

# Pregnancy and HIV infection: a European consensus on management

## Executive summary

The number of adults becoming infected in Europe continues to increase, with heterosexual contact accounting for a growing proportion of cases in Western Europe. There is particular concern for the increasing numbers of infected people reported from Eastern Europe, where the current infrastructure may be unable to cope with a rapidly evolving epidemic. HIV infection and transmission thus remains an important issue in Europe.

The risk of mother-to-child transmission of HIV infection can be substantially reduced from 15–20% without interventions to less than 2% with the use of antiretroviral therapy during pregnancy, during labour and in the neonatal period, with an elective caesarean section delivery and refraining from breastfeeding.

Potent and effective antiretroviral therapy [highly active antiretroviral therapy (HAART)] to delay progression of disease in HIV-infected adults has become the standard of care, and is usually applied before serious disease has developed. There is anecdotal evidence to suggest that HIV-infected women may now positively choose to become pregnant and that those who do become pregnant are less likely to have this pregnancy terminated, because their own disease is well managed and interventions to reduce the risk of vertical transmission are available.

Given the current situation in Europe, where the vast majority of paediatric HIV infections acquired from mother to child are preventable, the standard of care should be that all pregnant women, and even those planning a pregnancy, are not only offered, but recommended to have, an HIV test. Furthermore, a test should also be offered to their sexual partners.

If a woman is treated with antiretroviral drugs before becoming pregnant, a second trimester fetal anomaly scan may be reassuring. There are no data to suggest that these drugs are associated with an increased risk of teratogenicity, with the exception of efavirenz, zalcitabine and hydroxyurea, which are contraindicated during pregnancy.

An elective caesarean section delivery substantially reduces the risk of mother-to-child HIV transmission, with an independent effect on vertical transmission even in women with a low viral load and in those on effective antiretroviral therapy. HIV-infected women should therefore be given the option of delivering their child through a caesarean section performed before labour and before rupture of membranes. Advantages and disadvantages of this option should be discussed.

All HIV-infected women should be offered therapy during pregnancy, taking into account that it involves two different people; the infected pregnant woman and her infant, who is usually not infected. The choice of therapy and timing of initiation will depend on the clinical status of the woman and has to balance delaying disease progression and prevention of vertical transmission. The decision should be based on the woman's treatment history, clinical status and the available prognostic markers, CD4 lymphocyte counts and plasma HIV-RNA levels. These markers are related to the likelihood of disease progression in the mother and also to the risk of vertical HIV transmission.

For the prevention of mother-to-child transmission, zidovudine (ZDV) monotherapy remains the standard prophylaxis. Data from the 076 trial and observational studies indicate that selection of ZDV-resistant virus rarely occurs with the 3- to 6-month regimen used in pregnancy. Some clinicians suggest the use of HAART for all women to reduce the risk of vertical transmission, but there is no evidence to substantiate this suggestion and the issue remains controversial. Although the objective of achieving the lowest possible viral load in pregnancy may be appealing, even with maternal plasma HIV-RNA levels above 1000 copies/ml, more than 95% of infants will be uninfected with ZDV prophylaxis alone.

Early *in utero* transmission appears to be rare, although a few cases have been reported. Therefore, the impact of prophylaxis can be expected to be greatest in the third trimester and around delivery. There are also

arguments for not starting therapy too early in pregnancy to avoid exposure of the fetus at early stages of development and because partial suppression of viral replication may lead to the emergence of drug-resistant strains over a longer period of time. This is of particular concern with monotherapy or double combinations. Deferring antiretroviral prophylaxis until late-second trimester may be considered, unless there is an increased risk of pre-term delivery, such as with recurrent genital tract infections, cervical incompetence, uterine malformations, or twin pregnancy. In these cases, antiretroviral therapy should be introduced mid-second trimester.

When a woman becomes pregnant while receiving therapy, it is generally recommended to continue the same therapy. HAART should never be replaced by suboptimal combinations. Concerns about teratogenicity may lead to consider temporary, but complete, discontinuation of HAART during the first trimester. The risks and benefits of this approach are not known, and the decision should only be taken after a discussion between the pregnant woman and the treating expert physician.

ZDV should be included in all antiretroviral regimens during pregnancy. However, many women with prior therapy have already received ZDV in the past and switched to HAART without ZDV. In these cases, and where there was an informed decision to move away from ZDV, the current HAART should be continued.

For women who need treatment for their own health, HAART should be initiated after the first trimester, and should include ZDV. If there is a risk of pre-term delivery, HAART should be started soon after the first trimester, and earlier than mid-second trimester.

Women who do not require antiretroviral therapy for their own health should be started on the three-part ZDV regimen in the beginning of the third trimester, at 28–32 weeks, with an elective caesarean section at 38 weeks. Again, an earlier start is recommended for women at risk of pre-term labour. If a caesarean section is not an option, ZDV + lamivudine (3TC) may be considered. The addition of a two-dose nevirapine (NVP) regimen to the three-part ZDV regimen once labour is established should, in theory, reduce the risk of transmission.

Women not requiring antiretroviral therapy for their own health but with HIV-RNA > 10 000 copies should be offered HAART, including ZDV, starting after the first trimester.

Women presenting in late pregnancy without therapy

should be started on a three-part ZDV regimen (including 1 week post-partum) as soon as possible. Although the addition of the two-dose peri-partum NVP regimen is likely to reduce transmission, triple combination therapy of ZDV, 3TC and NVP may be a better approach to keep future options for the mother open.

Antiretroviral therapy should be continued as per normal right until the time of delivery, including the morning dose of the day of the scheduled caesarean section delivery. Regardless of the maternal antenatal antiretroviral regimen, ZDV is recommended intravenously during the intrapartum period and orally for the newborn for 4–6 weeks. If stavudine (D4T) is part of the ongoing regimen in the mother, this should be interrupted for the duration of the delivery, as D4T and ZDV are antagonists.

Women who received previous prophylactic ZDV may or may not have an indication for therapy for their own health at present. If the only indication is again prophylactic, the 076 trial regimen remains the standard of care. If ZDV drug-resistant virus is present, a decreased antiretroviral efficacy is to be expected. In these cases, HAART or a combined nucleoside reverse transcriptase inhibitor (NRTI) regimen without ZDV may be advisable.

For infants born to mothers receiving ZDV monotherapy or ZDV-containing combination therapy in pregnancy, treatment with ZDV should be started as soon as possible after delivery, regardless of maternal viral load. In very premature infants, intravenous ZDV is the only available choice. Adding NVP to ZDV neonatally is not recommended, as there is no evidence of additional effect.

For infants born to mothers receiving antiretroviral therapy not including ZDV in pregnancy, ZDV may still be the option for the infant, but the reasons why the mother is not taking ZDV need consideration. If the mother has documented resistance to ZDV, the infant should receive one of the NRTI from the maternal regimen. If the mother uses D4T and is not resistant to ZDV, one dose of D4T should be omitted near the time of delivery (as D4T cannot be taken simultaneously with ZDV), intravenous ZDV should be administered during delivery, and ZDV given to the neonate. After delivery, maternal D4T could be resumed.

