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Prophylaxis and treatment of HIV-1 infection in pregnancy – Swedish Recommendations 2017

Lars Naver¹,², Jan Albert³,⁴, Christina Carlander⁵, Leo Flamholz⁶, Magnus Gisslen⁷, Olof Karlström⁸,⁹, Veronica Svedhem-Johansson¹⁰, Jan Anders Sönnerborg¹¹,¹², Katarina Westling¹³,¹⁴, Aylin Yilmaz¹⁵ and Karin Pettersson¹⁶,¹⁷

¹Department of Pediatrics, Karolinska University Hospital, Stockholm, Sweden; ²Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden; ³Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden; ⁴Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institutet, Stockholm, Sweden; ⁵Department of Infectious Diseases, Västerås Hospital, Västerås, Sweden; ⁶Department of Infectious Diseases, Malmö University Hospital, Malmö, Sweden; ⁷Department of Infectious Diseases, University of Gothenburg, Gothenburg, Sweden; ⁸Medical Products Agency, Uppsala, Sweden; ⁹Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; ¹⁰Department of Medicine, Karolinska Institutet, Stockholm, Sweden; ¹¹Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; ¹²Department of Clinical Virology, Karolinska University Hospital, Stockholm, Sweden; ¹³Department of Obstetrics and Gynecology, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Prophylaxis and treatment with antiretroviral drugs have resulted in a very low rate of mother-to-child transmission (MTCT) of HIV during recent years. Registration of new antiretroviral drugs, modification of clinical praxis, updated general treatment guidelines and increasing knowledge about MTCT have necessitated regular revisions of the recommendations for ‘Prophylaxis and treatment of HIV-1 infection in pregnancy’. The Swedish Reference Group for Antiviral Therapy (RAV) has updated the recommendations from 2013 at an expert meeting 19 September 2017. In the new text, current treatment guidelines for non-pregnant are considered. The most important revisions are that: (1) Caesarean section and infant prophylaxis with three drugs are recommended when maternal HIV RNA >150 copies/mL (previously >50 copies/mL). The treatment target of undetectable HIV RNA remains unchanged <50 copies/mL; (2) Obstetric management and mode of delivery at premature rupture of the membranes and rupture of the membranes at full term follow the same procedures as in HIV negative women; (3) Vaginal delivery is recommended to a well-treated woman with HIV RNA <150 copies/mL regardless of gestational age, if no obstetric contraindications are present; (4) Treatment during pregnancy should begin as soon as possible and should continue after delivery; (5) Ongoing well-functioning HIV treatment at pregnancy start should usually be retained; (6) Recommended drugs and drug combinations have been updated.

KEYWORDS

HIV-1, Pregnancy, Prophylaxis, Guidelines

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CONTACT

Lars Naver
lars.naver@ki.se
Department of Pediatrics, K76-78, Karolinska University Hospital, SE-141 86 Stockholm, Sweden

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Mother-to-child transmission of HIV

More than 90% of all HIV-infected children acquire the infections during gestation, delivery or through breastfeeding. According to WHO approximately 2,100,000 children were living with HIV in 2016. The majority of HIV-infected infants are born in Sub Saharan Africa. In the absence of antiretroviral therapy (ART) or other preventive measures, and provided the mother does not breast-feed, the transmission rate is 15–25%. The risk of transmission is the highest at the end of pregnancy, and the vast majority of infected infants are infected during delivery. Breastfeeding without ART is associated with an additional 10–15% increased risk of MTCT (Level of Evidence 1a). Proper HIV treatment markedly reduces the transmission risk during lactation, to single percent levels [1].

Risk factors for mother-to-child transmission (MTCT) and pharmacological prophylaxis

Maternal plasma viral load is the strongest risk factor for MTCT [2] (Level of Evidence 1a). In well-treated women with undetectable viral load, the risk is as low as 0.4–0.5% [3,4], whereas an untreated women with a low viral load in is less protected against MTCT [5]. Obstetric risk factors of importance are vaginal delivery, preterm delivery < gestational week 34 and a long duration of ruptured membranes before delivery [6]. The timing of membrane rupture and mode of delivery have not been shown to be of importance when HIV RNA is <50 copies/mL [6–8]. The importance of prematurity is also unknown in this situation. Amniocentesis, the use of scalp electrodes for fetal monitoring, and other invasive procedures are associated with an increased risk of transmission [9]. However, the risk for transmission during amniocentesis when ART is provided and HIV RNA is <50 copies/mL is very low [10,11].

