ORIGINAL ARTICLE

Twenty-year experience in the management of pregnant women infected by HIV/AIDS at the Instituto Nacional de Perinatologia (National Institute of Perinatology) in Mexico City

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Abstract

Background: We undertook this study to review international recommendations and report the experience from the Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes (INPerIER) in the management of pregnant women with HIV/AIDS.

Methods: We reviewed medical records of 200 pregnant women with HIV/AIDS receiving care at INPerIER from 1988-2008 with specific focus on different scenarios of pregnant HIV/AIDS patients and different modes of antiretroviral prophylaxis. Treatment advances are also presented.

Results: The impact of diverse worldwide strategies can serve to decrease perinatal transmission of HIV. We report our experience at INPerIER in demonstrating a decrease in the rate of vertical transmission between 1988 and 1998 to 0%.

Conclusions: Early medical interventions with antiretroviral therapy has allowed us to reduce vertical transmission in pregnant women with HIV/AIDS to <2% over a 20-year period and to 0% since 1998.

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Introduction

In the CDC publication *Morbidity and Mortality Weekly Report*, Gobttlieb et al.[1] reported their observations made between October 1980 and May 1981 about a group of male homosexuals who presented uncommon clinical profiles related with pneumonia from *Pneumocystis carinii* (today known as *Pneumocystis jirovecii*). Their article reported the clinical evolution of four male homosexual patients living in California who presented *P. carinii* pneumonia, invasive mucocutaneous candidiasis, cytomegalovirus infections and Kaposi's sarcoma, which was associated with a strong cellular immunosuppression. This report allowed us to establish evidence of a new acquired cellular immunodeficiency.[1]

The first immunodeficiency reports including patients with hemophilia and persons with history of transfusion appeared in 1982, which modified the homosexual character of the disease to include blood transmission. The first case with suspected perinatal transmission was reported in 1983.*2*

Epidemiology

Evolution of HIV/AIDS epidemic has been dynamic, changing its presentation patterns in the population and it represents one of the most serious public health problems worldwide. UNAIDS (The Joint United Nations Programme on HIV/AIDS) reported in November 2007 that the percentage of persons living with HIV had become stable and highlights that the number of infections had

decreased, in part as the result of prevention programs. UNAIDS had considered that the number of persons living with HIV in that year was 33.2 million (30.6-36.1 million), 2.5 million new cases appeared (1.8-4.1 million) and 2.1 million patients (1.9-2.4 million) died from the disease.[3]

Currently, it is considered that >50% of persons infected are between 12 and 24 years of age. Even though in Mexico patients are predominantly male, females are the population group with the highest growth incidence in previous years, being the only group where mortality has increased during the last decade.

The evolution of HIV transmission in women has shown dramatic changes. In the early 1990s, the main transmission method in women was through the sharing of infected needles during the use of intravenous drugs. However, in the next decade, most infections in females were related to heterosexual transmission.

According to the November 2008 report from National Center for Prevention and Control of HIV/AIDS (CENSIDA) in Mexico, the estimated prevalence of the disease is 0.2% of the total population with 124,505 cases recorded officially. Male/female ratio has changed from 20:1 at the beginning of the epidemic to a 5:1 ratio and, disturbingly, in some states of the country this proportion has reached 3:1. Of the total of new female cases recorded in 2008, 99.2% presented a heterosexual transmission origin. On the other hand, and despite prevention programs for perinatal HIV transmission, 40 new pediatric HIV cases were reported in 2008, all as a result of perinatal transmission.[4]

Some reasons that may explain the increase of incidence and mortality rates in females are the vulnerability of this social group about their freedom of choice in sexual relations, having the ability to demand the use of prophylactics (condoms) during intercourse, inequitable access to healthcare services in some developing countries, as well as lack of knowledge from healthcare providers about clinical manifestations of the disease in this particular population group.

HIV Perinatal Transmission

HIV perinatal transmission is defined as HIV transmission from mother to child during pregnancy, labor and delivery, or breastfeeding.

Pregnancy. HIV transmission risk has been estimated to be 8% during pregnancy, but if this occurs at an early gestation stage, procedures to prevent transmission may be difficult. Also, if transmission occurs during the pre-embryonic period (3 to 5 weeks of gestation), this may trigger a spontaneous abortion, which has been demonstrated by HIV identification in fetal tissues.[5]

HIV-1 has been found through in situ hybridization in placental tissues and has been documented in amniotic fluid cultures from endothelial decidua cells and placental Hofbauer cells.

