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Research Article

Experience with Integrase Inhibitors in HIV-Infected Pregnant Women in the Madrid Cohort: A Paired Cohort Study

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Abstract

Background: Minimizing the time to achieve complete suppression of HIV replication, is critical in pregnancy to decrease the risk of mother-to-child transmission (MTCT). Integrase inhibitors(INSTIs) are characterized by a rapid drop in viral load (VL) and a good transplacental penetration. Our objective was to determine the effectiveness of INSTIs in MTCT and present the experience in the Madrid Cohort of HIV infected mothers-infant pairs.

Methods: Paired cohorts, multicentric and observational study, that includes retrospectively the cohort of pregnant women exposed to INSTIs during pregnancy and their infants (Cohort A) from 2000 to 2017, and another cohort of mothers without INSTIs treatment and their children matched by year of birth +/- one year (Cohort B). Maternal demographic, clinical and analytical characteristics were recorded. The follow-up of children was included.

Results: 67 pregnant women exposed to INSTIs from Madrid cohort (n:1423) and their children were identified. Another group of 67 pregnant women without INSTI treatment were selected. Both groups were similar in maternal age, ethnicity and route of transmission. The percentage of pregnant women with detectable VL at the first trimester was statistically higher ($p<0.01$) in cohort A (46.7%) than in B (6.7%). There were no statistically significant differences in the percentage of low birthweight and preterm newborn. There were no cases of MTCT, nor differences in congenital birth defects.

Conclusions: Regimens that include INSTIs in pregnancy are increasingly being used. They seem to have comparable safety and effectiveness to other families, and appear useful in MTCT prevention even in high-risk situations.

Keywords: HIV-1; Mother-to-child Transmission; Integrase Inhibitor; Pregnancy; Safety

1. Introduction

Prevention of mother-to-child transmission (MTCT) of HIV is the most important goal of antiretroviral therapy (ART) in pregnant women with HIV infection [1]. Even with a dramatic decline, in Western European countries there still ongoing perinatal transmission [2], mainly in children of mothers with poor viral load (VL) control during pregnancy or with late diagnosis [3].

Minimizing the time to achieve HIV viral suppression is critical in pregnancy [1] to decrease the risk of MTCT. The use of ART in HIV-infected women who become pregnant has significantly reduced the risk of perinatal HIV transmission [4]. Integrase inhibitors (INSTIs) belong to a family of antiretroviral drugs that are increasingly being used in current antiretroviral regimens, leading to a rapid decrease in VL. Thereby and together with their good penetration through the placenta, INSTIs are ideal candidates to avoid MTCT in high-risk situations during pregnancy.

In current recommendations, INSTIs are considered the third drug of choice in antiretroviral combinations [5, 6] and

often the women become pregnant while on treatment with these drugs. The recent publication of the Tsepamo observational study in Botswana, where dolutegravir (DTG) based first-line regimens were used, suggests that a higher risk neural tube defects (NTD) might exist in some settings in Subsaharan Africa in children from mothers treated with this drug by the time of conception [7]. Other INSTIs agents such as raltegravir (RAL) and elvitegravir (EVG) could also be prescribed in pregnant women with HIV [3]. RAL has been the most frequently used INSTI and it is the preferred one in pregnancy [3], while currently, EVG should not be used [5, 8] due to the low plasma levels achieved that jeopardize effectiveness.

Because of the high number of women of childbearing age with HIV infection and the gradual rise of first line regimens including INSTIs, it is important to accumulate more information regarding to safety and effectiveness of INSTIs during pregnancy. Our objective was to determine the effectiveness of INSTIs in MTCT adding general knowledge about their use in pregnancy presenting the experience in the Madrid Cohort of HIV infected mothers-infant pairs, contributing to collect information of their use in clinical practice in Western European countries.