A decreased risk for MTCT by use of prophylactic therapy was initially shown in the ACTG 076 study [12], where the mother was given oral zidovudine monotherapy during pregnancy, with addition of intravenous zidovudine during labour, and with zidovudine for the newborn during the first six weeks of life. Since then, zidovudine has been traditionally used as one part of ART regimens aimed at preventing MTCT ever since. However, there is no evidence supporting that zidovudine is superior to other nucleoside reverse-transcriptase inhibitors (NRTIs) for prophylaxis against MTCT or that intravenous zidovudine further decreases the risk for transmission if added to other ART in women with HIV RNA <50 copies/mL close to delivery [13]. Post-exposure prophylaxis after delivery has been proven to be effective for infants at high risk for infection and combination therapy to be more effective than monotherapy [14,15]. In a study of post-exposure prophylaxis, comparing two and three drug regimens, no difference in outcome was observed [16].

Mode of delivery

Elective caesarean section, as a sole means for preventing MTCT, decreases the risk of HIV transmission by approximately 50% [17] (Level of Evidence 1b). When the mother is also on ART and has low or undetectable virus levels, the transmission rate is approximately 0.4–0.5% [18] (Level of Evidence 1a). Comparably low transmission rates have been observed in cohorts of vaginally delivered women with effective ART and HIV RNA <50 copies/mL [19,20]. Following an increase until years 2002–2004, the frequency of elective caesarean deliveries has decreased in Western Europe [6].

For pregnant women on ART, with a viral load of <50 copies/mL, no additional benefit of elective caesarean section has been demonstrated in terms of lowering the rate of MTCT [6,21]. Caesarean section carries a risk of complications such as thrombosis, infection and haemorrhage. There is, therefore, no reason to recommend elective caesarean section to women on ART with a very low or undetectable viral load [18]. HIV may be present in the birth canal despite undetectable levels in plasma [22]. This has been shown to correlate to shorter duration of treatment [23], but it has not been linked to an increased risk for MTCT.

Swedish experiences

In Sweden, the MTCT rate of HIV-1 decreased from 25% to 8% when routine zidovudine prophylaxis was introduced in 1994. The transmission rate decreased further after 1998, when the use of elective caesarean section and ART increased. During the past 10 years, seven identified children have been infected by their mothers during pregnancy, delivery and breastfeeding. In four cases, the mother’s HIV infection was unknown at the time of delivery, why the mothers were not treated for the purpose of preventing transmission. In three cases, the mother’s HIV infection was identified and transmission to the infant potentially prevented. In two of these cases, the mother was well-treated throughout the pregnancy. The third mother came to Sweden late in pregnancy.
and received ART only a short time before delivery. Annually, 60–80 children are born to HIV-infected women in Sweden, indicating a transmission rate of <0.5% in women with known HIV infection. The majority of women living with HIV in Sweden deliver vaginally.

**HIV-2**

The risk of MTCT is lower with HIV-2 compared to HIV-1 infection, likely because the viral load is lower for HIV-2 than for HIV-1 infection [24]. However, also HIV-2 infected women should be treated regardless of virus levels.

The treatment of HIV-2 is complex since this virus shows a reduced susceptibility to multiple antiretroviral drugs [25]. Therefore, prophylaxis and treatment of pregnant HIV-2 infected women should be carried out in close cooperation with infectious diseases specialist experienced in HIV-2 treatment.

**Antiretroviral drugs during pregnancy**

ART during pregnancy can be motivated for two different reasons: to treat the HIV infection of the pregnant woman, and as prophylaxis to prevent viral transmission to the child. ART may sometimes be associated with side effects, where it can be difficult to determine if, for example, fatigue and gastrointestinal disorders are related to medication, pregnancy or both.

**Adverse events in the fetus and infant**

Although teratogenic effects have not been associated to prenatal antiretroviral exposure, recently approved drugs should be avoided due to uncertainties about possible adverse effects on the fetus/child. In the Antiretroviral Pregnancy Registry (APR), an ongoing prospective study of a predominantly American population, malformations were reported in 2.8% of 8583 live born infants exposed to antiretroviral drugs during the first trimester of pregnancy, which was comparable to those exposed during the latter part of pregnancy and to children born to HIV uninfected controls (2.8% and 2.7%, respectively) [26]. There is some support for an increased risk of malformations in untreated HIV during pregnancy [27].