Viral RNA can be detected in the plasma of newborns (NB) during the first 48 h of life, and it is considered that without interventions the NB may present an early development of the disease (before 12 months of age) in 30% of cases. It is important to mention that infected NB are generally asymptomatic at birth, with a possible bimodal presentation of the disease reported for the pediatric population, described in three groups of patients:

•Rapid progressors (20%): serious clinical manifestations during the first 6 months of life and AIDS development at 12 months of age; mortality presents at 3 years of age

•Average progressors (75-80%): mean age for diagnosis is 3 years of age with less aggressive clinical manifestations

•Slow progressors (1-5%): remain asymptomatic >8 years with a stable immunological panorama6 (Table 1).

Labor and Delivery. Labor and delivery is considered the most important phase for several reasons: HIV transmission can occur during labor through transplacental microtransfusions from mother to child or through direct contact with fluids during delivery. The virus has also been isolated in amniotic fluid from cervicovaginal fluids. Risk of infection has been calculated in 14-16% during this period; however, there are factors such as type of delivery, premature rupture of membranes, placental detachment, and fetal-monitoring invasive processes can all increase the risk percentage. Higher transmission risk in twin births has also been documented with a double-risk for the second twin possibly because of a longer labor exposure. Viral load in NB who have become infected during labor and delivery is initially low, increasing in the following 2 months of life and decreasing afterwards. It has been estimated that in 70% of cases, there is a late symptom presentation in these children (after 12 months of life). Transmission during labor and delivery has been the focal interest of most programs

Table 1. Risk factors associated with perinatal HIV transmission

Viral Phenotype Viral diversity No syncitio induction Macrophage tropism	Obstetric Length of membrane rupture Amount of materno-fetal transfusion Placental detachment Delivery type: vaginal, abdominal, forceps Fetal exposure to blood Invasive fetal tests: internal electrodes, hair/skin sampling, amniocentesis, umbilical cord sample
Maternal High viral load (mother) Acute HIV infection Advanced disease Low CD4 T-cell percentage High CD8 percentage Low neutralizing antibodies levels Use of recreational drugs Unprotected intercourse during pregnancy Vitamin A deficiency Sexually transmitted diseases	Fetal and neonatal Genetic susceptibility Cutaneous integrity Low gastric acidity Prematurity Low birth weight
Placental CD4 expression between placental cells Loss of integrity of placental barrier Chorioamnionitis Smoking	From breast milk Viral load in milk Specific antibodies

Modified from: Landers DV, Duarte G, Crombleholme WR. Human immunodeficiency virus during pregnancy. In: Faro S, ed. Infectious Diseases of Women. New York: McGraw-Hill; 2001. pp. 525-541.

to prevent vertical HIV transmission.[7,8]

Breastfeeding. The main transmission factor after birth is breastfeeding, estimating that up to 33% of worldwide AIDS pediatric cases are related to an elongated breastfeeding period. In spite of an estimated transmission risk between 4% and 22%,[9] a significant number of newborns exposed to breastfeeding present >700,000 virus copies daily in oral and gastrointestinal mucosa.10 It has also been documented that of 200 infected women, 58%11 present virus copies during breastfeeding. Nevertheless, advantages and disadvantages of breastfeeding are still being discussed in developing countries where there are no appropriate follow-up procedures. These transmission or protection mechanisms through human breast milk are not yet well defined, and HIV can pass into the gastrointestinal mucosal epithelium through miniscule continuity solutions.[12]

A low prevalence of HIV infections in pregnant women during the 1980s and 1990s was reported in Mexico. In 1988, the Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes (INPerIER) carried out a study including 600 blood serum samples from pregnant women living in the states of Oaxaca and Tabasco and through external consultation found a prevalence of 0.04% HIV infection.[13] Years later, CENSIDA carried out a sentinel study that documented a prevalence of 0.09% HIV infection in pregnant women.[14] However, it is with concern that a study carried out in 2004 in the General Hospital of Tijuana identified a prevalence of 1.3% HIV infection in pregnant women who attended the institution.[15] This scenario may be similar in other northern border cities in Mexico and it is imperative to establish constant surveillance programs. Unfortunately, there are legal obstacles in Mexico that limit the openness of these surveillance tests and it is mandatory that the patient receives counseling and provides informed consent in order to carry out the test. This delays the opportunity to detect a higher number of HIV-infected women.

