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Vertical Transmission of HIV — Medical Diagnosis, Therapeutic Options and Prevention Strategy

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1. Introduction

In the eight Millennium Development Goals, the World Health Organization proposed the improvement of HIV/AIDS epidemiological rates worldwide through disease prevention and treatment as a goal to achieve in 2015. Reaching the virtual worldwide eradication of vertical transmission (prevention of mother-to-child transmission [PMTCT]) is among such goals.

This chapter will address topics related mainly to diagnostic and therapeutic aspects that have been proven to be useful in the prevention of HIV vertical transmission (VT). The aim is to provide the reader with a clinical guideline for the management of an HIV(+) pregnant woman based on levels of evidence, grading of recommendation, and experts' opinions and to individualize those healthcare strategies that have demonstrated to be effective in the reduction of HIV vertical transmission. Such achievement will highlight the importance of ordering an HIV test to all pregnant women during prenatal control visit. The latter, in case of carrier status, will help to decrease viral load in HIV(+) mothers to undetectable or almost undetectable levels. It will also enable the formulation of a management strategy based on clinical and laboratory parameters, with the use of the most adequate pharmacological management, thus decreasing exposure of the newborn of an HIV(+) mother, to blood, genital secretions, or amniotic fluid, and to identify the best opportunity to program delivery and termination of breastfeeding.

This Clinical Guideline is intended for midwives, medical students, gynecology and obstetrics fellows/residents, maternal-fetal medicine fellows/residents, obstetricians serving at level 2 and 3 hospitals, and specialists in maternal-fetal medicine, who aim at updating their knowledge on the diagnosis and management of gestations affected by HIV/AIDS.

All the aforementioned will bring insights on why healthcare strategies intended to prevent fetal infection have become a paradigm of perinatal medicine since the application of such

biomedical interventions has been proven to be successful in the prevention of HIV transmission from an infected pregnant woman to her child, decreasing risk levels to 2%, as observed in the United States.

2. Developing the guide

The attempt at improving epidemiological rates of HIV/AIDS through the prevention and treatment of the disease is one of the eight Millennium Development Goals proposed by the World Health Organization. Worldwide, the virtual eradication of mother-to-child transmission is one of the goals to be accomplished [1, 2].

The present guide will be developed based on the method proposed by Harbour et al., which in turn is based on the formulation of various questions that will be answered according to levels of evidence, grading of recommendation, and experts' opinions [3].

Vertical transmission (VT) of HIV is defined as that occurring from mother to child during gestation, delivery, or breastfeeding. The VT rates range between 13% and 48%. [4-7]. Preventive strategies have been set out to lower VT rates to less than 2%. Pregnancy, delivery, and breastfeeding are the most susceptible periods for VT of HIV [8, 9]. Maternal viral load (VL) is the main independent risk factor for transmission. Certain sexually transmitted diseases (STD) also increase the risk of VT. Likewise, low maternal CD4 cell counts also constitute a risk factor for VT, which is independent from VL [10].

The prevalence of vertical transmission (VT) in the various regions of the world varies according to geographic site and specifically according to the contribution of economic resources invested by different countries worldwide in the various strategies for healthcare policies, aiming at the prevention and treatment of infected mothers [2].

In countries with low infection prevalence rates such as Chile, efforts have been targeted to the decrease of vertical transmission (VT), which is responsible for 99% of HIV infections among children younger than 13 years old [5, 11].

Mother-to-child transmission as route of exposure has decreased, from rates of approximately 30% in 1996, prior to the first VT prevention protocol (ACTG 076), to 0.7% for HIV and 0.6% for AIDS, during the 2006-2010 period [4, 12-14].

To optimize prevention of VT, the clinical approach to a seropositive pregnant woman must be based on a thorough assessment of her initial health status, with a full physical examination, focusing particularly on those signs that point toward an opportunistic infectious condition and evaluating her current immune status.

The strategy for prevention of VT has been based on the continuous review of the pooled evidence and has followed the impact factor of such evidence to suggest valid recommendations from expert opinions. It is of key importance to further evaluate new behaviors tending to identify, among other aspects: the eventual induction of resistance and toxicity of antivirals both in the pregnant mother as well as in the newborn, and their potential

effect on subsequent quality of life, the use of micronutrients and the identification of their impact on VT decrease, and the evaluation of vaginal delivery as an option in pregnant women with a low viral load [2, 14-20].