**Pharmacokinetics during pregnancy, placental drug transfer and passage to genital mucous membranes**

During pregnancy, a more rapid elimination (clearance) is reported for several drugs. This effect is most pronounced during the second and third trimester. After delivery, the pharmacokinetic pattern is normalized within a few days to weeks. Other pharmacokinetic changes described during pregnancy include altered absorption, an increase in the volume of distribution and a potential increase in free drug concentrations [22]. Due to altered pharmacokinetics, changes in drug dosage during pregnancy may sometimes be considered in women who harbour virus with significant drug resistance. As appears from the following text, some agents should be avoided.

**Nucleoside reverse-transcriptase inhibitors (NRTI)**

The pharmacokinetics for abacavir and lamivudine are affected to a limited extent in pregnancy [28,29] and there is no need for dose adjustment. The exposure to tenofovir and emtricitabine is moderately reduced. The decrease is not considered clinically relevant and does not require dose adjustment [30,31]. No data are available for tenofovir alafenamid (TAF), but a clinically relevant reduction seems unlikely.

**Non-nucleoside reverse-transcriptase inhibitors (NNRTI)**

During pregnancy, enzymes that metabolize drugs of this class are induced (induction of CYP2C9, CYP2D6 and CYP3A4). For efavirenz a modest, not clinically relevant, reduction of exposure is seen [32]. Rilpivirine exposure decreases by more than 30% [33]. Even this rather modest reduction may present a risk of impaired effect. Therefore, the European Medicines Agency recommends cautious use of rilpivirine in pregnancy (see Edurant Summary of Product Characteristics).

The exposure to nevirapine is reduced by approximately 20–30% [34,35], which is not clinically relevant when co-administered with two fully active NRTIs and standard dose may be administered. For etravirine, a slight increase in exposure has been reported. No dose adjustment is necessary [36].

**Protease inhibitors (PI)**

Darunavir concentrations decrease about 35% during the third trimester, as compared to postpartum levels, when administered together with ritonavir once daily (800 mg/100 mg) [37,38]. No dose adjustment is required, provided that there is no relevant PI resistance or other co-treatments that further reduce the darunavir exposure. The exposure of atazanavir (administered with ritonavir) decreases to approximately the same extent. As for darunavir, this is neither considered to be of
Lopinavir (in a fixed dose combination with ritonavir) is a well-proven drug in pregnancy. Despite the fact that the exposure decreases, no dose adjustment is required, provided there is no relevant PI resistance [40].

Cobicistat is an alternative booster as part of darunavir fixed dose products and atazanavir. Cobicistat exposure has been shown to decrease significantly during pregnancy (see next paragraph). There is reason to believe that exposure to darunavir and atazanavir, when combined with cobicistat, may be too low during pregnancy to ensure full effect.

**Integrase inhibitors**

No dose adjustment is required for treatment with raltegravir [41,42]. A 30% reduction in dolutegravir area under the curve (AUC) was observed during the second and third trimesters in a limited number of women [43]. This is likely a consequence of induction of IGT1A, the enzyme which accounts for the major part of the metabolism and which is induced during pregnancy. For patients without documented integrase inhibitor resistance, dose adjustment is not required. For elvitegravir (in fixed dose together with cobicistat/FTC/TDF or TAF), significantly decreased levels are reported during the second and third trimesters with an AUC reduction of more than 50% and $C_{\text{min}}$ values approximately 85% lower than after delivery. The reduction is significant and may present a risk for virological failure. Dose adjustment is not possible (only fixed dose products).

Medicinal products rarely used in Sweden are not discussed in these treatment guidelines. For detailed information, see https://aidsinfo.nih.gov/guidelines/htmltables/3/4868.

**Passage over placenta and genital mucosa**

Most NRTIs largely cross the placenta barrier (e.g., zidovudine, lamivudine, abacavir, emtricitabine, TDF). There is insufficient data for TAF. Nevirapine passes rapidly and completely across the placenta, resulting in high serum concentration in the fetus, if the mother takes the drug at least one hour before delivery [44]. This applies also on raltegravir [45,46]. Protease inhibitors have been shown to have poorer passage over the placenta barrier [47].

