

## **Recommendations for the Follow-up of HIV Infection: Reproduction, Pregnancy, and Prevention of Vertical Transmission**

**Expert Panel of the National AIDS Plan Committee (SPNS), the Spanish AIDS Study Group (GESIDA), Spanish Society of Gynecology and Obstetrics (SEGO), and the Spanish Association of Pediatrics (AEP).**

### **Abstract**

**Objective:** To provide updated information on the prevention of transmission of HIV from mother to child, both before conception and during pregnancy, labor, and in the postpartum period.

**Methods:** These recommendations have been drawn up and accepted by an expert panel from the National AIDS Plan Committee (SPNS), the Spanish AIDS Study Group (GESIDA), the Spanish Society of Gynecology and Obstetrics (SEGO), and the Spanish Association of Pediatrics (AEP). This process involved a review of the most recent and relevant clinical and epidemiological studies published and/or presented at scientific meetings and conferences with the aim of establishing recommendations that meet standards of quality.

**Results:** Serodiscordant couples can use assisted reproduction. In these cases, sperm washing is highly recommended. The action to be taken to prevent vertical transmission will depend on the point during pregnancy when the infection is diagnosed and whether or not the mother has already taken antiretroviral therapy with or without viral replication. Highly active antiretroviral therapy (HAART) is the treatment of choice and should include drugs with a suitable efficacy and safety profile. Every effort must be made to achieve an undetectable viral load in plasma at the time of birth, and breastfeeding must be ruled out. The newborn must always receive AZT during the first 8 hours of life and the relevant tests must be carried out.

**Conclusions:** Timely diagnosis of infection, suitable immunologic and virologic monitoring, administration of highly active antiretroviral therapy (HAART) to the mother, and postnatal follow-up of the child exposed to HIV and drugs are essential in order to be able to minimize the risk of vertical transmission.

**Key words:** Vertical transmission. Pregnancy. Birth. Exposed child. HIV. Assisted reproduction.

### **1. INTRODUCTION**

HIV infection has important consequences for reproduction, from the moment of conception (due to the risk of sexual transmission) until possible infection of the child and the subsequent need for antiretroviral therapy. Identification of infection and appropriate

treatment of the infected mother can prevent vertical transmission (VT). Every effort must be made to give women wishing to become pregnant suitable advice to protect them during pregnancy and to prevent the birth of HIV-infected children.

These recommendations are aimed at all health professionals who care for pregnant women and newborns. They have 4 main objectives, as follows:

1. To prevent the woman from going into labor without knowing her HIV status.
2. To review the state of the art and draw up guidelines for antiretroviral therapy, both to improve the health of the mother and to minimize the risk of VT, in addition to other aspects of caring for pregnant women. To discuss other strategies for reducing VT, such as elective cesarean delivery and treatment of the child.
3. To draw up guidelines for suitable follow-up of the child exposed to HIV and to antiretroviral drugs.
4. To evaluate existing options for reproduction, in the light of favorable changes in the prognosis of HIV infection and the desire to have children held by many couples.

The document insists on the need for a multidisciplinary approach that must involve, at least, a gynecologist, an infectious diseases specialist, a pediatrician, and a midwife, in addition to other health professionals.

We have applied the so-called **levels of evidence** based on the origin of the data used to support the suggestions, indications, and recommendations for action (Level A, comparative and randomized studies; Level B, cohort studies or case-control studies; Level C, descriptive studies or expert opinion).

## **2. Recommendations Before Pregnancy. Assisted Reproduction in the Framework of HIV Infection**

The currently favored ethical approach is to help couples to have children, bearing in mind 3 aspects: to reduce as much as possible the transmission of HIV during conception, to guarantee fertility, and to prevent infection of the newborn.

In the case of an HIV-infected man and a noninfected woman (serodiscordant couple), the objective is to achieve pregnancy without infecting the mother or the newborn.

Therefore, and in those cases where the patients do not have access to assisted reproduction, the patients should be advised based on the following principles:

- Explain the risk of each procedure, including open relations. It is important to stress that absence of transmission cannot be guaranteed and the data available on open relations are much scarcer than those on the methods described below. If the couple eventually chooses open relations (natural method), they must follow a protocol that includes the following:
  - a. Gynecologic study (hormones and ultrasound) for the woman and a spermogram for the man in order to rule out serious fertility problems.
  - b. The infected member must be taking HAART and have an undetectable viral load in plasma.
  - c. Unprotected sexual relations must be restricted to the most fertile periods.
  - d. The couple must understand that this is an exceptional situation.

Since the first series of pregnancies with serodiscordant couples using sperm washing,<sup>1</sup> several European teams have used different techniques for assisted reproduction (eg, sperm washing and intrauterine insemination [IUI], in vitro fertilization [IVF]) in more than 4000 cycles. They have achieved several pregnancies with no reports of infection of the couple or the newborn.<sup>2-9</sup> Although follow-up of these couples has not been as meticulous as might have been desired, most official bodies and scientific societies recommend sperm washing.<sup>10-14</sup>

### **Criteria for Reproductive Treatment in Serodiscordant Couples**

**Stable HIV infection.** The patient must be evaluated as a whole, and CD4+ T-lymphocyte counts and viral load in titers must not be limiting.

- Ribavirin: use of this drug by either of the members of the couple during the preceding 6 months is a contraindication for reproductive treatment.
- HAART: this should not be used to reduce viral load in semen, except if it is indicated by the patient's virologic situation.
- Informed consent: this must be specific and give details of the risks involved in the technique and of the concept of reducing (not eliminating) the risk of HIV infection. Both members of the couple must sign.
- Induction of ovulation: in order to maximize the yield, the cycle of IUI or IVF with sperm microinjections should be carried out by inducing ovulation using standard regimens. IUI or IVF should only be carried out once purified sperm is confirmed as negative by polymerase chain reaction. During the cycle of assisted reproduction, the woman should undergo testing for HIV antibodies and HIV viral load. This should be repeated 2 weeks after IUI or IVF in order to rule out infection resulting from the procedure.
- Semen samples and supernumerary embryos must be frozen in independent tanks.
- Every attempt should be made to carry out the PCR and the IUI or IVF on the day the sample is obtained.
- Laboratory: this must have suitable facilities, protocols, and procedures for the management of contaminated samples.

