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ORIGINAL ARTICLE

Evaluation of factors associated with vertical transmission of HIV-1 in fourteen years of a referral center in Southern Brazil[☆]

Avaliação dos fatores associados à transmissão vertical do HIV-1 em quatorze anos de um centro de referência no Sul do Brasil

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Abstract

Aim: To compare the prevalence and factors associated with vertical transmission of HIV-1 among pregnant women treated in the periods of 1998–2004 and 2005–2011 in a reference service for the care of HIV-infected patients in southern Brazil.

Methods: A descriptive and analytical study which used the databases of laboratories of Viral Load and CD4 National Laboratory Network of STD/AIDS, Ministry of Health. HIV-1 infected pregnant women were selected following an active search for clinical information and obstetric and neonatal data from their medical records between the years 1998 and 2011.

Results: 102 pregnant women were analyzed between 1998 and 2004 and 251 in the period 2005–2011 totaling 353 children born to pregnant women with HIV-1. It was observed that vertical transmission was 11.8% between 1998 and 2004 and 3.2% between 2005 and 2011 ($p < 0.001$). The increased use of antiretroviral drugs ($p = 0.02$), the decrease in viral load ($p < 0.001$) and

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time of rupture of membranes lower than 4 h ($p < 0.001$) were associated with the decrease of vertical transmission factors when comparing the two periods.

Conclusion: It was observed a decrease in the rate of vertical transmission in recent years. According to the studied variables, is suggested that the risk factors for vertical transmission of HIV-1 were absence of antiretroviral therapy, high viral load of pregnant women and the breakthrough time greater than 4 h membranes.

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Introduction

The mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 can occur during three major periods: in utero, at birth or during breastfeeding.¹ The HIV-1 can be transmitted intrauterine through transplacental cellular transport, through a progressive infection of the placenta's trophoblasts until the virus reach the fetal circulation or due ruptures in the placental barrier followed by microtransfusions that occur from mother to child.² The transmission during delivery occurs through the contact of the fetus with mother's infected secretions while passing through the birth canal, through ascending infection from vagina to fetal membranes and amniotic fluid or through absorption in the neonatal digestive tract. In the postpartum period, the main form of transmission is the breastfeeding.³

The vertical transmission route of HIV-1 can be influenced by several factors such as the delivery mode,⁴ the use of antiretroviral therapy,⁵ oral inflammations of newborn,⁶ prematurity and high maternal viral load.⁷ Besides these factors, the viral genetic diversity seems to play an important role in vertical transmission.^{1,8}

The epidemic of acquired immunodeficiency syndrome (AIDS) is found in process of stabilization, however it still presents high rates of transmission, especially among women, which characterizes the feminization of the disease.⁹ Therefore, it becomes important to understand the epidemiological profile of pregnant women and, this way, of MTCT, since the changes in prevalence depend on factors such as the use of antiretrovirals and the adhesion to prenatal care for pregnant women. These and other factors may lead to a fall in MTCT, thereby facilitating the adoption of preventive measures more effective.^{9,10} In Brazil from 1980 to June 2013 estimated that 718.230 people are living with HIV/AIDS.¹¹ According to the Brazilian epidemiological bulletin of 2013, analyzing information from 2010, the prevalence of HIV infection in pregnant women was 0.38%. Vertical transmission has become a major challenge to public health, epidemiological data show that 80% of HIV cases in children under thirteen years old had MTCT as the form of transmission.