There are no studies that directly correlate drug concentrations in vaginal secretion with protective effect against MTCT. However, on theoretical grounds the presence of antiretroviral drugs in the delivery channel may be protective against transmission. Zidovudine, lamivudine, TDF, emtricitabine, nevirapine, maraviroc, raltegravir and dolutegravir are detected in equal or higher concentrations in vaginal secretions compared to plasma. Concentrations of abacavir and PIs in vaginal secretion are significantly lower compared to plasma [48]. Efavirenz exhibit very low levels in vaginal secretion [49–52].

**HIV drug resistance**

Non-suppressive ART is associated with a risk of inducing viral drug resistance. Resistant virus is usually a result of previous therapeutic failure, but may also be a result of infection with a drug-resistant strain. Resistance in pregnant women may cause several problems such as: (1) increased risk for MTCT as it may be more difficult to reach the treatment goal $<50$ HIV RNA copies/mL, (2) drugs with limited safety data may have to be used, (3) limited therapeutic options for the infant if transmission would occur.

Single-dose nevirapine to the mother and the child was previously a strategy favoured by the WHO as prophylaxis against vertical HIV transmission in resource-limited settings. This approach is associated with a high risk of NNRTI resistance development, as a consequence of slow clearance and this agent’s low barrier to resistance [6]. The benefit in terms of reduced transmission was previously considered to outweigh the considerable risk of resistance in this setting. However, recommendations have been altered, and now the WHO recommends that all pregnant HIV-infected women start ART that should continue life-long. The addition of single dose nevirapine remains in the present recommendations when the treatment goal is not achieved at the time of delivery, as a means of further increasing the pre-exposure prophylaxis to the infant.

**Treatment target**

**Viral load in well-treated HIV infection**

In both pregnant and non-pregnant women, HIV treatment intends to result in undetectable plasma levels of HIV RNA ($<20$ copies/mL). A limited proportion of adherent patients, and where relevant resistance is not suspected, have detectable virus levels (20–150 copies/mL) with current virus quantification methods. When treatment and compliance are considered adequate, however, a detectable low-grade viremia ($<150$ copies/mL) is not considered treatment failure.
Recommendations

General

Pregnancy module InfcareHIV

RAV recommends that Swedish clinics use the pregnancy module in InfcareHIV [53] for follow-up and quality assurance of women’s and children’s ART during pregnancy and delivery. Hitherto, the pregnancies of 417 Swedish women are registered, 59 of which were pregnant in December 2017.

HIV screening of pregnant women

A prerequisite for undertaking proper preventive measures against MTCT of HIV is that the HIV infection of the pregnant woman is recognized. For this reason, The Swedish National Board of Health and Welfare (Socialstyrelsen) prescribe that all pregnant women in Sweden should be offered HIV testing and counselling about protection against infection and transmission of HIV at each pregnancy. Those testing positive should also be tested for Hepatitis B and C infection, having routes of transmission in mind.

The staff of prenatal clinics should be continuously educated and updated on HIV, to certify that testing and associated counseling are performed professionally. HIV-testing, prophylaxis and general medical care during pregnancy, delivery and post-delivery, should be made available for pregnant women residing illegally in Sweden, to the same extent as for those with citizenship or a residence permit.

Considerations before pregnancy

Treatment improvements during the recent years have resulted in an increasing number of HIV-infected individuals planning for family and children. The issue of contraception, the desire to have children as well as the risk for transmission with and without well-controlled HIV infection should be discussed in all relevant aspects.

Wish for children in discordant couples

The risk of infection is minimal through vaginal intercourse when the HIV-infected person has well controlled ART [54], and consequently discordant couples can choose a natural conception method. The possibility of normal family planning should be raised and discussed by the attending physician.

Fertility testing and treatment in women living with HIV

Reduced fertility is probably more common among HIV-infected compared to uninfected women [55].

In vitro fertilization of HIV-infected women has hitherto not been permitted in Sweden, since the risk of HIV transmission to the child has not been considered sufficiently low. In many Swedish regions, fertility testing is not offered to well-treated women living with HIV. The reference group is critical to this restriction and strongly recommends permission of fertility testing and assisted fertilization should be permitted for HIV-infected women with successful ART.

In 2018, a study of assisted fertilization for women living with HIV will be carried out at the Department of Reproductive Medicine, Karolinska University Hospital, Huddinge.

