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PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION

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Abstract We describe the impact of strategies to reduce HIV-1 vertical transmission on a cohort of pregnant women and evaluate toxicity related to antiretroviral (ARV) therapy and prevalence of birth defects. In this observational, retrospective, longitudinal and descriptive study, we have reviewed the data base and clinical charts from a cohort of 351 pregnant women with HIV infection admitted to a public hospital in Buenos Aires from April 1994 to August 2003. Eighty percent of women were infected by sexual transmission. Diagnosis of HIV infection was performed before pregnancy in 38.5% of cases; 241 patients received some kind of ARV therapy, combined therapy was administered in 123 of cases. The overall transmission rate was 9.6%, and antiretroviral therapy was the most significant factor associated with the transmission rate. HIV transmission odds were 0.04 for any ARV treatment versus no therapy. No cases of HIV transmission were observed among women given combination ARV therapy. More prevalent secondary effects associated to ARV therapy were anemia, hypercholesterolemia, increase of ALP and hypertrigliceridemia. In conclusion, antiretroviral therapy, particularly combined ARV therapy, irrespective of type of delivery, was associated with a reduced risk of HIV transmission without an increase in toxicity or incidence of congenital abnormalities in the short-term.

Key words: HIV-1, pregnancy, prophylaxis strategies, toxicity, safety

Resumen ***Prevención de la transmisión perinatal de HIV.*** En este estudio se describe el impacto de las estrategias implementadas para reducir la trasmisión vertical de HIV en una cohorte de mujeres embarazadas. Se evaluó, también, la toxicidad relacionada a la terapia antirretroviral y la prevalencia de malformaciones congénitas. Se revisaron, retrospectivamente, las historias clínicas y la base de datos de 351 mujeres embarazadas, con infección por HIV, admitidas en un hospital público de la Ciudad de Buenos Aires, entre abril de 1994 y agosto de 2003. Se obtuvieron datos completos de 351 pacientes. El 80% de las mujeres adquirieron la infección por HIV por vía sexual. El diagnóstico de infección por HIV fue previo al de embarazo en el 38.5% de los casos. Un total de 241 pacientes recibieron algún tipo de terapia antirretroviral durante el embarazo y 123, recibieron terapia antirretroviral combinada. El índice de transmisión global fue de 9.6%, y el uso de terapia antirretroviral fue el factor más significativo asociado al índice de transmisión. El *odds ratio* (OR) para la transmisión vertical del HIV fue de 0.04 para cualquier tipo de tratamiento antirretroviral *versus* la ausencia de tratamiento. No se detectaron casos de transmisión entre las mujeres que recibieron terapia combinada. Los efectos secundarios más frecuentes asociados a la terapia fueron: anemia, hipercolesterolemia, aumento en los niveles de fosfatasa alcalina e hipertrigliceridemia. En conclusión, la terapia antirretroviral, especialmente la terapia combinada, se asoció con reducción en el riesgo de transmisión vertical del VIH, independientemente del tipo de parto. No se detectó mayor toxicidad o incidencia de malformaciones congénitas, en el corto plazo.

Palabras claves: HIV, embarazo, estrategias de profilaxis, toxicidad, seguridad

In the absence of intervention, vertical HIV transmission is estimated to be 14 to 25% in developed countries, but in predominantly breastfed populations, it is estimated to range from 25 to 48%[1, 2].

There are three interventions known to be efficacious in the prevention of mother-to-child-HIV-1 transmission (MTCT): antiretroviral therapy in the mother and newborn, cesarean section before labor and ruptured membranes and complete avoidance of breastfeeding[3, 6].

However, most of the randomized clinical efficacy trials evaluating interventions to prevent mother-to-child-HIV-1 transmission were performed in breastfeeding populations from poor African countries, with a limited access to antiretroviral therapy[7].

On the other hand, data about the impact of antiretroviral therapy on the developing fetus and newborn are

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limited, but it has been suggested that exposure to antiretroviral therapy, especially to combination therapy, could have an impact on the short and longer term status[8, 9].

Argentina is a middle-income country, with an uneven distribution of resources that accounts for local differences in health care system access. Although this might influence HIV infected mothers' standard of care, recommended interventions to reduce the risk of vertical transmission, including antiretroviral therapy and formula feeding, are now fully available in the Public Hospitals of Buenos Aires City.