Due to the increasing number of infected pregnant women, actions as the development of governmental programs and the monitoring of pregnant women were implemented since 2000 in Brazil, infected women and exposed child have become a compulsory reporting.¹¹ According Sinan (Medical Care National System),¹¹ from 2000 to 2013 were reported 77.066 cases of HIV in pregnant women, the South region of Brazil is in second place with 31,3% of cases, behind only the Southeast region (41.7%) and

followed by the Northeast (14.9%), North (6.3%) and Midwest regions (5.7%). Comparing the detection rate of AIDS in children under five years (indicator used in Brazil to monitor the vertical transmission of HIV) between 2012 and 2003, it had a reduction of 35.8%.¹¹

This study aimed to compare the prevalence and factors associated with vertical transmission of HIV-1 among women treated in the periods from 1998 to 2004 and from 2005 to 2011 in a reference service for the care of HIV-infected patients in southern Brazil located at the University Hospital of Federal University of Rio Grande (HU-FURG), in the city of Rio Grande – RS.

Methodology

A descriptive and an analytic study were conducted, including 102 newborns from HIV-1 positive pregnant women in the period 1998–2004 and 251 in the period 2005–2011, a total amount of 353 births.

Despite of development of Brazilian governmental programs and monitoring of pregnant women were implemented in 2000, the health care to HIV patient began in the University Hospital Dr. Miguel Riet Correa Jr – FURG in 1994, due testing and subsequent observation of the high incidence of cases in the region. Such attention was ruled from normative of the Brazilian Ministry of Health and subsequently every care protocols met as such recommendations. Due changes, such as the higher prevalence of viral subtype C and the difference of the therapeutic and pharmacological model of the patient with HIV referenced in different analyzed periods, it was decided to stratify the data to become viable the analyzes. Moreover, it could report the effectiveness of care models recommended by Brazilian Ministry of Health.^{8,15}

Since 1998, all pregnant women attended at Dr. Miguel Riet Correa Jr. University Hospital of Federal University of Rio Grande (HU-FURG) were subjected to HIV/AIDS tests as recommended by guidelines from Brazilian Ministry of Health. Pregnant women that presented two positive serologic tests and one confirmation test or two consecutives tests with detectable viral load were classified as infected by HIV. The mothers signed an informed consent to participate in this research and this study was approved by FURG's Ethical Committee in Health Research (23116001368/2003-44).

The outcome was the MTCT of HIV-1 in newborns and the studied variables were: use of highly active antiretroviral therapy – HAART – (Biovir + Kaletra) during pregnancy, CD4⁺ T cells amount in the last three months of pregnancy,

Table 1 Comparison of factors associated with mother-to-child HIV-1 transmission between the periods 1998 and 2004 and 2005–2011 in a reference service.

Period	N	Membrane rupture times				p-value			
		>4 h	%	<4 h	%				
1998–2004	102	81	79.4	21	20.6	0.67			
2005–2011	251	27	10.8	224	89.2				
Total	353	108	30.6	245	69.4				
		Delivery mode							
	N	Cesarean	%	Normal	%				
1998–2004	102	39	38.2	63	61.7	0.67			
2005–2011	251	90	35.8	161	64.8				
Total	353	129	36.5	224	63.5				
		Mother-to-child transmission							
	N	HIV+	%	HIV–	%				
1998–2004	102	12	11.8	90	88.2	<0.001			
2005–2011	251	8	3.2	243	96.8				
Total	353	20	5.7	333	94.3				
		Antiretroviral therapy during pregnancy							
	N	Incomplete	%	Complete	%				
1998–2004	102	40	39.3	62	60.7	0.02			
2005–2011	251	67	26.7	184	73.3				
Total	353	107	30.3	246	69.7				
		T CD4+ cell amount							
	N	cell 0–199	%	cell 200–499	%	cell >500	%		
1998–2004	95	18	18.9	50	52.6	27	28.4		
2005–2011	251	13	5.2	94	37.5	144	57.3		
p-value	<0.001		<0.001		1.00				
		Maternal viral load – Log ¹⁰							
	N	0–2.99	%	3.0–3.99	%	4.0–4.99	%	≥5	%
1998–2004	95	27	28.4	23	24.2	35	36.8	10	10.5
2005–2011	251	173	68.9	49	19.5	26	10.3	3	1.2
p-value	<0.001		0.37		<0.001		<0.001		
		Children gender							
	N	Male	%	Female	%				
1998–2004	102	54	52.9	48	47.1	0.68			
2005–2011	251	127	50.5	124	49.5				
Total	353	181	51.3	172	48.7				

