

## Analysis of the mother-to-child transmission rate of HIV and maternal-fetal risk factors in exposed children born in a reference center in the state of Goiás

### *Análise da taxa de transmissão vertical do HIV e fatores de risco materno-fetais em crianças expostas nascidas em centro de referência do estado de Goiás*

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**ABSTRACT:** *Objectives:* To estimate the mother-to-child transmission (MTCT) rate of HIV and the maternal-fetal risk factors in children born in 2015 in follow-up during the years 2015 to 2017 in the largest reference center for HIV treatment in the state of Goiás. *Methods:* Retrospective cohort study of 111 HIV-exposed children born in 2015 of HIV-positive mothers, with 19 follow-up losses. *Results:* Among the mothers, 85 (92.4%) used ART during pregnancy. Of the 92 children who maintained follow-up, 4 (4.34%) acquired perinatal HIV infection. 81 (88%) newborns used antiretroviral prophylaxis. An important protective factor for HIV MTCT was neonatal prophylaxis (OR: 0.02, 95% CI: 0.00-0.56,  $p = 0.04$ ). Other investigated factors, such as ART during pregnancy, were not statistically significant for risk. *Conclusion:* The MTCT rate of HIV is still high in the state of Goiás and the challenges for its prevention consist in the loss of follow-up and failures in the strategic measures.

**Keywords:** HIV; Child; |Mother-to-child transmission; Epidemiology.

**RESUMO:** *Objetivos:* Estimar a taxa de transmissão vertical do HIV e os fatores de risco materno-fetais em crianças nascidas em 2015 em seguimento durante os anos de 2015 a 2017 no maior centro de referência para tratamento para HIV do estado de Goiás. *Métodos:* Estudo de coorte retrospectivo de 111 crianças expostas ao HIV nascidas em 2015 de mães HIV positivas. *Resultados:* Entre as mães, 85 (92,4%) utilizaram TARV durante a gestação. Das 92 crianças que mantiveram seguimento, 4 (4,34%) adquiriram infecção perinatal pelo HIV. 81 (88%) recém-nascidos fizeram uso de profilaxia antirretroviral. Um fator protetor importante de transmissão vertical do HIV foi a profilaxia antirretroviral do RN (OR = 0,02; IC 95%: 0,00-0,56;  $p = 0,04$ ). Outros fatores investigados, como uso de TARV durante a gestação, não foram estatisticamente significativos para risco. *Conclusão:* A taxa de transmissão vertical do HIV ainda se encontra elevada no estado de Goiás e os desafios para sua prevenção consistem na perda de seguimento e falhas nas medidas estratégicas.

**Palavras-chave:** HIV; Criança; Transmissão vertical; Epidemiologia.

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## INTRODUCTION

In 2019 there were approximately 38 million people in the world living with the Human Immunodeficiency Virus (HIV), of whom 1,8 million were children between 0 and 14 years of age; of these figures, 1.7 million and 150 thousand, respectively, were new cases reported in that year, both representing a historical reduction<sup>1</sup> that was followed by a reduction in childhood mortality due to Acquired Immunodeficiency Disease (AIDS)<sup>2</sup>, even though the treatment coverage for children is still unsatisfactory<sup>3</sup>. The rates of mother-to-child transmission (MTCT) – or ‘vertical transmission’ – of HIV have exhibited a substantial decrease in developed countries, falling to as low as 1%. This was possible thanks to the efficacy of the preventive measures that were adopted, such as enhancing access to antiretroviral therapy (ART) by infected pregnant women to avoid MTCT, which is the major HIV transmission route in the pediatric age group<sup>4</sup>.

In 2018 in Brazil there were 43,841 new cases of HIV infection, of which 8,621 were pregnant women. Such figures make up for a detection rate of 2.9 per thousand of live births, representing a trend of increase of this indicator, which is attributed, in part, to the expansion of prenatal diagnosis and subsequent prevention of HIV MTCT. Fortunately, the childhood mortality due to AIDS is decreasing in the country, but MTCT still accounts for 86.2% of cases in children younger than 13 years old<sup>5</sup>. Brazil, therefore, is in a context in which the elimination of the HIV MTCT is of great importance, and because of that the Brazilian Ministry of Health (MH) adopted the goal to eliminate or reduce the rate of HIV cases among children to less than 1% the total, according to the Guide for Certification of Elimination of HIV Vertical Transmission<sup>6</sup>.