For infants born to mothers who did not receive any therapy during pregnancy, one dose of NVP to the mother during labour plus one dose to the infant at 48–72 h could be combined with 6 weeks of ZDV. Alternatively, HAART as a post-exposure prophylaxis (ZDV + 3TC + NVP) for 6 weeks has been

suggested on a theoretical basis, although currently there are no data available to substantiate this recommendation.

If infants identified some time after delivery as being at risk of vertical transmission are breastfed, the mother should be advised to cease breastfeeding immediately to avoid further transmission risk. Although the window of opportunity is small relative to the duration of exposure, consideration could be given to initiating treatment immediately. If treatment is given in such circumstances, it is recommended to be HAART. *Pneumocystis carinii* pneumonia prophylaxis should be initiated immediately and continued until the child has been confirmed not to be infected.

The risk of mother-to-child transmission of HIV postnatally through breastfeeding is substantial, and HIV-infected women in Europe are strongly advised to

refrain from breastfeeding as safe infant-feeding alternatives are available. Whether administration of anti-retroviral drugs to either breastfeeding women or breastfed infants may provide protection from postnatal HIV infection remains to be verified.

Anaemia (usually mild and reversible) is the major toxicity associated with antenatal and neonatal exposure to ZDV. However, an increase in severe anaemia has been reported in association with increased use of combination therapy in pregnancy.

Long-term follow-up should be planned for all children exposed to antiretroviral therapy during pregnancy and the neonatal period to assess the risk of developing possible adverse effects and disease, such as cancer in adolescence and adulthood due to the potential carcinogenicity of NRTI. This should continue at least until school age but, where feasible, for longer.

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## Background

With antiretroviral prophylaxis, elective caesarean section and refraining from breastfeeding, the risk of mother-to-child transmission can be substantially reduced. In Western Europe, where these interventions are available, there were only 113 newly infected infants in 1999, and the rate of mother-to-child transmission has decreased from about 15 to 2% or less [1]. The prevalence of HIV infection in pregnant women varies widely between and within European countries but is generally less than 1%, although it can be higher in some groups or areas. For example, the overall HIV prevalence among pregnant women in London in 1999 was one in 400, but higher in some inner-city districts, and 10-fold higher than elsewhere in the UK. There is no evidence of a decrease in the number of adults becoming infected in Europe, and heterosexual contact accounts for a growing proportion of cases in Western Europe [2]. There is particular concern for the increasing numbers of infected people reported from Eastern Europe, where the current infrastructure may be unable to cope with a rapidly evolving epidemic. HIV infection and transmission thus remains an important issue in Europe.

Mother-to-child, or vertical, transmission of HIV-1 can take place before, during or after birth, with most transmission occurring around the time of delivery [3]. The risk is associated with maternal HIV disease status, fetal exposure to infected maternal body fluids and breastfeeding, but the exact mechanism of viral trans-

mission is not understood. Perinatal interventions to reduce mother-to-child transmission have been shown to be effective not only in clinical trials, but also in the general HIV-infected population, and are therefore becoming widely used [1,4–9].

Since the mid-1990s, potent and effective antiretroviral therapy (HAART) to delay progression of disease in HIV-infected adults has become the standard of care. Such regimens are now usually applied before serious disease has developed, and an increasing number of HIV-infected adults are receiving complex antiretroviral regimens. There is anecdotal evidence to suggest that HIV-infected women may now make a positive choice to become pregnant and that those who do become pregnant are less likely to have this pregnancy terminated, because their own disease is well managed and interventions to reduce the risk of vertical transmission are available.

Theoretical evidence suggests that exposure to antiretroviral therapy *in utero* or early life could have an adverse effect on the infant in the medium to long term but, although this effect is poorly quantified, it is likely to be rare [10]. There is also a lack of information on the impact of antiretroviral prophylaxis during pregnancy or caesarean section delivery on disease progression of HIV-infected women. The management of pregnancy in HIV-infected women, which allows for the optimum care of both woman and child, is becoming increasingly complicated, and there is a need for an agreed European approach.

## Antenatal screening

The rationale for testing pregnant women for a variety of conditions is to allow appropriate and timely interventions to be offered to benefit both the baby and the woman. Identification of HIV infection during pregnancy allows the infected woman to make an informed decision about the continuation of the pregnancy and, if the pregnancy continues, to be offered interventions to prevent vertical transmission of infection. Further benefits of testing include the appropriate management of the HIV-infected woman; for example, the timely initiation of antiretroviral therapy, and the opportunity to reduce the risk of her sexual partner becoming infected. Consideration may also be given to inviting the HIV-infected woman's sexual partner, and previous children, to undergo HIV testing.

Given the current situation in Europe, where the vast majority of paediatric HIV infections acquired from mother to child are preventable [1], the standard of care should be that all pregnant women, and even those planning a pregnancy, are not only offered, but recommended to have, an HIV test. Furthermore, health care providers have a responsibility to offer and recommend the test as an integral part of antenatal care, irrespective of whether this occurs in a public or private setting. However, a pregnant woman has the right to decline an HIV test and, in such a case, her wishes should be respected.

Although approaches to routine antenatal HIV testing are likely to vary on a national or regional basis, there are several principles that should be applied. An appropriate infrastructure needs to be in place to respond to the event of a positive result, even if this consists of referral to a centre of expertise. Testing must be carried out with both guaranteed confidentiality and informed consent. Obtaining verbal informed consent from the woman to be tested is sufficient, but this should be recorded by her health care provider. Prior to the test, women should be provided with clear information (written and oral) on the nature of HIV infection, how it is acquired, and what infection means for her health and that of her infant.

Test results should always be given in person and in private. Immediately after a positive test result, a woman needs detailed and specific counselling and support. Subsequent decisions about personal treatment, continuing the pregnancy and the use of interventions to reduce the risk of vertical transmission must be fully informed after a discussion about the risks and benefits of the various options. Information should be provided about the unknown long-term consequences for the women and the exposed infants of antiretroviral therapy. Although the risk of perinatal infection can be reduced, women should be made aware that infection

can still occur even in the presence of such interventions. Treatment of the woman's own HIV infection needs to be addressed and should be appropriate multi-disciplinary management of the pregnant woman, involving infectious disease specialists, obstetricians, midwives, neonatologists, paediatricians, and psychosocial professionals.

For women with negative test results, it is important to assess the presence of behavioural risk factors for HIV infection or infection with sexually transmitted diseases and to emphasize the need for appropriate measures of risk reduction, such as safe sex and avoidance of intravenous drug use. For women who have an initial negative test result and are known to be at high risk of HIV infection, repeat testing during pregnancy and post-natally is recommended, taking into consideration maternal infection close to delivery or transmission through breastfeeding [3]. Where not already done routinely, HIV-infected women should be offered testing for other infections that may be transmitted to the child, such as hepatitis B and hepatitis C, rubella, toxoplasmosis and cytomegalovirus.

