine in utero. Whether this is relevant for humans will have to be determined by long term studies and by linking registers of perinatal antiretroviral exposure to death and cancer registries.

**LAMIVUDINE**

Lamivudine is well tolerated in non-pregnant adults and children and has been extensively used with zidovudine in dual and triple therapy. In a South African study zidovudine (250 mg twice daily) was compared with lamivudine (300 mg twice daily) and with the two combined (zidovudine 250 mg twice daily, lamivudine 150 mg twice daily). Late pregnancy (therapy was initiated at week 38) did not significantly alter the handling of lamivudine, alone or in combination with zidovudine. In the neonates, clearance was slower than in older children and the recommended dose has been halved to 4 mg/kg/day. No toxicity was reported in the 20 mothers and children. Lamivudine crossed the placenta efficiently and was excreted in breast milk. In a retrospective study in Houston, 16 mothers were prescribed zidovudine with lamivudine during pregnancy from a mean of 18 (SD 7.8) weeks’ gestation with no side effects. Of the seven infants born at the time of review one developed anaemia, but did not require transfusion.

**DIDANOSINE**

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Nevirapine’s long half life (45 hours following a single dose in adults) is even longer in pregnant women (66 hours) and nevirapine crosses the placenta efficiently. A single dose of nevirapine administered to eight mothers during labour with an additional single dose given to the infant at 48–72 hours resulted in blood levels in the neonate which remained above the IC₅₀ for 7 days.⁷⁷ No adverse events were reported, but numbers are small and there are no data from use earlier in pregnancy. A severe skin rash is the most commonly recognised side effect of nevirapine and liver function tests may become abnormal. In a retrospective study in London no side effects were seen in nine children exposed to nevirapine during the second and third trimesters of pregnancy.⁴⁸ An international multicentre study, including European centres, is under way to evaluate whether the addition of nevirapine to existing therapy will further reduce the risk of mother to child transmission (PACTG 316).

**DELAVIRIDINE**

Delavirdine is generally well tolerated with rash and abnormal liver function tests the most common side effects. Thrice daily dosing and high tablet count (12/day) are disadvantages. It is licensed in the United States and available through an expanded access programme in the United Kingdom. There are no data from pregnant women.

**EFAVIRENZ**

Efavirenz (DMP266) is available through an expanded access programme but women must not be pregnant and must agree to use barrier and non-barrier methods of contraception. Although rodent studies had been normal teratogenicity was noted in cynomolgus monkeys, with severe defects (anencephaly and microphthalmia) in 3/13 fetuses (Dupont, communication to investigators, 1998).

**PROTEASE INHIBITORS**

Protease inhibitors (PIs) have become an integral part of combination therapy in adults and children. Recruitment to studies of pregnant women in the United States were temporarily halted following the observation of increased premature labour in women receiving combination therapy which included PIs.⁴⁹ These studies have resumed with more stringent entry criteria which exclude women with advanced HIV disease or a history of preterm deliveries.

**SAQUINAVIR**

Saquinavir has been the best tolerated of the PIs but only 4% of the dose of hard gel capsules is bioavailable in healthy volunteers. Bioavailability has improved with the new soft gel formulation but the recommended dose has also been increased from 600 mg to 1200 mg three times daily (18 capsules per day). A Thailand/UK pharmacokinetics study of zidovudine, lamivudine, and soft gel saquinavir is under way.

**RITONAVIR**

Ritonavir is more poorly tolerated, with perioral paraesthesia, nausea, vomiting, and diarrhoea, and as patients often require long term antiemetic and anti diarrhoeal therapy ritonavir may not be preferred in pregnancy. Recruitment to an ACTG pharmacokinetics study of ritonavir in pregnancy has started.

**INDINAVIR**

Indinavir is associated with new onset diabetes and a worsening of established diabetes and may therefore compound gestational hyperglycaemia. Hypercholesterolaemia and hypertriglyceridaemia occur within weeks of therapy, while changes in body fat distribution, particularly breast enlargement, may cause distress in some women. Elevated liver enzymes are common and hyperbilirubinaemia although conjugated may compound neonatal jaundice. Haemolytic anaemia has also been reported while crystallisation of indinavir in the renal tract precipitates renal stones which could damage the immature renal system. In the Swiss cohort one child exposed to indinavir, zidovudine, and lamivudine from the first trimester was born with biliary atresia,⁵⁰ a rare congenital malformation. A combination of indinavir, lamivudine, and zidovudine in pregnancy is being studied.