### **Women Infected by HIV Regardless of the Man's Serostatus**

If the man is not infected, or if there is a risk of reinfection if the man is infected (eg, different resistance profiles), the couple can engage in sexual relations with a condom and no spermicide. The semen content can then be emptied into the vagina. Semen can also be obtained by masturbation and injected into the vagina using a syringe. If both members of the couple are infected and taking active antiretroviral therapy, and there is no risk of reinfection, they can have unprotected sex. Given that infected women have a greater frequency of subfertility,<sup>15</sup> ovarian resistance, and tubal obstruction, it could be advisable to undergo a fertility study before trying to become pregnant.

**Assisted reproduction.** Until the end of 2005, little information was available on HIV-infected women and assisted reproduction.<sup>16</sup> Recently, 4 studies on IVF in HIV-infected women have been carried out.<sup>17-20</sup> In 2 of them, the pregnancy rate was lower in infected patients than in controls.

### **Action Protocol**

#### **Infected Women Wishing to Become Pregnant**

- Women must be informed of the risk of VT, antiretroviral toxicity, and obstetric risks (eg, prematurity, pre-eclampsia).
- Sexual transmission can be prevented by using a condom if both members of the couple are serodiscordant or have a different virologic pattern.
- The woman should receive antiretroviral therapy according to the recommendations for the infected adult. Drugs unsuitable for pregnant women should be excluded.

#### **Infected Women With Criteria of Sterility (>1 year)**

- Carry out a complete fertility study (eg, spermiogram, hysterosalpingography, baseline hormone study on the third day of the cycle).
- If assisted reproduction is required, the most appropriate technique will be indicated with the appropriate stimulation regimen.
- Inform about the possibility that the results may not be as good as expected, regardless of the number of embryos obtained.
- Stimulation protocols should take ovarian resistance into account. Ideally, only 1 embryo should be transferred in order to minimize the risk of a multiple birth. However, as the results of the process are expected to be poor in these patients, a less restrictive policy could be adopted.

- If pregnancy is not achieved, improvement of the immune status or an oocyte donation can be considered.

### **3. TREATMENT OF THE HIV-INFECTED PREGNANT WOMAN**

#### **Diagnosis of HIV Infection During Pregnancy**

In order to prevent VT, both pregnant women and those planning to become pregnant must be aware of their possible HIV-infected status. Therefore, all pregnant women must be offered suitable information and HIV serology testing. This first step is essential if VT is to be reduced.<sup>21,22</sup>

- HIV serology testing should be indicated at the first visit and carried out as soon as possible.
- If the woman's HIV status is unknown at the time of labor or immediately after, rapid serology testing must be performed. The feasibility and usefulness of these tests has been shown in an American multicenter study in which the time between extraction and the result was 66 minutes.<sup>23</sup> The United States Food and Drug Administration has also approved techniques for the detection of antibodies in saliva, although the specificity of the technique may be lower.<sup>24</sup>
- In the case of risk practices for HIV infection during pregnancy, it is important to educate about prevention. The test should be repeated once every trimester. If this is not possible, a rapid test should be indicated before labor.
- If the woman refuses to undergo serology testing, this should be reported in writing in her medical history (given the potential importance of the decision).

**Infected Pregnant Woman Diagnosed Before Pregnancy** The pregnant woman must be aware of the following:

#### **Antiretroviral Therapy**

- Initiation of HAART depends essentially on the woman's immunologic and virologic status and should follow the general recommendations for the treatment of adults. If it is not necessary, it should be recommended from the second trimester onward, with the aim of preventing VT.
- Pregnant women already taking HAART should not suspend it without instructions from their doctor.
- The pregnant woman must be aware both of the beneficial aspects of HAART (reduction of viral load and risk of VT) and of the possible impact on the pregnancy and, in the long term, on the newborn.<sup>25,26</sup> She should be informed about the connection between HAART and liver toxicity (nevirapine), mitochondrial toxicity, and lactic acidosis (nucleoside reverse transcriptase inhibitors [NRTI], hyperglycemia, and prematurity (protease inhibitors [PI], preeclampsia, and fetal death).<sup>27</sup> Therefore, close clinical and laboratory follow-up is necessary during pregnancy.
- HAART, even with a low viral load,<sup>28</sup> reduces VT; therefore, in principle, pregnancy is always an indication for ART.
- Special emphasis must be placed on the need for good adherence to treatment.

#### **Malformations**

There is no proof that HAART during pregnancy is associated with a greater risk of congenital malformations,<sup>29,30</sup> with the exception of efavirenz.<sup>31</sup>

#### **Method of Delivery**

The decision on the method of delivery should be agreed upon with the patient. Today, we know that vaginal delivery involves no greater risk if the patient has received HAART during pregnancy and has a low viral load during the last trimester, and if contact between maternal blood and the child is minimized.<sup>32</sup>

- If a cesarean delivery is indicated, or if the patient chooses this method, it is important to inform her about the greater morbidity associated with this surgical technique.<sup>33</sup> Informed consent must be signed.

#### **General Aspects**

- A suitable lifestyle (exercise, diet) must be recommended, as must supplements of folic acid, iodine, and iron.
- The patient should cut down on smoking and other toxic substances and abstain from unprotected sex with multiple partners during pregnancy.<sup>34</sup>
- The patient must not breastfeed her child during puerperium.

### **Infected Pregnant Woman Diagnosed During Pregnancy**

In addition to the usual reactions to a diagnosis of HIV infection (anxiety, fear of death, fear of rejection), the pregnant woman experiences the fear of transmitting HIV to her child and is concerned about the future.<sup>35</sup> Therefore, only patients with confirmed diagnosis of HIV infection must be informed about this by the obstetrician and by the infectious diseases specialist they are referred to. They should be given information about the following:

- General aspects of HIV infection (causal agent, natural history, modes of transmission, and preventive measures, both to prevent transmission to third parties and to avoid reinfection by a different viral strain).
- Health care: the patient must be informed that she will be cared for by a multidisciplinary team composed of an infectious diseases specialist and pediatrician with experience in HIV infection and, if necessary, by other specialists (social worker, psychologist, or psychiatrist). The patient must also be aware that all information will be treated in the strictest confidence at all times.
- The need to contact previous sexual partners so that they can undergo the relative diagnostic tests.