Maternity care and psychosocial support during pregnancy

For optimal medical and psychosocial support a multidisciplinary team consisting of HIV experienced gynaecologist/obstetricians, midwives, paediatricians, infectious disease specialists, HIV nurses and, when certain needs exist HIV experienced medical social worker, is preferable. Units handling only a few HIV-infected pregnant women should establish contact with an experienced centre. For this purpose, InfcareHIV may be helpful.

Blood sampling during pregnancy and delivery

Determination of CD4-cell counts

• According to regular routines [25].

Determination of plasma HIV RNA levels prior to initiation and change of ART

• Before initiation of treatment
• Before modification of treatment.
• Four weeks after initiated or modified treatment and then every four weeks until the treatment target is achieved. If treatment is initiated late during pregnancy, sampling is performed 1–2 weeks after treatment start.

Determination of plasma HIV RNA in well-treated patients

• At least once every trimester, approximately three weeks before elective caesarean section and at delivery.
If vaginal delivery is planned, HIV RNA should be determined every 14th to 28th day from gestational week 32.

**Resistance testing before initiation of prophylaxis/treatment and when treatment failure is suspected or manifested**

- Resistance testing should be performed before initiation of prophylaxis/treatment. Stored, frozen plasma or serum samples may also be used.
- When resistance is present, treatment decisions should be done together with an HIV experienced infectious disease specialist. Previous treatment history should be taken into consideration.
- Treatment failure is handled according to the general HIV treatment recommendations [25].

**Fetal diagnostics**

- If fetal diagnostics are indicated, combined ultrasound and biochemical test (CUB) is recommended for risk assessment. NIPT (non-invasive prenatal testing) should be offered to minimize the need for invasive procedures.
- If the risk of chromosomal aberrations is still considered high after non-invasive investigations and amniocentesis is indicated, the HIV treatment should if possible be optimized to achieve the treatment goal prior to the procedure.

**Cell sample**

Screening for cervical cancer with Pap and/or Human papillomavirus (HPV) test is recommended when visiting the midwife during pregnancy, unless recently done.

**External turnaround**

External turnaround of fetuses in breech/transverse position should be offered to well-treated women with HIV-RNA < 150 copies/mL in weeks 36–37.

**Antiretroviral treatment/prophylaxis to women before and during pregnancy**

**Women on ART at the time of confirmed pregnancy**

- Generally, effective ART regimens should be continued since modification of treatment may result in treatment failure.
- Rilpivirine-containing products (presently rilpivirine, rilpivirine/TDF/FTC or rilpivirine/TAF/FTC) should be replaced because of pharmacokinetical reasons.

This also applies to regimens where cobicistat is used as booster (elvitegravir/c/TDF or TAF/FTC, darunavir/c, darunavir/c/TAF/FTC, atazanavir/c).

**Previously untreated women starting ART during pregnancy**

- Treatment should be initiated as early as possible (Level of recommendation B).
- Suppression of HIV RNA to undetectable levels should be achieved as early as possible (Level of recommendation B).
- Consideration is given to possible resistance.
- The first line recommendation is abacavir/lamivudine in fixed-dose combination + darunavir/r alternatively abacavir/lamivudine or tenofovir/emtricitabine in fixed combination + efavirenz.
- Prior to initiating abacavir HLA B*5701 testing should be performed.
- TDF is recommended instead of TAF at treatment initiation during pregnancy, since documentation for TAF in pregnancy is limited.
- Raltegravir may be recommended as an option in advanced resistance and as an adjunct to standard treatment for women diagnosed with HIV in late pregnancy, for a more rapid reduction of viral load [56].
- Dolutegravir containing regimens may be an option. No increased risk when used during pregnancy has been registered.

**Previously drug experienced, presently untreated women restarting ART during pregnancy**

- Consider previous treatment and possible resistance. This is particularly relevant for resistance against NNRTIs.

**Co-infection HIV/hepatitis B**

- When concurrent chronic HBV-infection is present, tenofovir/emtricitabine is the recommended NRTI combination.

**Women with HIV-2**

- Same principles as for HIV-1 regarding treatment of the woman, mode of delivery and prophylaxis to the infant.
- HIV-2 specific combination therapy should be used in accordance with the general HIV treatment recommendation [25].
- Do not use NNRTIs.