**NELFINAVIR**

Nelfinavir appears to be better tolerated than ritonavir and indinavir but diarrhoea is a common and troublesome side effect. The ACTG 353 study will determine the pharmacokinetics of nelfinavir in pregnant women.

**Antiretroviral therapy to prevent HIV mother to child transmission**

Only zidovudine has been shown to prevent mother to child transmission in controlled studies. The ACTG 076 study was stopped following an interim analysis of the first 363 evaluable infants which showed a 67% reduction in transmission from 25.5% to 8.3%.⁴ The zidovudine regimen is detailed in table 2. The majority of women were in good health, only 5% had received prior zidovudine therapy and all had a CD4+ lymphocyte count greater than 200 × 10⁹/l. The median CD4+ lymphocyte count at baseline was 550 × 10⁹/l and the median plasma viral load (measured by RT-PCR and bDNA assays) was 5700 HIV RNA copies per ml. In the final analysis of all 402 evaluable infants transmission rates were 22.6% in the placebo arm and 7.6% in the zidovudine arm.⁶ Following the publication of these results the use of zidovudine monotherapy by pregnant women aware of their HIV infection has risen from 22% to 89%.²¹–²⁴ with transmission rates falling from 19% to 8% and from 14% to 5% in New York/Puerto Rico²¹ and France²² respectively. Evidence from the PACTG 185, study in which the women had a median baseline CD4+ lymphocyte count of 306 × 10⁹/l, a median viral load of 18 500 HIV RNA copies per ml plasma, and 21% had previously taken zidovudine for extended periods suggests that zidovudine is also effective in women with more advanced disease.⁷ This study of passive immunotherapy was terminated early because the overall transmission
This dose regimen has not yet been confirmed in pregnancy by pharmacokinetic studies.

†Continue until the cord clamped.

*Start as early as possible in established labour and at least 1 hour before elective caesarean section.

<table>
<thead>
<tr>
<th>Table 2 Recommended doses of antiretroviral therapy during pregnancy</th>
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<tbody>
<tr>
<td>ACTG 076*</td>
</tr>
<tr>
<td><strong>Zidovudine</strong></td>
</tr>
<tr>
<td>Maternal dose during 2nd and 3rd trimesters</td>
</tr>
<tr>
<td>Intrapartum</td>
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<tr>
<td>Maintenance dose</td>
</tr>
<tr>
<td>Neonatal dose</td>
</tr>
<tr>
<td>Lamivudine</td>
</tr>
<tr>
<td>Preparum weeks 38–40</td>
</tr>
<tr>
<td>At onset of labour</td>
</tr>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Preparum</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intrapartum</td>
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<td></td>
</tr>
<tr>
<td>Nevirapine</td>
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<tr>
<td>At onset of labour</td>
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<tr>
<td>Neonatal</td>
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<tr>
<td>During 2nd and 3rd trimesters</td>
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</table>

*Start as early as possible in established labour and at least 1 hour before elective caesarean section.
†Continue until the cord clamped.
‡This dose regimen has not yet been confirmed in pregnancy by pharmacokinetic studies.

rate was only 4.8% and a much larger study would be necessary to demonstrate any benefit of anti-HIV IgG. It is not possible to comment on the efficacy of lamivudine, didanosine, or nevirapine in preventing mother to child transmission from the aforementioned studies.

Although short duration improvement was seen with zidovudine monotherapy in patients with advanced AIDS, zidovudine alone does not prolong survival in asymptomatic subjects. Viral load is reduced by approximately 0.5 log₁₀ RNA copies per ml following which HIV-1 quasispecies with mutations which confer reduced sensitivity to zidovudine are selected and viral load returns to baseline after approximately 6 months of therapy. In the ACTG 076 study the median viral load reduction from baseline at the time of delivery was only 0.24 log₁₀ copies per ml but zidovudine was effective at all levels of viral load and it is unlikely that viral load reduction alone is responsible. Similar benefits of zidovudine have been noted with prophylaxis following occupational exposure; transmission is reduced from 0.3% to 0.1%. It is not known whether other therapies would have this prophylactic effect.