The ACTG 076 study carried out in 1994 showed the usefulness of prophylactic HIV treatment using zidovudine (ZDV), which was a positive factor because it reduced >70% vertical HIV transmission, opening the possibility for a positive impact on the pandemic, halting the primary form of HIV transmission in the pediatric population.[16]

During the 11th International Conference on AIDS

in Vancouver, Canada (1996), a global commitment was established so that by the end of the 20th century transmission rates were reduced to <2%. This commitment strengthened worldwide efforts that generated a number of global strategies to comply with this goal.[17,18]

As part of a comprehensive care program for HIV-infected pregnant women, we have established at INPerIER the goal to provide appropriate antiretroviral (ARV) treatment to all HIV-infected women who attend the institution for appropriate infection management and to reduce perinatal transmission rates. This experience at INPerIER began in December 1988, having cared for a total of 241 HIV-infected pregnant women until December 2008. This period could be divided into three stages: the first stage includes obstetric care of the mother and pediatric care of her offspring where perinatal results showed an incidence of 22% transmission.[19,20] At a second stage, prophylactic ZDV antiretroviral therapy was administered in these women, reducing perinatal transmission to 10%.[21,22] A third phase began in 1998 when we started combined ARV therapy, selective Cesarean delivery and breastfeeding inhibition, achieving a reduction of perinatal HIV transmission so that all children born under this program have been diagnosed as free of infection. We currently have three pregnant women and four children being followed-up, with the first viral load determination <50 copies/mL.[23]

Prophylactic Therapy vs. Highly Active Antiretroviral Therapy (HAART)

Azidothymidine (AZT, currently ZDV) was the first ARV drug used with known effectiveness since 1987. When used during the 1994 ACTG 076 study, it demonstrated its efficacy in the prevention of perinatal HIV transmission, reducing this risk in >70% of cases.[24]

Observed results represented a cascade of information about the benefit of ARV therapy against vertical HIV transmission, having a rapid increase in the number of worldwide studies with the same purpose.

The implementation of these efforts has radically modified management of pregnant HIV-infected women in the last 14 years, changing from passive obstetrical care to an aggressive intervention that has provided better results to contain this epidemic in the pediatric group.

There are two groups that classify scientific efforts: the first group contains prophylactic studies aimed towards reducing vertical HIV transmission with ARV drugs. The second group also offers a better option in the management of women, improving survival with a higher quality of life and reducing the risk of early ARV drug resistance (induced by monotherapies). Currently, this form of patient management is considered the best approach.

Short-treatment Period Studies

The interest in reducing the period of ARV therapy administration during pregnancy was based on the limited resources available in some developing countries that had difficulties in implementing protocol 076 either because of social or economic reasons. Among the problems, there was the inability to identify pregnant HIV-infected women at an early stage that allowed them to be included in a therapy regimen from the second trimester of pregnancy, as well as the absence of strict perinatal control in several countries. The most important problem related with the management of pregnant HIV-infected women was possibly economic due to the direct cost associated with the treatment required by each woman.

The shortened therapy was used in studies carried out in Thailand, Côte d'Ivore and Burkina Faso[25,26] and included pregnant HIV-infected women between their 36th and 38th week of gestation. The Thailand study demonstrated that the group treated with ZDV had a transmission rate of 9.2% vs. 18.6% from the placebo group, which represented a reduction of 51% in the risk of infection transmission.

The Côte d'Ivore and Burkina Faso26 repeated this scheme, including women from their 38th gestation week, and NB were breastfed. The Burkina Faso included 1 week therapy for mother after childbirth. Both studies showed a reduction of 37% and 38%, respectively, of the transmission rates.

Results from HIVNET 012 (Uganda) study were published in September 1999. This study evaluated the usefulness of high doses of ZDV during childbirth compared with a single dose of nevirapine (NVP) during childbirth. Results showed failure of ZDV under this scheme and NVP efficiency up to 13% to reduce infection transmission rate.[27] This represents an excellent last-minute alternative.

A multicenter study carried out in the U.S., Europe, Brazil and Bahamas included 1270 women with these characteristics. Of these women, 642 and their NB received an extra NVP dose along with their standard therapy and 628 women received placebo plus their standard therapy. Results showed the NVP group had nine cases of infection

when compared to ten infections in the placebo group, concluding there was no additional benefit when using this therapy to the standard therapy during labor.[28] On the other hand, a study presented in the 11th Retrovirus Conference (San Francisco, CA), questioned the benefit of this prophylactic method because even if the use of NVP combined with ZDV administered as a single dose during labor reduced infection transmission to 2%, this combination actually increased drug-resistant mutations, which was detected in up to 39% of mothers and >42% of exposed newborns. The most frequently observed mutations were K103N and Y181C, which may lead to a cross-resistance group and would make subsequent management of those patients difficult.[29]

Use of a combined therapy with two nucleoside ARV drugs (ZDV + 3TC, lamivudine) was a 1998 proposal to improve treatment efficiency and reduce monotherapy-associated risks.[30] PETRA project (perinatal transmission), carried out in African countries, evaluated this combination in three patterns, which revealed its efficiency in a group of HIV-infected women who breastfed their children.[31] The ZDV + 3TC combination showed similar results to the ACTG 076 study, and this therapy is still questioned because of its lack of effectiveness reducing viral load and the development of 3TC-resistant mutations. Therefore, this type of therapy is being recommended less often by the medical community as a prophylactic treatment.[32-34] Thus, no short-term treatments are currently recommended.