### **Infected Pregnant Woman Diagnosed During the Advanced Phase of Pregnancy or During Labor**

At present, in our setting, most infected children are children of mothers who were not diagnosed or who were diagnosed late. Therefore,

Any pregnant woman who has not been monitored or had a serology test or has an unknown HIV status must be informed about the convenience of taking a rapid test. If the result is positive and there is not sufficient time to confirm the result, she will be informed about the result and the possibility that it is a false positive.

After delivery, she will be informed about the suitability of completing the diagnostic workup.

### **Voluntary Interruption of Pregnancy**

Spanish legislation (Organic Law 8/1985, dated July 5, Article 417 bis of the Penal Code) allows a pregnancy to be interrupted, both in the case that it is necessary to prevent severe danger for the life or physical or mental health of the pregnant woman and when it is thought that the fetus will be born with severe physical or mental defects. In summary, any HIV-infected woman must be given rigorous information about the risks of VT and the preventive measures available, the efficacy of these measures and the generally favorable prognosis of the pregnancy; however, the woman must take the final decision to continue with the pregnancy or not.<sup>36</sup>

### **Antenatal Diagnosis**

Studies carried out during the pre-HAART era reported an increased risk of VT in women who underwent invasive procedures. A greater risk of infection was observed in women who underwent amniocentesis during the third trimester (OR, 4.1; 95% CI, 1.2–13.5).<sup>37</sup> Similarly, there was a greater risk of VT in 36% of women who underwent an invasive procedure. However, recent studies show that the risk of VT in women who undergo amniocentesis while taking ART is similar to that of other infected women.<sup>38-40</sup> Recently published results show that combining biochemistry and ultrasound during the first trimester in HIV-infected women achieves a detection rate of 88% for trisomy 21 and 75% for trisomy 18 with only 3.3% of false positives.<sup>41</sup> This would enable us to detect

pregnancies with a risk of chromosomal anomalies sufficiently early to start antiretroviral therapy and reduce as much as possible the viral load before carrying out the invasive procedure, ideally an amniocentesis in the second trimester, thus removing the need, where possible, to cross the placenta.

### **Recommendations**

1. The best available screening test for abnormalities and chromosome disorders should be applied as soon as possible, ideally during the first trimester and including measurement of the nuchal fold. If the screening test reveals an abnormality, the following are recommended:

- The procedure should be carried out under ART and, ideally, with an undetectable viral load (Level C).
- Try to avoid crossing the placenta during the procedure. If this is not possible, delay the procedure (Level C).
- Do not perform a chorion biopsy due to the theoretically greater risk of transmission (Level C).

2. To examine pulmonary maturity, rule out chorioamnionitis or carry out fetal surgery: evaluate the risk-benefit ratio and, if the procedure is to be performed, it should be done under the best suppressive therapy possible (Level C).

### **Monitoring the Pregnancy**

Some studies show greater risks of prematurity and fetal death and a more delayed growth in HIV-infected pregnant women,<sup>42,43</sup> and HAART has been associated with a higher incidence of preeclampsia.<sup>27</sup> Given the lack of data to clarify the causes of fetal death and preeclampsia in these women, pregnancy must be closely monitored (serial growth monitoring, fetal Doppler ultrasound, fetal monitoring) so that such situations can be diagnosed early. Therefore, monitoring of pregnancy must be based on the analytical parameters of HIV infection and pregnancy, awareness of the side effects of HAART, and on the monitoring of fetal well-being.

### **Recommendations for Coinfection by HIV and HCV**

- All pregnant women should undergo testing for HCV antibodies. Women with a low CD4+ T-lymphocyte count may not produce a serologic response to HCV; therefore, testing should determine the presence of the C virus in plasma (HCV RNA) (Level C).
- At least 1 quantitative measurement of plasma HCV should be carried out, preferably close to labor, since this is the main risk factor for transmission (Level C).
- Women for whom treatment of hepatitis C is indicated should take it before becoming pregnant (Level C). Interferon and ribavirin are teratogenic (Level A) and women should not attempt to become pregnant until 6 months after the end of treatment (Level C).
- The HCV viral load should be known; even though no practical treatment can be carried out during pregnancy, it is useful for preventing prolonged labor or delivery requiring the use of many instruments (Level C).
- Sufficient data are not yet available to indicate elective cesarean as a general measure based only on maternal HCV infection (Level C).

### **Coinfection by HIV and HBV Recommendations**

- Carry out complete HBV serology testing. If the woman reaches labor with an unknown HBV status, testing should be carried out as soon as possible (Level C).
- HBV viral load should be determined in any HBsAg-positive patient, regardless of the result for HBeAg. This information is useful when designing a HAART regimen that is effective against HIV and HBV (Level C).
- ART in a pregnant woman coinfecting by HIV and HBV will require the use of drugs that are active against both viruses (Level C).

#### 4. Antiretroviral Treatment During Pregnancy

The objective of ART during pregnancy is to prevent VT while preserving the health of mother and baby and preventing the appearance of resistance that limits future therapeutic options.

##### Recommendations

- The treatment of choice during pregnancy is HAART; monotherapy has little evidence to support it (Level B).
- If HAART is to be interrupted after delivery or during pregnancy due to toxicity or intolerance, when the regimen is composed of 2 NRTIs and nevirapine (NVP), the latter should be stopped 7 to 14 days earlier, given its long half-life (the optimal duration of the interval is unknown) (Levels B and C).
- In triple regimens with protease inhibitors (PI), all the antiretroviral drugs should be interrupted simultaneously (Level C).
- Resistance testing should be performed in pregnant women who have never received ART and in those taking ART with a detectable viral load at the beginning of the pregnancy (Level C).
- In the case of ART-experienced patients, previous ART regimens and the results of previous resistance studies should be considered in order to choose the optimum regimen during pregnancy (Level B).