The historical analysis shows that the adoption of preventive measures by the MH during the 1990/2000s – among them the recommendations of the Pediatric AIDS Clinical Trials Group 076 (PACTG-076), which reported a substantial decrease in the MTCT rate with prophylactic Zidovudine (AZT) for pregnant women infected with HIV<sup>7</sup> – resulted in significant reduction of the MTCT in Brazil<sup>8,9</sup>. In recent years, the detection rate of AIDS/HIV in children younger than 5 years old – utilized by the MH as a proxy indicator for monitoring the HIV MTCT rate – has exhibited a significant decrease, led by the Southern and Southeastern regions of the country<sup>5</sup>. Notwithstanding, Brazil maintains a rate higher than those of developed countries, and only two Brazilian cities received the Certification of Elimination of HIV Vertical Transmission<sup>10</sup>.

It is therefore quite important to seek a reduction of this HIV transmission route and, subsequently, the childhood mortality. In this regard, our study aims to estimate the rate of HIV MTCT and to evaluate the maternal-fetal factors among children exposed to the virus born in 2016 in Goiás, since this disease is eliminable

through preventive measures historically adopted by the MH and intensified in the recent years due to advancements such as the proper post-exposure antiretroviral prophylaxis for the newborn.

## METHODS

### *Design of the study*

This is a retrospective cohort study conducted in the service of Pediatric Infectiology HIV/AIDS of the *Hospital de Doenças Tropicais/Dr. Anuar Auad* (HDT/HAA) in Goiânia, Goiás, Brazil. This is a hospital school with specialized care and the main reference center in infectious diseases in the state of Goiás, linked to the public healthcare system, and that assists most cases of HIV/AIDS in the state, whose population is of 6,695,000 inhabitants and whose HDI is of 0.735, according to the 2016 census. This study was approved by the proper Research Ethics Committee (n° 2.314.473).

### *Studied population*

The population of the study was composed of all children born in 2015 between January 1st to December 31st to mothers infected with HIV and that were followed by the Pediatric Infectiology service of HDT/HAA. We aimed for a follow-up period of at least 18 months of age.

The inclusion criteria were being born to mothers proven to be HIV+, born in Goiás, and being followed by the service in HDT. The exclusion criteria follow-up at another medical service, abortion or fetal death, loss of follow-up, and delivery in other states.

### *Data sources*

We manually identified children as born to HIV+ mothers using their medical records as a secondary data source. We elaborated a data collection instrument with the following variables: gender, maternal age, number of pregnancies, time of maternal diagnosis of HIV, use of ART by the mother during the pregnancy, use of intravenous AZT intrapartum, type of ART regimen used the mother during pregnancy, type of delivery, gestational age, weight at birth, direct breastfeeding, prophylaxis for the newborn, HIV infection in the child, and seroreversion age in the children. In this study, direct breastfeeding in any given period and duration was defined as breastfeeding present.

According to the American Department of Health and Human Services (DHHS) guidelines, HIV infection in exposed children younger than 18 months of age is defined by two positive molecular tests (HIV-RNA or HIV-DNA) in two different samples. Therefore, the HIV-exposed children were considered not infected if they had two or more negative molecular tests, one of them being obtained at 1 month or more of age and the other at 4 months or more of age.

**Statistical analysis**

The SPSS version 21.0 (SPSS Inc. Chicago, U.S.A.) and OpenEpi version 3.01 ([http://openepi.com/Menu/OE\\_Menu.htm](http://openepi.com/Menu/OE_Menu.htm)) programs were utilized for the statistical calculations. The descriptive statistical analysis of the main characteristics of mothers and children was performed identifying the central tendency and dispersion values, and then the frequencies for the continuous and categorical variables. The chi-squared test ( $\chi^2$ ) was used to evaluate the proportion differences with statistical significance of 5% ( $p < 0.05$ ).

