

Prevention of vertical transmission and treatment of HIV infection in pregnant women

Recommendations of GESIDA-SEIMC, the Spanish Pediatric Association (AEP), National AIDS Plan and the Spanish Society of Gynecology and Obstetrics (SEGO)

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Current state of knowledge

Introduction

From the beginning of the AIDS epidemic, vertical transmission has been recognized as an important route of acquisition of HIV infection. In fact, the rate of vertical transmission has varied in different studies from 15%-48%, depending on where the study comes from and whether the mothers breastfed their infants¹. This is the route of HIV infection for more than 90% of infected children throughout the world and for almost 100% of infected children in the developing world.

This problem is extremely important if we bear in mind that more than 50% of infected persons in the world are women, most of whom are of fertile age. It has been calculated that 2.4 million infected women give birth every year, leading to 600,000 new infections in children (1,600 each day)². This health and social problem is mostly found in developing countries.

Furthermore, in the developed world, the success of highly active antiretroviral therapy (HAART) and the information in the media on different methods (antiretroviral

treatment, Cesarean, etc.) of reducing vertical transmission have renewed interest in having children among HIV-infected patients themselves, in couples where both partners are infected and in discordant couples.

Within the developed world, Spain is the western European country with the highest number of pediatric cases of AIDS³. The high number of children with HIV-1 infection can be explained by the high prevalence of this infection in women of fertile age^{4,5}. This consensus document by GESIDA-SEIMC, AEP, SEGO and PNS attempts to update the information available and join forces to obtain the lowest rate possible of vertical transmission in Spain, by means of free supply of antiretrovirals and high technical level of the different professionals involved in the treatment of these patients. Although the document is aimed almost exclusively at the use of anti-HIV drugs, the prevention of vertical transmission must be placed in a wider context, as it must stimulate responsible planning by women with respect to becoming pregnant (whether or not she is infected by HIV). Health education and the prevention of sexual transmission of HIV and other pathogens should be promoted, as should early diagnosis of HIV in women. Finally, we should consider whether it is

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necessary to use the legal option of abortion in the case of HIV-infected women.

Epidemiology of HIV infection by vertical transmission in Spain

According to the national register of AIDS cases, the first child diagnosed with AIDS by vertical transmission was reported in 1984. This was the route of transmission for a total of 857 children according to the latest available update (30-06-2000), with the highest number of cases in the Autonomous Regions of Madrid, Cataluña and Andalucía. The number of cases went up very quickly, reaching a peak of 90 children in 1988, and it remained between 80 and 90 from then until 1995. The drop in the incidence of cases of AIDS by vertical transmission has been very marked (80%) since 1995; thus, in 1999 (data not corrected because of delay) only 13 cases with this diagnosis were reported⁶.

In a study by the National Microbiology Center of the Instituto de Salud Carlos III and the National AIDS Plan Secretariat between 1995 and 1999, on samples received from 40 Spanish hospitals in 15 Autonomous Regions for diagnosis of HIV infection in children under one year, a significant reduction was detected in rates of vertical transmission (from 20.2% to 5.7%) from 1995 to 1997, with a change in trend from 1997 on⁷. Given its demographic character, this study includes neonates and breast-fed children of mothers with and without prophylaxis with antiretrovirals.

Data from the experience of some hospitals, for example 12 de Octubre in Madrid, collected during the decade 1987-97, report a notable reduction in vertical transmission from 17.5% (CI95%: 12.8-23) to 2.9% (CI95%: 0.15-13), according to whether prophylactic zidovudine (ZDV) had been administered⁴. The same situation was observed in Aranzazu Hospital, which has gone from 50% coverage with ZDV in 1994-1997 to 88% in 1998-1999 with a reduction in transmission of 21% to 3%, respectively⁸. The experience at the Gregorio Marañón and La Paz Hospitals, as reported by the members of the working group, is also a notable decrease in vertical transmission, with no cases since generalization of prophylactic antiretroviral use in a total of 170 diagnosed pregnant women treated with these drugs. These differences, between the aforementioned data for a group of hospitals and the particular details of the various hospitals mentio-

ned, may be connected with the fact that they correspond to studies with different designs.

The National AIDS Plan Secretariat, in collaboration with seven Autonomous Regions, since 1996 has been developing an anonymous, independent study on the prevalence of anti-HIV antibodies in neonates, as a method of calculating the prevalence of HIV infection in their mothers, that is, a sexually active female population being used as a sentinel population. From 1996 to 1999, more than 350,000 neonate sera have been processed, and as a whole, global seroprevalence has gone from 1 per thousand to 1.54 per thousand in 1999, a 54% increase resulting in a significantly upward trend. If we take into account the results from three other Autonomous Regions (Madrid, Cataluña and Valencia) which have carried out similar independent studies, we can affirm that the prevalence of HIV infection in the mothers of neonates in Spain can be calculated to be above 1.31 per thousand for the period 1996-1999⁵. The increase referred to may be related to a possible increase in the number of pregnancies which come to term thanks to the extension of highly efficacious therapies and of the effectiveness of the prevention of vertical transmission with ZDV and other drugs. However, it may also reflect an increase in the incidence of HIV in women of fertile age and/or a sub-diagnosis of infection in pregnant women.

If we apply a prevalence of between 1.3 and 2 per 1,000 to neonates in Spain in 1999, according to data from the National Institute of Statistics, we obtain an estimation of between 500 and 800 children born to HIV-infected mothers. If we extrapolate the HIV prevalence found for 1999 from the previous study, we can estimate that, of this total, between 15,000 and 20,000 fertile women (aged 15-49) are infected by HIV in Spain. An undetermined proportion of this number are not aware of their infection and, when pregnant, have a high risk of transmitting the disease to their children, if they are not diagnosed before or during gestation. These figures must be considered in the context, according to the calculations of the National AIDS Plan, that there are about 120,000 HIV-infected people in Spain.

Vertical transmission: when it occurs and the factors that influence it

HIV can be transmitted during pregnancy (antenatal transmission), during delivery

(intrapartum transmission) or afterwards by breastfeeding (post-natal transmission).

The rate of vertical transmission in those populations where breastfeeding is contraindicated varies between 15% and 25%. According to series, between 35%–45% of children who become infected do so before birth (intrauterine or ante-natal infection), whereas approximately 65%–55% become infected during delivery (intrapartum infection). In areas where infected women breastfeed their children, the transmission rates are higher (35%–45%). In these areas, ante-natal infection and intrapartum infection represent 30% and 50% of infections, respectively; breastfeeding explains the remaining 20%⁹. Several authors propose a definition based on laboratory tests to differentiate intrauterine infection from intrapartum infection:

- *Intrauterine infection.* Positive HIV or PCR-HIV culture (coculture) before 48 hours of life (blood from the umbilical cord is not valid because it is easily contaminated).
- *Intrapartum infection.* Negative HIV or PCR-HIV culture (coculture), or negative Ag p24, within the first week of life and positive HIV, PCR-HIV or Ag p24, between days 7 and 90 of life (in non-breastfed babies).

The factors involved in transmission include (table 1):

Factors other than viral load

1. *Maternal factors.* Immunological and clinical status of the mother: pregnant women in advanced stages of the disease or with AIDS criteria and those with CD4 counts below 500/mm³ have a higher risk of infecting their descendants^{10–15}.

2. *Viral factors.* Viral phenotype (slow/rapid-high) and viral genotype: pregnant women who present fast-growing and fast-replicating synthite-forming strains present a higher risk of infecting their children.

3. *Factors related to the placenta.* The mechanisms by which the virus can cross the uterus-placenta barrier have not yet been established. As pregnancy advances, the innermost layer of the placental cytotrophoblast becomes thinner and thinner thus increasing susceptibility to intrauterine infection. There is an increased risk of infection in situations where there is an alteration of placental inte-

TABLE 1. Factors involved in mother-to-child transmission

Viral factors
Phenotype
Viral diversity
Maternal factors
Advanced disease
CCR5 mutation
High viral load
Obstetric factors
Premature breaking of membranes
Type of birth
Breast feeding
Feto-placental
Premature birth
Chorioamnionitis

grity such as the presence of chorioamnionitis secondary to infection, or with factors which are known to be able to alter placental histology such as smoking or drugs. Thus, mothers with low CD4 counts who smoke have a three-fold greater risk of transmitting the infection¹⁴.

4. *Neonatal and fetal factors.* The age of the fetus at the time of exposure is a factor that is closely related to transmission. Although, at the beginning, it was thought children infected in the uterus were more likely to be premature as a consequence of HIV infection, it was later shown that prematurity itself was the factor which determined whether there was a greater risk of transmission and not vice versa¹⁵. It has been postulated that some factors related to the fetus itself could be associated with a lower susceptibility of fetal cells to infection, as is the case with the deletions in the gene which codifies the chymocine co-receptor CCR-5, certain HLA, or HLA discordance between the mother and the child. The immune response is also important in the newborn, especially the cytotoxic T response to the virus. Similarly, the integrity of the skin, which is connected with gestational maturity and the weight of the newborn are related to vertical transmission. Newborn babies who are underweight for their gestational age are at a greater risk of HIV infection¹⁴.

5. *Obstetric factors.* Invasive procedures during pregnancy (funiculocentesis, amniocentesis, etc.) represent a greater risk of infection for the fetus and are thus contraindicated as is invasive fetal monitoring during birth. Premature rupture of membranes,

which puts the fetus into contact with blood and cervico-vaginal secretions, is associated in several studies with a greater risk of infection, regardless of the type of birth. Thus, as described below, in the WITS study, the rate of transmission under these conditions was 25% versus 14% when the time elapsed was less than 4 hours. A recent meta-analysis shows that, in women where the viral load is not specified, and in those of whom a minority received antiretroviral treatment, each hour of ruptured sac leads to a 2% increase in the transmission rate⁶.