Sentinel site testing for HIV prevalence among pregnant women has been ongoing since 1997, when a national regulation for Perinatal AIDS was introduced in Argentina[10].

This regulation was intended to offer voluntary testing for all pregnant women and to provide standard antiretroviral treatment, based on the protocol 076 of the AIDS Clinical Trials Group (ACTG 076) results, for positive cases[11].

Data from these sources suggest that, in Argentina, the global prevalence of HIV among pregnant women ranged from 0.63% in 1998 to 0.45% in 2001. Other official data shows that the prevalence of HIV infection in pregnant women from Buenos Aires has been above 1% since 1998 to 2001 but below 1% in 2002 and 2003[12].

Because differences in strategies have been shown to exert a high impact on results, information about regional experiences is essential for the development of interventions in order to reduce HIV transmission and promote child survival.

In this report, we analyze the characteristics of our cohort of pregnant women and the efficacy of the strategies implemented in order to reduce the rate of HIV vertical transmission.

Material and Methods

We conducted a retrospective cohort study of HIV-1-infected women receiving antenatal care at Hospital José María Ramos Mejía in Buenos Aires.

The objectives were: to describe epidemiological features of HIV-infected pregnant women in follow-up at one multidisciplinary HIV Perinatal clinic in Buenos Aires, compare HIV transmission rates according to antiretroviral (ARV) therapy and mode of delivery and evaluate toxicity related to ARV and describe the occurrence of birth defects in this cohort.

Medical charts of all such women receiving care between April 1994 and August 2003 were reviewed, and the following data were abstracted: medical history (including opportunistic infections, date of diagnosis of HIV-1 infection, receipt of ARVs during pregnancy, dates of initiation and discontinuation of ARVs, CD4+ cell counts, viral load measurements (β-DNA, 2nd generation, Chiron), substance abuse; obstetrical history; maternal age at delivery; estimated date of confinement based on last menstrual period, ultrasound or obstetrical examination; mode of delivery; and adverse events (clinical events and laboratory abnormalities) during pregnancy. Adverse events were qualified according to the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events[14].

Receipt of ARVs during pregnancy was categorized as follows: none received; zidovudine alone received, further categorized as the complete ACTG 076 regimen (zidovudine administered orally during the antepartum period beginning as early as 14 weeks gestation, administered intravenously during the intrapartum period, and administered orally to the infant during the first six weeks of life) or an incomplete ACTG 076 regimen (at least one phase of the protocol, antepartum, intrapartum or prophylaxis with ZDV in the newborn was not completed); or a combination of ARVs received (two or more ARVs administered concomitantly). Mode of delivery was categorized as vaginal, elective cesarean section (ECS) (cesarean section performed before the onset of labor and before rupture of membranes), and non-elective cesarean section (NECS) (cesarean section performed after onset of labor and/or after rupture of membranes). Children were classified as HIV-1-infected based upon two positive HIV-1 PCR assays at or after four months of age, AIDS-defining events at any age, or positive HIV-1 ELISA and Western Blot assays at or after 18 months of age. HIV-1-uninfected children were those with two negative HIV-1-PCR assays (blood obtained through at separate venipuncture events), one of which was obtained at or after four months of age, and with negative serology results at or after 18 months of age.

For the cohort described in this paper, recommended interventions for prevention of mother-to-child transmission, including ARV therapy, formula feeding and C-section, were available during the entire follow-up period.

Predictors of transmission of HIV were studied with logistic regression analyses. These analyses were used to study the association of use of and type of antiretroviral treatment, type of delivery (elective cesarean, non-elective cesarean and vaginal), a history of an AIDS diagnosis and date of delivery with the odds of the infant begin HIV positive. Univariate and multivariate odds ratios and 95% confidence intervals (CIs) are cited. Multivariate odds ratios are derived from models with each of the predictors included.

Results

Data were collected from 351 patients. Fig. 1 delineates the exact number of women/children included in this analysis. Demographics characteristics at baseline are described in Table 1. Mean age of mothers was 26.8 years. AIDS related events were previously diagnosed in 12.53% of women, and 81% were infected by sexual transmission. As shown in Table 1, results from viral load and CD4 cell count, were not available for all mothers. Mean viral load and CD4+ cell count were 3.6 log (1.6-5.7) and 415 cells/ml (27-1485) respectively.