### Women attending late for antenatal care

In Europe, a small minority of pregnant women are late antenatal care attendees, usually those whose legal status is under consideration. In this situation, rapid HIV testing during or close to labour may be helpful, particularly for women from countries with a high prevalence or with a history of injecting drug use. However, although there may be limited time, informed consent is a pre-requisite. Rapid HIV tests are less reliable than standard tests and have a reported sensitivity of 98.8–100% and a specificity of 94.5–99.5%. This would imply that, for every 100 women tested, there could be as many as five false-positive results. Confirmation with two different antibody tests (either two different enzyme-linked immunosorbent assays, two rapid tests, or an enzyme-linked immunosorbent assay and a western blot) is therefore necessary. False-positive tests will cause considerable anxiety and may result in uninfected women and unexposed infants receiving prophylactic antiretroviral therapy. It is therefore important that there is a minimum delay between rapid and confirmatory testing. There are several types of rapid test available, although not all are licensed throughout Europe.

### Pre-conception counselling

Increasing numbers of women are already known to be HIV infected before becoming pregnant, and it is good clinical practice to involve both obstetrician and paediatrician at an early stage. HIV-infected women should not be denied access to available treatments, and issues relating to assisted fertility treatment may need to be discussed, and specialist referral required.

Counselling about HIV infection before conception is also important and should be reinforced and incorporated into care of HIV-positive women because of the potential benefits for the management of HIV disease and pregnancy outcome.

- Avoidance of unintended pregnancies and provision of information on safe sex and adequate contraception.
- General information can be given regarding the effect of pregnancy on the course of HIV infection, risks of antiretroviral treatment in pregnancy, risk of vertical transmission and strategies for its prevention.
- Maternal health status can be optimized for a possible pregnancy, through treatment of infections, adequate prophylaxis for opportunistic infection, nutritional interventions (including use of folic acid and other supplements), treatment of substance abuse, and discontinuation of all drugs with potential negative effects on the fetus.

## Management of pregnancy in HIV-infected women

Although the management of pregnancy in HIV infected women is generally similar to that in uninfected women, there are specific HIV-related issues that need to be considered. Both prevention of transmission of the virus to the infant and the management of the mother's HIV infection are related, and appropriate care for the mother should not hinder appropriate care for the child. Some procedures routinely carried out as part of antenatal care may carry a risk of HIV transmission. Although there is little data to quantify the risk of mother-to-child transmission of HIV through invasive obstetric procedures, it would be prudent to refrain from their use on the basis of theoretical risk, unless absolutely indicated. For example, the question has been raised regarding whether amniocentesis should be carried out in these women [11] and, if so, whether the procedure should be carried out under the cover of antiretroviral prophylaxis. This is becoming an increasingly pertinent question as heterosexually infected women become pregnant at older ages when the risk of cytogenetic disorders such as Down's syndrome is increased. These women would normally be offered invasive diagnostic tests to exclude fetal chromosomal abnormalities.

For women known to be HIV infected, including those where the diagnosis has been made in early pregnancy, non-invasive tests are recommended where possible as an alternative to amniocentesis. These non-invasive tests include a combination of nuchal fold assessment between 11 and 12 weeks of pregnancy, and biochemical tests. However, there will remain

cases where an amniocentesis is either indicated or requested. Consideration should then be given to carrying out the procedure under antiretroviral prophylactic cover. Monotherapy with ZDV would not be optimal, and triple therapy has been suggested. If the woman has a high viral load, triple combination therapy could be initiated at an earlier stage during pregnancy than would be the case if no amniocentesis was needed. Risk assessment should be on an individual basis, and it is prudent to seek the advice of an HIV expert.

If a woman is already treated with antiretroviral drugs before becoming pregnant, a second-trimester fetal anomaly scan can provide reassurance. There is no data to suggest that these drugs are associated with an increased risk of teratogenicity, with the exception of efavirenz, zalcitabine and hydroxyurea, which are contra-indicated during pregnancy.

Before performing an invasive procedure, it is good practice to review the woman's HIV, hepatitis B virus and hepatitis C virus status, because co-infection is common in Europe and all three are potentially transmissible to the fetus. As antenatal HIV testing is recommended for all women in Europe, this information would be available in most cases. However, where the woman declined to be tested for HIV, the procedure should be as for uninfected women, without antiretroviral cover.

The key objectives in the obstetrical care of HIV-infected women are the prevention, detection and treatment of risk factors for HIV transmission.

- Cervico-vaginal infections, sexually transmitted diseases, premature rupture of the membranes and pre-term labour are to some extent related, and prevention of any of these may have an impact on the others.
- When pre-term labour or premature rupture of the membranes occurs, the avoidance of subclinical bacterial infection is particularly important. In addition to antibiotics and tocolytic drugs, corticosteroids may be used when the benefit for fetal lung maturation outweighs the potential risk of increased HIV replication. This would be the case for severe prematurity (before 34 weeks), when even one loading dose before the delivery may be sufficient in reducing the risk of respiratory distress.
- Procedures that may favour maternal-fetal bleeding, such as external version, should be avoided.
- Use of tobacco and illicit drugs, especially cocaine, should be discouraged for reasons of general health.
- Unprotected sex with HIV-infected men or those at risk of acquiring infection should be avoided as it has been suggested that this may increase the risk of vertical transmission.

Follow-up of an HIV-infected pregnant woman is recommended every 4 weeks, including a general physical examination, and an assessment of her therapy, if any. CD4 cell counts and plasma viral load determination should be carried out at least once every trimester, with the frequency related to the use of antiretroviral therapy. Some virological assays do not adequately detect levels of RNA from non-B strain HIV virus. Therefore, when infection with a non-B strain is suspected, as in women from Africa, an appropriate plasma HIV-RNA assay must be used, after discussion with expert virologists. More intensive monitoring is required in cases of advanced immune deficiency and/or clinical symptoms. Tuberculosis screening should be routinely performed. Malaria prophylaxis is required when the woman intends to travel to a malaria-endemic country. Use of combination antiretroviral therapies must be carefully monitored (see below Antiretroviral therapy for the Pregnant Woman).

Vitamin supplements are indicated to prevent fetal toxicity associated with drugs; for instance, folic acid with anticonvulsants, sulphonamides, vitamin K with rifampicin or rifabutin. Folate antagonists (dapsone and pyrimethamine) may be associated with a risk of congenital malformations and their use should be avoided in the first trimester of pregnancy. *P. carinii* pneumonia prophylaxis is only recommended for women with CD4 cell counts below 200–250 cells/mm<sup>3</sup>, and can be safely stopped for women whose CD4 cell count has been above 200 cells for 3–6 months. Folic acid from pre-conception to the end of the first trimester of pregnancy is recommended in some centres for all HIV-infected women.

### Mode of delivery

An elective abdominal delivery substantially reduces the risk of mother-to-child HIV transmission [12,13]. HIV-infected women should therefore be given the option of delivering their child through a caesarean section performed before labour and before rupture of membranes. The caesarean section would normally be scheduled for 38 weeks of pregnancy, rather than 39 weeks, to avoid the initiation of labour or rupture of membranes. However, HIV-infected women, especially those receiving combination antiretroviral therapy, may go into labour 1 or 2 weeks earlier [14]. In these cases, it may thus be prudent at least to discuss this issue with the woman so that she will know to come to the hospital as soon as possible to allow an emergency caesarean section, with minimal delay and reduced duration of ruptured membranes.