6. *Factors associated with breast feeding.* The level and duration of viremia in milk, absence of protective mechanisms against viral infection, specific local immunity against HIV and duration of breastfeeding (prolongation of breastfeeding beyond 3 months, especially for more than 6 months, implies a high risk of post-natal infection). Breast feeding determines an additional 14% risk of infection for the neonate in those mothers with chronic HIV infection, and up to 29% when the mother's infection occurs close to birth⁹. The risk of infection by this route increases with the duration of breastfeeding (3.2% per year of breastfeeding after the first two months; the accumulated risk of transmission is calculated to be 3.5% at 6 months, 7% at 12 months and 10.3% at 24 months). Mixed feeding does not reduce the risk of infection, and it can also be greater than in mothers who breastfeed only¹⁸. Mastitis and vitamin A deficit also increase this risk. The results of a recent clinical trial determine that, in populations where breastfeeding is not contraindicated, 40% of infections are acquired by this mechanism, and the risk is much higher during the first months of breast feeding¹⁹.

Several different prospective studies have shown that, in those mothers who did not take prophylaxis for vertical transmission or antiretroviral treatment, the symptomatic illness, the CD4 count < 200/mm³, presence of circulating Ag p24 or high viral loads, prematurity (< 37 weeks), chorioamnionitis, cervico-vaginal infections, invasive procedures, intrapartum hemorrhaging, early rupture of membranes (> 4 hours) and low weight at birth are associated with a higher risk of transmission⁹.

In mothers who used prophylaxis with ZDV or antiretroviral treatment, baseline vi-

ral load and time of birth have shown themselves to be the best predictive markers of risk of transmission. Nevertheless, vertical transmission is possible even with an undetectable viral load. This demonstrates that several factors are involved: prematurity, CD4 count < 200/mcl, breaking of membranes > 4 hours early and chorioamnionitis^{9,10,20}.

Maternal viral load

Although the first studies which showed a clear correlation between maternal viral load and risk of transmission were published in the mid 1990s²¹⁻²³, it is only recently that it has been established as one of the principal determinants of risk of transmission. Thus, Mofenson et al have recently published data²⁴ from the PACTG 185 study, a clinical trial of passive immunoprophylaxis that included pregnant women with relatively advanced illness (median CD4 count of 310, 40% with exposure to ZDV before pregnancy) in which all the women received ZDV. They analyzed the maternal variables (immunological and virological), obstetric variables and variables of the newborn in 480 women and their children. Although there were several factors (low CD4 of the mother, maternal viral load at baseline and at birth, chorioamnionitis at birth) associated with transmission in the univariate analysis, the multivariate analysis showed that the only independent risk factor associated with transmission was maternal viral load at baseline (OR: 2.4 for each log; CI95%: 1.2-4.7) and at birth (OR: 3.4; CI95%: 1.7-6.8). In fact, no perinatal transmission was observed in 84 women with baseline viral load below 500 copies/ml or in 107 women with viral load at birth below 500 copies/ml (CI95%: 0-2.8).

In the same sense, García et al published data on viral load²⁵ in the WITS study («The Women and Infants Transmission Study»), a prospective, multicenter study on perinatal transmission and natural history of HIV infection in pregnant women and their children. It includes 552 women with HIV infection (41% of whom received ZDV during pregnancy) who gave birth to one live infant from 1989-1996. The overall rate of transmission was 20.6%. On analyzing the viral load (geometric mean of three determinations [0-18 weeks; 19-31; 32-birth and time of birth]) and transmission, an association of high VL and transmission was observed: 0% in

women with <1,000 copies/ml; 16.6% between 1,000 and 10,000 copies/ml; 21.5% between 10,001 y 50,000 copies/ml; 30.9% between 50,001 and 100,000 and 40.6% in women with more than 100,000 copies/ml. The upper limit of the 95% confidence interval for transmission in women with <1,000 copies is 5.1%. The following conclusions may therefore be drawn from the study: a) there is a clear correlation between maternal viral load and risk of transmission; b) there is no viral load above which transmission occurs in 100% of cases, and c) although no case of transmission was observed in children of mothers with a VL below 1,000 copies, the upper limit of the 95% confidence interval is 5.1% (a VL «threshold» below which it cannot be guaranteed that there is no transmission). An update of this data presented at the recent International AIDS Conference in Durban included data for 1,482 women collected between 1/90 and 9/99 and the following rates of transmission were observed: 0.9% for women with a VL lower than 400 copies; 6.4% between 400 and 3,000; 11.3% between 3,000 and 40,000; 21.1% between 40,000 and 100,000 and 30.1% for patients with more than 100,000 copies²⁶. The most outstanding fact is that there are 2 cases of transmission in women with less than 400 copies. Other studies carried out in Thailand also corroborate the observation that the risk of transmission increases with the level of maternal VL. They did not observe transmission in children born to mothers with an undetectable VL^{27,28}. They have also made it possible to confirm that, in those children who finally become infected, in 75% of cases, the infection occurs at the time of birth, and only 25% in the uterus. In both cases there is a clear correlation with the level of maternal viral load²⁷.

*The European Collaborative Study*²⁰ had a design similar to that of the WITS, and included data from the mothers of 373 children, recruited between 1987 and 1998. The global transmission rate was 15%. Although a correlation was also observed between maternal viral load and risk of transmission (41.7% for >100,000 copies; 17.5% between 10,000-100,000; 14.4% between 1,000-10,000), it is noteworthy that a transmission rate of 6% was observed in mothers with <1,000 copies. In fact, in seven of the infected children, the mothers had an undetectable VL. Some

methodological problems in this study, e.g., use of different techniques for viral load, use of samples which had been frozen several months before, lead us to doubt some of the results.

Before these studies, a meta-analysis published in 1998 included 10 American and European studies²⁹, which found the same association between VL and risk of transmission. In this meta-analysis, a 5.9% transmission rate was observed for children born to mothers with <1,000 copies. It is important to insist on the fact that there is no threshold of viral load below which the absence of transmission is guaranteed: thus in a recent meta-analysis³⁰ of seven different prospective studies from Europe and the U.S.A., transmission was observed in 8/834 (0.96%; CI95%: 0.4-1.9) patients treated with antiretrovirals, and in 36/368 untreated patients (9.8%; CI95%: 7-15.4), which shows the importance of antiretroviral treatment even in mothers with a low viral load.

One of the mechanisms that might explain such an important association between viral load and rate of vertical transmission would be the correlation existing between viral load in plasma and in vaginal secretions. The birth canal, cervix and vagina, represent one of the compartments where HIV is found. Recent studies establish a correlation between viral load and that present in the cervico-vaginal secretions of non-pregnant women. It was observed that viral load could be maintained for even one year at undetectable levels in vaginal secretions in the vast majority of mothers who reach undetectable viral load with combined antiretroviral therapy³¹. Nevertheless, other studies have not established such a clear association between viral load in vaginal secretions and proviral load in cervico-vaginal cells³². This stresses the need to use antiretroviral prophylaxis during birth and on the neonate regardless of the maternal viral load^{33,34}.

To summarize, materno-fetal transmission of HIV may be said to occur by one of these three routes: intrapartum transmission, intrauterine transmission or postpartum transmission by breastfeeding. Each route has its own mechanisms, risk factors and potential preventive intervention. For each form of transmission, the characteristics of the host (mother), receptor (child) and virus can contribute to possible transmission³⁵. However,

and especially for pregnant mothers who receive ZDV and who later do not breast feed their children, the level of maternal viral load has become the best predictor of transmission, although with two important limitations: there is no threshold of maternal viral load below which we can say with confidence that there will not be transmission; neither is there a threshold above which transmission will be 100%.

Intervention during pregnancy for the prevention of vertical transmission

General concepts

For a correct prevention of vertical transmission of HIV infection is it essential for the pregnant woman to know that she is infected. Therefore, from a clinical point of view, it is *compulsory* to offer all pregnant women HIV serology testing, with suitable information, regardless of their epidemiologic history. This first step is basic to effective reduction of vertical transmission.

The strategies used to attempt to reduce the risk of vertical transmission are associated with factors which influence transmission and include, in the west, the following, either alone or in combination:

1. Reduction of maternal viral load using antiretroviral treatment
2. Avoidance of invasive manipulation of the fetus during pregnancy (e.g., amniocentesis) and birth
3. Reduction of exposure of the child to maternal secretions or blood (e.g., through caesarean or fast birth).
4. Administration of prophylactic antiretroviral treatment to the child.
5. Avoidance of breastfeeding.

Of all these strategies, those considered most important in recent years, as well as avoiding breastfeeding, have been antiretroviral treatment and elective Caesarean, and these will be the key to trying to reduce vertical transmission^{35,36}. Neither vitamin A supplements³⁷, nor hyperimmune immunoglobulin³⁸ has been effective in reducing vertical transmission of HIV. Cleansing the birth canal with chlorhexidine has not been effective either³⁹, although it may have a protective effect in those cases with more than 4 hours of ruptured sac. Recently, vaginal disinfection has been tried with benzalconium chloride, which

is well tolerated. However, its potential effectiveness has yet to be demonstrated⁴⁰.

Clinical trials with antiretrovirals

Randomized clinical trials (RCT) published in the field of materno-fetal transmission⁴¹⁻⁴⁶ have enabled us to draw a series of conclusions which are clearly applicable to daily clinical practice. Table 2 condenses the basic data from these trials.

The first RCT to show the efficacy of an antiretroviral in reducing vertical transmission of HIV was published in 1994⁴¹. This trial, known as PPACTG 076, was carried out in the U.S.A. and France on antiretroviral-naïve, HIV-infected pregnant women, who did not later breastfeed their children. It compared a regimen of oral ZDV (ZDV) (500 mg/day beginning between weeks 14 and 34 of pregnancy, intravenous ZDV during the birth and oral ZDV for the neonate, for 6 weeks) against placebo. In the ZDV arm, transmission (measured at 18 months in the child) was 8.3%, compared with 25.5% in the placebo group, with 68% relative efficacy (reduction of transmission) of ZDV (CI95%: 40.7-82.1; p=0.00006). As a result of this RCT, this regimen began to be used in the west, with the result that the incidence of pediatric HIV infection in the U.S. has fallen by 66%⁴⁷, as it did also in Spain^{4,8} and other European countries¹².