Once the effectiveness of biomedical patient benefits in VT prevention has been demonstrated, it is important to ensure the collection of epidemiological history in order to generate an adequate means of notification, which constitutes data required for reassessing the design and the effectiveness of preventive programs. To attain such goals, it is key to maintain and improve diagnosis and primary prevention of infection in women in childbearing age. Furthermore, it is important to avoid the high rate of unwanted pregnancies and abortions, which represent indirect indicators of risk behaviors in such population. Likewise, one should aim at reaching 100% of screening during the first trimester, at the possibility of repeating such screening during the third trimester and at training maternity staff in rapid testing for the detection of carrier status during labor for pregnant women not having previously undergone such screening [2].

3. Medical diagnosis

3.1. Early diagnosis

Most women discover their carrier status or disease during pregnancy or after delivery upon the detection of the infection in the newborn. With regard to the latter, and despite the fact that there is no consensus on the recommendation of universal screening to all women upon their pre- and/or postconception visit, the American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynecologists United kingdom recommend performing the test on a routine basis, a behavior commonly adopted in many countries worldwide [21, 22]. In fact, most of such countries have also integrated a mandatory pretest counseling, the need for an informed consent, and the willfulness of people upon deciding to undergo the testing. Thus, sample collection requires the participation of staff trained in "counseling". The latter has reinforced the decision of women to undergo the test and has resulted in a significant rise of adhesion to preventive behaviors and therapy (Uganda and Rwanda) [23, 29, 30].

The recommended test for screening is the fourth-generation ELISA. Such laboratory examination enables the simultaneous detection of Ag p24 and its respective antibodies, and therefore the window period is reduced to approximately 30 days with a sensitivity of 99.9% and a specificity of 99.5%. Despite the latter, it is important to stress that the positive predictive value of such test during pregnancy is approximately 50%, as a result of being applied on a low prevalence population. Thus, a confirmation test is required, and therefore patients with positive ELISA test should undergo a confirmatory test with Western blot. The confirmatory Western blot technique is carried out with a nitrocellulose strip onto which HIV envelope proteins have been added. When patient serum is transferred to the strips, any antibody against the virus present in serum will bind to the respective specific antigen on the strip. Western blot results are interpreted by observing the colored bands that are identified according to their

position and particular characteristics. When results are indeterminate, a new sample must be ordered after 3 months to reevaluate eventual positivity [2, 31, 32, 36].

Furthermore, for pregnant patients with unknown serological status that seek healthcare because of labor initiation or medical situations in which pregnancy interruption is imminent, health services should be equipped with rapid diagnostic techniques (visual or instrumental). Despite their nonoptimal specificity and sensitivity, in the event of being positive, such techniques would enable the recommendation of peripartum preventive measures, with prior provision of the informed consent by the patient. Such emergency evaluations may be performed even by individuals lacking a specific training when other human resources are unavailable [33-36].

3.2. HIV detection test requisition among pregnant women: who is eligible?

With regard to the indication of universal HIV testing for women at their preconception consultation and/or at the beginning of their antenatal follow-up visit, the American College of Obstetricians and Gynecologists recommends that it is carried out on a routine basis, as it is the common practice in many countries of the world. In fact, most women are aware of their carrier status during pregnancy or during the puerperium upon screening for neonatal infection. As for the latter, it has been demonstrated that ordering the test together with pre- and posttest counseling improves awareness on the disease, adherence to therapy, and development of behaviors in the carrier to prevent transmission to her individual environment [22-27]. With regard to pre- and postconception counseling, defined as a "confidential conversation between a patient and a counselor that aims at the acquisition by the former of skills to face the stress related to an eventual carrier status, at achieving HIV/AIDS-related decision making during pregnancy, and learning of strategies for the prevention of vertical transmission," it is advisable to address the following topics:

• Information about basic aspects of HIV/AIDS transmission and prevention

• Signature of the informed consent or statement of declination of the test

• Evaluation of the HIV detection test final result, with posttest counseling

• Reinforcement of preventive strategies for HIV and other STD during pregnancy

• Supply of emotional support in the case the result of one or both tests is reactive or positive

• Provision of information on pregnancy control and/or follow-up procedures at the special-ties level and consequent referral in cases with reactive or positive test results