2. Materials and Methods

2.1 Characteristics of the study population and variables

The Madrid Cohort of HIV-1-infected mother-infant pairs is a multicenter, prospective, observational and cohort study of HIV-1 infected pregnant women and their infants. This is a large cohort that prospectively collects information on clinical and epidemiologic characteristics of HIV-1 infected pregnant women until delivery and their children in 9 public hospitals in Madrid, Spain: Hospital Universitario 12 de Octubre, Hospital Universitario Fundación Alcorcón, Hospital Universitario de Getafe, Hospital General Universitario Gregorio Marañón, Hospital Universitario La Paz, Hospital Universitario Severo Ochoa, Hospital Universitario de Móstoles, Hospital Universitario Príncipe de Asturias and Hospital Universitario Clínico San Carlos. The information was collected from the medical records of the mothers and their infants, according to a standardized follow-up protocol. The baseline characteristics of the cohort have been previously reported [9, 10].

Maternal demographic characteristics, clinical data, HIV-1 infection features (year of diagnosis, previously ART administrated, transmission route, stage of infection according to the criteria of the US Centers for Disease Control and Prevention [CDC]), ART regimens and changes of treatment during pregnancy were recorded. Blood count, biochemistry panel, HIV-1 VL and CD4+ lymphocyte counts and percentage at first trimester and at the last one or delivery were also collected. VL less than 50 RNA plasma copies/mL (1.69 $\log_{10}$) was defined as 'undetectable'.

The obstetric features included: gestational age, type of pregnancy (single or twin), mode of delivery and administration of intrapartum prophylaxis. The mode of delivery was classified as: vaginal delivery, elective Caesarean section (if it was done before starting labor and without rupture of membranes) and urgent Caesarean section (if it was performed after labour and/or with rupture of membranes). 'Premature birth' was defined as a neonate born before 37 weeks of pregnancy and 'extreme preterm birth' as a neonate born before 28 weeks of pregnancy. 'Low birth weight' was considered if children were born with less than 2500 g.

Children follow-up included medical history, physical examination, blood and complementary standardized tests to HIV-1 perinatal infection diagnosis and detection of possible ART toxicity [9]. Infants visits were scheduled at birth, after 2 or 3 and 6 weeks and thereafter at 3, 6, 12 and 18 months. Children with two plasma HIV-RNA PCR negative were considered uninfected if one of them was done after 3 months of age. The abnormalities in the newborn were classified in birth defects or minor anomalies, according to EUROCAT (European Surveillance of Congenital Anomalies) [11]. With regard to neonatal prophylaxis regimens, we classified them as: zidovudine (AZT) monotherapy for 4-6 weeks, combination therapy with two drugs [AZT + lamivudine (3TC) or AZT plus single dose of nevirapine (NVP) at birth], and triple therapy with AZT and 3TC for 4 weeks, plus NVP for 2 weeks.

The current study is a paired cohort study that includes retrospectively the cohort of pregnant women exposed to INSTIs during pregnancy and their infants (Cohort A) from 2000 to 2017 from the hospitals belonging to the Madrid Cohort, and another cohort of mothers without INSTIs treatment and their children (Cohort B) pertaining to the same Madrid Cohort. The criterion used for matching these patients was the year of delivery (+/- one year), to select comparable groups in terms of obstetric practices and prevention MTCT measures. From the pairs of twins, one of them was randomly selected. This study is a subanalysis of the research projects of the Fundación para la Investigación del SIDA en España (FIPSE) initiated in 2000, approved by the Clinical Research Ethics Committee at the participating hospitals [9, 10].

2.2 Statistical analysis

Once ad hoc database was created in the Microsoft Access program (Microsoft Corporation, Redmond, Washington, USA). Qualitative variables were summarized as a frequency distribution and normally distributed quantitative variables as mean ± standard deviation. The continuous non-normally distributed variables were summarized as median and interquartile range (IQR).

For compare the variables between the two paired cohorts, in case of normal distribution variables the paired t test was used, in case of non-normally distributed variables the Wilcoxon paired test was used. To compare the paired categorial variables the Mc Nemar test was used. The null hypothesis was rejected in each statistical test when $p < 0$, 05. Analysis was performed using windows SPSS version 21.0.