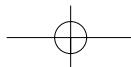
The basic problem for generalized worldwide use of ZDV has been the high price which developing countries have been unable to pay. Furthermore, the later publication of a PPACTG 076 data sub-analysis showed that only part of the efficacy of ZDV in reducing vertical transmission was correlated to a reduction in maternal viral load, thus establishing a hypothesis that the greater part of the effect could be attributed to a prophylactic effect⁴⁸, similar to its ability to reduce the probability of occupational post-accident infection⁴⁹. All of this has led to RCT with shorter ZDV regimens or, even, regimens with other drugs. In this sense, in March 1999, three RCT were published which explored short ZDV regimens:

1. In Thailand⁴², the usefulness of a short regimen of ZDV (300 mg oral twice a day, starting in week 36 of pregnancy, combined with 300 mg oral every 3 hours during labor) was compared with a

TABLE 2. Clinical trials with antiretrovirals

Study/ number of patients	Intervention	Antiretroviral regimen				Breast feeding	Measure of transmission	Transmission %	Realtive efficacy	Cost	
		Antepartum	Intrapartum		Postpartum						
			Mother	Child	Mother						Child
PPACTG 076 (477)	ZDV	100 mg PO 5 times per day, beginning between weeks 14-34 of pregnancy	Continuous infusion of one dose of ZDV at 2 mg/kg i.v. during the first hour, followed by 1 mg/kg/h until the cord is clipped		No	2 mg/kg oral every 6 h for 6 week	No	Infection at 18 months	8,3%	68% p<0,05; CI95%: 40,7-82,1	US\$ 800-1,000 Developing countries 200-400 \$
THAILAND (597)	V.S. placebo ZDV	500 mg PO twice a day, beginning in week 36 of pregnancy	500 mg oral every 5 h		No	No	No	Infection at 6 months	25,5% 9,4%	50% p<0,05 CI95%: 15,4-70,6	US\$ 200-400 Developing countries 50-100 \$
Côte d'Ivoire Study. RETROCI Study (280)	V.S. placebo ZDV	500 mg PO twice a day, beginning in week 36 of pregnancy	500 mg oral every 5 h		No	No	Yes	Infection at 3 months	18,9% 15,7%	57% p=0,07 CI95%:-5-65 -5-65	200-400 \$ 50-100 \$
Burkina Faso Côte d'Ivoire Study (DITRAME) (451)	V.S. placebo ZDV	500 mg PO twice a day, beginning in week 36-58 of pregnancy	600 mg PO at beginning of labor		300 mg oral twice a day for one week	No	Yes	Infection at 6-18 months	24,9% 18/21,5%	58%/50% p=0,027/ns CI95%: 0,05-60/ -2-52	US\$ 210-560 Developing countries 70-210 \$
HVI-NET 012 Stuy (Uganda) (626)	V.S. placebo NVP	No	NVP 200 mg at a single dose at the onset of labor ZDV 600 mg at the onset of labor and 500 every 5 h until delivery		No	NVP single dose 2 mg/kg, for 5 days following birth ZDV 4 mg/kg, twice a day, for 7 days in infant in, mother no	Yes	Infection at 4 months	27,5/50% 15,1%	47% p<0,05 CI95%: 20-64	4\$
PETRA Study South Africa, Uganda and Tanzania (1754)	ZDV ZDV+3TC (arm 1)	From week 36 until the onset of labor (ZDV, 300 mg/12 h; LMV, 150 mg/12 h)	ZDV, 500 mg/5 h and LMV, 150 mg/12 h		Same doses for one week	ZDV, 4 mg/kg oral twice a day and LMV 2 mg/kg oral twice a day, both for one week	70%Yes	Infection and death 6 weeks and 18 months	25,1% 9,2/20,7%	No significant differences at 18 months	500-600 \$ (3 partes) 85 \$ (dos partes)
	ZDV+3TC (arm 2)	Nothing	ZDV, 500 mg/5 h and LMV, 150 mg/12 h		Same doses for one week	ZDV, 4 mg/kg oral twice a day and LMV 2 mg/kg oral twice a day, both for one week			12,6/24,4%		
	ZDV+3TC (arm 3)	Nothing	ZDV, 500 mg/5 h and LMV, 150 mg/12 h		Nothing	Nothing			18,4/25,7%		
	ZDV+3TC (arm 4)	Placebo	Placebo		Placebo	Placebo			20,7-26,6%		

ZDV: zidovudine; NVP: nevirapine; 3TC: lamivudine; \$: dólares; CI: confidence interval.



placebo in pregnant women who later did not breastfeed their babies. The rate of infection in children (measured six months after birth) was 9.4% in the ZDV group compared with 18.9% ($p=0.006$) in the placebo group (a 50% reduction in transmission; CI95%: 15.4-70.6).

2. In Côte d'Ivoire⁴³ (RETROCI study) the same regimen was used, but in women who later breastfed their children. The rate of infection in children measured at three months was 15.7% in the group which received ZDV compared with 24.9% in the placebo group ($p=0.07$), with a relative efficacy of 37% (CI95%: from -5 to 65).
5. Another RCT performed in Côte d'Ivoire and Burkina Faso⁴⁴ (DITRAME study) compares the use of another ZDV regimen (300 mg oral twice a day from week 36-58 of pregnancy in combination with 600 mg oral as a single dose at the onset of labor followed by 300 mg oral twice a day for one week in the mother) compared with placebo in mothers who also breastfed their children. The rate of transmission at six months was 18% in the ZDV group compared to 27.3% in the placebo group, with a relative efficacy of 38% (CI95%: 0.05-60; $p=0.027$). Later, data from the same study at 15 months after birth were published, reporting a 21.5% transmission rate with ZDV and 30.6% with placebo, and a relative efficacy of 30% (CI95%: from -2 to 52)⁵⁰.

In late 1999, an RCT carried out in Uganda was published. This compared nevirapine (NVP) in a single dose during labor and at 48-72 hours in the neonate with an ultra-short regimen of oral ZDV during labor (300 mg/3 h) and 4 mg/kg every 12 hours for 7 days in the neonate, with 13.1% transmission rates in the NVP group compared to 25.1% for the ZDV group ($p=0.0006$), with a relative efficacy of 47% (CI95%: 20-64). This approximation is the cheapest of all (four dollars)⁴⁵. At the recent International AIDS Conference, the appearance of resistance mutation in position K103N in 7 out of 30 (23%) women analyzed and treated with NVP at 6 weeks postpartum⁵¹ was reported. In two of them, other mutations were also involved. Furthermore, in two of seven analyzed children who were infected, resistance mutations were also detected.

In 1999 preliminary data from an RCT which combined ZDV and lamivudine (LMV) were reported. This was a double-blind study, carried out in Africa, which compared 4 different arms: ZDV + LMV from week 36, intrapartum, and postpartum for one week both in the mother and in the infant; ZDV + LMV only intrapartum and postpartum; ZDV + LMV only intrapartum and placebo. The transmission rates at 6 weeks were: 8.6% (RR: 0.5; CI95%: 0.33-0.77; $p=0.001$); 10.8% (RR: 0.65; CI95%: 0.42-0.94; $p=0.02$); 17.7% (RR: 1.05; CI95%: 0.73-1.45; $p=ns$) and 17.2% (RR: 1)⁴⁶. Although in this study there was no arm in which therapy was exclusively for the newborn, it may be deduced that the regimen used only during the birth is not effective in reducing transmission, and that early administration to the newborn could be effective, as has been demonstrated by other studies with ZDV⁵² (or with the same association ZDV-LMV)⁵³.

The fundamental doubt brought about by these studies was their long-term effectiveness in women who breastfed their children. In this sense, at the recent International AIDS Conference in Durban, some data were updated. Thus, in a joint analysis of the DITRAME and RETROCI studies, at 24 months of life, the transmission rate was 30.1% in the placebo group, compared with 22.1% in the ZDV group (difference of risk: 8%; CI95%: 2-15.4)⁵⁴. The risk of post-natal transmission was about 9%. In the PETRA study, however, which includes 1754 women, 70% of whom breastfed their children, the rates of transmission + death at 18 months were: 20.7%; 24.4%; 25.7% and 26.6% for the ante (from week 36) + intra + postpartum (1 week) treatment arms; intra and postpartum; intrapartum only and placebo⁵⁵. This data, associated with the fact that a three-fold higher mortality has been described in HIV-negative orphans born to seropositive mothers⁵⁶ question the real effectiveness of short regimens in the prevention of transmission when the children are breastfed. Moreover, at the same Congress two studies were presented which explore other short treatments:

1. Study BMS 094, which includes 204 mother-child pairs (no breastfeeding), in a preliminary analysis performed at six weeks, suggests, a similar reduction in transmission if ZDV is used (6.3%), stavudine (4.2%), didanosine (1.9%) or

didanosine + stavudine (2%). Administration of the drugs is antepartum (from week 34–36), intrapartum and postpartum to the children for six weeks⁵⁷.

- The SAINT study compares NVP (single dose for the mother and newborn; 652 mother-child pairs, with breast feeding) with ZDV + LMV (birth and postpartum for 1 week, both mother and child; 654 patients). At 10 weeks a similar transmission was calculated in both arms (12.7% for NVP and 9.5% for ZDV + LMV; $p > 0.1$)⁵⁸.

Finally, data from the PPACTG 316 RCT study⁵⁹ to evaluate the safety and efficacy of intrapartum and postpartum NVP added to standard antiretroviral therapy compared to placebo have just been reported. Of more than 1,500 women selected at random, 49% of whom had a viral load of less than 400 copies/ml at the time of birth, and 34% gave birth by elective Cesarean, the global transmission rate was 1.5% (CI95%: 1–2.7); this occurred in 9/594 mothers who received NVP (1.5%; CI95%: 0.7–2.8) and 8/580 in the placebo group (1.4%; CI95%: 0.6–2.7). This indicates that, in the west, in «controlled» mothers, the addition of NVP at the time of birth does not reduce the risk of transmission. This, together with the risk of developing resistance to NVP (see below), warns against the generalized use of NVP at the time of birth in this group of women.

Observational studies with antiretrovirals

In addition to the previously mentioned clinical trials, some experiences and some studies with combinations of antiretrovirals have been published⁶⁰ and these are mentioned below.