Table 1. Dosing of antiretrovirals to the woman at delivery and to the infant as post-exposure prophylaxis.

To the woman

HIV RNA >150 copies/mL at delivery aiming at sufficient drug exposure to the infant as soon as possible.

_Intravenous infusion of zidovudine:_ 2 mg/kg should be given over 1 h. After this, the infusion rate should be 1 mg/kg until the child is born. When a caesarean section is planned, the infusion should be initiated 4 h prior to surgery. When delivery is expected within an hour or when emergency section within approximately the same interval, the infusion is initiated as soon as possible and the loading dose 2 mg/kg may be administered in 30 min instead of 1 h.

_Tablet nevirapine:_ 200 mg (alternatively 20 mL oral solution 10 mg/mL) single dose 4–12 h before estimated delivery. If the women did not receive nevirapine >2 h before delivery (sufficient amount did not pass the placental barrier) an additional dose of 2 mg/kg is given to the infant as soon as possible after delivery.

To the infant

Routinely to all infants if there is no indication for individualized treatment

- Zidovudine (oral solution 10 mg/mL)
  - Infants born ≥ week 35:
    - Zidovudine 4 mg/kg q12h for 4 weeks (oral solution)
    - If oral treatment not is possible: intravenous zidovudine 3 mg/kg q12h
  - Start treatment within 4 h after delivery
  - Treatment for a total of 4 weeks
- Infants born gestational week 30–34:
  - Zidovudine 2 mg/kg q12h (oral solution) or 1.5 mg/kg q12h intravenously
  - After 2 weeks dose adjustment to 3 mg/kg q12h or 2.3 mg/kg q12h intravenously
- Infants born < gestational week 30:
  - Zidovudine 2 mg/kg q12h (oral solution) or 1.5 mg/kg q12h intravenously for 4 weeks

Other treatment options when extended prophylaxis is indicated:

- Abacavir (oral solution 20 mg/mL)
- Abacavir 2 mg/kg q12h for 4 weeks
- Lamivudine (oral solution 10 mg/mL)
- Lamivudine 2 mg/kg q12h for 4 weeks
- First line therapy in combination prophylaxis together with zidovudine
- Tenofovir (oral powder 33 mg/g)
  - Single dose tenofovir 13 mg/kg
- Nevirapine (oral solution 10 mg/mL)
  - If maternal HIV RNA at delivery >150 copies/mL and the mother received nevirapine before delivery according to above, single dose nevirapine 2 mg/kg orally to the child at 48–72 h of age. If the mother did not receive nevirapine >2 h before delivery (sufficient amount did not have time to pass the placenta) an additional dose of 2 mg/kg is given to the infant immediately after birth
- Lopinavir/r (oral solution 80 mg lopinavir/20 mg ritonavir/mL)
  - Infants <14 days old:
    - Caution because of case reports of suspected toxicity in prematurely born infants (transient adrenal insufficiency, life-threatening brady arrhythmia, cardiac insufficiency, lactic acidosis, acute renal failure, central nervous system and respiratory depression. Toxicity may be due to the drug itself and/or propylene glycol 15.3%, and ethanol 42.4% contained in the oral solution). If there is lack of options and lopinavir/r is given to infants <14 days of age and/or younger than gestational age 42 weeks, administration should be done in hospital under close observation (Grade of recommendation D).
  - Lopinavir/r 300 mg lopinavir/75 mg ritonavir/m² q12h.

Antiretroviral treatment/prophylaxis for the women before delivery

_HIV RNA >150 copies/mL before delivery (last two weeks before estimated/planned delivery)_

- If HIV RNA >150 copies/mL at the last planned sampling occasion, repeated HIV RNA testing with rapid reply is recommended.
- If HIV RNA >150 copies/mL persists or repeated testing is not feasible, contact with an expert in treatment of pregnant HIV-infected women is recommended. In addition, elective caesarean section is recommended even if vaginal delivery was originally planned.
- If treatment failure is suspected, intensified treatment based on treatment history and resistance pattern should be considered.
- Addition of raltegravir or dolutegravir may be an alternative to achieve rapid decrease in HIV RNA.