• Support to therapy adherence, exams, and periodic follow-up if applicable

• Record of the activity in the pertaining documents

The trend worldwide regarding HIV test ordering has progressed toward mandatory pro-grams. These are more efficient and less harmful than those that are voluntary or the routine programs with implicit but revocable consent. International organizations (WHO/UNAIDS) recommend guidelines regarding avoidance of compulsoriness of HIV testing and prioritiza-

tion of guidance, education, and advise for its performance [25, 27, 28]. The recommendations/ guidelines should be undertaken regardless of seropositivity prevalence in the population. Such management protocols would enable an adequate control of mother-to-child transmission at the population health level, while protecting mother rights and preventing stigmatization and discrimination. To the WHO, national policies and practices regarding compulsoriness of HIV testing should be reviewed to eliminate any testing that is not voluntary. Mandatory testing or testing under coercion on individuals belonging to vulnerable groups or groups with high risk of infection such as pregnant women should not be performed. Voluntary testing amplification and counseling must include a better protection of risk behavior and seropositivity related stigma and discrimination. Additionally, more support for bonding and connection to prevention, treatment, care, and support services should be provided. Despite the latter and the trends seen in both poor as well as in developed countries, there are some exceptions, such as several states at the United States of America and countries like Chile. In Chile, the HIV/AIDS law has been in force since 2005 but does not accept compulsoriness; however, the 2011 Decree of the Ministry of Health indicates that HIV testing is mandatory for pregnant women [23-27].

It is imperative, therefore, for women at the last trimester or those at due date with unknown serology for HIV antibodies to undergo an urgent HIV screening rapid test. Similarly, counseling must be offered in this case and the corresponding informed consent obtained [23-27]. Should such test be reactive, the vertical transmission prevention protocol should be applied immediately (Level 4 evidence) [19-21, 35, 36].

Based on experts' opinion, HIV testing should be offered to all pregnant women by their second control visit at the latest. Should the result of the test be negative, the latter should be repeated between 32 and 34 weeks of gestation in women under higher risk of acquiring HIV during the first trimester of pregnancy (pathological alcohol consumption, drug addiction, sex workers, multiple sexual partners, etc.), i.e., Grade D recommendation.

3.3. Medical examinations and specialty consultations that should be ordered in HIV(+) pregnant women

Every patient with confirmed serology should be referred to consultation, and immediate coordination should be implemented in order to provide the patient with assessment by a multidisciplinary team (Grade D recommendation).

Routine exams different from those performed on the nonpregnant HIV-positive women are not justified in the pregnant patient with recent positive serology, with the exception of those clinically warranted (Grade D recommendation).

Other STDs should be actively ruled out. Hepatitis B and hepatitis C serology as well as tuberculin skin testing (PPD) should also be performed (Grade D recommendation). Lymphocyte count, viral load, and viral genotyping should be ordered by the immunologist or the infectologist (Grade D recommendation).

The following are listed laboratory tests that should be routinely carried out [2]:

- Rubella serology: both IgG and IgM are evaluated to evidence current or past infection. If there is no evident immunity against rubella, postpartum vaccination is recommended.

- Urine culture: aiming at ruling out an infection of the urinary tract.

- Hepatitis B virus surface antigen: to evaluate the presence of disease, since the transmission mechanism and the risk of vertical transmission are similar, and in the event of a synergic effect in disease progression

- RPR or VDRL: these are nontreponemic tests for syphilis detection. They are highly sensitive but poorly specific. Therefore, if a positive result is obtained, it should be confirmed with a more specific test detecting antibodies against *Treponema pallidum*, such as FTA-ABS (fluorescent treponemal antibody absorption). The presence of such microorganism is associated with increased vertical transmission [9].

- Hepatitis C serology: the purpose of this test is to rule out the carrier status since it is common among HIV-infected patients. It is considered an opportunistic infection and might be patient death cause.

- PPD (purified protein derivative) testing for tuberculosis: to evaluate a tuberculosis diagnosis. In HIV-carrier patients, a cutaneous reaction measuring 5 mm is enough to be considered positive (at least 10 mm should be seen in the remainder of patients). False-positive results may exist, for instance, in patients previously vaccinated with BCG (bacillus Calmette-Guérin). This infectious association should be considered since it worsens patient prognosis.

- *Toxoplasma gondii* serology: to detect the potential opportunistic infection, mainly with encephalic involvement. In a carrier, a latent *T. gondii* infection may be reactivated as a result of a deterioration of cellular immunity in these patients.

- Cytomegalovirus cytology: CMV is the most common viral opportunistic disease in AIDS. It is associated with severe immunosuppression, and the reactivation of a latent disease is its usual form of onset. The disease usually has high mortality rates.

- Gonococcus, chlamydia, mycoplasma, and Ureaplasma cultures: since they share in common their mechanism of transmission, other sexually transmitted infections should be ruled out.

3.4. Immunological parameters

3.4.1. CD4 T-cell count and viral load assessment (PCR)

These are prognostic factors for vertical transmission, and they are determinant factors for the appropriate time to initiate ART. They are also parameters for the assessment of the therapeutic response.

3.4.2. Genotyping

Its evaluation is critical to assess resistance to antiretroviral therapy.