We observed changes in the chronological relationship between pregnancy and HIV diagnosis since 1994 to 2003. Between 1994 and 1996, 60 to 80% of HIV diagnosis were made during pregnancy. In the last three years HIV infection was performed during pregnancy in less than 30% of cases (data not shown).

Proportion of patients receiving treatment during pregnancy has increased since 51.7% in 1995 to 88.5% in 2003.

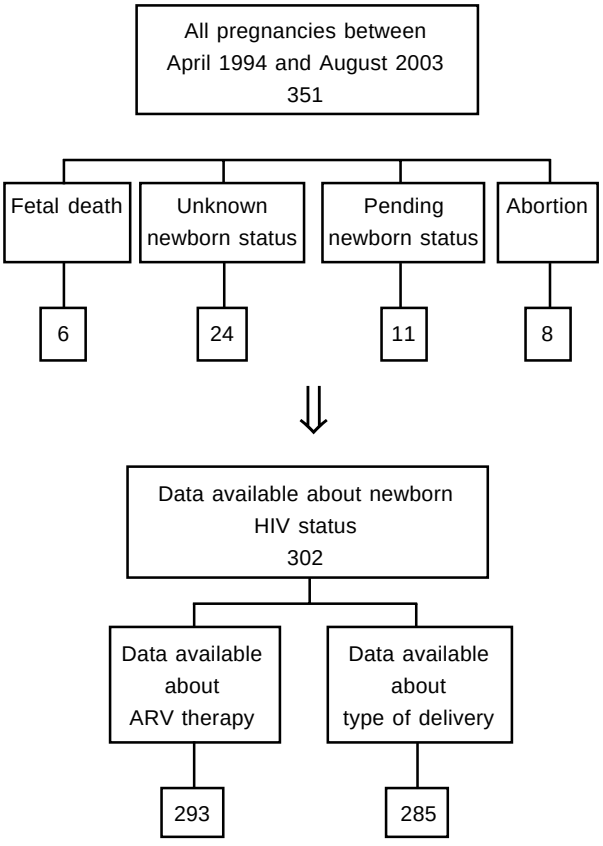

Fig. 1

Characteristics of mothers, according to newborn status, have shown that type of delivery was vaginal in the 59.3% of the HIV positive transmission group, and 58.9% in the negative transmission group, elective cesarean in 22.2% vs. 31.8% and nonelective cesarean in 18.% vs. 9.3% respectively. Zidovudine was the Nucleoside Reverse Transcriptase Inhibitor (NRTI) used in more than 80% of mothers who did not transmit the HIV infection (Table 2).

Six cases of fetal death, eight abortions, twenty four cases of unknown HIV newborn status because lost of follow-up and eleven pending results were excluded from the analysis of the transmission rate.

The relationship between ARV therapy and transmission rate was evaluated in 293 cases, with a global transmission rate of 9.6%; 241 patients received some type of antiretroviral therapy: 94 received complete ACTG 076 while 24 received incomplete ACTG 076 and 123 combined therapy. As regards combined therapy, 51 patients received two NRTIs, 35 received two NRTIs plus nevirapine and 37 received two NRTIs plus one protease inhibitor.

Transmission rate was 4.3% in the complete ACTG 076 group (4/94), 20.8% in the incomplete ACTG 076 group (5/24), and 36.5% in the no-therapy group (19/52). No cases of vertical transmission were detected in the combined therapy group.

We obtained data about type of delivery in 285 patients. Vaginal delivery was performed in 168 patients and cesarean in 117 of them (88 elective and 29 non elective).

Transmission rate was 9.5% in the vaginal group (16/168), 6.8% in elective cesarean (6/88) and 17.2% in the non elective cesarean group (5/29).

The relationship between antiretroviral therapy, type of delivery and transmission rate is described in Table 3. These data suggest that non elective cesarean in the no-therapy group, may be the worst scenario, although the number of women in this subgroup is small.