It has been suggested that elective caesarean section to reduce the risk of vertical transmission may not have sufficient benefit compared with the possible disadvantages for women who are successfully treated with

HAART with a low (< 1000 copies/ml) or undetectable viral load near the time of delivery. However, recent findings from observational studies continue to confirm the independent effect of elective caesarean section in approximately halving the risk of vertical transmission, even in women with low viral load, and those who are treated with combination antiretroviral therapy [1,15–18]. An elective caesarean section has been shown to remain a cost-effective intervention over a large spectrum of assumptions [19,20]. It is important, therefore, to have an open and frank discussion with each woman to address the relative benefits of caesarean section delivery for her, so that she can make an informed choice.

A caesarean section delivery can have potential adverse effects for the mother, which should be acknowledged [21]. Abdominal deliveries carried out electively before labour and with intact membranes have a low risk of complications, whereas caesarean procedures performed on an emergent basis have a higher risk of complications. Although HIV-immunodeficient women may have a higher chance of developing infective complications than non-infected women, in the European randomized mode of delivery trial [12] there was no significant increase in serious infective complications in women delivered by elective caesarean section. Optimal antibiotic prophylaxis and strict aseptic procedures limit the incidence of infections. A study is currently in progress in Europe to document the extent of adverse effects in the post-partum period, by mode of delivery (I. Hoesli, S. Fiore, personal communication, 2001).

### Women who go into early labour or who have premature rupture of the membranes

If premature labour with or without rupture of the membranes occurs at or after 34 weeks of pregnancy, it is advisable to deliver by caesarean section immediately, as it is known that prolonged rupture of membranes is associated with increased vertical transmission risk [22]. If the pregnancy is of less than 30 weeks duration, conservative handling to delay the delivery is recommended as the risk to the neonate is higher due to complications of prematurity than due to the risk of HIV transmission. When the premature labour occurs between 30 and 34 weeks, the best course of action depends on the individual circumstances of both the mother (including HIV virological and immunological parameters) and the fetus, and discussion with an HIV-expert obstetrician is advisable.

### Antiretroviral therapy for the pregnant woman

ZDV was the first drug to be proven effective for prevention of vertical transmission in a clinical trial [4],

while information on the effect of different monotherapy or combination therapy is based on other trials and ongoing observational studies [6,16]. For treatment of HIV infection, the standard of care today is combination therapy known as HAART. When indicated for the treatment of the woman, the drug regimen should be consistent with current knowledge on the pathophysiology of HIV infection and issues of drug resistance, and should not compromise the long-term efficacy of therapy. At the same time, there are considerations unique to pregnancy, the most important being concern over potential adverse effects in the fetus and the newborn.

All HIV-infected women should be offered therapy during pregnancy, taking into account that it involves two different people; the infected pregnant woman and her infant, who is usually not infected. The choice of therapy and timing of initiation will depend on the clinical status of the woman and has to balance delaying disease progression and prevention of vertical transmission. The decision is therefore based on the woman's treatment history, clinical status and the available prognostic markers, CD4 lymphocyte counts and plasma HIV-RNA levels. These markers are related to the likelihood of disease progression in the mother and also to the risk of vertical HIV transmission.

Antiretroviral HIV treatment to delay disease progression in general, as well as the use of combination therapy in pregnancy, has become widespread. In particular the use of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors has increased substantially. Recently modified guidelines for the initiation of therapy in infected adults in France are based on clinical and immunological markers only, and not on RNA load. If the CD4 cell count falls below 350 cells/mm<sup>3</sup> or below 20%, or if the CD4 cell count declines substantially, HAART would be indicated. UK guidelines recommend initiation of therapy at CD4 cell count levels of 200–350. The current American guidelines for adult treatment are similar, but in addition recommend HAART when HIV-RNA levels increase to or are at levels above 50 000 copies/ml [assessed by reverse transcriptase polymerase chain reaction (PCR)]. These recommendations are valid irrespective of pregnancy.

For the prevention of mother-to-child transmission, ZDV monotherapy remains the standard prophylaxis. Concern has been expressed about the use of ZDV monotherapy for a limited period of time, because of theoretical concerns about selecting resistant virus strains, thereby reducing future therapy options. Data from the PACTG 076 trial [4] and observational studies indicate that selection of ZDV-resistant virus rarely occurs with the 3- to 6-month regimen used in pregnancy. The use of HAART to reduce the risk of

vertical transmission has not been investigated in a randomized, controlled trial.

The use of other antiretroviral drugs in combination with ZDV is increasing [6,16,23]. Data from observational studies confirm that, with combination therapy, rates of vertical transmission can be reduced further than with ZDV alone. NVP was studied in a phase III clinical trial (ACTG 316) [6] in the United States and Europe, as a single oral dose at delivery and a single oral dose to the neonate at 48–72 h, in women who already received other antiretroviral therapy, many of whom delivered by elective caesarean section [6]. However, the trial was stopped early, as the rate of vertical transmission was found to be so low, about 1.5% in both arms, as to make the required sample size not feasible. 3TC in combination with ZDV has been evaluated in Africa (the UNAIDS PETRA trial) and in a French study (ANRS 075), where 3TC was started at 32 weeks, and where this dual combination therapy was associated with a 1.6% rate of vertical transmission [23,24]. From a clinician's perspective, the objective of achieving the lowest possible viral load in pregnancy may be appealing but, even with maternal plasma HIV-RNA levels above 1000 copies/ml, more than 95% of infants will be uninfected with ZDV prophylaxis alone.

Most cases of transmission occur late in pregnancy or during delivery [3]. Early *in utero* transmission appears to be rare, although a few cases have been reported. Therefore, the impact of prophylaxis can be expected to be greatest in the third trimester and around delivery. There are also arguments for not starting therapy too early in pregnancy to avoid exposure of the fetus at early stages of development and because partial suppression of viral replication may lead to the emergence of drug-resistant strains over a longer period of time. This is of particular concern with monotherapy or double combinations. Deferring antiretroviral prophylaxis until late-second trimester may be considered, unless there is an increased risk of pre-term delivery, such as with recurrent genital tract infections, cervical incompetence, uterine malformations, or twin pregnancy. In these cases, antiretroviral therapy should be introduced in mid-second trimester.

### **Women requiring antiretroviral therapy for their own health**

When a woman becomes pregnant while receiving therapy, it is generally recommended to continue the same therapy. However, there are circumstances under which a switch in drugs may be considered, such as intolerance in the mother or use of a drug with known teratogenic potential, such as efavirenz and hydroxyurea. HAART should never be replaced by suboptimal combinations because this may lead to the emergence of drug resistance. Concerns about teratogenicity may

lead to consider temporary, but complete, discontinuation of HAART during the first trimester. The risks and benefits of this approach are not known, and the decision should only be taken after a discussion between the pregnant woman and the treating expert physician.

To date, it has been recommended that ZDV be included in all antiretroviral regimens during pregnancy. However, many women with prior therapy have already received ZDV in the past and switched to HAART without ZDV. A switch back to ZDV may lead to decreased efficacy if ZDV-resistant strains are present; although when the viral load is undetectable it may not be possible to test for resistance. In these cases, and where there was an informed decision to move away from ZDV, the current HAART should be continued, with intra-partum and neonatal drug choice as described below.