Antiretroviral treatment/prophylaxis of the women during delivery

_If HIV RNA is <150 copies/mL at delivery in women on well-functioning ART_

- Vaginal delivery is recommended if no obstetric contraindications exist. The woman is recommended to take her antiretroviral drugs as usual during labour (Table 1).
- If caesarean section is performed, the woman is recommended to take her regular antiretroviral drugs prior to the operation, even though ‘nil by mouth’ may be prescribed prior to the procedure.

_If HIV RNA is or is suspected to be >150 copies/mL at delivery_

- Delivery by caesarean section.
- Intravenous zidovudine during delivery, as pre-exposure prophylaxis to the infant.
Table 2. Follow-up of infants born to HIV-infected mothers.

**Clinical evaluation and blood sampling**

- **0–3 days**
  - HIV RNA. Umbilical cord blood should not be used, due to the risk of contamination with maternal blood. Sampling may be performed at the same time as the PKU test at >48 h of age to minimize the number of sampling occasions.
- **6 weeks**
  - HIV RNA
- **4 months**
  - HIV RNA
- **20–24 months**
  - HIV antibodies

This scheme applies to children with an indeterminate or negative HIV status. The number of sampling occasions is decreased compared to previous recommendations and it is important that all samplings are performed on recommended time and that results is received on all tests. Otherwise the diagnosis of an HIV-infected infant may be seriously delayed. If an HIV infection is suspected or established, antiretroviral treatment should be considered, and the follow-up and sampling schedule should be intensified.

- Single-dose nevirapine orally to the woman 4–12 h before the estimated delivery, as pre-exposure prophylaxis to the infant.
- Single-dose nevirapine orally to the infant at 48–72 h of age and further post-exposure prophylaxis with a dual combination for 4 weeks to the infant (Table 1) (Level of Recommendation C).

**Women who have not been HIV-tested during pregnancy**

- If a woman arrives in labour without previous HIV testing during pregnancy, an HIV test handled with rapid response should be provided at the delivery ward. If this test is positive, see below.

**Diagnosis of HIV-infection during delivery**

- Drugs with extensive placental passage should immediately be administered to the woman as pre-exposure prophylaxis to the infant; intravenous zidovudine, oral nevirapine 200 mg (Table 2), oral tenofovir 490 mg (two tablets ≈ 245 mg) and oral raltegravir 400 mg (Level of Recommendation D).
- If possible, an emergency caesarean section should be performed prior to rupture of the membranes and labour (Level of Recommendation D).
- Maternal blood should be sampled for later determination of plasma HIV RNA, CD4+ cell count and drug resistance.
- After delivery, the Infectious disease clinic should be contacted for further ART to the woman.
- If the woman did not receive nevirapine >2 hours before delivery (sufficient amount has not had time to pass the placenta) an extra dose is given orally to the infant as soon as possible, but no later than at 4 h of age, and one dose at 48–72 h of age.
- Further post-exposure prophylaxis with a dual combination for four weeks to the infant. Zidovudine and lamivudine are recommended. Start as soon as possible and at latest at four hours after delivery and continue for four weeks (Table 1) (Level of Recommendation D).
- In cases where mother’s HIV infection is diagnosed after delivery, the above-mentioned recommendation concerning prophylaxis to the infant may be followed. Prophylaxis may in these cases be initiated up to 48 h after delivery.

**Antiretroviral treatment/prophylaxis to the woman after delivery**

**General**

- The antiviral therapy should be continued after delivery and a visit to infectious disease clinic should be planned if the woman started treatment during pregnancy or if there were problems in any aspect of treatment during pregnancy. If possible, synchronize this visit with the child’s follow-up visit to the paediatric clinic.

**Mode of delivery**

**Elective caesarean section**

- Elective caesarean sections are planned according to the same recommendations as for other indications, that is, usually about one week before expected delivery. If the indication for the section is HIV RNA >150 copies/mL despite treatment, consider performing the procedure approximately 10–14 days before the estimated date of delivery to avoid spontaneous start of labour.
- If a woman who is planned to deliver by elective caesarean section is already in labour, an emergency caesarean section should be considered, unless labour is too advanced. Each case should be assessed individually depending on the indication for elective caesarean section.
- The recommendation for antibiotic prophylaxis does not differ from that in HIV-negative women (Level of Recommendation D).

**Vaginal delivery**

- Vaginal delivery is recommended for women on well-functioning ART, HIV RNA <150 copies/mL and no obstetric risk factors when tested <2–4 weeks prior to delivery (Level of Recommendation B). Scalp electrode and blood sampling from the scalp for fetal
monitoring should be avoided. Vacuum extraction/forceps delivery should only be performed only on strict obstetric indications.