##### Drugs

The criteria applied to the use of antiretroviral drugs in pregnant women are different from those applied to adults, since the safety of both the mother and the child must be taken into consideration.<sup>44</sup> Potential teratogens such as efavirenz (EFV) must be avoided. Drugs whose safety is well known should be used. Where possible, antiretroviral drugs about which little is known during pregnancy should not be used. The drug with which we have most experience during pregnancy is zidovudine (ZDV) and this must form part of HAART where possible, except when there are reports of resistance or intolerance (Table 1).

It must be remembered that the woman's safety is affected by mitochondrial toxicity, liver toxicity,<sup>45,46</sup> and metabolic alterations, especially hyperglycemia.<sup>47</sup>

##### Safety of ART for the Child During Pregnancy

Noninfected children exposed to NRTIs may experience mitochondrial damage, as shown by the high prevalence of asymptomatic hyperlactatemia during the first 3 to 6 months of life,<sup>48</sup> although spontaneous reversion suggests that this damage has no symptoms in most children.<sup>49,50</sup>

A study from the Swiss cohort suggests that the incidence of prematurity could increase after ART with a PI. These data are consistent with those of a European collaborative study. A recent study evaluating 233 pregnant women taking ART with PIs found a 22% prematurity rate, similar to that of the same population before the use of PI. The multiple regression analysis revealed that prematurity was not associated with the PI used or with the duration.<sup>51,52</sup>

**Tabla 1. Use of antiretroviral drugs in pregnant women**

	Recommended	Alternatives <sup>a</sup>	Not recommended due to lack of data during	Contraindicated
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			pregnancy	
<b>Nucleoside reverse transcriptase inhibitors (NRTI) and Nucleotide reverse transcriptase inhibitors (NNRTI)</b>	Zidovudine (ZDV)	Didanosine (ddl)	Emtricitabine (FTC)	D4T+DDI <sup>b</sup>
	Lamivudine (3TC)	Abacavir (ABC)	Tenofovir (TDF) <sup>c</sup>	Zalcitabine (ddC)
		Stavudine (d4T)		
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</b>	Nevirapine (NVP) <sup>d</sup> CD4 < 250 cells/uL			Efavirenz (EFV) <sup>e</sup>
<b>Protease inhibitors (PI)</b>	Lopinavir/r (LPV/RTV) 400/100 Saquinavir/r (SQV/RTV) 1000/100 12h	Indinavir/r (IND/RTV) 400/100 <sup>f</sup> Nelfinavir (NFV) 1250/12 h	Atazanavir/r (ATV/RTV) <sup>f</sup> Fosamprenavir/r (FPV/RTV) Tipranavir/r (TPV/RTV)	
<b>Protease inhibitors (PI)</b>			Enfuvirtide (T-20)	

<sup>a</sup>Use when first-choice agents cannot be used.

<sup>b</sup>Risk of severe lactic acidosis.

<sup>c</sup>Potential risk of abnormalities of the kidneys, bones, and calcium-phosphorus metabolism in animals when administered at high doses. No data on pregnancy.

<sup>d</sup>Greater risk of liver toxicity in pregnant women coinfecting with HCV or HBV or who have a CD4 T lymphocyte count > 250 cells/mm<sup>3</sup>.

<sup>e</sup>Category D teratogen.

<sup>f</sup>Hyperbilirubinemia, potential risk of kernicterus. Increased nonconjugated bilirubin has been reported in adults who take this drug. However, in a small series of pregnant women treated with this drug, no greater incidence of hyperbilirubinemia was reported in neonates than in the general population.

### When to Start and When to Switch ART

As a general rule, in a treatment-naïve pregnant woman, ART should be started between weeks 10 and 14. Switching ART during pregnancy will depend on adverse effects or lack

of efficacy.<sup>44,53</sup> However, if the woman was already receiving therapy, the first measure should be to switch any potentially teratogenic drugs (EFV, hydroxyurea, zalcitabine) and any nonrecommended drugs (tenofovir, fosamprenavir, amprenavir, atazanavir). This first evaluation of the drugs leaves us with 2 possible situations: viral replication or no viral replication.

### **ART-Experienced Woman With No Viral Replication**

Current recommendations are to maintain therapy, switching potentially teratogenic antiretroviral drugs depending on the ART history and previous resistance studies. If the patient is taking a ZDV-sparing regimen, several authors advise that it be included, as long as there are no ZDV resistance mutations.

The combination of ZDV with 3TC is well known, efficacious, and safe in pregnant women and is the first-choice combination. d4T+ddI (risk of mitochondrial toxicity) and tenofovir (no data in pregnant women) are not recommended and should be replaced by other NRTIs. Despite the similarity between 3TC and FTC, the paucity of information on the latter in pregnant women means that it should be replaced by 3TC. Starting a regimen containing abacavir is limited by the risk of hypersensitivity reaction. However, the approach is different if the woman was already taking the drug and other options were not possible.

In the case of scheduled cesarean in patients taking d4T (due to anemia, resistance to ZDV), the morning dose should be suspended and intravenous ZDV should be administered, as there is antagonism between these drugs.

EFV is totally contraindicated due to its teratogenic potential (category D), and it must be replaced as soon as pregnancy is suspected or confirmed. High-resolution echography must be carried out to rule out disorders of the neural tube.

In women who become pregnant while on NVP, we must take into account the following<sup>54,55</sup>: a) it could be wise to replace it with a PI; b) the risk of severe toxicity is low in patients who have been on NVP for a long time; and c) switching to a PI could involve toxicity in patients who were perfectly tolerant of their previous regimen.

Current guidelines for adults recommend regimens containing PI boosted with ritonavir (RTV), although there is more experience with nelfinavir (NFV) during pregnancy. Saquinavir (SQV) boosted with RTV (1000/100 mg) twice daily is another option, as is the coformulation lopinavir/ritonavir. Recent pharmacokinetic studies in HIV-positive pregnant women have shown the efficacy and safety of SQV/RTV once daily at a dose of 1200/100 mg.<sup>56</sup> If a woman taking one of these regimens has an undetectable viral load, then the regimen should be maintained.