A controlled, non-randomized study analyzed the efficacy of the combination ZDV (same regimen as in PACTG 076) and LMV (LMV) at standard dose (150 mg twice a day) from week 32 until delivery, and then to the neonate at 2 mg/kg twice a day for six weeks⁵⁵. The authors include the prospective French cohort and compare the results with patients from the cohort treated with ZDV monotherapy. They report data from the first 200 mother-child pairs with more than six months of follow-up on the child (440 women in total are included) and compare them with 899 pairs treated with ZDV only.

Mother-to-child transmission was 2.6% for the combination group compared with 6.5% for the ZDV group ($p < 0.05$).

Three observational studies^{61–65} presented data from 255 mother-child pairs in combination therapy. Of these, 148 included protease inhibitors. Transmission data are available in 193 cases, with no case of vertical transmission documented with a 95% confidence interval between 0% and 2%.

A retrospective American PPACTG 367 substudy⁶⁴ analyzes vertical transmission between January 1998 and May 1999 in 462 women with varied therapy. Among the 347 children on whom there were evaluable data, global transmission was 3.5%. Worthy of note are the low transmission rates in combination treatments (CI95% in parenthesis): ZDV + LMV: 0% (0%–0.5%); triple PI-sparing: 0% (0%–2.1%); triple with PI: 1.7% (0.2%–6%). Table 3 shows the update of these data presented at CROI 2000⁶⁵.

An update of the WITS presented at the Durban AIDS Conference²⁶, contributes transmission data on 1,482 women enrolled between January 1990 and September 1999. The transmission rates were: 20.7% for 381 untreated women, 19.4% for 206 women treated with ZDV before 1994; 7.7% for 530 women treated with ZDV only after 1994, 3.9% for 179 women in combination therapy with protease inhibitors; and 1.1% for 186 women who received HAART.

There are other small studies, which, because of their design⁶⁶, or low number of patients⁶⁷, contribute information that is still insufficient. There is little data on the use of regimens that include NVP during gestation. In an open-ended study, an English group recently reported their experience with 45 pregnant women treated from week 14 with a highly effective triple therapy with NVP with good tolerance⁶⁸.

TABLE 3. PPACTG 367 study (462 women)

Therapy	No. (%)	Transmission (% CI)
None	125 (15)	26 (18.8–54.8)
ZDV	179 (19)	7.8 (4.5–12.4)
ZDV + LMV	189 (20)	1.1 (0.2–5.5)
Multi without PI	76 (8)	3.4 (1–10.4)
Multi with PI	378 (40)	1.1 (0.5–2.5)

ZDV: zidovudine; LMV: lamivudine; PI: protease inhibitors; CI: confidence interval 95%.

To summarize, it may be said that, although there is not a great deal of information on combination therapies, the addition of LMV to ZDV reduces vertical transmission to approximately 3%, and that the use of HAART can place the rate of vertical transmission at around 0%-2%²⁶.

Data on the safety of antiretroviral drugs

Safety in the child. Data on the safety of antiretrovirals, with regard to both teratogenicity and fetal development are, in general, limited. Table 4 shows the FDA classification of antiretroviral safety. From the available data, we can point out the following:

ZDV is safe, at least in the short and medium term: Sperling et al⁶⁹ publish the follow-up to 18 months of life of children born to mothers included in the PACTG 076 protocol. The only adverse effect noted was anemia during the first six weeks of life with no further consequences. Data from non-infected children in the same protocol, with follow-up from birth to a median age of 4.2 years (3.2-5.6), show no differences between those whose mothers received ZDV or placebo⁷⁰. Neither have tumors been observed in more than 700 children exposed to ZDV in utero and followed up for a median period of 6 years after birth⁷¹.

The publication by a French group⁷² on mitochondrial dysfunction in 8 non-infected children born to mothers treated with ZDV (4 children) or ZDV+LMV (4 children), of whom two died, generated considerable concern for safety in using antiretrovirals during pregnancy. This was not confirmed by other studies^{73,74} or by the excellent review in the USA of five large databases including more than 20,000 children born to HIV-infected mothers⁷⁵. However, the recent report of isolated cases of fetal death in connection with maternal lactic acidosis (see below) continues to cause concern, in spite of its low incidence.

There is less information on the safety of other drugs.

A small observational study⁶⁰ of 30 children born to mothers treated with combinations of antiretrovirals (17 with PI; of these, 9 with indinavir), found preterm birth in 35%, one case of cerebral hemorrhage and another of atresia of the biliary vessels.

In observational studies which include protease inhibitors, preterm birth was observed in 13%-29%^{62,63,76} as was low birth weight in those children born to mothers treated with PI (2,551 vs 3,111 kg; $p=0.002$)⁶¹. This difference in preterm birth and weight at birth has not been so clear in other studies⁶⁴. In any case, it is unknown whether this rate of preterm birth is connected with the use of antiretrovirals, or, with HIV infection itself, as a large American cohort study seems to suggest⁷⁷. In fact, in PACTG 185, the rate of preterm birth was 17%, similar to that of non-infected women from minority populations, which are influenced by several factors in the highest incidence of preterm births⁷⁸. A recent collaborative European study (which also includes the previously mentioned Swiss cohort) observed a rate of preterm birth of 29% in 101 mothers treated with PI⁷⁶.

A register established in 1989, which prospectively collects data on exposure to antiretrovirals and outcome of children, evaluated 916 cases up to July 1999. The prevalence of birth defects among those exposed during the first term of pregnancy was 2% of liveborn babies, a figure that does not differ significantly from that of unexposed newborns (2.17%)⁷⁹.

The safety of other drugs is even less well known, although the majority are classified as «C», and given the results of teratogenicity

TABLE 4. Safety of antiretroviral drugs during pregnancy

Drug	FDA	Step ratio NB/mother	Carcinogenicity in animals	Teratog in rats
ZDV	C	0.9	Tumors in rats	Yes
Zalcitabine	C	0.3-0.5	Tumors in rats	Yes
Didanosine	B	0.5	No	No
Estavudine	C	0.8	Not completed	No
LMV	C	1.0	No	No
Abacavir	C	Yes (rats)	Not completed	Yes
Saquinavir	B	Minimum step in rats	Not completed	No
Indinavir	C	Yes (rats)	Not completed	No
Ritonavir	B	0.15-0.64	Not completed	No
Nelfinavir	B	?	Not completed	No
Amprenavir	C	?	Not completed	Yes
Lopinavir	C	?	Not completed	Yes
NVP	C	1	Not completed	No
Efavirenz	C	Yes (rats)	Not completed	Yes

ZDU: zidovudine; 3TC: lamivudine; NVP: nevirapine; FDA: Food and Drug Administration; NB: new born; B: either animal-reproduction studies have not demonstrated a fetal risk but there are not controlled studies in pregnant women; C: either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

studies in animals, or the little information available, the following antiretrovirals tend not to be used: zalcitabine, efavirenz, abacavir, amprenavir, hydroxyurea. If there are alternatives, indinavir is also advised against because of the risk of jaundice in the neonate. Information available on lopinavir is also very limited⁸⁰.

Risk of toxicity in pregnant women. In addition to the specific secondary effects of each antiretroviral, during the last year data have appeared on mitochondrial toxicity and lactic acidosis to which pregnant women may be more predisposed. Several entities have been linked to mitochondrial toxicity: neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis and lactic acidosis. Of these, symptomatic lactic acidosis and hepatic steatosis may be more prevalent in women⁸¹. Some researchers have associated these syndromes with a recessively inherited mitochondrial disorder that prevents the fetus/infant from oxidizing fatty acids. Given that the mother could be a heterozygotic carrier of the abnormal gene, there may be an increased risk of hepatic toxicity due to inadequate oxidation of fatty acids both of the fetus and of the mother⁸².

Lactic acidosis with microvacuolar hepatic steatosis has been reported, although rarely, in association with HIV-infected patients who have been treated for long periods. Although it was initially associated with the use of ZDV, the involvement of other analogs has also been described, especially stavudine. In a publication of 106 cases of HIV-infected adults (no pregnant women) with this syndrome, the typical initial symptoms were; nausea, vomiting, abdominal pain, dyspnea/tachypnea and weakness⁸¹. Metabolic acidosis with high serum lactate and hepatic enzyme figures was usual⁸⁵. In this series, patients were more often women who were somewhat overweight. Although rare, the incidence of this syndrome is far from negligible: 0.13%-1.2%/patient/year^{84,85}.

The incidence of this syndrome in HIV-infected pregnant women in antiretroviral therapy is unknown. In 1999, an Italian group published the case of a pregnant woman in therapy with stavudine and LMV who presented symptoms and fetal death in week 38⁸⁶. The recent report⁸⁷ by BMS of three maternal deaths (and two of the fetuses) in the immediate postpartum due to lactic acidosis, two of

them with pancreatitis, of women treated with stavudine and DIDANOSINE, in combination with other antiretrovirals (NVP or protease inhibitors) throughout pregnancy and whose clinical picture started late on in their pregnancy, should alert physicians to suspect this picture at the smallest symptom. This risk can probably be extended to other nucleoside analogs, in prolonged therapy, as there have recently been reports of isolated cases of severe, non-lethal, lactic acidosis in pregnant women with other drugs of the group⁸⁸.

In this sense, pregnant women undergoing treatment with analogs should be monitored both clinically and analytically, with greater frequency during the third quarter. At present, no need has been established to determine lactic acid in plasma, as there are no protocols for early diagnosis⁸⁵.

Risk of development of resistance. Any antiretroviral therapy that is not radically suppressive carries a potential risk of developing resistance⁸⁹. This gives cause for concern as the development of resistance could condition the possibilities of a later successful antiretroviral treatment, both in the child and in the mother. In this sense, already in the mid 1990s, there were reports of transmission of strains from mother to child⁹⁰⁻⁹². Although initial data suggested that the fact that the mother might present mutations to ZDV did not increase the risk of transmission⁹⁵, a recent study, in which 25% of 142 mothers presented some mutation to ZDV, found a clear association between resistance and higher risk of transmission (OR: 5.16; CI95%: 1.4-18.97)⁹⁴. Similarly, recently⁹⁵ there have been reports of a trend towards greater transmission (OR: 5.8; CI95%: 0.98-34.31) between phenotypic resistance to ZDV and vertical transmission regardless of viral load in a group of women with moderately advanced illness (mean: 289 CD4/ml). Although little is known about which viral populations are transmitted and how they are selected⁹⁶, it is a demonstrated fact that these populations are transmitted (up to 20% of infected children in the French cohort⁹⁷). Even though it has been suggested that these children infected with resistant strains are at greater risk of disease progression⁹⁸, this hypothesis may not be real given that it is exactly those mothers who receive ZDV who have a more advanced form of the disease, which is associated with faster

progression in the child when there is vertical transmission. With regard to the mother, data are scarce and, in the only study available, in a mean follow-up of 4.2 years, there were no differences between women who took ZDV and those who took placebo in PACTG 076⁹⁰.