Antiretroviral prophylaxis to the infant

**General**

- Prophylactic treatment is provided for 4 weeks (except nevirapine which is given as an oral single dose to the mother before delivery and to the infant at 48–72 h) (Table 1).
- Treatment is initiated as soon as possible and within 4 h after delivery.

**The mother has well-functioning antiretroviral treatment and HIV RNA <150 copies/mL before delivery**

- Zidovudine monotherapy is given to the infant as soon as possible and within 4 h after delivery.

**Maternal HIV RNA is >150 copies/mL before delivery**

- Intravenous infusion with zidovudine to the mother during delivery/caesarean section.
- Single-dose nevirapine orally to the mother 4–12 h before estimated delivery.
- Single-dose nevirapine orally to the infant at 48–72 h of age.
- If the woman did not receive nevirapine ≥2 h before delivery (sufficient amount has not had time to pass the placenta) an extra dose should be given orally to the infant as soon as possible, but no later than at 4 h of age.
- Further post-exposure prophylaxis with a dual combination for 4 weeks to the infant. Zidovudine and lamivudine are recommended. Start 4 h after delivery and continue for 4 weeks (Table 1) (Level of Recommendation D).
- In case of known or suspected drug resistance of the maternal virus, prophylactic treatment to the child is given after individual assessment. Contact with infectious disease specialist experienced in HIV resistance is recommended.
- For preparation and dosages, see Table 1.

**Procedures associated with an increased risk of exposure to maternal blood when HIV RNA is <150 copies/mL**

- If a procedure that resulted in increased exposure to maternal blood has taken place (e.g. scalp electrodes, scalp blood sampling, vacuum extraction/forceps delivery with abraded skin or accidental incision injury associated with caesarean section), the following should be considered despite maternal HIV RNA <150 copies/mL: post-exposure prophylaxis with one dose of nevirapine to the infant as soon as possible but no later than at 4 h of age and one dose at 48–72 h of age, and further post-exposure prophylaxis with two drugs for 4 weeks (Table 1) (grade D).

**Infant feeding**

Children to HIV-infected women should not be breastfed (Level of Recommendation A). Breastfeeding during ART has not been sufficiently studied and according to the Swedish Communicable Diseases Act, HIV-infected women are not allowed to breastfeed (Level of Recommendation A). The woman should be provided support to interrupt the milk production and to bottle feed the infant.

**Follow-up of children to HIV-infected mothers**

**General**

- To establish whether or not HIV transmission has occurred (Table 2), children born to HIV-infected women should be followed-up with clinical examinations, as well as with blood samplings at a unit with competence regarding paediatrics and HIV.
- Early diagnosis of a possible HIV infection is important, since the risk of rapid disease progression and immune failure is relatively high during the first months of life.

**Determination of infectious status**

- A possible HIV infection in the infant can generally be diagnosed at 1–4 months of age, since most infected children have high viral loads at that time.
- Since the debut of viremia may be delayed in infants infected during ongoing prophylactic treatment, sampling 2 weeks after discontinued prophylaxis is recommended.
- For the diagnosis of HIV to be considered certain, virus detection from samples taken at two different occasions is required.
- If there are two negative HIV-1 PCR tests at different sampling occasions after the age of one month, the likelihood of HIV infection is minimal, assuming that the child is not breast-fed.
- It is very important that all samplings, as presented in Table 2, are performed on recommended time and that results are obtained on all tests. Otherwise the
diagnosis of an HIV-infected infant may be seriously delayed.

- After 20 months of age, the disappearance of passively transferred maternal HIV antibodies should be confirmed. This establishes that viral transmission has not occurred.

- There are no proven adverse long-term effects of exposure to antiretroviral drugs during pregnancy. The number of children followed for long-term is limited. Long-term follow-up of uninfected children is therefore valuable, but difficult to perform in clinical practice.

Vaccination

- Children of women with HIV infection can follow the Swedish immunization program in its entirety.

- BCG vaccination of children in groups at risk for tuberculosis exposure, should be administered according to standard principles, if tests according to Table 2 have been negative for HIV infection up until 4 months of age.

- HIV-infected children in Sweden should not receive the BCG vaccine.

Disclosure statement

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