Some light on the contribution of the prepartum, intrapartum, and postpartum components of the 076 regimen has been shed by two recent publications. In an observational study from New York State transmission rates were 28.8% in mother-infant pairs who did not receive zidovudine, 5.2% in those who started zidovudine antepartum, and 9.2% among 87 infants where zidovudine was only commenced during delivery or the neonatal period. Starting zidovudine more than 48 hours after delivery did not offer any protection. In Thailand, zidovudine 300 mg twice daily from the 36th week of gestation and every 3 hours by mouth during labour has been compared with placebo. All women were provided with formula feeds and advised not to breast feed but there was no neonatal component. There were 17/193 (9.2%) transmissions to the children exposed to zidovudine compared with 35/198 (18.6%) in the placebo arm, a 51% reduction. The median CD4+ lymphocyte count in the mothers at baseline was 428 and 410 respectively. The smaller effect found in Thailand (compared with the ACTG 076 study) may have been due to the omission of the neonatal component, the deferred start of prepartum component, differences between the cohort, or obstetric factors. These data suggest that zidovudine should be offered to all mothers and their infants however late in pregnancy they present.

**Maternal viraemia and mother to child transmission**

Many maternal factors have been associated with an increased risk of mother to child transmission including more advanced disease, lower CD4 counts, and higher viral loads, all of which are closely related. A meta-analysis of nine studies of transmission based on 1115 mother-infant pairs describes the relation between viral load and transmission. In the absence of zidovudine viral loads ≥10 000 copies per ml were associated with 37% transmission loads of 1000–9999 with 15%. While zidovudine was associated with a 50% reduction in transmission both above and below 10 000 copies per ml, the scope for further improvement especially in those mothers with higher viral loads is clear. In Europe, Mayaux et al found that viral loads of 1000 copies per ml were associated with 2% transmission while 40% of babies are infected if the maternal viral load is >100 000 copies per ml. Although viral load is more predictive, stratification by CD4 lymphocyte count produces similar results. In the PACTG 185 study, the risk of transmission with zidovudine therapy was 3.3% if maternal CD4 lymphocyte count was >200 ×10⁹/l compared with 9.5% if the count was <200 ×10⁹/l. It is anticipated that regimens which reduce plasma viraemia to below 500 copies per ml will substantially reduce the risk of transmission. However, transmissions have occurred when plasma viraemia was undetectable (less than 1000 to less than 200 copies/ml), perhaps because viral load in genital tract secretions can differ from that in plasma. As many women with HIV in the United Kingdom have non-B HIV genotypes, which may give falsely low or undetectable results in viral load assays we recommend using two assays, which utilise different nucleotide sequences to bind or amplify the target.

Viral load reduction in pregnancy with lamivudine 300 mg twice daily alone or lamivudine 150 mg twice daily plus zidovudine 250 mg twice daily appears to be the same as in non-pregnant adults, about 1.5 log₁₀. In the South African study, lamivudine and/or zidovudine were given only from the 38th week of pregnancy so the duration of response was not determined. However, in a small study in Lon-
don, where women with more advanced HIV disease (CD4 count <200 \times 10^3/ml or viral load >30 000 HIV RNA copies per ml plasma) were treated with zidovudine and lamivudine from the start of the second trimester, a 1.5 log10 reduction in viral load was observed at the time of delivery, after a mean of 17.6 weeks on therapy. Although no transmissions occurred the M184V mutation in the RT gene which denotes reduced lamivudine sensitivity was detected in plasma from four of five mothers at or before delivery. The rapid appearance of M184V is well recognised in non-pregnant populations.