3. Results

During the study period, 67 pregnant women exposed to INSTIs were identified from the 1423 pregnant women with HIV-1 infection collected in the Madrid Cohort. The pregnancies with treatment regimens that included INSTIs occurred during 2008-2017 period, representing 11.9% of the mothers with HIV-1 infection followed in that period. Most pregnant women with INSTI in their treatment schedule were identified in recent years [58 women (86.5%) between 2012-2017)]. Another group of 67 pregnant women without INSTI treatment and their children were selected for comparison. Both groups were similar in maternal age, ethnicity and transmission route. The baseline characteristics of the mothers are detailed in Table 1.

Maternal age p = 0.323	**Cohort A** Mean (+/- SD)	**Cohort B** Mean (+/- SD)
	31.8 (+/- 7.2)	32.2 (+/- 6.1)
Home country p = 0.367	**Cohort A** n (%)	**Cohort B** n (%)
Spain	19 (32.2)	15 (25.4)
Africa	25 (42.4)	22 (37.3)
Latin America	13 (22)	19 (32.2)
Eastern Europe	2 (3.4)	3 (5.1)
Transmission way p = 0.526	**Cohort A** n (%)	**Cohort B** n (%)
Heterosexual	30 (44.8)	37 (55.2)
MTCT	7 (10.4)	5 (7.5)
Blood transfusion	2 (2.9)	2 (2.9)
Parenteral drug user	0 (0)	1(1.4)
Unknown	28 (41.8)	22 (32.8)

Cohort A: Pregnant treated with INSTIs

Cohort B: Pregnant treated without INSTIs

SD: Standard deviation

MTCT: Mother to child transmission

Table 1: General features of pregnant women.

Although there was a trend for a higher number of mothers diagnosed of HIV-1 infection during the current pregnancy in Cohort A (n = 17; 25.8%) than in Cohort B (n = 9; 13.6%), there was no statistically significant differences between groups (p = 0.115). However, the proportion of women without ART prior to the current pregnancy was statistically higher (p = 0.009) in Cohort A (n = 24; 37.5%), than in Cohort B (n = 10; 15.6%). The percentage of pregnant women with detectable VL at the first trimester of gestation was also statistically higher (p < 0.01) in Cohort A (n = 14; 46.7%) than in Cohort B (n = 2; 6.7%). The CD4+ lymphocyte counts at the beginning of pregnancy were similar in both cohorts (Cohort A: 501/µL +/- 286/µL and Cohort B: 693/µL +/- 320/µL; p = 0.1). The evolution of VL and CD4+ lymphocyte counts between the first and at the time point closer to delivery in each cohort, is presented in Table 2.

In the group of mothers treated with INSTIs: RAL was used in 54 mothers (18 in first trimester), DTG in 10 (8 in first trimester) and EVG in 3 (2 in first trimester). The number of women with more than three antiretrovirals was statistically higher (p < 0.01) in Cohort A (n = 28; 41.8%) than in Cohort B (n = 1; 1.5%). The treatment regimens are shown in Table 3.

Cohort A	**1º trimester**	**3º trimester**	**p value**
Median CD4+/µL (IR); (N = 28)	441 (331-690)	545 (371-681)	0.194
Undetectable VL [n (%)]; (N =37)	22 (59.5)	30 (81.1)	0.021
Cohort B	**1º trimester**	**3º trimester**	**p value**
Median CD4+/µL (IR); (N = 35)	682 (531-801)	669 (460-828)	0.711
Undetectable VL [n (%)]; (N = 48)	45 (93.8)	47 (97.9)	0.625

Cohort A: Pregnant treated with INSTIs

Cohort B: Pregnant treated without INSTIs

IR: Interquartile range

VL: Viral load

Table 2: Analytical features of mothers.

Cohort A		**n (%)**
	2 NRTIs + 1 INSTI	34 (50.7)
	2 NRTIs + 1 PI + 1 INSTI	23 (34.3)
	1 NRTI + 1 PI + 1 INSTI	3 (4.4)
	2 NRTIs + 1 NNRTI + 1 INSTI	3 (4.4)
	Others	4 (5.9)
Cohort B		**n (%)**
	2 NRTIs + 1 PI	42 (62.6)
	2 NRTIs + 1 NNRTI	21 (31.3)
	Others	4 (5.9)

Cohort A: Pregnant treated with INSTIs

Cohort B: Pregnant treated without INSTIs

NRTI: Nucleoside and nucleotide reverse transcriptase inhibitors

NNRTI: Non-nucleoside reverse transcriptase inhibitor

PI: Protease inhibitor

INSTI: Integrase inhibitor

Table 3: Treatment regimens.