133 pregnant women viral load, delivery mode, breakthrough
 134 time and newborns weight (Kg) after delivery. The use of
 135 antiretroviral therapy was classified as: (a) Complete – when
 136 the mother received antiretrovirals during pregnancy and in
 137 the moment of delivery as well as the newborn; and, (b)
 138 Incomplete – when at least one of the three procedures
 139 were conducted or when the mother did not use antiretro-
 140 viral. Socio-demographic variables were not standardized

141 between these periods. So it was not possible to perform the
 142 demographic profile of the population in this study (Table 1).

143 The data was analyzed using Stata version 8.0 statisti-
 144 cal software (StataCorp, CollegeStation, TX). An analytical
 145 descriptive analysis of numerical variables was performed
 146 according to the studied periods, which were presented by
 147 their frequencies, mean values, standard deviation and a
 148 significant *p* value of 0.05 of a two-tailed test.

Results

In this study, were analyzed 353 children born from HIV-1 positive pregnant women between the years 1998 and 2011, attended at HU-FURG in the city of Rio Grande/RS.

This study showed that the rates of mother-to-child transmission obtained between the years 1998 and 2004 and 2005 to 2011 fell significantly ($p < 0.001$) from 11.8% to 3.2% respectively. It becomes interesting to observe the results in different periods, in which the transmission rate between the years 1998 and 2000 was 11.8%, from 2001 to 2004 the rate was 7.7%, from 2005 to 2008 the rate was 2.7% and from 2009 to 2011 the transmission rate was 2.9% (Fig. 1).

For the analyzed variables in both studied periods, could be observed that between the periods from 1998 to 2004, 79.4% of the pregnant women had a membrane rupture time longer than 4h. In contrast, for the period between 2005 and 2011, only 10.8% of pregnant women had a membrane rupture time longer than 4 hours ($p < 0.001$).

There was no significant difference in the mode of delivery between the two studied periods, neither in the average weight of newborns after delivery. The use of antiretroviral therapy throughout the gestational period was done by 69.7% of the pregnant women. Between the years 1998 and 2004, 60.7% of pregnant women adhered to HAART and, between the years 2005 and 2011, the adherence rate was 73.3% ($p < 0.02$) suggesting that the adherence to the antiretroviral therapy by pregnant women appears to be an important factor in the reduction of mother-to-child transmission. It was considered complete use of ART when mothers reported having used the drug during the antenatal period, at delivery and her newborn have received prophylaxis with oral suspension of Zidovudine (AZT) for six weeks after delivery. The use of injecting AZT and oral AZT was checked with the drug dispensing control spreadsheets during hospitalizations of the patient, according to the protocol established by Health Ministry of Brazil. Since 1998, the PMTCT attention was performed following the recommendation to AZT monotherapy. In 2001 it was recommended the triple therapy combining three ARTs, inserting the Bivir and Nelfinavir. In 2007, following the recommendation of the Brazilian Health Ministry, Kaletra was introduced, replacing Nelfinavir.

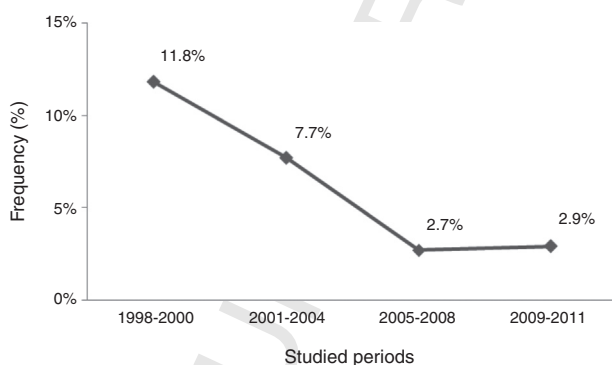


Figure 1 Comparison of the mother-to-child HIV-1 transmission rates between the periods from 1998 to 2011 in a reference service.