This information indicates that HIV(+) pregnant women should be assessed and treated by a multidisciplinary medical team (Infectologist, immunologist, pharmacist, obstetrician, and neonatologist) (Level 4 evidence) [16-21]. Additionally, as previously mentioned, screening for various STDs found to be related with increased VT is of key importance. Such screening should include herpes simplex virus 2 and *T. pallidum* (Level 2+ evidence [2-9].

4. Pre- and postnatal treatment

4.1. Therapeutic options

In pregnant HIV carriers, the transmission of the infection to the fetus can occur mainly during delivery (65%), but also during pregnancy and breastfeeding with approximate rates of 35% and 15%, respectively. Such risk for transmission increases with certain factors such as maternal primary infection during pregnancy, intercurrent sexually transmitted infections, decreased CD4 counts, and high viral loads (27). In relation with the latter, and despite the fact that viral loads lower than 1000 copies/ml present a significantly lower risk for vertical transmission, there is no viral load exemption from VT risk. Thus, triple-drug highly active antiretroviral therapy (HAART) regimens have been proven to reach the goal of undetectable viral load levels with a reasonable risk versus benefit quotient, especially during the peripartum period where the risk of infection of the product of conception is higher. It is during that same period that it is advised to incorporate zidovudine to the regimen, since it has demonstrated its efficacy in abbreviated regimens prescribed during the intrapartum and postpartum periods [2, 37-50].

Moreover, the study of the teratogenic risks entailed by the different drugs used in ART regimens has not evidenced a higher incidence of congenital defects than that observed in general population. Likewise the APRI (Antiretroviral Pregnancy Registry International) study on the prevalence of congenital defects was 2.2 per 100 live births when assessing the use of ART at any stage of pregnancy and was 3% when therapy was used during the first trimester. With the exception of efavirenz, which is categorized by the FDA as D, because of its association with neural tube defects, the rest of ARV is categorized as B or C [2]. There are reports in which AZT might be related to an increase of hypospadia rates among the exposed human population, and others where delavirdine might be associated with increased cardiac septal defects in animals [46-49].

The following drugs or combinations should not be indicated during pregnancy: efavirenz, nelfinavir, and the association of d4T (stavudine) and ddI (didanosine). They all share teratogenicity and the risk of toxicity to the mother-child binomial [46-51]. Finally, to optimize the update in side effects, it is essential to fully and continuously report to the competent organizations such as APRI about the possible secondary teratogenic effects and to comply strictly with regulations on the indication for therapy initiation and drug choice according to the stage of pregnancy [46-49, 51].

Although it is true that the first attempt to control VT with a successful pharmacological regime was achieved by the protocol known as ACTG 076, a protocol attaining a decrease in VT from

29% to 5.6% in 2001, new evidence has demonstrated that triple ART was more effective than monotherapy or bitherapy in VT prevention [14, 42-45]. Thus, a protocol that associated biomedical preventive measures (cesarean section and elimination of breastfeeding) with the indication of a combination of three antiretroviral drugs (nucleosidic and nonnucleosidic inhibitors of reverse transcriptase and protease inhibitors, regimens known together as Highly Active Antiretroviral Therapy or HAART) was designed [14, 42-45].

4.2. Antiretroviral therapy during pregnancy

The purpose of pharmacological therapy during pregnancy is to prevent vertical transmission through the reduction of the viral load in the mother to undetectable levels without resulting in teratogenic effects on the fetus. There are currently 14 commonly prescribed antiretroviral drugs (Table 1) that should be used to customize regimens in which selection is based on the eventual prior treatment of the pregnancy, the status of the disease, the viral load, CD4 cell counts, and the associated toxic and teratogenic effects according to FDA (Tables 1 and 2). Despite other drugs having been demonstrated efficacious in preventing vertical transmission, it is advisable to include the use of zidovudine within the antiretroviral scheme since it is the only drug that has proven efficacy and, most of the times, to be innocuous to the fetus in protocolized regimens (AIDS Clinical Protocol 076-ACTG 076) [2].