HAART during Pregnancy

HAART is the current preferred treatment for pregnant HIV-infected women because it reduces viral load and vertical HIV transmission rate[35] and also decreases the risk of developing resistance to ARV drugs (when used as monotherapy).

Stringer[36] carried out an analysis of studies presented at medical congresses during 1999 and was one of the first investigators to recommend the use of HAART to treat HIV-infected pregnant women. Stringer observed that of 553 women who received HAART, only two transmitted the disease to their children, thus resulting in a transmission risk <1%. Thorne,37 in 2000, reported after analyzing 2633 cases of pregnant women from eight countries that 41% received HAART with ≥3 ARV (13th World AIDS Conference, Durban, South Africa).

On the other hand, the important decrease in vertical HIV transmission in the U.S. from 4.3% in 1998 to 1.3% in 2000 was because 86% of pregnant women received HAART during pregnancy, reducing cesarean procedures to 29% of deliveries.[38]

Results from PCTG 316 study showed that of 2756 women who received HAART, only 1.3% of their NB contracted the infection.[39]

In Mexico, the INPerIER began the use of combined ARV therapies in 1999 as part of the program for integral care of HIV-infected pregnant women. HAART is used nowadays, following recommendations from ARV management of HIV/AIDS patients, with a higher prevalence of the ZDV + 3TC + nelfinavir scheme with very favorable results, maintaining a vertical HIV transmission rate of 0% in 2008 when administered to pregnant women for at least a 4-week period. Because of the international alert about nelfinavir, this drug has been replaced by lopinavir/ritonavir.[40]

Pregnant HIV-infected women should receive HAART according to their particular clinical profile as detailed in Tables 2 and 3. This information was obtained from the 2008 Guide for Management of Patients with HIV/AIDS.[40]

Strategies to Reduce Perinatal HIV Transmission

Vertical HIV transmission can be prevented; therefore, most pediatric HIV/AIDS cases can be prevented. According to CENSIDA's guidelines, prevention policies should include:

•Optimal treatment for the mother, which reduced vertical HIV transmission rate and preserves their health over a longer period

•Avoiding the use of monotherapy because this has a higher failure rate due to previous resistance and also limits the effectiveness of ARV drugs for future treatment of the mother or her child

•Availability in Mexico of combined antiretroviral treatment for all women who require it during pregnancy and after childbirth

HAART should be used regularly, having the following benefits: 1) reduce vertical HIV transmission in >98% of cases; 2) increase the probability of maintaining and restoring mother's immune function and delay her disease progression; and 3) reduce the risk for developing ARV resistance in the mother and her child.

In October 2007 we initiated an early HIV diagnosis program at INPerIER with rapid oral HIV tests with patients' approval, alleviating the services of external consultation and STD Service. Results are available in 20 min. A total of 5983 tests have been carried out up until January 2009, detecting five HIV-infected women who were unaware of their condition, including three pregnant women.

ARV Safety and Effectiveness during Pregnancy

Despite the documented benefit of HAART for both prevention of vertical HIV transmission and improvement of the quality of life for mothers, there are reservations about the risk of teratogenesis or damage to the mother or her newborn from the use of such medications.

Drugs that have demonstrated the highest safety and efficiency are nucleoside analogues that inhibit the reverse transcriptase enzyme, including ZDV and the ZDV + 3TC combination.

These drugs are well tolerated and pass through the placenta appropriately, and teratogenesis has not been demonstrated so far in humans or animals when recommended dosages are used. Adverse effects have been observed in animals that received dosages 30 times higher than recommended during the first trimester of gestation.[41]

In a group of 400 women who were exposed to ZDV + 3TC during their first trimester of gestation, there were no higher incidences of alterations or birth defects than those reported in Metropolitan Atlanta Congenital Defects Program (CDC, USA).[42]

Nevertheless, there are reports of at least eight cases that support the possibility of mitochondrial dysfunction shown by myopathy, myocardiopathy and neuropathy in pediatric patients exposed in utero to these medications.43 However, the benefit achieved in >16,000 children treated only in the U.S. and who have not become infected is far greater than the possible risk involved.[44] In spite of this potential risk, experts have not explained why the fetus and NB exposed to these ARVs do not express adverse effects.[45]

The same toxicity manifestations can be found in the mother with the most common being myopathy, myocardiopathy, neuropathy and pancreatitis.