There was an increase in the CD4⁺ T cells amount (CD4⁺ T cells > 500) when comparing both studied periods. According the analyzed data, between the years 1998 and 2004, was observed a frequency of 29.4% of pregnant women with CD4⁺ T cells amount higher than 500. However, in the period of 2005–2011, the percentage of pregnant women with CD4⁺ T cells amount higher than 500 increased to 57.3% ($p < 0.001$).

When analyzing the maternal viral load, can be observed that pregnant women with viral load between undetectable and log of 2.9 was 68.0% in the period of 2005–2011 and 28.4% in the period of 1998–2004 ($p < 0.001$).

Discussion

Brazil has as goal the elimination of HIV-1 vertical transmission (less than 1% of transmission) until 2015.¹¹ Studies have shown that it is possible to prevent new HIV infection in children, since HIV-positive pregnant women have timely and appropriate access to prenatal care and to HAART.¹³ In the present study was observed a rate of vertical transmission of 5.7% from a total of 353 children born from seropositive mothers for HIV-1 between the years 1998 and 2011. However, it is interesting to analyze the rate of mother-to-child transmission in different periods. In this study can be noted that between the years 1998 and 2000 the MTCT rate was 11.8%, from 2001 to 2004 the rate was 7.7%, from 2005 to 2008 the rate was 2.7% and from 2009 to 2011 the MTCT rate was 2.9%, this demonstrates that the MTCT rates are relatively low when analyzes at different times. There has been a small increase in MTCT rates between the years 2005 and 2008 (2.7%) and 2009–2011(2.9%), which may be justified due to the fact that a portion of pregnant women HIV positive still do not make use of chemoprophylaxis during the pregnancy, especially drug users and currently the specific use of the illicit drug CRACK. Data showed that pharmacy records can help identify less-than-optimal adherence to treatment.¹⁴ Because of stabilization of values of the referenced MTCT rates not only in this study as well as in Brazil, the Brazilian Ministry of Health implemented in 2012 the use of Nevirapine (NVP) (Technical Note n. 388/2012). In Brazil has been advocating the use of AZT associated with NPV for the prevention of newborns to HIV since a recently published study demonstrated that the oral treatment with a solution containing AZT during six months associated to an oral suspension with NPV, three doses in the first week of life, significantly reduce the rate of mother-to-child transmission from pregnant women who did not use chemoprophylaxis during pregnancy.¹¹

Taking into account the aim of this study, observing the rates obtained between the years 1998 and 2004 and 2005–2011, it is noticed a drastic drop in the transmission rates from 11.8% to 3.2% respectively, result that clearly demonstrates the decline in mother-to-child transmission rates. Comparing these results with studies conducted in the same Brazilian region, a studied published in 2006 observed a MTCT rate of 11.8% in infants born between the years 1998 and 2003.¹⁵ Later in another study published in 2010 from the same region, was observed a MTCT rate of 4.8% between the years 2003 and 2007⁸ and, in the present study, was observed a MTCT rate of only 2.9% when analyzed only the period from 2007 to 2011. These results clearly demonstrate that there

was a decrease in the MTCT rates of HIV-1, which highlights the effectiveness of the national policy and program for the control of mother-to-child transmission.