If a woman is not already on therapy, HAART should be initiated after the first trimester, with ZDV included in the antiretroviral regimen. If there is a risk of pre-term delivery, HAART should be started soon after the first trimester, and before mid-second trimester.

### **Women not requiring antiretroviral therapy for their own health**

These women should be started on the three-part ZDV regimen in the beginning of the third trimester, at 28–32 weeks, with an elective caesarean section at 38 weeks. Again, an earlier start is recommended for women at risk of pre-term labour. If a caesarean section is not an option, ZDV + 3TC (based on the PETRA and the ANRS 075 trial results [23,24]) may be considered. But this may lead to selection of 3TC-resistant virus, thus jeopardizing future treatment options for the mother. The addition of a two-dose NVP regimen to the three-part ZDV regimen once labour is established should, in theory, reduce the risk of transmission. However, the high risk of development of NVP resistance in the mother must be considered. In such cases, therefore, a short-duration triple therapy that will protect all classes of therapy and can be stopped after delivery is probably the best option.

### **Women not requiring antiretroviral therapy for their own health, but with HIV-RNA > 10 000 copies**

Because of the high transmission risk, and to achieve optimal and timely viral load reduction in the mother in the later stages of pregnancy and during delivery, HAART should be considered, including ZDV, starting after the first trimester.

### **Women presenting in late pregnancy without therapy**

The three-part ZDV regimen (including 1 week post-partum) should be started as soon as possible, while taking into account the resistance issue raised earlier. Although the addition of the two-dose peri-partum NVP regimen is likely to reduce transmission, triple combination therapy of ZDV, 3TC and NVP may be a better approach to keep future options for the mother open.

### **Intra-partum and neonatal prophylaxis**

Antiretroviral therapy should be continued as per normal right until the time of delivery, including the morning dose of the day of the scheduled caesarean section delivery.

In all the presented scenarios, regardless of the antenatal regimen, ZDV is recommended intravenously during the intrapartum period, as this is the only drug for which evidence from a trial is available, and orally for the newborn for 4–6 weeks. ZDV and D4T are antagonists and thus, if D4T is part of the ongoing regimen in the mother, this should be interrupted for the duration of the delivery.

### **Women off therapy when becoming pregnant, but previously treated**

This usually involves two different clinical situations: women who received ZDV prophylaxis for a previous pregnancy, and women who received treatment for their own HIV infection and stopped therapy. In both cases, testing for resistant virus may be useful but should be carried out in an expert laboratory, on the appropriate sample (i.e. either while still on treatment or shortly after stopping treatment), and interpreted with adequate expertise.

Women who received previous prophylactic ZDV may or may not have an indication for therapy for their own health at present. If the only indication is again prophylactic, the 076 trial regimen remains the standard of care [4]. A decrease in the prophylactic efficacy of ZDV monotherapy among pre-treated women has been reported, but was not confirmed by data from the ACTG 185 trial. If ZDV drug-resistant virus is present, a decreased antiretroviral efficacy is to be expected. In these cases, HAART or a combined NRTI regimen without ZDV may be advisable.

In women in whom antiretroviral therapy is indicated for their own health, factors that may influence the choice of therapy are, in addition to CD4 cell counts and plasma HIV-RNA, the resistance profile and the woman's reasons for interrupting therapy. These may be related to side effects, poor adherence to therapy, and concern over tolerance in view of pregnancy.

## Toxicity

The safety of antiretroviral drugs is a key issue for the management of HIV-infected women. Pregnancy may modify the pharmacokinetics of drugs and the risk of adverse effects of some drugs for the mother. As most drugs are known to cross the placenta (although most PI do not cross to a significant degree), the main cause for concern is the risk of toxicity to the fetus [25–27]. Women should be informed that data on safety of antiretroviral drugs are limited, both for the mother and for her offspring. The risk of specific toxicities already known should be illustrated.

Pre-clinical reproductive toxicity studies, carcinogenicity and mutagenicity studies have been reviewed extensively. According to the US Food and Drug Administration classification, ZDV, D4T, 3TC, abacavir, indinavir, amprenavir, lopinavir/ritonavir, NVP, efavirenz and delavirdine are in category C. This categorization means that safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus. The drugs didanosine, saquinavir, ritonavir and nelfinavir are in category B, meaning that animal studies fail to demonstrate a risk to the fetus, and that adequate and well-conducted studies of pregnant women have not been conducted. Efavirenz has shown teratogenic potential in cynomolgus monkeys. It should be noted that antiretrovirals have not been routinely tested for reproductive toxicity in primates, and that the doses used in rodent studies varied widely.

Data regarding the safety of these drugs in human pregnancies remains scarce. In the French study [23], the combination of ZDV and 3TC was remarkably effective in reducing the risk of vertical transmission, but was associated with increased toxicity for the infant in a minority of cases [23]. The likelihood of acquiring resistance was associated with the CD4 cell count, viral load and duration of 3TC. In a European study [14], duration of pregnancy was associated with the use of antiretroviral therapy. Women who had received combination therapy during pregnancy were significantly more likely to deliver prematurely than those who had not received treatment, especially when including PI and when started early or before pregnancy.

Recently, three cases of lactic acidosis resulting in maternal deaths have been reported, as well as four non-fatal cases in pregnant women. In all cases, these women received a combination of drugs including didanosine and D4T. Lactic acidosis is a known toxic effect of nucleoside analogues, but there are no data to indicate whether its occurrence is higher in pregnancy

than it is outside of pregnancy. Careful monitoring for this syndrome is essential when these drugs are used in pregnancy. In these cases, although neither can be used as a screening test, elevated liver enzymes are an early significant sign, with elevated pancreatic enzymes and lactate levels occurring later. Clinical signs include nausea and should not be confused with pre-eclampsia. Clinicians should be alert to the possibility that when a woman presents late in pregnancy with these symptoms, it could be related to her HIV medication rather than to the pregnancy itself. In selecting nucleoside analogues for treatment, use of the didanosine + D4T combination should be based on a risk/benefit assessment, considering the possibility of a potentially fatal lactic acidosis syndrome.

Severe, life-threatening and, in some cases, fatal hepatotoxicity has been reported in adults patients treated with NVP. In these reports, most of events occurred in the first 12 weeks of treatment. Pregnancy may also induce cholestatic effects. If NVP is started in pregnancy, possible occurrence of liver toxicity should be closely monitored through laboratory and clinical assessments.

Both PI and pregnancy may determine *per se* alterations in lipid and glucose metabolism. Use of PI treatment in pregnancy may therefore theoretically carry an additional risk of glucose intolerance, diabetes and hyperlipidaemia. An appropriate diagnostic and monitoring approach to glucose and lipid metabolism is essential when use of PI is planned during pregnancy.

## Resistance

Although drug resistance is mostly an issue in women who have been treated, the prevalence of resistant virus is increasing, both in primary infection and in pre-treated patients. NRTI resistance is currently more common than PI or non-nucleoside reverse transcriptase inhibitor resistance, as the NRTI have been used more widely and for longer. As clade variation may affect sensitivity and specificity of the test, expert advice should be sought before testing. The main issue in this context is selection of 3TC and NVP resistance during prophylactic treatment [23].