### **ART-Experienced Woman With Viral Replication**

ART should be adjusted by applying the criteria set out in the previous section, the objective being suppression of viral replication, at least during the last weeks of pregnancy.<sup>44</sup> To attain this, it is sometimes necessary to turn to second-choice drugs. Suspension of ART would depend on the possible adverse effects for the newborn and the mother.<sup>44,57</sup> ART should be suspended when there are actual or suspected drug-related adverse effects such as lactic acidosis, HELLP syndrome, preeclampsia, or other conditions that could represent a severe risk for the mother and the fetus. The drug should be suspended until the adverse effect has resolved and caution should be exercised with regard to the use of other drugs during the last weeks of pregnancy.

In women who were prescribed ART with the sole aim of preventing VT, suspension could be justified by laboratory data 1 month after delivery, although there are no universally accepted recommendations to this effect. In the case of HAART including NVP, the NRTIs should be continued for 1 to 2 weeks after suspending NVP in order to reduce the possibility of resistance. In the case of PI-containing regimens, all drugs should be suspended at once.

## Recommendations

- The objective of ART during pregnancy is to prevent VT while preserving the health of mother and baby (Level C).
- It is indicated in all pregnant women, regardless of the viral load (Level A).
- The benefits for mother and child outweigh the potential risks (Level A).
- The objective is to obtain an undetectable viral load (Level B).
- The treatment of choice is that composed of 2 NRTIs combined with a PI (Level B).
- The choice of drugs should be based on the resistance study, drug safety, and ease of adherence (Levels B and C).
- ART should be initiated between weeks 10 and 14 of pregnancy (Level B).
- If the woman is already taking ART, then she should continue; however, potentially teratogenic drugs should be switched, as should those with which experience is limited (Levels B and C).
- ZDV should be included in the HAART regimen, as long as there is no resistance (Level A). Lamivudine is the second NRTI of choice (Level B).
- The combination d4T+ddl should not be used due to its toxicity. EFV and drugs with which there is little experience—tenofovir, amprenavir, fosamprenavir, and atazanavir—should not be used (Levels B and C).
- NVP should not be used to start ART in women with CD4+ T-lymphocyte counts above 250 cells/ $\mu$ L. Potential liver toxicity should be monitored in patients with chronic HBV and HCV hepatitis (Level B).
- In the case of scheduled cesarean in patients taking d4T during pregnancy, the morning dose should be suspended on the day of the cesarean and switched to intravenous ZDV (Level C).
- Changes in HAART should be based on safety, adverse effects, and efficacy (Level C).
- Control of VT in HIV-infected patients requires the creation of multidisciplinary teams (Level C).

### 5. Threat of Premature Birth. Early Rupture of Membranes.

Significantly higher rates of prematurity have been observed in HIV-positive pregnant women,<sup>57</sup> although studies usually highlight the presence of confounders,<sup>58</sup> such as drug addiction or the absence of antenatal care. Other aspects that would lead to an increase in the frequency of preterm births are impaired maternal immune status<sup>59,60</sup> or ART,<sup>61-63</sup> especially in the case of patients on HAART before the pregnancy.<sup>64</sup>

### Recommendations for Treating the Threat of Premature Birth

#### *Prevention of the Threat of Premature Birth*

- Offer good antenatal care (Level B).
- Given the greater risk of premature birth, provide screening for vaginal infections (cultures), especially bacterial vaginosis, in HIV-infected women,<sup>65</sup> although this measure has not proven efficacious in the general population (Level C).
- Reduce the consumption of toxic substances (tobacco, alcohol, drugs of abuse) (Level B).
- Attain a good nutritional status during the pregnancy (Level B).
- If previous surgery of the cervix is required, evaluate its use during the first trimester and evaluate the need for cerclage (Level C).
- In HIV-infected women, weekly checkups should be started earlier (week 34-35) and should involve fetal monitoring and a vaginal examination (Level C).

### ***Diagnosis and Treatment of the Threat of Premature Birth***

- Follow the same regimens as in the general population,<sup>59</sup> including the use of corticosteroids to reduce morbidity and mortality caused by prematurity, except in the case of a severe infection (chorioamnionitis, tuberculosis) (Level B).
- Only administer antibiotic prophylaxis if there are other indications (premature rupture of membranes, vaginal colonization by group B streptococcus, or nonspecific symptoms of infection) (Level B).
- If contractions are regular, even though the cervical changes are minimal, tocolytic treatment should be accompanied by intravenous ZDV at 2 mg/kg/h for the first hour followed by 1 mg/kg/h until the dynamic symptoms stop (Level C).
- If the situation cannot be resolved and labor begins and/or the amniotic sac ruptures, and conditions are not suitable for a vaginal birth, a cesarean delivery should be performed in good time (Level C).

### ***Recommendations for Treating Premature Rupture of Membranes***

As the risk of fetal infection in patients with premature rupture of membranes and a very low viral load and/or who are on HAART is unknown, treatment of premature rupture of membranes in the HIV-infected woman is not clear. Management will depend mainly on gestational age:

- 22 weeks or less: inform the patient of the possibility of a voluntary interruption of pregnancy given the risks of infection and neonatal complications (eg, lung hypoplasia) (Level C).
- More than 22 weeks and less than 26 weeks: use conservative treatment<sup>66</sup> due to the risk of severe sequelae resulting from prematurity. All patients should receive HAART and take the usual measures (prophylactic antibiotics and corticosteroids, maternal and fetal monitoring) (Level C).
- Between 26 and 30 weeks: provide individual treatment according to health status of the mother and fetus, the mother's virological status, whether or not she has taken HAART, and the neonatal results of the center (Level C).
- Between weeks 30 and 34: complete the pregnancy. In very specific cases, amniocentesis can be considered to determine the maturity of the fetus' lungs according to the expected neonatal results for the relevant week of pregnancy (Level C). In pregnancies of under 36 weeks, elective cesarean delivery is recommended. This recommendation is based on the small trend of an increased risk of transmission in preterm pregnancies with premature rupture of membranes, even if the mother is receiving HAART (Level C).
- 36 weeks or more: if the prognosis for labor is good (Bishop index  $\geq 6$ ), and vaginal delivery is not contraindicated, use oxytocin. On the contrary, a cesarean delivery is recommended (Level C).
- For women with a full-term pregnancy and premature rupture of membranes, induce labor immediately if the Bishop index is favorable and vaginal delivery is not contraindicated (Level C).