Generic name	FDA category
Nucleoside reverse transcriptase inhibitors	
Abacavir	C
Didanosine (ddl)	B
Lamivudine (3TC)	C
Lamivudine + zidovudine (Combivir)	C
Stavudine (d4T zalcitabine)	C
Zidovudine (ZDV, AZT)	C
Nonnucleoside reverse transcriptase inhibitors	
Delavirdine	C
Evavirenz	X
Nevirapine	C
Protease inhibitors	
Amprenavir	X
Indinavir	C
Nelfinavir	X
Ritonavir	B
Saquinavir	B

Table 1. Antiretroviral agent categories according to FDA

Category	Interpretation
A	Controlled studies fail to demonstrate risk
B	No evidence of risk for humans
C	The existence of risk cannot be ruled out; should only be used when potential benefits justify potential risk to the fetus
D	Proven risk
X	Contraindicated in pregnancy

Table 2. FDA pregnancy categories

4.2.1. ART toxicity and side effects

One of the aspects that need to be assessed for the selection of a pharmacological therapy is the eventual toxic effect of such medications on the mother-child binomial. Thus, studies have reported that approximately 80% of treated pregnant women developed certain side effects such as anemia, nausea, vomiting, abnormal liver enzyme results, or hyperglycemia [44-49]. As a consequence of the aforementioned, it is essential to know the side and toxic effects of the drugs generally used (Table 3) in order to identify them and act accordingly in the event of using them.

4.2.2. Protease inhibitors

In the general population, protease inhibitors have been linked to the induction of variable degrees of carbohydrate intolerance. The latter should be considered when prescribing the patient such drugs to the pregnant woman since they might trigger the development of gestational diabetes [44-49].

4.2.3. Nucleoside—reverse transcriptase inhibitors

There is evidence that nucleoside reverse transcriptase inhibitors may induce mitochondrial dysfunction by virtue of their high affinity for gamma DNA-polymerase found in mitochondria. Among the drugs of such family that are more intensely related to such adverse effect are d4T (stavudine) and ddI (didanosine) and, to a lesser extent, ZDV (Zidovudine), 3TC (lamivudine), ABC (abacavir), and TDF (tenofir). The association between such type of drugs and lactic acidosis with or without concomitant liver steatosis is also known. Such conditions are more commonly seen in association with the use of d4T (stavudine) (0.8%-1.2%) [44-49]. The clinical picture resulting from such entity is similar to Hellp syndrome, a condition that may or may not be associated to polyneuropathies, fatty liver, myopathies, cardiopathies, and lactic acidosis. Finally, there are literature reports on children from mothers exposed to zidovudine or zidovudine/lamivudine (AZT/3TC) who developed mitochondrial dysfunction-related symptoms, a finding that was not observed in the cohort of patients following the ACTG/076 protocol [2].

AR	Main toxicity	Other toxicities
AZT	Anemia - Neutropenia	Gastrointestinal-headache-rash
d4T	Polyneuropathy, lipoatrophy, lactic acidosis	Pancreatitis, hepatic steatosis
3TC	-	Gastrointestinal-headache
ddl	Pancreatitis, polyneuropathy	Gastrointestinal, Hyperuricemia
Abacavir	Hypersensitivity reaction	Gastrointestinal
Tenofovir	-	Gastrointestinal, Renal
Efavirenz	CNS: Vertigo, Psychosis	Rash, hepatotoxicity, dyslipidemia
Nevirapine	Rash, Hepatotoxicity	
PI (except for Atanazavir)	Lipodystrophy, dyslipidemia, diabetes	Liver toxicity, gastrointestinal, osteonecrosis
Indinavir	Metabolic, hyperbilirubinemia, kidney stones	Gastrointestinal
Atanazavir	Hyperbilirubinemia, rash	Gastrointestinal

Table 3. Antiretroviral agent toxicity

4.3. Opportunity for ART initiation in pregnancy

Several cohort studies show that the late initiation of ART is associated both with higher VT as well as with longer duration of VT. The latter is based on the fact that when therapy duration was 9.5 weeks, VT was significantly higher than when therapy duration was 16 weeks ($P < 0.001$) [21]. Conversely, in a study conducted at the United Kingdom and Ireland VT was significantly higher among patients with a delayed initiation of therapy (25 + 6 vs. 30 + 1 weeks, <0.001; level of evidence: 2++) [2, 14]. Conditions of ART initiation during pregnancy are listed as follows:

- A pregnant woman without prior therapy should initiate ART from 20 weeks of gestation (Grade B recommendation).

- When VL is higher than 100,000 copies/ml, ART should be initiated by week 14 (Grade B recommendation).

- If the pregnant woman has clinical or immunological criteria for ART initiation, or if seroconversion occurs during gestation, ART must be initiated immediately (Grade B recommendation).

- A low frequency of VT (5%) has been observed during the second trimester of pregnancy. Thirty-four percent of VT occurs during the antepartum and 66% occurs during delivery [2, 7, 10, 12]. However, placental transmission may occur from 13 weeks (Level 2++ evidence C).