The information available on what happens with other drugs, although limited, is also worrying. Thus, in the previously mentioned French cohort⁵⁵, 39.4% of the 152 women examined at six weeks after birth who received LMV presented the mutation in position 184 (although none of the 11 who took it for at least four weeks did). In the study which shows the superiority of a single dose of NVP over ZDV⁴⁵, it is worrying that the appearance of the mutation in position K103N was observed in 7 of 30 women treated with NVP (23%) at 6 weeks postpartum^{51,100}. In two of them, other mutations were also involved. Moreover, in two of the seven analyzed children who were infected, resistance mutations were also detected. These data have been confirmed by PACTG 316 (blind study in which pregnant women receive antiretroviral treatment [not NNRTI] they are randomized to receive NVP or placebo, as well as the treatment they were already receiving), in which 4/32 women (13%; CI95%: 4-25) with viral load above 3,000 copies/ml at the time of birth who received NVP, presented resistance mutations, compared with 0/38 in the placebo group¹⁰¹. This same group in the same trial, reports that the same occurs in women with more than 400 copies/ml¹⁰² (5/46; 11%; CI95%: 3.6-23.6). Although the future significance of this mutation in these viral quasispecies is uncertain^{36,100}, the rapid selection of resistances caused by NVP in the absence of complete viral suppression is worrying.

Elective cesarean

The elective cesarean, defined as that carried out before birth, has been associated with a protective effect against vertical transmission in some observational studies^{15,105-106} but not in others^{10,107-110}. Therefore, its role as a potential instrument for reducing vertical transmission of HIV has been controversial. Two studies published last year (a meta-analysis of cohort studies and a randomized clinical trial) have contributed data which allow us to situate the role of elective Cesarean in the prevention of vertical transmission.

The meta-analysis analyzed data from 15 prospective cohort studies. It included data

from 8533 mother-child couples, and after adjusting for other factors which also influence the risk of transmission (antiretroviral treatment, maternal stage of disease and birth weight), the probability of transmission in those cases where Cesarean was performed before rupture of membranes fell by about 50% (OR: 0.45; CI95%: 0.33-0.56). The probability of transmission fell by 87% for those cases of elective Cesarean and antiretroviral treatment with ZDV (antepartum, intrapartum and postpartum) compared with other forms of delivery and non-use of antiretrovirals (OR: 0.13; CI95%: 0.09-0.19). In fact, among mother-child couples receiving ZDV antepartum, intrapartum and postpartum, the rate of vertical transmission was 2% among 196 mothers who underwent elective Cesarean and 7.3% among 1,255 mothers with other forms of delivery¹¹¹. Therefore, this meta-analysis concludes that elective cesarean is effective in reducing vertical transmission by about 50%, even in women receiving ZDV. This meta-analysis has two fundamental limitations: 1) It does not include patients in combined antiretroviral therapy with transmission rates which are already very low (see below), and 2) It has been questioned whether a meta-analysis of cohort studies (and not of randomized clinical trials) can give evidence of sufficient quality to support extensive and definitive clinical recommendations¹¹².

A more rigorous study to investigate the protective effect of cesarean is a European, randomized multicenter study, for which we have information on the first 370 children¹¹³ (a total of 436 women were included): the women randomized to elective cesarean had a significantly lower vertical transmission rate than those randomized to vaginal delivery (1.8% vs 10.5%; $p < 0.001$). However, in patients who received ZDV, the reduction in transmission was smaller and not significant (4.3% in vaginal delivery vs 0.8% in cesarean; OR: 0.2; CI95%: 0-1.7). Therefore, the only randomized trial available provides insufficient evidence that cesarean substantially reduces perinatal transmission in women treated with ZDV and does not analyze the role of cesarean in women who receive combined therapies (or HAART) during pregnancy.

Another aspect to be considered is the operative morbidity of cesarean, an area where data, although limited, do exist. In this sense, in 1995, an Italian group published a case-

control study¹¹⁴ which compared the morbidity of cesarean in 156 HIV-infected patients with another 156 who were not infected. They observed greater complications in 3.8% of the HIV+ patients compared to 0.6% of the negative patients (OR: 6; CI95%: 0.9-38.5). The less serious complications (especially post-operation fever) were three times more common in HIV+ patients (OR: 3.1; CI95%: 1.3-7.6). In the multivariate analysis, the only factor associated with morbidity was advanced immunodepression (<200 CD4/mm³). In the same sense, in 1999, two series were reported^{115,116} in which a total of 91 HIV-infected women underwent elective Cesarean, compared with 1,518 who had a vaginal delivery or non-elective cesarean. Both studies describe complications that are twice as frequent in patients who underwent elective cesarean. Also in 1999, a German group published a case-control study that compared complications in 62 HIV-infected women compared to 62 non-infected women who underwent cesarean¹¹⁷. The rate of more severe complications (defined as: fever for more than 48 hours needing antibiotics; need for further surgery or blood transfusion) was 32.3% in HIV+ patients compared with 11.3% in HIV- patients (OR: 3.1; CI95%: 1.4-7.2).

To summarize, it may therefore be said, that cesarean reduces the risk of vertical transmission in children born to mothers who do not receive antiretroviral therapy. There are data that suggest (although they do not show definitively) the potential use of cesarean in women treated with ZDV. It is unknown whether cesarean can contribute in any way to the reduction of vertical transmission in women who have combined antiretroviral treatment with undetectable viral load (at low risk to start with). Furthermore, it is necessary to remember that cesarean is accompanied by an increased risk in post-operation morbidity.

Recommendations

General principles

Pre-conception advice

Any healthcare professional attending a woman who is planning to get pregnant must explain how important it is for her to know her situation with regard to HIV, and offer a test before conception, in which case, the test should also be offered to the partner.

Identification of HIV-infected pregnant women

For correct prevention of vertical transmission of HIV it is essential that the pregnant woman know she is infected. Therefore, from a clinical point of view (table 5):

1. All pregnant women MUST be offered, regardless of their epidemiologic history, HIV serology testing accompanied by suitable advice. This first step is basic for us to be effective in reducing vertical transmission.
2. This must be pointed out during the first visit, to gather previous information as quickly as possible. If the serological situation is unknown at the time of birth or immediate postpartum, this must be ordered urgently using rapid serology testing and the results of the mother's test must be known immediately.
3. Given the potential importance of this decision, a refusal by the woman to take the test must be reflected in the clinical history.
4. In women with habits that risk transmission during pregnancy, especially if the partner is infected or is at risk of being infected, it is important to educate the patient about preventive measures that reduce the risk of transmission. Furthermore the test must be repeated at least once per quarter.

Need for suitable treatment in the mother

Although there will rarely be «conflicts of interest» between the mother and child, the general principle must be suitable treatment of the mother. In fact, suitable control of vi-

TABLE 5. Identification of HIV infection in pregnant women

HIV serology must be carried out
On all pregnant women at the first check-up
If there are risk factors: HIV-positive partner or partner who takes drugs intravenously, check-up every quarter
During delivery, if the pregnancy has not been monitored or if HIV serology has not been performed beforehand
On the neonate, only in the exceptional case that it has not been possible to perform serology on the mother. In this situation, urgent serology should be requested. Any postpartum serology represents a failure of early identification and limits the possible benefit in the prevention of vertical transmission

HIV: human immune deficiency virus.

ral replication in the mother is probably the best way to reduce the risk of vertical transmission¹¹⁸. Suitable treatment of the mother involves other factors, as well as antiretroviral therapy, in relation to the specific needs which may exist: fast access to methadone programs, prophylaxis of opportunistic infections... In this sense, the initial evaluation of the HIV-infected pregnant woman must include at least:

1. Immunological situation by determination of CD4 lymphocytes.
2. Risk of progression via determination of viral load.
3. Hepatitis B and C virus serology.
4. Current and previous antiretroviral history.
5. Gestational age.
6. Support requirements (social, psychiatric, methadone, etc.).
7. Antiretroviral resistance testing. If HIV infection is diagnosed during pregnancy, it may be useful to optimize therapy, especially in a patient with virological failure. In a stable patient with undetectable viral load, apart from the technical difficulties in determination in this situation, it is not indicated.
8. Obstetric requirements. As we have already mentioned these pregnant women present other problems (smoking, alcoholism, small ponderal increase, etc.), other medical conditions (HCV coinfection, sexually transmitted diseases, cervical dysplasia and cancer of the cervix, tuberculosis, etc.), the need for other treatments (psychodrugs, etc.) as well as psychosocial factors (lack of family or social support) which can complicate pregnancy and involve, regardless of HIV infection, a more exhaustive monitoring of the patient.

For all these reasons, these pregnant woman have a higher risk of presenting obstetric pathologies such as premature rupture of membranes, premature birth (especially in patients treated with HAART) and retarded intrauterine growth. If we take these aspects into account, periodic check-ups should be more frequent, a complete study should be made of sexually transmitted diseases, cervicovaginal smear test, and the necessary vaccinations should be given (tetanus, HBV) and seroconversion to infections with perinatal risk should be ruled out (toxoplasma, CMV).

Obstetric ultrasound scans: antiretroviral drugs do not produce malformations, but these studies should be made to rule out uteroplacental insufficiency. During the peripartum period, a study of fetal well-being should be performed using antenatal monitoring.

In the case of severe secondary anemia after taking antiretrovirals, transfusions of red blood cell concentrates should be made to reduce the risk of intrapartum hypovolemic shock (the average loss of blood during a vaginal delivery is 500 cc and during a Cesarean 1000 cc).