In a logistic regression model, the odds for HIV transmission, regarding the group of therapy, were 0.04 (IC

TABLE 1.– *Baseline demographic characteristics*

Mean age (range)	27 years(17 – 43)
AIDS Y/N (%)	44 / 349 (12.6%)
Risk factor for HIV transmission	
Sexual	282 (80.8%)
IDU	62 (17.8%)
Transfusion	5 (1.4%)
Mother HIV diagnosis timeline	
Before pregnancy	135 (38.5%)
During pregnancy	94 (26.9%)
Post pregnancy	14 (4.0%)
Unknown	106 (30.0%)
Concomitant events	
HCV	16
HBV	13
HPV	5
Syphilis	13
Vaginal candidiasis	2
Giardia intestinalis	1
Herpes zoster	1
Chronic renal failure	1
Pneumocystosis	1
Trombocytopenia	1
Vulvar sarcoma	1
Pleural TB	1
Acute toxoplasmosis	1
CNS toxoplasmosis	1
CD4+ cell/count = Mean/ Median (range) n = 108	415 / 375 (27-1485)
HIV- RNA $\log_{10}$ cps/ml = mean (range) n = 94	3.61 (1.6-5.7)

IDU: intravenous drug user, HCV: Hepatitis C virus, HBV: Hepatitis B virus, HPV: Human Papilloma Virus, TB: Tuberculosis, CNS: Central Nervous System

TABLE 2.– *Characteristics of mother HIV+according to newborn HIV status*

	HIV+	HIV-	Unknown HIV	Abortion or Still Birth	Total
N	28	266	43	14	351
Type of delivery (%)					
Elective cesarean	22.2	31.8	16.7	0.0	28.9
Non-elective cesarean	18.5	9.3	3.3	42.9	10.2
Vaginal	59.3	58.9	80.0	57.1	60.9
Mean CD4+ count (No. with data)					
Baseline	331.5 (2)	404.2 (91)	364.7 (12)	684.8 (5)	411.3 (110)
Delivery	302.5 (2)	458.1 (81)	634.5 (2)	573.0 (1)	463.9 (88)
Age (Years) (No.)	38.5 (6)	38.7 (130)	38.6 (14)	26.0 (2)	38.5 (152)
Prior AIDS (%) (No.)	7.1 (28)	13.2 (266)	14.0 (43)	14.3 (14)	12.8 (351)
Mean HIV RNA (log_{10} copies/ml) (No.)					
Baseline	3.63 (1)	3.73 (94)	3.82 (8)	3.17 (4)	3.71 (107)
Delivery	4.51 (1)	2.70 (91)	2.49 (4)	4.18 (1)	2.74 (98)
Antiretroviral drugs (%)+					
ZDV	32.1	83.5	51.2	28.6	73.2
d4T	0.0	2.3	0.0	14.3	2.3
ddC	0.0	1.9	0.0	0.0	1.4
ddI	0.0	1.9	2.3	0.0	1.7
NFV	0.0	9.4	0.0	0.0	7.1
NVP	0.0	13.5	7.0	21.4	12.0
NVP at birth	0.0	5.6	0.0	0.0	4.3
RTV	0.0	1.1	2.3	0.0	1.1
SQV	0.0	3.0	0.0	7.1	2.6

ZDV: zidovudine, d4T : stavudine, ddC: zalcitabine, ddI: didanosine, NFV: Nelfinavir, NVP: Nevirapine, RTV: ritonavir, SQV: saquinavir

TABLE 3.– *Relationship between antiretroviral therapy, type of delivery and transmision rate*

ARV	Vaginal delivery		Elective cesarean		Non elective cesarean		n
HIV status of the newborn	+	–	+	–	+	–	
Complete ACTG 076	4	71	0	12	0	6	93
Incomplete ACTG 076	2	12	2	4	1	2	23
Combined therapy	0	47	0	59	0	15	121
No therapy	10	22	4	7	4	1	48
Total	16	152	6	82	5	24	285

95% 0.02-0.13) for any ARV therapy versus no treatment (p = 0.0000), 1.01 (IC 95% 0.33-3.16) for elective cesarean versus vaginal delivery, and 2.97 (IC 95% 0.79-11.24) for non elective cesarean versus vaginal delivery (Table 4). When the analysis was restricted to women who had not received any ARV therapy, OR was 1.22 (IC 95% 0.27-5.47) for elective cesarean and 14.5 (IC 95% 0.99-21.32) for non elective cesarean, both versus vaginal delivery (Table 4).