4.4. Choice of drugs to start ART

Triple ART or HAART (highly active antiretroviral therapy) is the preferred choice. The use of zidovudine (AZT) in association with lamivudine (3TC) 600 and 300 mg per day, respectively, is recommended for the prevention of HIV vertical transmission. A preparation

including both drugs in a fixed drug combination of 300 mg AZT and 150 mg 3TC is commercially available (grade of recommendation: A). Lopinavir/ritonavir (800/200 mg daily) or saquinavir/ritonavir (2000/200 mg daily) are recommended as a third drug (Grade C recommendation). The use of nevirapine (NVP) as a third drug may be considered in patients with CD4 T-cell counts lower than 250 cells/mm^3 (200-400 mg daily) (Grade C recommendation).

A higher incidence of malformations failed to be demonstrated on 3,000 pregnancies exposed to AZT and 3TC. The 3TC+AZT combination has evidenced a higher efficacy in the prevention of VT than AZT as monotherapy. Cohort studies have reported a reduction in HIV mortality and transmission with the use of AZT+3TC (Level 2+ evidence). There is not enough comparative evidence of the efficacy of other ARV combinations on VT prevention (Level 2+ evidence) [19, 20, 43, 45].

The use of NVP in pregnant women with CD4 T-cell counts between 250 and 350 cells/mm^3 failed to confirm an increase of the risk of suffering severe adverse effects. The benefits of using NVP in pregnant women outweigh the risks (Level 2+ evidence) [19, 20, 43, 45].

4.5. Procedures for monitoring ART during pregnancy

Efficacy of ART is measured through the decrease of viral load. ART is effective if the decrease is near 1 log of VL 2 weeks after the initiation of therapy and 1.5 log at 4 weeks. Achieving a decrease of 2 logs between 28 and 34 weeks of gestation is also considered effective [19]. The viral load should be assessed upon the first control visit. Viral load should be controlled 2 and 4 weeks after the initiation of therapy or after a change in therapy. Subsequently, VL should be controlled on a monthly basis until becoming undetectable. At gestation weeks 34-36, a VL assessment should be performed to define the route of delivery, eventual additional ART, and to plan ART for the newborn (Grade D recommendation).

In patients starting ART before week 24, a VL every 2 months (8 weeks) and at week 34 is recommended (Grade D recommendation).

Several clinical guidelines propose such management based on expert recommendations (Level 4 evidence) [15-17, 19-21].

4.6. What are the best moment and the recommended route for delivery?

A cesarean section should be indicated at 38 weeks of gestation in women with HIV infection without ART during pregnancy, in women without a VL result at gestation week 34, or in cases of VL >1,000 copies/ml (Grade B recommendation).

A vaginal delivery may be allowed in mothers under ART from 24 weeks of gestation or earlier, with VL <1,000 copies/ml at week 34, CD4 T-cell counts above 250, and that additionally meet the following conditions:

- Gestational age greater than 37 weeks

- Single fetus in cephalic presentation

- Favorable obstetric conditions

- Care provided by specialist physician

- Informed consent from the patient

Invasive maneuvers (amniocentesis, chorionic villus biopsy, internal monitoring, artificial rupture of membranes) and instrumental delivery (forceps, spatulas) should be avoided (Grade D recommendation) though oxytocin may be used for labor guidance. The use of methylergonovine for the management of uterine inertia should be avoided if the patient is using protease inhibitors.

Elective cesarean section at 38 weeks of gestation, before an eventual rupture of membranes or initiation of spontaneous labor, substantially reduces the risk of HIV transmission. On its own, elective cesarean section reduces the risk of HIV transmission in 50%. Cesarean section together with antiretroviral therapy during the antenatal period, during delivery and administered to the newborn with the addition of termination of breastfeeding, achieves decreases close to 90% with final vertical transmission rates under 2% (Level 2++ evidence) [52-57].

Studies with large patient numbers have failed to show benefits in favor of cesarean section in women undergoing ART with VL <1,000 copies/ml. Shapiro showed transmission rates for vaginal delivery of 0.8 v/s 0.5 for cesarean section (OR 1.4 (0.2-6.4)) in patients with viral load lower than 1,000 copies/ml. (Level 2+ evidence) [53]. Moreover, cesarean section has been seen to cause 7-10-fold increases in morbidity, mainly infectious, as compared to vaginal delivery (Level 2+ evidence) [57]. Obstetric procedures that increase the risk of fetal exposure to maternal blood such as amniocentesis, villus biopsy, and invasive monitoring have been implicated by some researchers as transmission risk factors (Level 2+ evidence) [30]. The use of oxytocin is not contraindicated; however, ergot derivatives accumulate in patients receiving protease inhibitors because of the inhibitory action of the latter on cytochrome 3A4, and exaggerated vasoconstriction and ischemia have been described in relation with their use in association (Level 4 evidence) [15-20].