At present, obstetricians make regular ultrasound and analytical studies to detect patients who may present genetic alterations (Down's syndrome). In the case of personal or family history, advanced maternal age or the presence of a biochemical or ultrasonographic marker, it may be necessary to diagnose the fetal cariotype. HIV infection should not be a formal contraindication in the case of considerable risk or suspicion. In these cases only amniocentesis would be considered acceptable (chorial biopsy and cordocentesis carry an excessive risk) after suitably informing the mother about the risks and benefits of the technique. Every attempt must be made to carry out the technique with effective HAART, thus avoiding crossing the placenta.

Coordination with other services and professionals

Quality care for the HIV-infected woman demands suitable coordination and communication at least among the infectious diseases specialist, obstetrician and pediatrician. In addition, in selected cases, a psychiatrist and/or social support are necessary.

Information on aspects related to vertical transmission and its prevention. The patient should be informed of the possibilities of treatment (as detailed below), of its usefulness in reducing vertical transmission and ignorance concerning its complete safety in the long term. It is also important to inform the patient, throughout pregnancy, of the usefulness of elective Cesarean in selected cases. Similarly, the doctor should inform the patient that current legislation allows abortion. It is the physician's obligation to respect the mother's final decision with regard to treatment. Periodic checking of hemogram, biochemistry, viral load and CD4 lymphocytes is indicated. It is essential to plan monitoring of the viral load close to birth, towards week

32-34, to decide whether or not programmed Cesarean is to be performed (see below).

In daily clinical practice, a printed Informed Consent Form for antiretroviral treatment is essential (see annex 1). If a Cesarean is to be performed, the center's own consent form should be used. Furthermore, the clinical history must record all such decisions made by the patient, whether HIV serology, or if applicable, antiretroviral therapy are accepted or not.

Specific situations in the mother

Pregnant women with no previous antiretroviral therapy

Treatment indicated due to the situation of the mother. Women in whom highly efficacious antiretroviral treatment is recommended because of their clinical/immunological condition or because of high risk of progression, must ideally begin treatment from week 14 on (avoiding use of high teratogenic-risk drugs, such as efavirenz, ddC and hydroxyurea, or those with high risk of toxicity to the fetus, such as indinavir, as well as those with as yet undefined risk-amprenavir, abacavir, lopinavir). In this case, it is essential that one of the components of the combi-

nation be ZDV (ZDV), which must be used in its three parts.

Treatment not indicated due to the situation of the mother. Where no immediate treatment is indicated for the mother, and where the main reason for treatment is to reduce the risk of vertical transmission, the following should be explained to the mother:

1. The use of ZDV in its three components (gestation, intrapartum and postpartum) reduces the risk of vertical transmission to 5%-8%^{41,58} and is reasonably safe in the short and medium term.
2. The combination of LMV (LMV) with ZDV can reduce the risk to about 3% with no reports of toxicity in the short term⁵⁵.
3. The use of triple regimens containing NVP (NVP) or protease inhibitors (PI) may manage to reduce transmission to 0% and 2%, although their safety in the medium and long term is unknown.
4. When deciding on the type of therapy, the lack of data on long-term safety should be weighed against the greater risk of transmission if an undetectable viral load is not achieved and the risk of resistance developing both in the mother and in the child with the difficulties implicit for further optimal antiretroviral therapy that this can involve.
5. If a sufficiently low viral load is not achieved (e.g., below 1000 copies/ml), or the mother should decide not to start any antiretroviral therapy or to do so only with ZDV, elective cesarean is indicated in week 37-38. The use of elective cesarean in the context of double and triple treatment is unknown, with the result that (taking into account the higher risk of morbidity in non-infected women) it cannot be systematically advised in this context. It might be indicated where, in spite of antiretroviral therapy, a sufficiently low viral load (e.g., below 1,000 copies/ml) is not achieved.

ANNEX 1

Informed consent for antiretroviral therapy for the prevention of vertical transmission of HIV

I
 Has been informed by Dr. of
 Hospital

On the usefulness and efficacy of antiretroviral therapy, with currently marketed drugs, in the reduction of vertical transmission (from mother to child) of the human immune deficiency virus (HIV). I have also been informed that if I accept, I shall be obligated to carry out the necessary periodical check-ups with medical visits and blood analyses.

I have been informed of the possible risks this treatment can involve both for me and for my child.

I accept antiretroviral therapy ()
 I do not accept antiretroviral therapy ()

Patient:
 Name Date Signature

Doctor:
 Name Date Signature

This document should be included in the patient's Clinical Records

Pregnant women with previous antiretroviral therapy

General aspects. As already mentioned, information available on antiretroviral safety during the first quarter of pregnancy is very limited. Therefore, when a woman who is receiving antiretroviral therapy becomes pregnant, the options are either to continue or sus-

pend it during the first weeks. This decision must consider the response to the current combination, tolerance during pregnancy and possible adverse effects on the fetus. All therapy may also be suspended during the first quarter and restarted from the second quarter on, or it may be continued. If the decision is to suspend treatment, all drugs must be stopped simultaneously and begun again simultaneously, from the 14th week of pregnancy on. In any case, in clinical practice, as the patient does not usually refer to her pregnancy until week 6-8; therapy is usually maintained.

There are a few circumstances in which a drug must be withdrawn from the previous regimen, however, this probably only includes ddC, efavirenz, abacavir and, perhaps, indinavir, for reasons previously mentioned. Furthermore, an antiretroviral therapy which maintains the patient stable and with an undetectable viral load should not be replaced by a sub-optimal therapy, except for very clear potential toxicity.

Specific situations. Antiretroviral treatment including ZDV and with undetectable viral load. This is the least complex scenario and does not require any change in therapy unless the regimen contains drugs which are not recommendable (indinavir, efavirenz, abacavir), and must be replaced by ritonavir, nelfinavir, saquinavir or NVP, although there is still little data on the potential toxicity of the latter during pregnancy, especially in the first quarter.

As already commented, during the first quarter, it is possible to suspend all treatment and restart it from the second quarter on, or to maintain it without interruption. If it is decided to suspend treatment, all drugs must be withdrawn simultaneously, and begun again simultaneously, from week 14 of pregnancy. In any case, in clinical practice the patient generally does not mention that she is pregnant before 6-8 weeks, with the result that treatment is usually maintained.

Antiretroviral therapy with ZDV and with undetectable viral load. Two therapeutic regimens are possible:

1. A first therapeutic regimen in which stavudine is preferred. In this case, the regimen may be replaced by ZDV, since there is more information on the protective effect of ZDV. In any case,

some clinicians, taking into account pharmacodynamic and pharmacokinetic data on stavudine and a recent study⁵⁷, prefer to maintain the initial regimen, and suspend stavudine until delivery begins, when it is substituted by intravenous ZDV.

2. A second therapeutic regimen is chosen because of previous failure with a regimen containing ZDV. In this case, there are two alternatives: Maintain the same treatment as long as viral load remains undetectable. Although there is not much evidence on the effectiveness of therapeutic regimens during pregnancy without ZDV, recent data on the efficacy of ritonavir in Thailand⁶⁶, or on triple therapies with vertical transmission rates below 2% with combined regimens, some without ZDV⁶⁴, support the fact that the drop in viral load to undetectable levels close to delivery is associated with a reduction in vertical transmission.

Replace stavudine with ZDV. In a ZDV-experienced mother whose regimen was replaced because of virological failure, there may be risk of ZDV-resistant strains being stored and, consequently, the substitution of stavudine by ZDV involves a theoretical risk of introducing a less effective antiretroviral, while leaving the patient with only two active drugs and possible virological rebound. Therefore, the usefulness of adding a fourth drug to boost the regimen must be discussed with the patient (possibly NVP for NNRTI-naive patients; or saquinavir combined with ritonavir or nelfinavir). The decision to maintain ZDV in the regimen would be based on two types of data: first, even in mothers who have previously been treated and who have resistant strains, ZDV has shown its efficacy⁹⁵. Second, it has been also demonstrated that part of the benefit conferred by ZDV is independent of the reduction in viral load (just as in post-exposure prophylaxis)⁴⁸. Consequently, the decision must be made on an individual basis. Therefore, based on currently available information, even in those mothers for whom it is decided to maintain the ZDV-sparing regimen, intravenous ZDV during birth and oral ZDV administered to the newborn during the first six weeks would still be indicated.

Patients with virological failure with (out) previous ZDV. These patients, with detectable viral load, are those at greatest risk of transmission. In this situation, ZDV must also be used (at least during birth, as it is known that it is incompatible with stavudine), and elective cesarean around week 37-38 of gestation is necessary. The exact time when the change should be made has not been established. In this situation, a resistance study would be indicated to guide antiretroviral therapy. Two situations may arise:

1. *Pregnancy and birth without incident.* When virological failure occurs, a change of therapy will have been tried, if possible guided by a genotypic resistance test and a new intense regimen with three or four drugs will be recommended. If, despite the new treatment, a sufficiently low viral load is not obtained (e.g., below 1000 copies/ml), elective cesarean is programmed at around week 37-38). In this situation, although some clinicians support the association of a single dose of NVP immediately before cesarean, others consider that in the absence of complete suppression of viral replication, the addition of NVP could select strains which are resistant to non-analogs, and limit future treatment. It is likely that recent data showing development of resistance in one of every four women using NVP, rule out the generalized use of NVP in this context. In any case, in view of currently available information, even those mothers for whom it is decided to maintain the regimen without ZDV, administration of intravenous ZDV during delivery and oral ZDV to the neonate during the first six weeks would be indicated.
2. *Pregnancy and birth complicated by transmission risk factors* such as pre-term birth, prolonged rupture of sac, intrapartum maternal fever and bleeding. In such situations, the newborn is at high risk, and intensified antiretroviral prophylaxis for the baby is justified (see below).