### ***Recommendations for Management of Labor in HIV-Infected Pregnant Women***

#### ***Patients on HAART and at Week 36 or More:***

- The main objective is to reach the lowest viral load possible at the time of labor. A last test should be carried out between weeks 34 and 36 (Level B).
- If the viral load is low ( $<1000$  copies/mL), elective cesarean delivery<sup>67</sup> does not seem to improve the reduction of VT. The patient must be made aware of the risks and benefits of cesarean delivery (increased morbidity and mortality)<sup>68</sup> and of vaginal delivery, and she must be able to decide (Level B).
- If the patient decides to have a vaginal delivery, apply obstetric measures aimed at minimizing VT: do not place electrodes on the fetus' scalp, do not make fetal

microtomes, avoid the use of instruments and episiotomy, and try to maintain the amniotic sac intact for as long as possible.<sup>69</sup> (Level B).

***Patients with less than 36 weeks of pregnancy, ART regimens other than HAART, a viral load >1000 copies/mL, or a late diagnosis:***

- Program elective cesarean at weeks 37-38 to avoid, on the one hand, fetal respiratory distress and, on the other, spontaneous initiation of delivery and/or premature rupture of membranes (Level C).
- In the case of a cesarean delivery: administer antibiotic prophylaxis, since the risk of puerperal infection is greater than in a noninfected pregnant woman.<sup>68,70</sup> (Level C).
- Administer intravenous ZDV during the birth, or before cesarean delivery (emergency or elective), regardless of maternal viral load at the time of labor and whether or not she has received HAART during pregnancy (Level C).
- If possible, during labor use the HAART regimen that was used during the pregnancy (Level C).
- In the case of treatment-naïve women, administer ART during labor with NVP<sup>71,72</sup> and add ZDV and 3TC to reduce resistance. Continue until resistance can be evaluated by an infectious diseases specialist (Level C).

## **6. NUTRITION OF THE NEWBORN OF AN HIV-INFECTED MOTHER IN OUR SETTING**

Several cohort studies from different countries have found that the rate of VT is higher in breastfed children than in those who are formula-fed.<sup>73,74</sup>

The factors associated with increased VT are greater HIV viral load, greater HIV viral load in breast milk, increased maternal immunologic impairment, mastitis, and bleeding lesions on the nipples.

### **Recommendations**

HIV-infected mothers must not breastfeed their children. They must use formula (Level A).

## **7. MONITORING AND DIAGNOSIS IN THE CHILD EXPOSED TO HIV**

Diagnosis of HIV infection in the newborn must be made during the first weeks of life so that ART can be started early. The usual diagnostic techniques (ELISA, Western blot, and immunofluorescence) determine the presence of IgG antibodies against viral proteins. They are not useful in the newborn, since the antibodies detected are those transferred by the mother. Therefore, virological tests are mandatory; however, given that at least 50% of children are infected during labor, testing for the HIV-1 genome could give negative results during the first 48 hours of life (a positive result indicates prenatal infection). Therefore, testing should be repeated between weeks 2 and 3 of life, when the sensitivity of the test reaches 95%. (See Recommendations for Antiretroviral Therapy in Children and Adolescents 2008).

If the mother is positive for HBsAg, follow the guidelines set out below in the section on vaccination. As for HCV, if the mother is seronegative and there is a risk of acquiring HCV during pregnancy, the child must undergo PCR for HCV and serology testing at 1 year. If the mother is infected by HCV, serology testing is not necessary until after 12 months. PCR for HCV should be performed at birth and when a blood sample is taken for PCR for HIV. Regardless of the mother's history, TORCH (toxoplasma, syphilis, rubella, cytomegalovirus, herpes) serology testing must be performed, preferably during the first week of life, at the same time it is performed for the mother. Detection of CMV in urine (shell-vial or real-time PCR) is also recommended.

### **Monitoring and Control of ART Toxicity**

Although all antiretroviral drugs are classified as B and C, except for efavirenz (currently category D), the number of malformations does not seem to have increased in exposed children, according to current registries.

It is important to follow up newborns and infants in order to identify early clinical abnormalities arising from mitochondrial dysfunction. A metabolic study should be performed only in these cases.

### **Vaccination**

The currently recommended infant vaccination schedule in our setting should be followed. There is 1 exception: the newborn of an HBsAg(+) mother. In this case, follow the vaccination schedule at 0, 1, and 6 months, and administer anti-hepatitis B specific immunoglobulin during the first 72 hours of life, preferably during the first 6-12 hours. Serology testing should be carried out after the second vaccination dose, and the dose should be repeated if a poor serological response is observed.

### **Prophylaxis for *Pneumocystis jiroveci* Pneumonia and Tuberculosis**

Trimethoprim-sulfamethoxazole: 5-10 mg/kg/d of trimethoprim (1-2 doses), 3 days per week (consecutive or alternate).

- Recommended from 4 weeks of life onward when HIV infection cannot be ruled out. At present, this is only necessary in exceptional circumstances.
- If infection is confirmed, it must be administered until 12 months of life and suspended once immune recovery has been achieved.
- It is important to have information on the tuberculosis status of the mother and of the people who live with her. If any of these people have the disease, the child must be separated from that person until he/she is no longer carrying the bacteria. PPD testing and chest X-ray should be performed and primary chemoprophylaxis should be started with isoniazid once tuberculous disease has been ruled out.
- BCG vaccine is contraindicated in children infected with or exposed to HIV.