4.7. Antiretroviral drugs used during delivery or cesarean section

Intrapartum intravenous AZT shall be used in the indicated dose, regardless of the chosen route for delivery (Grade B recommendation), as follows:

- Loading dose: 2 mg/kg, infused over 1 h (in case of cesarean, 4 h prior to surgery)

- Maintenance dose: 1 mg/kg/h during cesarean section (to run 3 h after the loading dose) or during labor, until the cord is clamped

- In case AZT 200 mg is unavailable, the oral administration of AZT/3TC upon the initiation of labor or 4 h prior to scheduled cesarean section is recommended

Nevirapine 200 mg single dose before cesarean section shall be added in any of the following settings (Grade B recommendation):

- The late initiation of the protocol (later than 34 weeks and patients that failed to complete 4 weeks of ART upon delivery)

- VL week 34 >1,000 copies/ml

- Intrapartum HIV (+) diagnosis that did not receive ART

When NVP is used intrapartum, AZT/3TC should be added for 7 days postpartum to decrease the risk of developing resistance to NVP (Grade B recommendation).

The use of IV AZT during delivery enables reaching effective fetal plasma levels thus generating a preexposure prophylaxis. The latter, together with the oral administration of AZT suspension to the newborn for 6 weeks, enables a postexposure prophylaxis that as a whole has an impact on VT regardless of the patient having received AZT within her ART regimen during pregnancy or even, in the case of an eventual resistance to AZT (Level 2+ + evidence) [53-55].

4.8. Breastfeeding management

Pharmacological cessation of breastfeeding shall proceed in all HIV(+) women even if such result is just from the rapid intrapartum test (Grade B recommendation). Based on four studies in which mothers acquired HIV-1 after birth, the estimated risk of transmission is 29% (95% CI 16-42%). The analysis of five studies showed that when the mother became infected before delivery, the additional risk of transmission through breastfeeding, beyond *in utero* or intrapartum transmission, is 14% (95% CI 7-22%) (Level 2+ evidence) [56, 57].

5. Special situations

5.1. What to do with HIV(+) pregnant women who received previous ART and are currently without ART?

A CD4 T-cell count, a VL, and a viral genotyping study are recommended in women previously exposed to ART and who discontinued therapy. The latter will enable designing the therapeutic regimen based on patient history and current genotype. Viral load should be assessed after 4 to 6 weeks of the initiation of ART, and a new genotyping study should be performed in case of failure, for adjustment of the latter. Zidovudine should be included in the ART regimen when possible (Grade D recommendation).

Several clinical guidelines propose such management based on expert recommendations (Level 4 evidence) [15-20].

5.2. What to do with HIV(+) women undergoing ART who become pregnant?

Women undergoing ART who become pregnant are recommended to maintain ART if their VL is undetectable. If the regimen includes drugs that increase toxicity (D4T) or contains Efavirenz, these should be withdrawn and replaced with lopinavir/ritonavir or by saquinavir/ritonavir, including, when possible, AZT in the regimen (Grade D recommendation). The WHO guidelines do not recommend the use of the antiretroviral medication efavirenz (EFV) during the first trimester of pregnancy because of its potential fetal teratogenic effects, mostly

involving defects of neural tube closure. Nevertheless, there are no categorical studies supporting such recommendation (Level 3 evidence). Likewise, the use of the ddI/d4T combination should be terminated [15-21].

The genotyping study should be performed on pregnant women undergoing ART with VL >1,000 copies/ml, particularly in pregnancies that have not achieved such goal at 34 weeks of gestation. Moreover, the addition of a single dose of nevirapine at the moment of delivery is suggested (Grade D recommendation).

Several clinical guidelines propose such management based on expert recommendations (Level 4 evidence) [15-21].

5.3. What to do with HIV(+) pregnant women who reach 32 weeks of gestation without ART?

In pregnant women reaching the 32nd week of gestation or more without ART, it is recommended to assess CD4 T-cell levels and VL and to initiate immediately ART with AZT/3TC coformulated, together with a protease inhibitor (PI). Nevirapine (NVP) can be used instead of a reinforced PI when CD4 T-cell counts are lower than 250 cells/mm^3 (Grade D recommendation).

There is wide experience on the use of NVP during pregnancy. The drug has a risk of severe hepatotoxicity with CD4 >250 cells/mm^3, especially in coinfection with HBV and HCV. Several clinical guidelines propose such management based on expert recommendations. When NVP is used during delivery, AZT/3TC needs to be used subsequently to prevent drug resistance induced by NVP (Level 4 evidence) [15-21].