Otras situaciones

1. *Pregnant patients who are aware of their HIV-infected condition close to de-*

livery. This situation represents a failure in prevention that must be avoided by recommending HIV serology testing for all pregnant women or all those planning to become pregnant. In any case, if this situation arises, at least combined antiretroviral therapy including ZDV and NVP must be offered, as well as recommending elective cesarean given the scant possibilities of achieving a sufficiently low viral load (e.g., below 1,000 copies/ml) in a short space of time. Follow-up by the infectious disease specialist who designed the initial regimen is essential.

2. *HIV-infected patient who wishes to become pregnant.* The recommendations are similar to those in previous sections with two nuances: Pregnancy should be discouraged in woman with virological failure. If they are not receiving antiretroviral therapy, it is probably worthwhile to delay starting therapy until the second quarter. If she is in antiretroviral therapy and with undetectable VL, the possibility of maintaining or suspending medication during the first term must be discussed with the patient.
5. *State of maternal infection unknown at time of birth.* Diagnosis is urgent (in this sense, two pilot studies have shown the usefulness and feasibility of a rapid test^{119,120}) to find out whether the pregnant woman is infected by HIV or not. If the test is positive, therapy with intravenous ZDV, probably combined with NVP and LMV (drugs with a long half-life), must be started immediately. For the newborn, immediate treatment will be indicated as described in the section on children. In the case of rupture of the amniotic sac, especially after more than 4 hours, an attempt must be made to shorten delivery and cesarean considered. Although no benefit of urgent cesarean has been shown, the objective is to reduce the time of exposure of the child during birth since the risk of transmission is directly proportional to the time of rupture of the sac, increasing to about 2% per hour of exposure both in vaginal delivery and in cesarean delivery. Nevertheless, the risk is much greater in mothers with advan-

ced disease, probably in relation to the greater viral load in plasma and vaginal secretions¹²¹.

In any of the above situations, during delivery, intravenous ZDV is compulsory at 2 mg/kg for the first hour and afterwards at 1 mg/kg/h until the cord is tied. Moreover, as soon as possible, usually during the first 6-8 hours after birth, the newborn must continue to receive oral ZDV at 2 mg/kg every 6 hours during the first 6 weeks.

Therapeutic approach to the neonate

General considerations

In the child, early intervention is extremely important, as it has been shown that preventive antiretroviral treatment is effective when started early. There are three possible situations.

Specific situations

Child of infected mother treated during pregnancy. This is the most common situation. The recommended regimen is prophylaxis with oral ZDV at 2 mg/kg every 6 hours for the newborn during the first 6 weeks. It should be begun as soon as possible, ideally during the first 8 hours after birth. If oral medication is not possible, 2/3 of the oral dose can be administered intravenously. The recommended dose in children under 34 weeks is 1.5 mg/kg every 12 hours PO during the first weeks, followed by 2 mg/kg every 8 hours up to six weeks of treatment. The 6-week duration is arbitrary and is based on the duration used in PPACTG 076.

Child born to a mother who is unaware of her infection. This is more infrequent, although it does occur occasionally. As commented above, rapid HIV diagnosis is urgent, and if positive, therapy must be administered immediately to the mother, if still possible, and to the newborn. There are two possible situations:

1. *Identification of the pregnant woman at delivery with time for HAART in the mother.* Intravenous ZDV must be started as soon as possible. Combination with LMV could increase the protective effect of ZDV, as suggested by the PETRA study⁴⁶, and the French experience⁵³, compared to regimens with ZDV only, although there are no direct com-

parative studies. The indirect evidence, however, suggests that this combination should always form part of prophylaxis in this situation. In the Ugandan study⁴⁵, the administration of NVP at birth and to the newborn also showed its efficacy in monotherapy, although its additional effect in combination with other antiretrovirals is unknown. If the infection is identified in the mother close to delivery, the combination with NVP may increase the protective effect, although this has not been definitively established. NVP should always be used as a third drug. If, in the mother, triple therapy is initiated with IV ZDV associated with LMV and NVP, in the child therapy should be started with ZDV and LMV, and at least a single dose of NVP at 48-72 hours. In situations of increased risk of transmission, prophylaxis in the child with NVP up to 4-6 weeks, as well as with ZDV and LMV must be evaluated. The recommended doses of ZDV are 2 mg/kg every 6 hours, and of LMV 2 mg/kg every 12 hours. The first dose of 2 mg/kg of NVP must be administered at 48-72 hours from birth followed by a continuous daily dose of 4 mg/kg once a day from day 5 up to the end of 4-6 weeks.

Periodic monitoring of transaminases is recommended before starting NVP and throughout prophylaxis. The withdrawal of LMV and NVP at 2 weeks if diagnostic tests for infection (PCR-DNA) are negative during the first 48 hours and may be evaluated at 15 days. Nevertheless, caution is required, because, although the test is highly sensitive from day 15 on, sensitivity in children who receive early combined therapy is unknown. Therefore, it is preferable to continue prophylaxis for 4-6 weeks until a second negative postpartum PCR-DNA is obtained.

2. *Identification of the pregnant woman at delivery without time for HAART in the mother.* Treatment with ZDV and LMV must be started in the child before the first 48 hours, as there is no evidence of protection after this time. A very wide observational study showed that ZDV alone reduces the risk of transmission to 9% in comparison with 26% in untreated mothers with similar cha-

racteristics⁵². This protection is similar to after accidental injection of contaminated blood, although the risk is much greater in the case of the child. Therefore, the need to combine other antiretrovirals with ZDV during the first weeks seems evident.

One of the greatest problems in the development of antiretroviral drugs in pediatrics is the need to carry out tolerance and pharmacokinetic studies at different ages, especially in the neonate. Only the tolerance and pharmacokinetics of ZDV and, to a certain extent, those of LMV and NVP, are well known in the neonate. Therefore, and by analogy to what is recommended in adults in the case of accidental injection of contaminated blood, a combination of drugs should be used in the neonate. These combinations could be ZDV and LMV or ZDV, LMV and NVP. NVP should always be used as the third drug. Due to its theoretically greater efficacy in prevention and its greater antiviral effect if the child were to become infected, the combination of triple therapy seems more appropriate, although this has not been established, and there is still concern over the possible increase in toxicity in the child. Nevertheless, in situations of greater risk, such as prolonged rupture of membranes, pre-term birth, intense maternal bleeding or infection of the maternal genital tract, a triple combination of ZDV, LMV, every 12 hours and NVP is recommended for the neonate. The recommended doses of ZDV are 2 mg/kg every 6 hours, and of LMV 2 mg/kg every 12 hours. The first dose of 2 mg/kg NVP should be administered, if possible, during the first 12 hours followed by the same dose at 72 hours from birth. Therapeutic levels of the drug are thus reached during the first week and, later, a continuous daily dose of 4 mg/kg once a day from the 7th day until the end of 4-6 weeks. The withdrawal of LMV and NVP or NVP can be evaluated at 2 weeks if the diagnostic tests for infection (PCR-DNA) are negative during the first 48 hours and at 15 days. Nevertheless, caution is required, because, although at 15 days sensitivity of the test is high, it is not 100%, and is unknown in children who receive early combined therapy. Therefore, it is preferable to continue prophylaxis for 4-6 weeks until a second negative result of PCR-DNA is obtained.

There is no evidence of the protective effect of prophylaxis if the child is identified after the first 48 hours. Nevertheless, triple therapy is also recommended as in the previous section.

With all these measures, the risk of transmission is presumably very low, but occasionally, the newborn is infected. It must not be forgotten that, even when prevention fails, the objective must be the preservation of long-term normal immune functioning. This requires early diagnosis, which, with currently available techniques, can be carried out during the first 4-6 weeks in almost all infected children. During the first weeks after infection, there is an explosion of viral replication with dissemination to the entire organism, even the central nervous system. The neonate's capability of containing viral replication is very limited, and as a consequence, the viral load is higher and the set point takes longer to be reached. Early treatment provides unquestionable benefits for the child, such as avoiding dissemination of the virus, reduction of the viral load at set point, and preservation of the immune function, an objective which has been shown to be possible, at least in the short term^{125,124}.

Reproduction and HIV in serodiscordant couples

The spectacular changes observed in recent years in the prognosis of HIV infection have led to a series of new problems. One of the most important is the frequent desire among serodiscordant couples to have children, although this is also the case in couples where both members are infected. In the first case, two situations may arise: woman infected-man not infected, and, more often, man infected-woman not infected.

Woman infected-man not infected

Generally, in these cases, household methods of self-insemination are recommended (sperm collection and introduction into the vagina by syringe). If, after several attempts, this is not effective, other alternatives can be considered. In this sense, if the methods are not effective after one year, the case would resemble normal sterility and thus warrant study and eventual treatment. The existence of HIV in the woman should not be reason

for discrimination in her access to these programs.

Man infected-woman not infected

In spite of the fact that most of the data published on HIV and reproduction refer to vertical transmission in infected women, it must not be forgotten that in our environment most of those infected are men (80% of fertile age (average age at time of diagnosis 37.1 years)¹²⁵. Therefore, the most frequent consultation is that of serodiscordant couples who want to have children and the man is the infected partner. This situation implies risk of infection for the partner through contact with semen, given that semen is a clearly established vehicle for HIV infection^{126,127}.

It is difficult to define precisely the risk of transmission by coitus. Quinn et al¹²⁸ published data on heterosexual transmission in 415 serodiscordant couples in Uganda. They observed, in a prospective follow-up of 30 months, a seroconversion incidence of 11.8% persons per year. This figure seems unacceptably high. However, in the same study, the authors do not observe any cases of transmission among 51 patients with VL below 1,500 copies/ml. Although it seems logical that the risk of transmission also decreases dramatically in serodiscordant couples where the infected male is correctly treated and has an undetectable VL, no studies confirm or refute this assumption. Furthermore, although several studies have shown a strong correlation between reduction of viral load and genital secretions^{35,34,129,130}, others have recovered virus *in vitro* in patients treated with HAART^{151,152,135}. In a recently published study¹⁵⁴ of 67 men with VL below 400 copies/ml compared with 55 non-treated infected patients, the following was observed:

Semen	Treated	Not treated	OR	CI95%
Plasma RNA-VIH+	1.8%	67.0%	0.01	0-0.05
Cellular DNA-VIH+	16.0%	58.0%	0.52%	0.12-0.80

Before these studies were available, it was known that, despite the fact that the semen is infected, the spermatozoa are theoretically unharmed as they do not have HIV receptors¹⁵⁵. In 1992, Semprini reported 12 pregnancies achieved in serodiscordant couples

by artificial insemination after separating the mobile spermatozoa from the rest of the ejaculate (seminal washing) without detecting any infection in the mother or in the new born¹⁵⁶. Since then, this and other groups have used the same methodology:

Semprini reported a larger series of patients with more than 1000 artificial inseminations in 350 serodiscordant couples with 200 pregnancies and no case of infection either in the women or in the newborns¹⁵⁷.