It is unclear whether there is a relationship between resistance and vertical transmission, and results from a limited number of studies are conflicting. Similarly, the clinical implication of drug resistance are not clear. Drugs could, to some extent, still be effective even with resistance, but not optimally so. In this context, it is important to realize that resistance may develop very rapidly, even after a short regimen or with one dose (such as with NVP). The consequences of this for future treatment options for the woman and for prophylaxis in further pregnancies are unknown [28,29].

Resistance testing may be recommended in pre-treated women who are failing on treatment [30]. Resistance testing may be advisable also in other circumstances, such as use of ZDV alone or where the woman is known to be exposed to multiple drug-resistant virus. In this case, one may not want to give ZDV monotherapy in the case of primary resistance, but to use combination therapy instead. We are not in a position to recommend routine resistance testing for all drug-naïve women, although this issue may need to be reconsidered in the future if the prevalence of primary resistance continues to increase.

## Conclusion

The challenge today is to help individual HIV-infected women to make reproductive decisions and choose a strategy that is most appropriate for her and her child, based on her individual treatment history, and immunological and virological markers. Such a choice requires discussion of the potential benefits as well as the potential adverse effects of each possible medical and obstetrical intervention.

An increasing number of HIV-infected women receive combination antiretroviral therapies for their own health. However, little clinical safety data is yet available concerning *in utero* exposure to these drugs, including PI. Close monitoring of individual women, including a second-trimester fetal anomaly ultrasound scan, with assessment of fetal well-being in the third trimester, as well as the provision of experienced neonatal care is recommended. Further evaluation is required in registers, prospective cohorts and clinical trials. Careful collection of data on short-term outcome and follow-up are a crucial responsibility of all clinicians and public health specialists.

## Antiretroviral treatment of the newborn

Even though ZDV prophylaxis has been standard of care for a number of years now, the relative impact of each of the three parts of ZDV prophylaxis in reducing the risk of mother-to-child transmission of HIV is not quantified. Because the majority of perinatal infections occur around the time of delivery, the rationale for the infant component of the prophylactic regimen is based on data on the efficacy of post-exposure prophylaxis both in humans and animal models. It is assumed that a considerable part of the effect could be associated with the immediate post-exposure prophylaxis of the infant, in addition to the viral load reduction in the mother. The importance of the neonatal component has been confirmed in observational studies where women had not received the pregnancy or intra-partum antiretroviral prophylaxis [7]. Retrospective case-control studies of health care workers with nosocomial exposure to

HIV-infected blood showed that ZDV administration soon after exposure was associated with about 80% reduction in the risk of contracting HIV infection. These results have been confirmed in animal models, and post-exposure prophylaxis with NVP has been shown to provide protection from HIV in the chimpanzee model [25]. Data from adult post-exposure prophylaxis studies suggest that treatment (NRTI) should be started as soon as possible, within 24 h.

## Treatment scenarios

### *Infants born to mothers receiving ZDV monotherapy or ZDV-containing combination therapy in pregnancy*

Treatment with ZDV should be started as soon as possible after delivery, regardless of maternal viral load. In very premature infants, intravenous ZDV is the only available choice [31,32]. Adding NVP to ZDV neonatally is not recommended, as there is no evidence of additional effects. The hypothesis that HAART during pregnancy may be so efficient in reducing the risk of vertical transmission that the infant component may no longer be necessary remains unconfirmed.

### *Infants born to mothers receiving antiretroviral therapy not including ZDV in pregnancy*

In these cases, ZDV may still be the option for the infant, but the reasons why the mother is not taking ZDV need consideration. For example, if she has documented resistance to ZDV then the infant should receive one of the NRTI from the maternal regimen. NVP should not be used in this situation, as resistance would occur very rapidly. If the mother uses D4T and is not resistant to ZDV, one dose of D4T should be omitted near the time of delivery (as D4T cannot be taken simultaneously with ZDV), intravenous ZDV should be administered during delivery, and ZDV should be given to the neonate. After delivery, maternal D4T could be resumed.

### *Infants born to mothers who did not receive any therapy during pregnancy*

In these cases (e.g. those identified late in pregnancy or during labour through rapid testing), one dose of NVP to the mother during labour plus one dose to the infant at 48–72 h could be combined with 6 weeks of ZDV. Alternatively, HAART as a post-exposure prophylaxis (ZDV + 3TC + NVP) for 6 weeks has been suggested on a theoretical basis, although currently there are no data available to substantiate this recommendation.

### *Infants identified some time after delivery as being at risk of vertical transmission*

If these infants are breastfed, the mother should be advised to cease breastfeeding immediately to avoid further transmission risk. In these cases, although the window of opportunity is small relative to the duration of exposure, consideration could be given to initiating treatment immediately. If treatment is given in such

circumstances, it is recommended to use HAART as a post-exposure prophylaxis, although there is no evidence to substantiate this. If the infant was not breastfed, and the period between delivery and identification of the infant is long, post-exposure prophylaxis is not effective. In all cases, virological testing should be carried out to establish infection status, and *P. carinii* pneumonia prophylaxis should be initiated immediately and continued until the child has been confirmed not to be infected.

### Duration of therapy

Apart from the results from a trial in Thailand suggesting that where maternal treatment was initiated at about 28 weeks, neonatal treatment could be as short as 3 days [9], there is no trial evidence to confirm or quantify the effect of duration of neonatal therapy. In clinical practice there is much variation in duration, although expert opinion generally agrees that 4–6 weeks would be appropriate.

### Side effects

To check possible side effects of the drugs used, haematological parameters and serum chemistry (such as lactate, glucose, creatinine levels and liver function) should be investigated at the beginning and at the end of therapy, and on a clinical basis where appropriate. The prevalence of anaemia in neonates born to infected women is rising as there is increased exposure to combination therapy *in utero*. Paediatricians need to be vigilant regarding the emergence of anaemia in newborns on antiretroviral prophylaxis and consideration may be given to stopping prophylaxis early in infants with severe anaemia rather than risking the need for a transfusion.

### Adherence

Parents should be informed about the importance of neonatal treatment and the possibility of side effects, and supported throughout treatment. A treatment plan, including a written schedule, may be developed before delivery, to be discussed with parents. The possibility of long-term follow-up of uninfected children should also be discussed. Intravenous ZDV for 10 days, keeping the infant in the hospital, could be an appropriate option in cases where adherence is expected to be a problem (e.g. where the mother is an active illicit drug user) [31].

### Diagnosis

Maternal antibodies cross the placenta and can be present in the infant for up to 18 months. The early diagnosis of infection in infants born to HIV-infected women is thus dependent on virological tests, most commonly a DNA PCR. There are no data to indicate an effect of exposure to antiretroviral therapy before birth and during delivery, and in the neonatal period on delaying the timing of diagnosis of infection in those infants who become infected despite interven-

tions. An early diagnosis of infection is optimal, and the usual diagnostic testing schedule is once in the first days of life, once between 3 and 6 weeks, and then at 3 months. A child is considered to be uninfected when at least two DNA PCR tests are negative, one of which should be based on a sample after the first week of life. However, it is prudent to keep children in follow-up and to confirm absence of infection with antibody testing at 18 months of age.

It is generally recommended that DNA and RNA PCR tests are best carried out in laboratories with sufficient expertise. Low-titre false-positives are common with sensitive viral RNA quantification assays, and such results should be treated cautiously.