5.4. What to do with HIV(+) pregnant women close to delivery date without prior ART?

The following are to be observed:

- Ideally assess CD4 T cells and VL.
- Intravenous zidovudine as per regimen.
- Single dose of nevirapine.
- Resolution of delivery through cesarean section.
- Use AZT/3TC for 1 week, add PI, until evaluating the best regimen to continue therapy (Grade D recommendation).

Several clinical guidelines propose such management based on expert recommendations (Level 4 evidence) [15-21].

5.5. What to do with HIV(+) pregnant women who have been treated with ribavirin?

Because of the potential teratogenesis of ribavirin, its preconception withdrawal for at least 4 months in women and at least for 7 months in case the couple had received such drug should be counseled. In case of an eventual use during pregnancy, it should be immediately withdrawn, and a consultation visit should be arranged to assess maternal liver function.

5.6. What to do with HIV(+) pregnant women with threat of premature delivery?

The administration of IV AZT 2 mg/kg/h, together with tocolytic therapy, during the first hour followed by 1 mg/kg/h until dynamics ease up, according to ART administration policy during delivery, is recommended in the presence of regular uterine dynamics, despite cervical modifications being scarce. If unable to slow down the situation and if delivery is triggered and/or rupture of membranes ensues, a cesarean section shall be performed sufficiently in advance (Grade C recommendation).

Premature delivery constitutes a risk factor for perinatal transmission of the virus: a maternal viral load (VL) of <400 c/ml in a delivery occurring before 34 weeks was related to an 8-fold increase in the risk of transmission as compared to term delivery (Level 2+ evidence) [58].

5.7. What to do with HIV(+) pregnant women with premature rupture of membranes?

All patients should receive ART and undergo the usual control and therapeutic measures such as the administration of prophylactic antibiotics, steroids, and eventually the use of magnesium sulfate as neuroprotector. In case of a suspected infection or loss of fetal well-being, pregnancy interruption must be carried out. The recommended delivery route is cesarean section. The management of each case depends on the gestational age (Grade D recommendation).

In pregnancies of less than 26 weeks, a conservative therapy is recommended in view of the risk of severe sequels as a result of prematurity and high neonatal mortality (Grade D recommendation). Between weeks 26 and 30, each case shall be evaluated according to maternal and fetal status, the virological status of the mother, if she has been administered a therapy or not, and the neonatal outcomes of the center (Grade D recommendation). Between 30 and 34 weeks, the general behavior that is recommended is to terminate pregnancy. In view of the higher tendency to an increase of reported VT in premature deliveries with PROM even while receiving ART, the preferred route for delivery shall be cesarean section (Grade D recommendation)

There is a clear difference in the risk of severe sequels between gestational ages (61.5% at week 23 and 10% at week 28). In view of the higher risk of VT in preterms, a cesarean section shall be considered (Level 2+ evidence) [21, 56, 58].

Before the use of ART during pregnancy, several studies found a relationship between the duration of the rupture of membranes and the VT, particularly if such duration was greater than 4 h. In women with less than 24 h since the rupture of membranes, for every hour that elapses after the rupture, the risk of vertical transmission rises in 2%. Because the risk of fetal infection in patients with PROM and very low plasmatic viral load and/or under ART is unknown, treatment of PROM has not been fully clarified. Several clinical guidelines propose such management based on expert recommendations (Level 4 evidence) [15-21].

6. Conclusion

Recommendations and protocols discussed above are easy to implement in countries with adequate resources, consolidated healthcare systems, and proven functional system with trained healthcare personnel and high literate population. Countries must strategically choose their models for the provision of services, taking into consideration the type of epidemics, cost-effectiveness, equity in access, and available resources. The WHO at present collaborates with poor countries, proposing a "Health Systems Platform for HIV/AIDS." Such idea comprises the following areas that are considered as crucial: (1) labor systems that ensure the availability of a sufficient number of trained healthcare providers that work in an adequate facility and in safe conditions, (2) systems to purchase and distribute medications and other supplies, (3) fair funding systems to prevent people from being pushed into poverty when they become ill, and (4) healthcare information systems to alert the administrators of healthcare assistance and those in charge of elaborating policies addressing risks for persons in situations that might severely worsen. Of all these necessities, the most urgent is the availability of a sufficient number of health professionals. Nevertheless, there are some experiences gained through the participation of untrained personnel in some stages of the process; for instance, in the diagnosis of the condition of HIV carrier, this should not be de-emphasized.

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