Pregnant women who receive ARVs also have the risk for developing fatty liver or lactic acidosis, with potential risk of death, especially when using didanosine (ddI) + stavudine (d4T) associated with another ARV. This combination should be prohibited as part of the HIV infection treatment.[46] On the other hand, ddI has been associated with up to 6.3% of malformations observed in a group of exposed NBs during the first trimester of gestation vs. 1.1% of cases that were exposed later on.47 There is insufficient clinical experience with other medications such as emtricitabine (FTC) and tenofovir to be able to recommend their usage during gestation.[48]

Of non-nucleoside analogue reverse transcriptase inhibitors, NVP is the ARV with the highest efficiency when used during pregnancy; however, 1% of pregnant women who receive this drug may present toxic hepatitis that can be fatal.[49] High resistance levels in short treatments have also been demonstrated and higher toxicity levels in the mother when compared with schemes that replaced NVP by a protease inhibitor (PI).[50]

Efavirenz should be avoided during pregnancy because studies in pregnant primates documented congenital alterations such as anencephaly, anophthalmy and syndactyly.[51] On the other hand, a January 2005 analysis of prospective studies showed childbirth defects in 5/206 deliveries of women exposed to efavirenz. Avoidance of this medication is justified when considering the three previous cases of neural tube defects. A similar scenario was observed with delavirdine, which has been associated with heart defects in rodents exposed to this medication while in utero.

The use of PIs during pregnancy has greatly increased and they are the most powerful complement to reduce viral load of the mother during gestation. They appear to present a minimal transplacental passage[52] and no teratogenic effects have been reported to date in humans.

Safe and Efficient ARV Schemes

Even though optimal dosage has not been identified for new ARVs during pregnancy, toxic effects seem to be similar in both pregnant and non-pregnant women when ZDV + 3TC associated with a PI are used. Until 2007, nelfinavir was the protease inhibitor with ample safety margins during gestation; however, its efficiency was questioned because of its low ability to reduce high viral loads and present a low genetic barrier resistance level. Therefore, because of the international alert on contamination and possible temporary withdrawal of this medication in Mexico, we recommend its replacement by lopinavir/ritonavir or saquinavir/ritonavir as an alternative that will improve

treatment of HIV-infected mothers and will confirm its safety in pregnant women in an open clinical phase. It is important to adjust dosage during the last month of gestation, increasing lopinavir to 600 mg and ritonavir to 150 mg/12 h according to pharmacological bioavailability studies because suboptimal concentrations have been reported due to physiological conditions of pregnancy[53-55] (Tables 2 and 3).

A descriptive and observational study was carried out at INPerIER. The study included 26 non-infected children born from mothers who received ARV therapy during gestation. All patients were subjected to comprehensive physical examination and development evaluation using size and height parameters comparing to normal developmental tables in Mexican children. Also, neurological evaluation was carried out using Amiel-Tison scale, language development evaluation, intelligence quotient (IQ) measurement and audiometry test. Results showed that 25/26 newborns were delivered with appropriate gestational time, average age of children was 18 months (12 months to 10-year interval). There were 23% of patients who had developmental alterations: two patients presented alterations in passive muscular tone, two patients had language alterations, one patient presented dyslalia, and seven patients presented mild neuromotor evaluation alterations. Audiometry was normal in evaluated patients. Despite the small number of cases followed-up, observed alterations are regarded as common in pediatric patients, and some may be temporary with multifactorial etiology and a low level of association with uterine exposure to ARV drugs. Therefore, when analyzing obtained information and comparing it with current international literature, we observed there was no evident increase of neurological damage associated with HIV or ARV drug exposure in uterus when compared to data from non-exposed children.[56]

References

1.Gobttlieb MS, Schorrf R, Schamker HM, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981;305:1425-1431.

2.Centers for Diseases Control: Unexplained immunodeficiency and opportunistic infections in infants. MMWR Morb Mortal Wkly Rep 1982;31:665-667.

3.UNAIDS/WHO. Report on the global HIV/AIDS epidemic. December 2007.

4.Panorama epidemiológico del VIH/SIDA e ITS en México.

5.Consejo Nacional para la prevención y control del VIH/SIDA. Noviembre 2008. Available at: www.ssa.gob.mx/censida

6.Anderson JR. A Guide to the Clinical Care of Women with HIV. Rockville, MD: ATIS; 2001.