## Infant feeding: breastfeeding and HIV transmission

Mother-to-child transmission of HIV can occur post-natally through breastfeeding, and HIV-infected women in Europe are strongly advised to refrain from breastfeeding as safe infant-feeding alternatives are available. Whether administration of antiretroviral drugs to either breastfeeding women or breastfed infants may provide protection from post-natal HIV infection remains to be verified. Ongoing trials in developing countries of short-course ZDV prophylaxis in breastfeeding populations have confirmed the efficacy of the peri-partum antiretroviral prophylaxis even in these breastfed children [5,8,33].

In the rare cases where, despite advice to the contrary, an HIV-infected woman chooses to breastfeed, she should be advised to do so exclusively and not to introduce other feeds or drinks for 4–6 months (this advice is based on observational data relating to HIV risk, and general knowledge regarding optimum infant-feeding practices) [34]. The duration of breastfeeding should be as short as possible, with a rapid cessation. However, national guidelines in Europe state that HIV-infected women should be advised, rather than instructed, not to breastfeed. The legal position of women who choose to breastfeed has not yet been tested in court.

There is no data to suggest that providing antiretroviral therapy to the breastfeeding mother is safe, but a change in therapy for the mother is not recommended for fear of an upsurge in viral load in both plasma and breastmilk.

## Post-natal care for women

The medical care for HIV-infected women after delivery is no different from that for infected

women who have not been pregnant, but multidisciplinary support for the HIV-infected woman and her family is essential to ensure adequate care for both women and infants. The post-natal transfer of care to other members of the multidisciplinary team should already be planned during pregnancy. Specific problems such as drug abuse should be managed appropriately.

HIV-infected women are at higher risk of urinary tract and wound infection after caesarean section and of infection at the episiotomy site after vaginal delivery than uninfected women. HIV-infected women should be advised to contact the obstetrician or infectious disease specialist if any signs of infection, which may be related to delivery, occur shortly after leaving the hospital. The puerperium is a period at risk of post-natal depression, and women with HIV may require additional support while there is uncertainty regarding the infection status of their infants.

In cases where antiretroviral therapy was given only to reduce the risk of vertical transmission, continuation of treatment should be reassessed in the post-partum period, and treatment can be stopped if there are no maternal indications to treatment.

If perinatal maternal therapy also included NVP, which has a long half-life, it is recommended to stagger the cessation of other drugs over 4–7 days to reduce the risk of resistance, thus keeping future treatment options open. Although current data suggest that prophylaxis with ZDV has only minor and transient effects on the mother, a careful clinical and laboratory follow-up of the mother for adverse events and virological and immunological markers is essential.

Where women need to continue HAART for their own health, maternal adherence (which is generally excellent during pregnancy) can be more problematic post-natally, and continued support is needed.

From the gynaecological point of view, the follow-up of the women once or twice per year is also recommended for cervical smears, as the risk of dysplasia is higher for women with immuno-suppression than for other women, and for the detection and treatment of other sexually transmitted infections. At these follow-up occasions, assessment of contraceptive needs and discussion about her wish to have another child can be carried out. There is no evidence to suggest that pregnancy accelerates HIV progression, and data from the European Collaborative Study suggest that more than two-thirds of women will still be alive 10 years after delivery, and survival is further improving with the more widespread use of HAART.

## Contraception

At the post-partum follow-up visit 6–10 weeks after delivery, most women have had their first menstruation period. Ideally, the issue of contraception should have been discussed already during pregnancy so the woman can have an idea of what method she would prefer. Women with HIV infection may infect their uninfected partner, and with condom protection at least one of the parents would remain uninfected. In case both parents are infected, the possibility that unprotected intercourse may favour sexual transmission of HIV strains with different sensitivity to antiretroviral drugs should be discussed. Many couples choose to use condoms only, both for protection against HIV and unplanned pregnancies.

The efficacy of hormonal contraception may be reduced in women who are already receiving a number of antiretroviral drugs [35]. Clinicians treating women who are at risk for drug interaction should review the need for possible use of alternative methods of contraception or dose adjustment for the interacting agent. The insertion of intra-uterine devices may be appropriate for women without a history of pelvic inflammatory disease and with CD4 cell counts above 400 cells/mm<sup>3</sup>, after screening the couple for the presence of genital tract infections.

## Follow-up of children born to HIV-infected women

Anaemia (usually mild and reversible) is the major toxicity associated with antenatal and neonatal exposure to ZDV [4]. However, an increase in severe anaemia has been reported in association with increased use of combination therapy in pregnancy [23].

Long-term follow-up should be planned for all children exposed to antiretroviral therapy during pregnancy and the neonatal period to assess the risk of developing possible adverse effects and diseases, such as cancer in adolescence and adulthood due to the potential carcinogenicity of NRTI [10,36]. This should continue at least until school age but, where feasible, for longer. This is particularly important for the large number of uninfected children who are likely to be discharged from care as soon as the absence of infection has been confirmed. The issue of confidentiality must be addressed and also whether information regarding exposure to antiretroviral therapy *in utero* and neonatally should be recorded on the child's ongoing medical record.

Animal studies have suggested a possible risk of cancer as a long-term risk of exposure to antire-

troviral therapy. Follow-up of infants exposed to ZDV *in utero* and in early life has been reassuring regarding the short-term risk for cancer, with no malignancies observed in more than 700 children in the PACTG 076 trial and the Women and Infants Transmission Study [36]. However, long-term risk for cancers or organ-specific toxicities is unknown. Follow-up of children with antiretroviral exposure at least once a year for as long as is feasible is now recommended in some European countries, to allow detection of rare cases of cancer, unusual or unexpected disease and mitochondrial abnormalities.

Mitochondrial dysfunction has been reported in a small number of infants in France exposed *in utero* or neonatally to ZDV with or without 3TC [23,37,38]. Similar findings have not been reported from elsewhere, but focused investigations have not been carried out in countries other than France. Although it may be rare that mitochondrial abnormalities cause clinical disorders, the possibility of drug-related adverse effects needs to be discussed with the pregnant woman when starting therapy.

In 1998, three unexpected adverse events (one case of intracerebral haemorrhage at term, one case of biliary atresia and one case of congenital glaucoma) were reported in the Swiss cohort of 74 children born to HIV-infected mothers who were exposed to antiretroviral therapy before, during and immediately after birth [26].

These reports, together with the increasing use of HAART regimens in infected women and the continuing introduction of new drugs in clinical practice, highlight the importance of maintaining and expanding registries and surveillance systems on the safety of antiretroviral use in pregnancy and in children exposed to these drugs *in utero*.