The occurrence of adverse events (AEs) was determined in 271 patients who received any kind of antiretroviral therapy: 13 received monotherapy with ZDV and 133 combined therapy. Combined therapy included two NRTIs in 54 patients, two NRTIs plus nevirapine in 41 and two NRTIs plus one PI in 38.

One hundred eighty seven episodes of adverse events (AEs) were reported in 88 of women who had received some kind of ARV therapy.

The frequency of AEs according to ARV therapy used is described in Table 5.

More prevalent adverse events were: anemia 38.5% (72/187), hypercholesterolemia: 17.6% (33/187), hypertriglyceridemia 10.7% (20/187), increase of phosphatase alkaline: 10.7% (20/187), increase of GOT/GPT levels 6.9% (13/187) and gastrointestinal upset 5.3% (10/187). Less frequent toxicities related to ARV therapy included: trombocytopenia, neutropenia, rash, hypergly-cemia and high levels of amylase and CPK. Characteristics of AEs are described in Table 6.

Mothers who did not receive ARV therapy did not attend subsequent examinations. Thus, control data for this group are not available for analysis.

Causes of fetal death were determined in four of the six cases: one congenital abnormality, one placental abruption, one premature membrane rupture and one acute fetal distress. Congenital abnormality and placental abruption cases came from mothers in the combined therapy group while premature membrane rupture and

TABLE 4.– *Logistic Regresion Summary: Odds of HIV ARV therapy*

Covariate	Odds Ratio	95% CI	P-value
ARV treatment (vs. no treatment)	0.04	0.02-0.13	0.0000
Elective cesarean (vs. vaginal)	1.01	0.33-3.16	0.98
Non-elective cesarean (vs. vaginal)	2.97	0.79-11.24	0.11
Elective cesarean restricted to group with Not ARV therapy (vs. vaginal)	1.22	0.27-5.47	0.79
Non-elective cesarean restricted to group with Not ARV therapy (vs. vaginal)	14. 5	0.99-21.32	0.05

TABLE 5. – *Frequency of AEs according to ARV therapy*

ARV	No. AEs	%
ZDV	19	10.1
2 NRTIs	66	35.3
2NRTIs + 1 NNRTI	46	24.6
2 NRTIs + 1 PI	56	29.9
Total	187	100.0

NRTI: nucleoside reverse transcriptase inhibitor, PI: protease inhibitor

TABLE 6.– *Characteristics of AEs*

Grades	1	2	3	4	Total	%	Discount
Anemia	43	26	2	1	72	38.5	–
Neutropenia	1	–	–	1	2	1.1	1
Trombocytopenia	4	–	–	2	6	3.2	–
⇑ ALP	17	–	1	2	20	10.7	–
⇑ ALT/AST	6	7	–	–	13	6.9	–
Hypercholesterolemia	33	–	–	–	33	17.6	–
Hypertriglyceridemia	18	2	–	–	20	10.7	–
Hyperglycemia	3	–	–	–	3	1.6	–
⇑ amilase	2	–	–	–	2	1.1	–
⇑ CPK	2	1	–	–	3	1.6	–
GI upset	8	2	–	–	10	5.3	–
Rash	1	2	–	–	3	1.6	2
Total	138	40	3	6	187	–	1.60%

AEs: Adverse events, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transferase, CPK: Creatine phosphokinase, GI: Gastrointestinal

acute fetal distress cases came from mothers who had received no therapy.

Eight cases of congenital abnormalities were detected (2.3%), six in the monotherapy group: one renal agenesis, two imperforate anus, one gastrosquisis, two harelips, one mielomeningocele and one miocardiopathy and two in the non therapy group.

Discussion

A retrospective review of medical records of a cohort of pregnant women from Buenos Aires was carried out.

These results confirm the benefits of the ARV therapy that has been established in clinical trials. Although ARV therapy was available healthcare access is unevenly distributed in our country, and our results may reflect this background.

Therefore, in this context, the prevalence in Buenos Aires of more than 1% of HIV infection among pregnant women before 2001, indicates that the epidemic setting had not yet been put tightly under adequate control.

Data show that the main source of HIV transmission among women is sexual intercourse and that pregnancy occurs during early stages of HIV infection. As 26.9% of the diagnoses of HIV infection were made during pregnancy, it is highly advisable to recommend HIV screening in all pregnant women.