With the approval of Law No. 9313 on November 13, 1996, Brazil began to rely in its legal system with one legislation that ensures the access to antiretroviral by people living with HIV/AIDS. Thus, Brazil became the first emerging country to provide antiretroviral therapy to patients that need it. In 2009, the Secretary of Substitute Health Surveillance started to use fast HIV tests in pregnant women, according to the authority conferred by the Article 45 of the Decree No. 6860 of May 27, 2009.^{9,11} Therefore, it can be suggested that these control measures had an influence in the decline of the HIV infection rates in infants between the studied periods, result that demonstrates the importance of these control measures in public health services. Similar decreases in mother-to-child transmission rates are found in several countries that adopt control measures, especially the use of antiretroviral therapy by HIV positive pregnant women.¹⁶ In the present study, could be observed that 69.7% of mothers made use of antiretroviral throughout the gestational period, suggesting a decline in the vertical transmission rate. In a study published in 2011 was observed that, from 25 seropositive children, 9% were born from mothers that received inadequate antiretroviral therapy during pregnancy, a fact that occasioned a rate of only 1.7% of vertical transmission.¹⁷

When analyzing the different periods of this study, it can be observed that, between the years 1998 and 2004, 60.7% of pregnant women adhered to the use of antiretroviral therapy and, between the years 2005 and 2011, there was an increase in pregnant women that adhered to antiretroviral therapy during pregnancy with a percentage of 73.3%. This suggests a low viral load in pregnant women and a decrease in vertical transmission rates between the periods from 2005 to 2011, whereas it is only 3.2%. These results corroborate with a previous study, which demonstrated that the mainly risk factors for HIV transmission were the failure of antiretroviral therapy, late maternal diagnosis and, consequently, high viral load of pregnant women at delivery.⁸ The antiretroviral therapy during pregnancy is extremely important in order to prevent vertical transmission and it can be used during any period regardless the clinical condition in which the mother is found.¹⁸ Studies have reported that a high viral load and a low CD4⁺ T cells amount during pregnancy are significant factors for mother-to-child transmission to occur.^{8,19}

It is noteworthy that a time lower than 4h for the membrane rupture is extremely important to reduce mother-to-child transmission of HIV-1.²⁰ In this study, it can be observed a significant decrease ($p < 0.001$) in rupture time when analyzing the studied periods, since there was a frequency of 79.4% of pregnant women who had a rupture time higher than 4h between the period from 1998 to 2004. In contrast, in the period 2005–2011, the frequency was 10.8% of pregnant women who had a rupture time higher than 4h. The significant difference between membrane rupture time in both studied periods is the result of the update of care protocols for HIV pregnant women. In 2004 started the encouragement of HIV testing during prenatal care and proper implementation of prevention actions of vertical transmission of HIV, with the first published protocol in

2007. According to the Brazilian guide for recommendations for prophylaxis of the transmission of HIV and antiretroviral therapy in pregnant women, the active management of labor should occur to prevent prolonged membrane rupture time, once the less time decreases the risk of vertical transmission.⁹

Despite of the effort to reduce the MTCT, the residual risk of that transmission is still relatively high in comparison of what it is observed elsewhere in the HAART area.²¹ The fact that the Southern of Brazil is characterized to have more prevalence of HIV-1 subtype C, which is intrauterine more transmissible,⁸ it can help to explain the rate of MTCT found in the present study. Beyond this fact, late entrance and lack adherence to prenatal care, especially in drug users, favor the MTCT. A study showed that low prenatal screening coverage of maternal HIV infection, impairing maternal treatment or prophylaxis; and the incorrect use of the rapid screening test at admission for delivery are impediments to the effective reduction of MTCT of HIV.²² For the attention to pregnant women with low adherence to prenatal be expanded in the region of this study, especially those drug users, the referral service of University Hospital Dr Miguel Riet Correa of FURG/Rio Grande conducts active search of women in favor of the effectiveness of compliance with care protocols to prenatal care as recommended by the Brazilian Ministry of Health.

Therefore, this study may suggest that the increase of antiretroviral therapy during pregnancy, the time for membrane rupture lower than 4h and low viral load contributed to the decline of mother-to-child HIV-1 transmission in both studied periods. These results agree with the data obtained in the literature.^{2,7,23} However, more studies should be conducted to establish which factors are involved in mother-to-child transmission.

Conflicts of interest

The authors declare no conflicts of interest.

Uncited reference

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