### **Recommendations**

- A definitive diagnosis of HIV infection in the child of an infected mother requires 2 positive virologic test results from 2 different samples of the child's blood (Level B).
- Carry out the first test at 24-48 hours of life, the second at 2-3 weeks, and the third at 6-12 weeks.
- Definitive diagnosis in the noninfected child during the first year of life requires 3 negative virological test results, at least one of which must have been carried out at 6-12 weeks of life (Level B).
- In cases where there is an increased risk of transmission of HIV (ie, those newborns who receive 3 antiretroviral drugs), PCR for HIV should be carried out at 48 hours, 2 weeks, and 6 weeks. A fourth should be carried out at 3 and 6 months (Level B).
- Children of mothers with possible infection by non-B HIV serotypes should undergo specific virologic tests (Level C).
- Children aged over 18 months must show negative anti-HIV antibodies in 2 tests separated by a 1-month interval. In children with a negative result in previous virological tests, monitoring of antibodies is sufficient (Level B).

## 8. PRACTICAL CONSIDERATIONS AND SPECIFIC SITUATIONS. TREATMENT AND MANAGEMENT ALGORITHMS

### 8.1. Pregnant Woman With Known HIV Infection and no Previous ART

Pregnancy	Labor	Newborn	Comments
<p><b>If PVL is undetectable (&lt;1000 copies/mL):</b> prophylaxis with AZT from wk 14 onward<sup>a</sup></p>	<p>If delivery before wk 34-35, elective cesarean. PVL tested wk 32-36</p>	<p>AZT always during first 8 hours postpartum, at 2 mg/kg/6 h for 4 wk (1 cc:10 mg).<sup>c</sup></p>	<p>If the woman does not agree with the proposed treatment schedule, this must be recorded in her medical history (given the importance of the decision).</p> <p>EFV, ddC, and the combination of d4T and ddl must be avoided (contraindicated), as must be drugs with which the patient has no experience, or limited experience (TDF, ATV/r, FPV/r, TPV/r, enfuvirtide).</p> <p>Choose drugs with which the patient has most experience.</p> <p>ART can be withdrawn from the mother if there is no indication for treatment for the mother, taking into account the half-life of the drugs so as not to administer covert monotherapy or dual therapy. If the mother has to continue with ART, this can be adapted to her new situation (see text and GESIDA/PNS Recommendations on ART).</p>
<p><b>If PVL is detectable:</b> AZT + 3TC<sup>b</sup> + PI or AZT + 3TC<sup>b</sup> + NVP (latter schedule only in women with CD4 &lt;250/μL. Start preferably from week 14.</p>	<p><b>Maintain HAART</b> Intravenous AZT 2 mg/kg in 1 h in bolus at beginning of labor, followed by 1 mg/kg/h until clamping</p> <p><b>Elective cesarean wk 37-38</b> Recommended if PVL near labor &gt;1000 copies/mL Consider if PVL &lt;1000 copies/mL, but detectable. AZT in iv perfusion minimum 2 h before cesarean</p>		

Abbreviations: ART, antiretroviral therapy; ATV, atazanavir; AZT, zidovudine; ddC, zalcitabine; ddl, didanosine; d4T, stavudine; EFV, efavirenz; FPV, fosamprenavir; NVP, nevirapine; PI, protease inhibitor; PVL, plasma viral load; r, low-dose ritonavir as a booster; TDF, tenofovir; TPV, tipranavir; 3TC, lamivudine.

<sup>a</sup> Before starting monotherapy with AZT, ensure that the undetectable PVL is real (that it is not a laboratory error or a different viral subtype).

<sup>b</sup> If for any reason 3TC cannot be used, ddl is a reasonable alternative.

<sup>c</sup> Newborn: If oral administration is not possible, the iv dose is 1.5 mg/kg/6 h. In premature babies with a gestational age of  $\leq 34$  weeks, the dose is 1.5 mg/kg/12 h from birth to 2 weeks, with a subsequent increase to 2 mg/kg/8 h between weeks 2 and 6 orally. Intravenous dose: 2/3 of the oral dose.

## 8.2. Pregnant Woman With Known HIV Infection and Previous ART

Pregnancy	Labor	Newborn	Remarks
<p><b>If PVL is undetectable:</b></p> <p><b>1. AZT-containing regimen</b> Maintain same treatment (as long as there are no teratogenic drugs or high toxicity)</p> <p><b>2. AZT-sparing regimen</b> If there is no resistance (or suspected resistance) or toxicity due to AZT, consider switching an N(t)RTI for AZT, given the wide experience with this drug and its efficacy. In any case, always replace teratogenic or highly toxic drugs. If possible, replace those drugs with which experience is limited (see last column)</p>	<p>PVL tested at wk 32-36</p> <p><b>Always administer AZT iv</b> at 2 mg/kg in 1 h in bolus at beginning of labor, followed by 1 mg/kg/h until clamping</p> <p><b>Elective cesarean wk 37-38</b> Recommended if PVL near labor &gt;1000 copies/mL. Consider if PVL &lt;1000 copies/mL, but detectable. AZT in iv perfusion minimum at least 2 h before cesarean</p>	<p><b>Mother with undetectable PVL:</b></p> <p>AZT always during first 8 hours postpartum, at 2 mg/kg/6 h for 4 wk (1 cc:10 mg).<sup>a</sup></p> <p><b>Mother with PVL</b> &gt;1000 copies/mL despite ART, advise triple therapy in child. <b>AZT</b> always during first 8 hours postpartum, at 2 mg/kg/6 h for 4 wk. 3TC during first 12 hours; at 2 mg/kg/12 h for 4 wk. If risk factors for transmission (prematurity, ruptured membranes more than 4 hours, genital tract infection, or bleeding), add NVP during first 12 h and at 48-72 hours. Evaluate continuing with NVP at 4 mg/kg once daily from the 5<sup>th</sup> day until 14<sup>th</sup> day of life</p>	<p>Limited safety data for antiretroviral drugs during first trimester. EFV and ddC, must be avoided (contraindicated). Avoid also d4t+ddl (if there are alternatives) and, where possible, drugs with which there is no experience, or experience is limited (TDF, ATV/r, FPV/r, TPV/r, enfuvirtide).</p> <p>Choose drugs with which experience is broad.</p> <p>If NVP is a component of current ART, there is no need to change it regardless of the woman's CD4 count.</p>
<p><b>If PVL is detectable:</b> Use a new 3- or 4-drug regimen depending on the patient's history of ART, resistance, and drug safety during pregnancy. The objective is to obtain an undetectable viral load, at least during the last trimester.</p>			<p>Resistance study indicated to enable a better selection of drugs.</p>

Abbreviations: ART, antiretroviral therapy; ATV, atazanavir; AZT, zidovudine; ddC, zalcitabine; ddl, didanosine; d4T, stavudine; EFV, efavirenz; FPV, fosamprenavir; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, low-dose ritonavir as a booster; TDF, tenofovir; TPV, tipranavir.