Since 1998, HIV-infection and pregnancy diagnosis have been contemporary in more than 60% of cases. Nevertheless, in the last few years, a marked shift has been noticed, and there have been an increasing number of pregnancies detected among chronic infected women. This new trend could reflect the efficacy and safety of the HIV vertical transmission prevention program. At the same time, this situation could also be due to the maintenance of risky sexual behavior, particularly among discordant couples.

Other evidence for the positive influence of prevention programs on transmission is the increasing proportion of pregnant women with HIV infection under ARV treatment.

We have found that the transmission rate in women without treatment was higher than previously reported in ACTG 076 Study, and this may be due to the fact that our group might have had higher viral load levels at time of delivery. Unfortunately this data is not available, because these patients did not have an adequate follow-up and in many cases, their HIV status was just known during or after labor.

It is important to highlight the role of zidovudine in the prevention of vertical transmission, since in this cohort, 83% of women who did not transmit HIV were treated with zidovudine alone or in combination, whereas only 32.1% of the women who did transmit HIV had received it.

No infections were reported among the offspring of patients under combined therapy, and this fact suggests this should be the standard treatment.

However, it is not clear yet which should be the best choice for patients without current virologic and immunologic criteria of treatment, so as not to jeopardize the outcome of future treatments.

In our cohort, these patients received treatment with two NRTIs (mostly ZDV and 3TC) until labor. However, a long follow-up period would be needed in order to evaluate the results in terms of development of viral resistance.

Recent studies have reported the emergence of resistance mutations in patients who had received a single dose of nevirapine before labor[15, 16].

In our cohort, only 4.3% of patients received a single dose of nevirapine before labor, and no data are available about the development of resistance mutations during follow-up.

According to current guidelines, vaginal delivery was recommended for all patients reaching labor with less than 1000 copies/ml, unless a specific obstetric contraindication was given[6].

In the multivariate analysis, ARV treatment was the only factor affecting the transmission rate. Among those patients who did not receive ARV treatment during pregnancy, the transmission risk was higher when non elective cesarean was performed.

As regards toxicity development, adverse events were mostly mild, and treatment interruption was exceptionally required. The most frequent side effect was anemia, and since it is also a very common feature in general pregnant population, it is difficult to establish a cause-effect relationship with ARV treatment.

Hypercholesterolemia and hypertriglyceridemia grade I were reported in all treated groups, and two cases of hypertriglyceridemia grade II were also reported in patients receiving nelfinavir.

In spite of the expected digestive distresses during the first trimester of pregnancy, treatment was, in general, well tolerated. Digestive intolerance was more frequent in patients who had received Protease Inhibitors (PIs) containing regimens.

The congenital abnormalities rate was no higher than the rate registered among the general population, according to data of surveillance studies from the Center for Diseases Control (CDC). The global annual prevalence determined in the general population in USA was 3.1%[17]. Local data, available from 12 614 deliveries in Buenos Aires, have determined an occurrence of 273 congenital abnormalities, since January 2004 to March 2005 (rate = 2.16%)[18].

So far, the bulk of data seems to confirm the main role of HIV screening at pregnancy, the efficacy or ARV treatment, and the potential benefit of elective cesarean in those patients not reaching a low viral load level at delivery.

Combined regimens with NRTIs alone or plus NNRTIs or PIs yielded better outcomes than ZDV monotherapy, with no evidence of more toxicity on the mother and newborn in the short term, but an extended follow-up of children exposed to ARV drugs would be needed in order to verify safety of antiretroviral therapy during pregnancy.

Controlled trials are also needed to define the best regimen for those patients not fulfilling current treatment criteria, but nonetheless receiving therapy for the prevention of vertical transmission. These trials should focus on determining the most appropriate regimen for minimizing risk of resistance development which could eventually compromise the outcome of subsequent ARV therapy.

This study has several limitations. A retrospective analysis of data obtained form clinical records does not allow us to control for many potential confounding variables. In particular, safety data for women not taking ARV therapy was not collected. Missing information on CD4+ T lymphocytes and viral load results precluded analyses of the correlation of these variables and perinatal transmission.

There are limited data on the use of ARVs agents during pregnancy in Latin America. In this context, we think these results are important because they confirm the benefits of antiretroviral therapy to decrease perinatal HIV transmission.

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