Maternal considerations

It has become clear from the Multicenter AIDS Cohort Study that plasma viral load is the single most useful prognostic marker in HIV-1 infected men. In this cohort, for people with a baseline CD4+ cell count of <350 \times 10^3/ml the probability of progressing to an AIDS defining illness within 9 years of the baseline blood sample was 95.6% if the plasma viral load was >30 000 copies per ml (as measured by bDNA testing) but about 30%, if the viral load was <3000 copies per ml.

Limited viral load reduction is seen with zidovudine monotherapy (<0.5 log10); a more sustained 1.5 log10 reduction with two NARTIs while viral load reductions in the order of 2.5 log10 are routinely observed with triple combinations. The duration of response is also much longer (but may not be indefinite) and the majority of patients can anticipate a reduction in viral load to below 500 copies per ml. Significant clinical benefit with combination NARTI therapy compared with monotherapy and a good correlation between viral load reduction and clinical response has been demonstrated. However, failure to fully suppress viral replication results in viral resistance and although resistance is not the only cause of therapeutic failure cross resistance occurs between some NARTIs. Compared with dual therapy significant improvement in clinical outcomes with triple therapy has been reported. The optimal time to start therapy has not been determined but plasma viral load, CD4+ lymphocyte counts, and clinical status are used as guides. Similarly the optimal combination even for non-pregnant women is uncertain but published guidelines recommend initiating therapy with at least three drugs, commonly two NARTIs and a PI or NNRTI.

Recommendations for the pregnant mother

ASYMPTOMATIC MOTHERS WITH HIGH CD4 LYMPHOCYTE COUNTS AND LOW PLASMA VIRAEMIA (FIG 1 TRACK A) How “high” CD4+ lymphocyte count and “low” viral load are defined will vary not only between centres, in part owing to the use of different viral quantification assays, but over time as experience with antiretroviral therapy in non-pregnant subjects modifies practice. Therefore, a range rather than absolute values is suggested in figure 1. Antiretroviral therapy would not be recommended if these women were not pregnant. Rouxioux et al estimated that less than 2% of mother to child transmission occurred before the third trimester. Data from the International Twin Registry and mode of delivery studies also highlight the importance of labour in mother to child transmission. We therefore conclude that zidovudine monotherapy according to the ACTG 076 regimen (see table 2) remains a reasonable option for these women but recommend that treatment is deferred until the third trimester to reduce the likelihood of resistance developing and to reduce fetal drug exposure. Although it would appear from the Thai data that the maternal component may be started as late as gestational week 36, there is a risk that mothers may miss therapy altogether when premature labour, which is associated with increased transmission risk, occurs. Transmission rates of <2% achieved when zidovudine monotherapy is combined with an elective caesarean section suggest that this is a valid option although short course, combination therapy may be preferred by some mothers.

Is dual therapy justified in a pregnant woman? While there is clear evidence that dual therapy with NARTIs defers progression to AIDS and prolongs life compared with monotherapy, triple therapy in drug naive patients is more effective than dual therapy and initial dual therapy may reduce the efficacy of subsequent triple therapy, even with a complete change of therapy.

WOMEN WITH ADVANCED HIV DISEASE, HIGH VIRAL LOAD, OR LOW CD4 COUNTS (FIG 1, TRACK B)

For women with relatively advanced disease we recommend triple therapy. However, the decision to treat and the choice of treatment are based on fetal and maternal considerations. With the exception of zidovudine there are few or no safety data in human pregnancies with ART and with combination therapy the fetus could be exposed to several potentially toxic agents. Table 3 illustrates how many babies are exposed to a drug to protect a baby in Europe from HIV as additional therapies are added to a regimen. On the other hand the risk of mother to child transmission increases with viral load, is inversely related to CD4 counts, and is related to maternal health and remains at least 18% if the maternal viral load is greater than 10 000 copies per ml despite zidovudine therapy. Since further viral load reduction is likely to reduce transmission triple therapy may also outweigh the potential, unknown hazards for the neonate as well as being beneficial to the mother. Some mothers in this category are reluctant to expose their baby to combination antiretroviral therapy. To these women we recommend zidovudine monotherapy (track A) plus an elective caesarean section.