Marina et al have reported 101 artificial inseminations in 63 serodiscordant couples with 37 pregnancies with the same result¹⁵⁸.

Veiga, Coll et al have carried out 155 inseminations in 64 couples with 32 pregnancies and no infections¹⁵⁹.

Therefore, as far as this type of patient having children is concerned, the following possibilities are available:

1. Inform patients of the results of the Quinn study, with the uncertainty stemming from not knowing whether these results can be applied to patients in whom a low or undetectable viral load is obtained using therapy. If the couple decides to use this natural method, it is essential: To be sure that the man's viral load is very low, preferably undetectable. To rule out sterility, to avoid running unnecessary risk. This can be done via: Seminogram with a study of the characteristics of the semen. Gynecological study of the woman, especially if this is her first pregnancy
2. Inform patients of the existence of reproduction teams that perform semen washing and artificial insemination. This requires: A full study of the couple, similar to that carried out in sterile couples, in order to rule out associated pathology that might make application impossible. From the point of view of infectious diseases, the most important criteria for an infected man to be included in this study is that his infection be stabilized. Furthermore, in order to increase the rate of pregnancy and minimize the number of inseminations to be performed, it is recommended that ovulation be stimulated using ovulation-stimulating drugs (gonadotrophins) in the same way as couples for

Control and treatment of HIV infection and prevention of vertical transmission

Situation A. Pregnant women with known HIV infection and no previous antiretroviral therapy (HAART)

Gestation	Birth	Neonate	Comments
If VL undetectable: prophylactic ZDV from week 14 of pregnancy If VL detectable: ZDV+LMV or triple therapy (ZDV+1 RNTI+NVP or ZDV+1 RNTI+1 IP). Begin preferably from 2nd quarter on	Always ZDV IV 2 mg/kg in bolus at the beginning of birth and then 1 mg/kg/hour until cord is clipped If maternal VL near birth is < 1,000 copies/ml. Vaginal delivery If maternal VL near birth > 1,000 copies/ml elective cesarean at 37-38 weeks. ZDV perfusion to begin IV at least 4 hours before cesarean	Always ZDV in the first 8 hours postpartum, at 2 mg/kg/6 h, for 6 weeks (1 cc: 10 mg)*	If immediate HAART is not indicated in the mother, begin immediately after first quarter. The advantages and disadvantages should be explained to the woman. Two-drug regimens will only be used if the mother so wishes. The following are to be avoided: ABV, ddC, EFV, IND, hydroxyurea, amprenavir and, in general, lopinavir

VL: viral load in plasma; ZDV: zidovudine; NVP: nevirapine LMV: lamivudine; IRNYI: reverse transcriptase nucleoside inhibitor; PI: protease inhibitor; HAART: antiretroviral therapy; ddC: zalcitabine; ABV: abacavir; EFV: efavirenz; IND: indinav. *Neonate: if therapy cannot be administered orally, the IV dose is 1.5 mg/kg/6 h in premature babies ≤ 34 weeks gestational age: dose 1.5 mg/kg/h from birth to weeks, with later increase to 2 mg/kg/8 h between weeks 2 and 6 PO. IV dose: 2/3 of oral dose.

Situation B. Pregnant women with previous HAART

Gestation	Birth	Neonate	Comments
With undetectable viral load 1. HAART. Including ZDV. Maintain therapy 2. HAART does not include ZDV (never used): ZDV can be included in the new regimen by suspending stavudine. Or maintain initial regimen 3. HAART does not include ZDV (used previously): Maintain same regimen. Or change stavudine to ZDV and a fourth drug	Always ZDV IV 2 mg/kg in bolus at the onset of birth and then 1 mg/kg hour until the cord is clipped If maternal VL close to birth < 1,000 copies/ml. Vaginal delivery If VL close to birth > 1,000 copies/ml. Elective cesarean at 37-38 weeks. Initiate perfusion ZDV IV at least 4 hours before cesarean	Always ZDV during the first 8 hours postpartum, at 2 mg/kg/6 h, for 6 weeks (1 cc: 10 mg)*	Antiretroviral safety data are limited in the first quarter of gestation. The following should be avoided: ABV, ddC, EFV, IND
With detectable viral load »With (out) ZDV. Use new regimen with three or four drugs, at least during last quarter			Genotype resistance study indicated

*New born: if oral route unavailable, IV dose is 1.5 mg/kg/6 h. In preterm babies ≤ 34 weeks of gestational age: dose 1.5 mg/kg/12 h from birth to 2 weeks, with later increase to 2 mg/kg/8 h between weeks. 2 and 6 PO IV dose: 2/3 of oral dose.

whom insemination is indicated for other reasons. These drugs entail a greater risk of multiple pregnancies, which is even higher in serodiscordant couples since, unlike other couples who use the same treatment, their fertility is not handicapped. Thus, caution is required with stimulation protocols which must be adapted to this special situation. Non-aggressive protocols of ovarian stimulation are recommended.

If the woman does not become pregnant after 4 attempts at insemination, or if, in prior study, a severe pathology which contraindicates insemination is detected, some of these teams offer more complex techniques such as FIV-IC-SI, with results which can be extrapolated to those obtained after applying the same techniques in couples which are not serodiscordant^{140,141} or which may even be superior.

Situation C. Pregnant women who are aware of their HIV condition very close to the time of birth. This situation represent a failure in prophylaxis

Gestation	Birth	Neonate	Comments
End of pregnancy: HAART including ZDV and NVP	Always ZDV IV 2 mg/kg in bolus at the onset of birth and then 1 mg/kg hour until the cord is clipped If maternal VL > 1.000 copies/ml or unknown. Elective cesarean at 37-38 weeks. Begin ZDV IV perfusion at least 4 hours before cesarean cesarean	Always ZDV during the first 8 hours postpartum, at 2 mg/kg/6 h, for 6 weeks (1 cc: 10 mg)* Always LMV during first 12 hours; 2 mg/kg/12 hours for 6 weeks** (1 cc: 10 mg) If risk factors for transmission (preterm, sac ruptured more than 4 hours, infections of genital tract or bleeding).	Undetectable VL not usually achieved. No determination may be available
At birth: there is no time for HAART	Always ZDV IV 2 mg/kg in bolus at the onset of birth and then 1 mg/kg hour until the cord is clipped cesarean	Evaluate adding NVP during first 12 h at 48-72 hours. Evaluate continuing NVP at dose of 4 mg/kg once per day form 7th day up to 6 weeks**	After delivery offer woman HAART according to virological condition

HAART: highly active antiretroviral treatment. * Newborn: if oral route not available, IV dose is 1.5 mg/kg/6 h preterm \leq 34 weeks of gestational age: dose 1.5 mg/kg/12 h from birth to 2 weeks, with later increase to 2 mg/kg/8 h between weeks 2 and 6 orally IV dose: 2/3 of oral dose. ** Evaluate withdrawal of LMV and NVP after 15 days if HIV diagnostic tests are negative at birth and at 15 days. Nevertheless, the diagnostic validity of PCR-RNA or PCR-DNA at 15 days is unknown when combined therapy is administered to newborn.

Situation D. Pregnant women not identified during pregnancy or birth. This situation represents the greatest failure of prophylaxis for vertical transmission. Remind all pregnant women that they should have HIV-testing during pregnancy and, if not possible, during or immediately after birth

Gestation	Birth	Newborn	Comments
No HAART	No treatment	Always ZDV during first 8 hours postpartum, at 2 mg/kg/6 h, for 6 weeks (1 cc: 10 mg)* Always LMV during first 12 h postpartum at 2 mg/kg/ every 12 h for 6 wks (1 cc: 10 mg) <i>Identification of newborn before 48 hours</i> Evaluate adding NVP at 2 mg/kg during first 12 hours, and at 48-72 hours. Usually, NVP is continued form the 5th day on with a dose of 4 mg/kg uonce per day up to 6 weeks** (1 cc: 10 mg). <i>Identification of newborn before 48 hours</i> NVP introduced 48-72 hours, or as soon as possible, and continued from day 5 on with a dose of 4 mg/kg once a day up to six weeks** (1 cc: 10 mg)	Although the dose of LMV and NVP are unknown in preterm babies, it seems justified to use the same dose as in full term baby in situations of risk of vertical transmission

*Newborn: if oral route not available, IV dose is 1.5 mg/kg/6 hours. In preterm babies \leq 34 weeks of gestational age: dose 1.5 mg/kg/12 h from birth to two weeks, with later increase to 2 mg/kg/8 h between weeks 2 and 6 orally. IV dose: 2/3 of oral dose. ** Withdrawal of LMV and NVP will be evaluated after 15 days if HIV diagnostic testes have proved negative at birth and at 15 days. However, diagnostic validity of PCR-RNA or PCR-DNA at 15 days is unknown when combined therapy administered to newborn.

In conclusion, we can confirm that the results obtained to date by the different teams who have used this technique suggest that semen washing followed by insemination in serodiscordant couples is a safe and reproducible technique. The same can be said when FIV-ICSI must be used instead of insemination. Although the risk of infection for the woman after insemination can-

not be completely ruled out, the risk seems to be minimal as shown by experience to date.

Furthermore, the basic mission both of this technique and of putting Quinn's data into practice is not the total disappearance of the risk these couples live with, but the reduction of risk when the desire to have children is important.

At present, and at the request of the National AIDS Plan Secretariat, the General Directorate of Health Planning (S.G. of Health and Social Programs, Certification of Quality and Services) and the Instituto de Salud Carlos III (Health Technology Assessment Agency), inclusion of semen washing and artificial insemination in the National Health Service is being evaluated.

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