7.Cashat CM, Villalobos AP, Agüero EW. Infección por VIH en pediatría: prevención, diagnóstico y tratamiento. In: Pérez LM, ed. Manual para la atención del paciente con VIH/SIDA. México: Publicaciones Permanyer; 2005. pp. 233-248.

8.Mofeson LM. Epidemiology and determinants of vertical HIV transmission. Semin Pediatr Infect Dis 1994;5:252-265.

9.Ortiz IF, Rangel FS. El manejo de la mujer embarazada con infección por el VIH y profilaxis postexposión. In: Pérez LM, ed. Manual para la atención del paciente con VIH/SIDA. México: Publicaciones Permayer; 2005. pp. 233-248.

10.Lawrence RM, Lawrence RA. Breast milk and infection. Clin Perinatol 2004;31:501-528.

11.Lewis P, Nduati R, Kreiss JK, et al. Cell free human immunodeficiency virus type 1 in breast milk. J Infect Dis 1988;1771:34-39.

12.Nduati RW, John GC, Richardson BA. HIV-1 infected cells in breast milk; association with immunosuppresion and vitamin A deficiency. J Infect Dis 1995;172:1461-1468.

13.Kourtis A, Butera S, Ibegbu C, Belec I, Duerr A. Breast milk and HIV-1 vector of transmission or vehicle of protection? Lancet Infect Dis 2003;3:786-793.

14.Del Rey PG, Lara SJ, Gómez MA, Arredondo GJL. Prevalencia de indicadores de exposiciòn de exposición e infección aguda para toxoplasma, rubéola, CMV, VIH y hepatitis B en mujeres embarazadas. Ginecol Obstet Mex 1991;59:17-20.

15.Magis C, Pedrosa L, Soler C, Panebianco S, Loo E, Martínez F. Offering HIV detection to pregnant Mexican women. Conference on global strategies for the prevention of HIV transmission from the mother to infant. Washington DC; 1997. p. 9.

16.Viani R, Ruiz CJ, López EG, et al. HIV prevalence during pregnancy in Tijuana, Baja California. AIDS 2003;17:1113-1114.

17.Coonor EW, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment: Pediatric AIDS Clinical Trials Group Protocol

Table 2. Antiretroviral treatment recommendations for pregnant women without previous treatment and their children

Scenarios		Recommended treatment	Alternate treatment	Newborn treatment	Mother postpartum
Infection detection before 36th gestation week	CD4 >350	Oral ZDV 250-300 mg/12 h +	Oral ABC 300 mg/12 h+ 3TC 150 mg /12 h+ SQV/r 1000 mg/100 mg /12 h Hepatic function surveillance	ZDV 4 mg/kg /12 h +	Suspend ART and refer to specialized adult management center during first month postpartum. Avoid breastfeeding.
	CD4 < 350	Oral ZDV 250-300 mg/12 h + 3TC 150 mg /12 h + LPV/r 400/100 mg/12 h Third trimester: oral LPV/r 600/150 mg/12 h Return to first dosage 2 weeks after birth#			Suspend ART and refer to specialized adult management center during first month postpartum. Avoid breastfeeding.
Infection detection after 36th gestation week	Any CD4 count	Oral ZDV 250-300 mg /12 h+ 3TC 150 mg /12 h+ LPV/r (600/150 mg)/12 h until immunological/ virological evaluation postpartum#		ZDV 4 mg/kg /12 h+ 3TC 2 mg/kg /12 h from 6th hour of birth during 4 weeks (unless mother VL <1000 c/mL close to birth)	Refer to specialized adult management center during first month postpartum. Avoid breastfeeding.
Mother did not receive treatment				ZDV 4 mg/kg /12 h + 3TC 2 mg/kg /12 h from 6th hour of birth for 4 weeks	

≠If VL >1000 c/mL close to delivery, extend treatment 4 weeks.
+If newborn <34 gestation weeks, start 1.5 mg/kg/6 h and adjust to 2 mg/kg/h on 14th day after birth.
#Lopinavir/ritonavir dosage is similar to kaletra tablets (200/50 mg).
AZT, zidovudine; 3TC, lamivudine; LPV/r: lopinavir/ritonavir; ABC, abacavir; SQV, saquinavir/ritonavir.