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**Table 1A.** Prophylactic antiretroviral therapy (ARVT) during pregnancy

Clinical scenarios	ARVT recommendation	Options	Recommendation for delivery
Women not requiring ARVT for their own health	Start three-part ZDV regimen at 28–32 weeks		Elective CS at 38 weeks GA If CS not possible, combination ARVT may be recommended
Women requiring ARVT for their own health Already on ARVT	Continue the same therapy Stop known teratogenic drugs	When possible, include ZDV	Elective CS at 38 weeks GA In addition to any oral ARVT, intravenous ZDV is recommended intrapartum and orally for the baby (4–6 weeks). If D4T is part of maternal ARVT, stop for the duration of delivery
Women not yet treated but requiring ARVT for their own health, with HIV-RNA > 10 000 copies/ml	HAART during pregnancy and during delivery, starting after first trimester	When possible, include ZDV	Elective CS at 38 weeks GA (If on HAART and HIV-RNA viral load < 1000 copies, some experts would not recommend elective CS) Intravenous ZDV is recommended intrapartum and orally for the baby (4–6 weeks). If D4T is part of maternal ARVT, stop for the duration of delivery
Women presenting late in pregnancy	Start a three-part ZDV regimen in the third trimester, including 1 week post-partum	ZDV + 3TC + NVP	Elective CS at 38 weeks GA Intravenous ZDV is recommended intrapartum and orally for the baby (4–6 weeks).
Women off therapy when becoming pregnant, but previously treated Women who received ZDV as prophylaxis for a previous pregnancy Women who received ARVT for their own health and stopped	Start three-part ZDV regimen in the third trimester, including 1 week post-partum	Test for resistance may be appropriate Test for resistance, assess reasons for interrupting ARVT	

CS, Caesarean section; D4T, stavudine; GA, Gestational age; HAART, highly active antiretroviral therapy; NVP, nevirapine; ZDV, zidovudine.

**Table 1B.** Antiretroviral treatment prophylaxis for the newborn

Scenario	Recommendation	Options
Infants born to mothers receiving ZDV only or a ZDV-containing combination	Start ZDV as soon as possible after birth for 4–6 weeks	Intravenous ZDV may be the only choice for premature infants
Infants born to mothers receiving ARVT not including ZDV	Use NRTI from maternal regimen	Consider the reason why the mother did not take ZDV
Infants born to mothers who did not receive any therapy	Neonatal ZDV for 6 weeks	NVP during labour and at 48–72 h after birth could be added

ARVT, Antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; ZDV, zidovudine.

## Appendix 2. Guidelines for pregnancy and HIV from different countries

**Table 2.**

United Kingdom	<a href="http://www.bhiva.org/guidelines">http://www.bhiva.org/guidelines</a>
Spain	<a href="http://www.msc.es/sida/asesor/home.htm">http://www.msc.es/sida/asesor/home.htm</a>
France	<a href="http://www.prn.org/prn_nb_cntnt/vol4/num4/article4_frm_set.htm">http://www.prn.org/prn_nb_cntnt/vol4/num4/article4_frm_set.htm</a>
Italy	<a href="http://www.sanita.it/aids">http://www.sanita.it/aids</a>
Germany	<a href="http://www.rki.de">http://www.rki.de</a>
Switzerland	<a href="http://www.shcs.ch">http://www.shcs.ch</a>

**Table 3A.** Nucleoside analogue reverse transcriptase inhibitors

NRTI	Animal carcinogenicity	Reproduction/ fertility animal studies	Teratogenicity/ developmental toxicity animal studies	Placental and breastmilk passage	Human studies in pregnancy	FDA pregnancy category
Zidovudine	Vaginal squamous tumours in rodent adult female — due to a urine concentration of unmetabolized zidovudine with vaginal reflux: this mechanism is not present in humans	No shown effect	No specific patterns of defects seen	Rapidly crosses placenta and is excreted in breastmilk	PACTG 076	Category C
Didanosine	Long-term screening studies showed no effect	No shown effect	No shown effect	Only phase I + II. Is excreted in lactating rats; not known if it does so in human breastmilk	PACTG 249, phase I study on 14 women	Category B
Lamivudine	Long-term screening studies showed no effect	No shown effect	No shown effect	Rapidly crosses placenta and is excreted in breastmilk	ZDV + 3TC, ref	Category C
Stavudine	Some <i>in vitro</i> mutagenesis and clastogenetic tests are positive	No shown effect	No shown effect	Crosses the rat placenta <i>in vivo</i> and is excreted in breastmilk of lactating rats	PACTG 332, phase I/II study	Category C
Zalcitabine	High doses associated with thymic lymphoma in rodents	No shown effect	Hydrocephalus occurred in rats given high doses. Skeletal defects with modest doses	Crosses the placenta in studies on primates. Unknown if excreted in breastmilk	No studies in pregnant women or neonates	Category C
Abacavir	Studies not completed	No shown effect	Decreased fetal weight. Increased % of anasarca and skeletal defects	Crosses the rat placenta <i>in vivo</i> and is excreted in breastmilk of lactating rats	No studies in pregnant women or neonates	Category C

FDA, US Food and Drug Administration; NRTI, nucleoside reverse transcriptase inhibitor. <http://www.bhiva.org/guidelines>

**Table 3B.** Non-nucleoside reverse transcriptase inhibitors (NNRTI)

NNRTI	Animal carcinogenicity	Reproduction/ fertility animal studies	Teratogenicity/developmental toxicity animal studies	Placental and breastmilk passage	Human studies in pregnancy	FDA pregnancy category
Delaviridine	Studies not completed	No shown effect	Teratogenic in rats. Embriotoxicity and maternal toxicities in rabbits	Unknown	No studies in pregnant women or neonates	Category C
Efavirenz	Studies not completed	No shown effect	Primate teratogenetic studies have never been conducted	Crosses the rat placenta <i>in vivo</i> and is excreted in breastmilk of lactating rats	No studies in pregnant women or neonates	Category C
Nevirapine	Studies not completed	No shown effect	Teratogenic effects in rats have not been observed	Crosses human placenta and is excreted in human breastmilk	PACTG 250 HIVNET 012 PACTG 316	Category C

FDA, US Food and Drug Administration. <http://www.bhiva.org/guidelines>

**Table 3C.** Protease inhibitors and other drugs

Protease inhibitor	Animal carcinogenicity	Reproduction/fertility animal studies	Teratogenicity/developmental toxicity animal studies	Placental and breastmilk passage	Human studies in pregnancy	FDA pregnancy category
Indinavir	Studies not completed	No shown effect	No evidence of teratogenesis in rats	Crosses the placenta in rats and dogs. Unknown if excreted in breastmilk	PACTG 358, phase I/II	Category C
Ritonavir	Carcinogenetic studies are negative	No shown effect	No teratogenic effects have been observed in rats	Unknown	PACTG 354, phase I/II	Category B
Nelfinavir	Studies not completed	No shown effect	No effects	Unknown	PACTG 353, phase I/II	Category B
Saquinavir	<i>In vitro</i> tests have been negative	No shown effect	No teratogenic effects have been observed	Unknown	PACTG 386, phase I/II	Category B
Amprenavir	Studies not completed	No shown effect	Increased abortion and minor skeletal variations	Unknown	No studies in pregnancy	Category C
Hydroxyurea	Genotoxic on a wide range of <i>in vivo</i> and <i>in vitro</i> animal tests. Transpecies carcinogen, potential risk for humans	Testicular atrophy, decreased spermatogenesis in rats	Potent teratogenic effects have been observed in all animal species tested	Crosses the placenta in animals and is excreted in human breastmilk	Reports on 16 women, treated for haematologic illnesses	Category D

FDA, US Food and Drug Administration. <http://www.bhiva.org/guidelines>