With regard to the newborn cohorts, they were comparable in mean birth weights [Cohort A: 2920 g (+/-713) and Cohort B: 3034 g (+/- 508)] and gestational age [Cohort A: 37.9 weeks (+/-2.8) and Cohort B: 38.3 weeks (+/- 2.1)]. There were two extreme preterm birth (24+6 weeks and 26 weeks respectively) in the group of mothers treated with INSTIs. There were no statistically significant differences in the percentage of low birthweight babies or preterm delivery (Table 4).

The proportion of neonates with combined antiretroviral prophylaxis was significantly higher (p = 0.03) in children of mothers treated with INSTIs at pregnancy (Table 3).

Birth weight (p = 0.6)	**Cohort A** **n (%)**	**Cohort B** **n (%)**
< 2500 g	12 (18.8)	9 (14.1)
≥ 2500 g	52 (81.3)	55 (85.9)
Gestational age (p = 0.7)	**Cohort A** **n (%)**	**Cohort B** **n (%)**
< 37 weeks	11 (17.7)	9 (14.5)
≥ 37 weeks	51 (82.3)	53 (85.5)
Rupture of membranes (p = 1)	**Cohort A** **n (%)**	**Cohort B** **n (%)**
≤ 4 hours	13 (59.1)	12 (54.5)
> 4 hours	9 (40.9)	10 (45.5)
Apgar score (p = 1)	**Cohort A** **n (%)**	**Cohort B** **n (%)**
< 7	1 (1.7)	59 (98.3)
≥ 7	1 (1.7)	59 (98.3)
Neonatal prophylaxis (p = 0.03)	**Cohort A** **n (%)**	**Cohort B** **n (%)**
AZT	43 (67.2)	57 (89.1)
AZT + 3TC	2 (3.1)	1 (1.6)
AZT + NVP	1 (1.6)	2 (3.1)
AZT + NVP + 3TC	18 (28.1)	4 (6.3)

Cohort A: Pregnant treated with INSTIs

Cohort B: Pregnant treated without INSTIs

AZT: Zidovudine

3TC: Lamivudine

NVP: Nevirapine

Table 4: Newborn features.

There were no cases of MTCT in either group. The number of birth defects was three in both groups (4.2%), and the percentage of minor anomalies was 11.8 (n = 8) in Cohort A and 5.8 (n = 4) in Cohort B, without statistically significant differences (p = 0.424). The abnormalities in the newborn are detailed in Table 5.

Congenital anomalies	**Defect**	**n (%)**
Cohort A	Atrial septal defect (ostium secundum)	1 (1.4)
	Ventricular septal defect	1 (1.4)
	Polydactyly	1 (1.4)
Cohort B	Down syndrome	1 (1.4)
	Tetralogy of Fallot	1 (1.4)
	Mild supravalvular pulmonar stenosis	1 (1.4)
Minor anomalies	**Defect**	**n (%)**
Cohort A	Umbilical hernia	4 (5.9)
	Persistent foramen ovale	4 (5.9)
Cohort B	Umbilical hernia	3 (4.4)
	Persistent foramen ovale	1 (1.4)

Cohort A: Pregnant treated with INSTIs

Cohort B: Pregnant treated without INSTIs

Table 5: Birth defects.

4. Discussion

We compared specifically a cohort of mothers treated with INSTIs during pregnancy with another one of women treated with other antiretroviral families, due to the interest of adding information in this regard, because of a recently identified potential safety issue related to NTD in the fetuses of women who were using DTG at the time of conception [7, 12]. In our series, pregnant women with regimens that included INSTIs mostly presented in recent years, showing the increasing trend to use them in high risk situations of MTCT.