Table 3. Antiretroviral management recommendations in pregnant women with previous treatment and their children

Scenarios	Gestation time	Management of pregnant women	Newborn management
With treatment	Measure VL and CD4 regardless of gestation time	Continue ART if VL <50 c/mL, avoid risky ART (efavirenz, stavudine, didanosine). If VL between 50 and 1000 c/mL identify adherence problems and adjust HAART. If VL >1000 c/mL after control period (virologic failure), carry out resistance test and refer to specialized center for adults. Caesarean delivery is recommended if birth is due soon.	ZDV 4 mg/kg /12 h+ 3TC 2 mg/kg /12 h from 6th hour of birth during 1 week. If VL <1000 c/mL close to birth‡ If oral intolerance, start IV ZDV 1.5 mg/kg /6 h* Avoid breastfeeding
Without treatment	Measure VL and CD4 regardless of gestation time	Start triple therapy according to ART history, avoid risky drugs. Without history start oral ZDV 250-300 mg /12 h+ abacavir 300 mg /12 h+ lopinavir/ritonavir 400/100 mg/12 h. Increase lopinavir/ritonavir dosage during third trimester. Program caesarean delivery. Replace ZDV with tenofovir when ZDV toxicity is found. When lopinavir/ritonavir are contraindicated, consider saquinavir/ritonavir. Carry out resistance test on virologic failure and refer to specialized center.	ZDV 4 mg/kg /12 h + 3TC 2 mg/kg /12 h from 6th hour of birth during 1 week. If VL <1000 c/mL close to birth‡ Avoid breastfeeding

ART, antiretroviral treatment; HAART, highly active antiretroviral therapy; ZDV, zidovudine; 3TC, lamivudine; VL, viral load; c/mL, copies/mL; CD4, CD4 T-cell count; O, orally; IV: intravenously.
#If VL>1000 c/mL close to birth, extend treatment 4 weeks.
***If newborn has <34 gestation weeks, start with 1.5 mg/kg/6 h and adjust to 2 mg/kg/h on 14th day after birth.**
ΩART with potential teratogenicity are zalcitabine, delavirdine, efavirenz and hydroxyurea.
****Chosen treatment should be done according to guidelines of rescue therapy described in Chapters 2.4 and 2.5 of this Guide.**
Modified from: CENSIDA: Guide for management of persons who live with HIV/AIDS. 4th ed. 2008. www.salud.gob.mx/conasida

076 Study Group. N Engl J Med 1994;331:1173-1180.

18.Conference on global strategies for the prevention of HIV transmission from the mother to infant. Washington DC; 1997.

19.Conference on global strategies for the prevention of HIV transmission from the mother to infant. Montreal, Canada; 1999.

20.Arredondo-García JL, Ortiz-Ibarra FJ. SIDA de transmisión perinatal: Experiencia del Instituto Nacional de Perinatología. Bol Med Hosp Infant Mex 1992;49:573-579.

21.Arredondo-García JL, Hernández-Trejo M, Figueroa-Damian R, Ortiz-Ibarra FJ, Ahued-Ahued R. SIDA y embarazo. Ginecol Obstet Mex 1997;66:8-12.

22.Ortiz-Ibarra FJ. Programa de atención integral del Instituto Nacional de Perinatología para la mujer embarazada infectada por el VIH. In: Uribe P, Magis C, eds. La respuesta mexicana al SIDA: Mejores prácticas. México: CONASIDA/UNISIDA; 2001. pp. 186-190.

23.Ortiz-Ibarra FJ, Casta-Cruz M. Prevención de la transmisión perinatal del VIH: una meta alcanzable. Bol Med Hosp Infant Mex 2003;60:643-654.

24.Ortiz-Ibarra FJ. Infección por el VIH/SIDA en el embarazo y la lactancia. Gac Med Mex 2006;142:57-64.

25.Greenblatt RM, Hessol NA. Epidemiology and natural history of HIV infection in women. In: Anderson JR, ed. A guide to the clinical care of women with HIV. Rockville, MD: ATIS; 2001. pp. 1-32.

26.CDC. Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission Thailand 1996-1998. MMWR Morb Mortal Wkly Rep 1998;47-48:151-154.

27.Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'voire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. Diminution de la Transmission Mère-Enfant. Lancet 1999;353:786-792.

28.Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. Lancet 1999;12:1735-1744.

29.Dorenbaum A, Cunningham C, Gelber R, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission. A randomized trial. JAMA 2002;288:189-198.