CONCEIVING WHILE ON TREATMENT (FIG 1, TRACK C) This is becoming more common as antiretroviral therapy is increasingly prescribed to asymptomatic patients and as patients become more
confident about their prognosis. It is likely that by the time the newly pregnant mother realises her condition and presents to the clinic embryonic development will be complete. In these circumstances stopping treatment may be too late to prevent congenital abnormalities while subjecting the fetus to additional risk of transmission as the viral load rebounds. Therefore, continuation of the preconception regimen is recommended although the addition of, or change to, zidovudine should be considered while this remains the only agent proved to reduce mother to child transmission in humans. Some mothers planning a pregnancy may detect conception at 2–3 weeks and discontinue antiretroviral therapy until the end of the first trimester. There is no evidence to confirm or refute this practice. A transient increase in viral load above pretreatment levels has been observed in 4/5 individuals stopping treatment after 8–19 days but this may be more relevant to the risk of transmission to the neonate through breast feeding following peripartum antiretroviral therapy, than to intrauterine infection.

LATE PRESENTATIONS (FIG 1, TRACK D)
For the mother who presents too late in pregnancy to allow formal immunological and virological assessment the 076 regimen should be started with the possible addition of lamivudine and/or nevirapine (see table 2 for doses).

The pretreated mother
In the ACTG 076 study, only 1/36 mothers prescribed zidovudine had detectable genotypic resistance at the time of delivery, although in London mutations were detected in 2/10 women on zidovudine monotherapy. In the PACTG 185 study 20% of mothers had past exposure to zidovudine but the transmission rate was still lower than in the ACTG 076 study at 4.8% while in the French cohort the transmission rate was 20% in pretreated mothers. It is advisable to monitor pretreated mothers for resistance mutations not only before therapy (when wild type genotype may be detected) but during therapy to detect early recurrence of mutant virus. For mothers with zidovudine resistant virus, combination therapy with an alternative NARTI should be considered. With increased prescribing of ART

Table 3  Ratio of babies exposed without benefit to babies exposed with benefit for each additional antiretroviral agent added to maternal therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>At risk</th>
<th>Protected</th>
<th>Exposed, no benefit</th>
<th>Ratio of exposed:protected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>17</td>
<td>12</td>
<td>88</td>
<td>7.3:1</td>
</tr>
<tr>
<td>Second agent</td>
<td>5</td>
<td>3</td>
<td>97</td>
<td>32.3:1</td>
</tr>
<tr>
<td>Third agent</td>
<td>2</td>
<td>2</td>
<td>98</td>
<td>49:1</td>
</tr>
</tbody>
</table>
The possibility of primary infection with drug resistant HIV should be considered. Mother to child transmission of zidovudine resistant viruses has been reported.

Monitoring of exposed infants

The outcome of all pregnancies exposed to antiretroviral therapy should be reported to the Antiretroviral Pregnancy Registry (which in Europe is managed by GlaxoWellcome Ltd, Greenford Road, Greenford, UB6 0HE, tel: 0800 413524; fax: 0181 966 2338) so that any risks can be identified as quickly as possible. Infants exposed to combinations, particularly those containing protease inhibitors and other more recently licensed drugs, should be monitored for renal and hepatic toxicity in the early period after delivery until the profile of these drugs is better known. Until HIV infection has been excluded, infants should receive Pneumocystis carinii pneumonia (PCP) prophylaxis with co-trimoxazole. Although the available data suggest that zidovudine monotherapy does not delay the diagnosis of HIV infection in the infant this remains a theoretical risk for combination therapy. In the United Kingdom all pregnant women with HIV infection should be reported anonymously to the Royal College of Obstetricians and Gynaecologists’ study which is linked to the paediatric reporting scheme run by the Royal College of Paediatrics and Child Health Surveillance Unit (Contact Ms Pat Tooke, RCOG, 27 Sussex Place, Regent’s Park, London NW1 RG1, tel: 0171 829 8686). This database is linked to national death and cancer registries.

The guidelines have been prepared following widespread discussions with physicians, obstetricians, and paediatricians caring for women with HIV in London. The guidelines were debated at the British HIV Association meeting in Oxford, 1998, following which they were modified to represent the consensus opinion in the United Kingdom.

et al.


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