Currently, INSTIs have become the preferred combinations with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) as first line therapy for patients with HIV-1 infection [6]. This has led to an increase of women who get pregnant being on treatment with INSTIs. On the other hand, their potential advantage of leading to a rapid decline in maternal VL [3, 13] and its good placental transfer has also generated a rise of its use in pregnant women with poor control of viral replication or with a late diagnosis in pregnancy. This is probably the reason why in our serie, the proportion of mothers without ART before the current pregnancy was higher in those treated with INSTIs, and also why they had worse virological suppression in the first trimester than the mothers belonging to the other cohort.

Minimizing MTCT is best achieved when ART is started before conception and the mother VL is low and controlled [14]. As mentioned above, RAL has been the most used INSTI in pregnancy, and it has shown high effectiveness in late presenting pregnant women reaching VL suppression before delivery [2, 15]. There also exist important cumulative evidence of low maternal adverse effects and good fetus safety profile [3, 5, 13, 16, 17], that makes it one of the most widely ART used in pregnancy.

The use of ART in pregnant women requires consideration of safety for the mother and the fetus [18]. Information about this has been generated progressively to consider reasonably safe a series of drugs, although this is still limited and most of data come from observational studies.

In this respect, the communication of preliminary analysis of an ongoing 4-year observational study in Botswana, resulted in a global warning because of the finding of 0.9% (4/426) of babies whose mothers became pregnant while taking DTG who had NTD compared with 0.1% (14/11173) of newborns whose mothers took other antiretroviral medicines [7]. In August 2019, with increased exposure numbers, NTD prevalence had decreased to 0.3% of deliveries, but it slightly remained significantly different from other comparison categories [12].

Other recent studies provide reassuring information in this regard. An observational study using the Brazilian ART database, included 1468 women who became pregnant while on ART containing DTG (382) or efavirenz/RAL (1806), and DTG-exposure was not associated with NTD [19]. On the other hand, the revision of central nervous system defect cases reported to Antiretroviral Pregnancy Registry (a voluntary, international, prospective exposure registry) observed only 2 cases of NTD among 8040 birth outcomes with periconceptional ART exposure. Overall these frequencies are consistent with the observed low NTD prevalence (0.01%-0.1%) in developed countries where food folic acid fortification and antenatal folic acid supplementation are the standard of care, reducing overall NTD occurrence [20].

Despite WHO (World Health Organization) now recommends DTG as the preferred first/second line for all adults and children with dosing information, currently in high-income countries, the use of DTG is contraindicated in the first trimester of pregnancy and should not be used in women who wish to become pregnant, or women of childbearing age who do not use effective contraceptive measures [5, 6].

In our cohort of HIV-1 infected pregnant women, the proportion of congenital anomalies and minor birth defects did not differ between both groups, and probably the higher number of heart defects detected compared to the general population, is due to the active surveillance in the newborns in our cohort. Furthermore, there were no statistically significant differences between both groups in preterm delivery or low birth weight.

As noted earlier in many studies, treatment with INSTIs showed a rapid VL drop contributing to MTCT prevention, even in pregnant women with late diagnosis or high VL during pregnancy, leading to a statistically significant increase ($p = 0.021$) in the proportion of women with undetectable VL at third trimester compared to the first one. There was no vertical transmission despite high risk, although the use of combined prophylaxis in newborns might have also contributed to avoid any perinatal transmission.

The main limitations of our study are its retrospective nature and the relative small sample size that make it impossible drawing definitive conclusions and extend our findings to other settings. In addition, active surveillance of birth defects was not done in all newborn with complementary tests or imaging studies. However, our study

provides relevant information on a large number of pregnant women treated with INSTIs, with a control group with similar conditions, highlighting their utility in high risk MTCT situations and adding experience of their use in Western European countries. Furthermore, it reports the absence of major congenital birth defects in our cohort.

5. Conclusions

ART regimens that include INSTIs in pregnant women are increasingly being used. They seem to have comparable safety and effectiveness to other antiretroviral families. They appear useful in MTCT prevention, even in high-risk situations, although more studies are necessary to establish the safety profile for the newborn and effectiveness with the aim of eliminating perinatal transmission of the HIV.

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Conflicts of Interest

The authors declare no conflicts of interest.

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