30.Martison N, Morris L, Gray G, et al. HIV resistant and transmission following a single dose nevirapine in PMTCT cohort. 11th CROI. February 2004 (oral abstracts 38).
31.Moondley J, Moondley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when co-administered with zidovudine in human immunodeficiency virus type 1 infected pregnant woman and the off spring. J Infect Dis 1988;178:1327-1333.
32.The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa and Uganda (Petra study): a randomized double blind placebo-controlled trial. Lancet 2002;359:1178-1186.
33.Dao H, Mofenson LM, Ekpini R, et al. International recommendations on antirretroviral drugs for treatment of HIV-infected woman and prevention of mother to-child HIV transmission in resource-limited setting: 2006 update. Am J Obstet Gynecol 2007;(suppl 9): S42-55.
34.Fowler M, Lampe M, Jamienson D, et al. Reducing the risk of mother to child human immunodeficiency virus transmission: past successes, current progress and challenges and future directions. Am J Obstet Gynecol 2007;(s uppl 9); S2-9.
35.Duran AS, Losso MH, Salomon H, Nisdi Perinatal Study Group. Drug resistance among HIV-infected pregnant women receiving antiretroviral for prophylaxis. AIDS 2007;21:199-205.
36.García PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and risk of perinatal transmission. N Engl J Med 1994;331:1173-1180.
37.Stringer J. Transmisión perinatal del VIH. Resúmenes del XIX Congreso Interamericano de Infectología Pediátrica. Zacatecas, México; December 2002.
38.Thorne C. European Collaborative Study. Antiretroviral therapy and cesarean section to reduce vertical transmission of HIV in Europe. Program and abstracts of the XIII International AIDS Conference; 2000 July 9-14; Durban, South Africa: Abstract MoOrC240.
39.Shapiro D, Tuomala R, Pollack H, et al. Mother-to-child HIV transmission risk according to antiretroviral therapy, mode of delivery, and viral load in 2895 US women (PACTG 367). Oral presentation at the 11th Conference on Retrovirus and Opportunistic Infections; 2004 February; San Francisco, CA (abstract 99).
40.Duarte G, Read JS, Gonin R. Mode of delivery and postpartum morbidity in Latin American and Caribbean countries among women who are infected with human immunodeficiency virus -1: the NICHD international site development initiative (NISDI) perinatal study. Am J Obstet Gynecol 2006;195:215-229.
41.CENSIDA: Guía para el manejo de las personas que viven con el VIH/SIDA. 4ª ed. 2008. Available at: www.salud.gob.mx/conasida
42.Olivera OA, Anderson LM, Diwan BA, et al. Transplacental effects of 3-azido-2--3-dideoxythymidine (AZT): tumorigenicityin mice and genotoxicity in mice and monkey. J Natl Cancer Inst 1997;89:1602-1608.
43.Wilmington NC. Antiretroviral pregnancy registry; 2001 May; Interim report 1/1/89-1/31/01.
44.Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999:354:1084-1089.
45.Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. J Acquir Immune Defic Syndr 2000;25:261-268.
46.Blanche S, Tardieu M, Benhammou V, et al. Mitochondrial dysfunction following perinatal exposure to nucleoside analogues. AIDS 2006;20:1685-1690.
47.FDA/Bristol Myers Squibb issues caution for HIV combination therapy with zerit and videx in pregnant women. FDA Talk Paper; January 5, 2001: 1-3.
48.Serious adverse events attributed to Nevirapine regiments for postexposures worldwide 1997-2000. MMWR Morb Mortal Wkly Rep 2001;49:1153-1156.
49.Maternal toxicity with continuous Nevirapine in pregnancy: results from PACTG 1022. J AIDS 2004;36:772-776.
50.Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1V transmission in the United States. Safety and toxicity of individual antiretroviral agents in pregnancy. 2005 November 17 (Suppl).
51.Mirochnick M, Dorenbaum A, Holland D, et al. Cord blood protease inhibitor (PI) concentration following

in utero exposure. Pediatr Infect Dis J 2001;20:803-805.
52.CDC. Revised recommendations for HIV testing for adults, adolescents, and pregnant women in the health-care settings. 2006;55 RR-14:1-17.
53.Jamienson DJ, Clark J, Kourtis AP, et al. Recommendations for human immunodeficiency virus screening, prophylaxis and treatment for pregnant women in the United States. Am J Obstet Gynecol 2007;(suppl):S26-32.
54.Roche retira Nelfinavir del Mercado Europeo. EMEA. Agencia española de medicamentos y productos. Roche; 2007. Available at: www.gtt-vih.org
55.Riddler SH, Haubrich R, DiRienzo, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2000;358:2095-2106.
56.Best B, et al. 15th CROI, Boston: 2008, #629; 2 Eley T, et al. ibid, #624.
57.Figueroa-Medrano L, Figueroa DR, Arreola-Ramírez G, Ortiz-Ibarra FJ, Ahued-Ahued R. Neurologic development among perinatally exposed infants to HIV infected women. In: Monduzzi, ed. Barcelona: International Proceeding Divison; 2002. pp. 51-55.