<sup>a</sup> Newborn: If oral administration is not possible, the iv dose is 1.5 mg/kg/6 h. In premature babies with a gestational age of  $\leq$  34 weeks, the dose is 1.5 mg/kg/12 h from birth to 2 weeks, with a subsequent increase to 2 mg/kg/8 h orally between weeks 2 and 6. Intravenous dose: 2/3 of the oral dose.

### 8.3. Pregnant Women Who Learns of Her HIV Infection Close to the Birth

This situation means that early detection has failed.

Pregnancy	Labor	Newborn	Remarks
<p><b>End of pregnancy:</b> ART including AZT+3TC+third component (PI or NVP), taking into considered the limited ability of PI to cross the placenta and the potential toxicity of NVP (see text).</p>	<p><b>Always administer AZT iv</b> at 2 mg/kg in 1 h in bolus at beginning of labor, followed by 1 mg/kg/h until clamping</p> <p>If maternal PVL &gt;1000 copies/mL or unknown, elective cesarean at 37-38 weeks. Begin perfusion with iv AZT at least 2 hours before the cesarean.</p>	<p>AZT always during first 8 hours postpartum, at 2 mg/kg/6 h for 4 wk (1 cc: 10 mg).<sup>a</sup></p> <p>Always 3TC during first 12 hours; at 2 mg/kg/12 h for 4 wk (1 cc: 10 mg).<sup>b</sup></p> <p>If risk factors for transmission (prematurity, ruptured membrane more than 4 hours, genital tract infection, or bleeding): add NVP during first 12 h and at 48-72 hours. Evaluate continuing with NVP at 4 mg/kg once daily from 5th day until 14th day of life</p>	<p>Possibly no determination of PVL.</p> <p>After delivery, ART should be maintained or withdrawn from the mother according to her immunologic-virologic status. Take half-life of drugs into consideration so as not to administer covert monotherapy or dual therapy and thus generate resistance.</p>
<p><b>During labor:</b> no time for ART</p>	<p><b>ABSOLUTE INDICATION FOR ELECTIVE CESAREAN</b></p> <p>Always administer iv AZT at 2 mg/kg in 1 h in bolus at beginning of labor, followed by 1 mg/kg/h until clamping.</p> <p>If possible, administer AZT+3TC+NVP to the mother. Continue with this regimen after labor, and adjust ART according to the mother's CD4 count during the peripartum. Withdraw ART gradually in order to prevent resistance (see text) if the mother does not require ART.</p>		<p>See remarks in the birth column for approach to ART in the mother after birth.</p>

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; NVP, nevirapine; PI, protease inhibitor; PVL, plasma viral load.

<sup>a</sup> Newborn: If oral administration is not possible, the iv dose is 1.5 mg/kg/6 h. In premature babies with a gestational age of  $\leq$  34 weeks: the dose is 1.5 mg/kg/12 h from birth to 2 weeks, with a subsequent increase to 2 mg/kg/8 h orally between weeks 2 and 6. Intravenous dose: 2/3 of the oral dose.

<sup>b</sup> If the results of HIV diagnostic tests are negative at birth and 15 days, consider withdrawing 3TC and NVP from day 15 onward. However, the diagnostic validity of PCR-RNA or PCR-DNA at 15 days is unknown when the newborn receives combination therapy.

#### 8.4. Pregnant Woman Not Aware of HIV Infection During Pregnancy or Labor

This situation is the worst failure in prevention of vertical transmission. All pregnant women must undergo an HIV test during pregnancy, and, if this is not possible, during labor, or in the immediate postpartum.

Pregnancy	Birth	Newborn	Remarks
		<p>AZT always during the first 8 hours postpartum at 2 mg/kg/6 h for 4 weeks (1 cc = 10 mg)<sup>a</sup></p> <p>3TC always during the first 12 hours postpartum at 2 mg/kg/12 h for 4 weeks (1 cc = 10 mg)<sup>b</sup></p> <p><u>Detection before 48 hours</u> NVP should be added at 2 mg/kg during the first 12 hours, and at 48-72 hours. Normally, NVP will be continued after the 5<sup>th</sup> day at 4 mg/kg QD until 2 weeks have been completed<sup>b</sup> (1 cc = 10 mg)</p> <p><u>Detection before 48 hours</u> NVP should be added at 48-72 hours, or as soon as possible, and continued after the 5th day at 4 mg/kg QD until 4 weeks have been completed<sup>b</sup> (1 cc = 10 mg)</p>	<p>Although the doses of 3TC and NVP are unknown in premature babies, it seems justified to use the same dose as in the full-term child in situations of risk of vertical transmission.</p> <p>The mother should be evaluated as should the need for ART. In any case, follow-up will be in a specialized unit.</p>

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; NVP, nevirapine.

<sup>a</sup> Newborn: If oral administration is not possible, the iv dose is 1.5 mg/kg/6 h. In premature babies of  $\leq 34$  weeks of gestational age the dose is 1.5 mg/kg/12 h from birth to 2 weeks, with a subsequent increase to 2 mg/kg/8 h orally between 2 and 6 weeks. IV dose, 2/3 of oral dose.

<sup>b</sup> Assess withdrawal of 3TC and NVP after 15 days if the HIV diagnostic tests are negative at birth and 15 days. However, the diagnostic validity of PCR RNA or PCR DNA at 15 days is unknown when combination therapy is administered to the newborn.



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