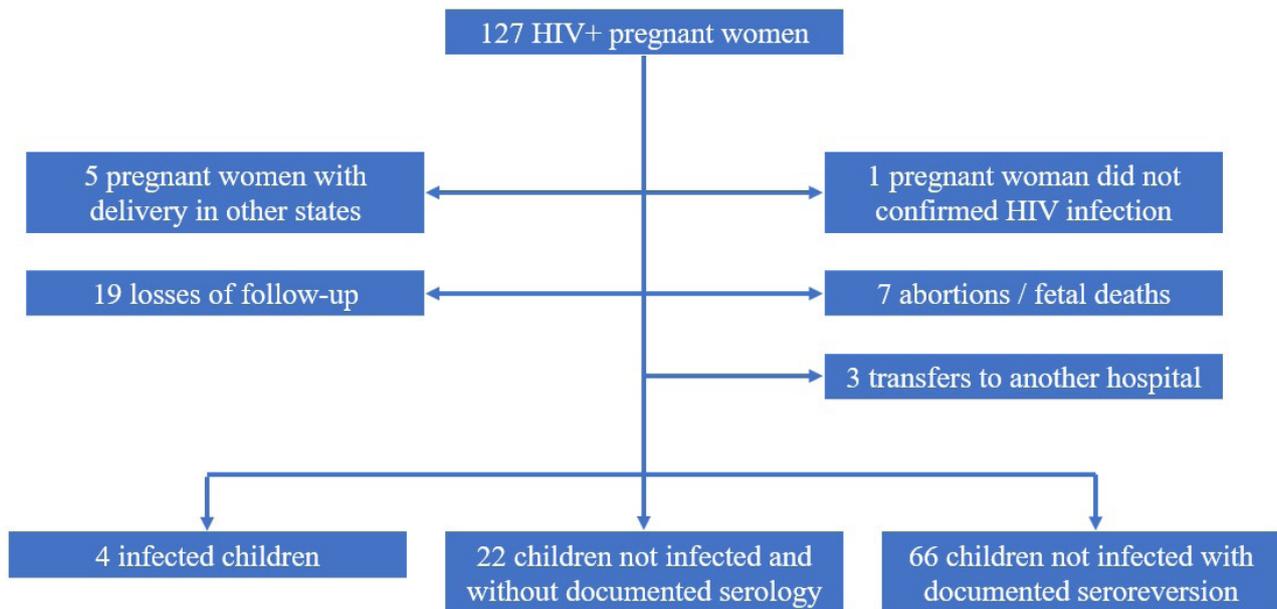
The HIV MTCT rate was estimated with a confidence interval of 95% (CI 95%), the numerator being the number of infected children, and the denominator being the number of children exposed to HIV.

We performed an univariate analysis to evaluate the factors associated with the MTCT of HIV in the exposed children.

**RESULTS**

A total of 127 pregnant women with HIV infection and their children born in 2015 were initially included for analysis. Of these women, we excluded 5 whose delivery occurred in another state, 7 who had abortions or fetal deaths, 3 who were transferred to another hospital (all of them to the Hospital das Clínicas of the Federal University of Goiás), and 19 who had loss of follow-up. We excluded 1 child whose mother repeated the tests and did not confirm the HIV diagnosis. Therefore, there remained for analysis 92 children exposed to HIV.

Of these 92 children, 4 were infected, 66 were not infected with documented seroreversion, and 22 were not infected without documented anti-HIV serology, according to the DHHS guidelines (Figure 1). With these figures, we calculated, for our sample, a rate of HIV MTCT of 4.34%.



**Figure 1:** Flowchart of the exclusion criteria for children in the study. HIV+: infection by the Human Immunodeficiency Virus; \*children with 2 undetectable viral load tests, but without documented anti-HIV serology (according the DHHS guidelines).

Table 1 shows the maternal-fetal characteristics of the 92 analyzed children. As for gender, 46 were male and 46 were female. As for the maternal age, 7 (7.6%) mothers were 20 years old or less, 63 (68.5%) were older than 20 years of age, and 22 (23.9%) did not have this information in their records. 15 (16.3%) women were in their first pregnancy, 62 (67.4%) in their second or further pregnancy, and 15 (16.3%) did not have this information.

As for the moment of maternal diagnosis of HIV, 35 (38%) were before the pregnancy, 41 (44.6%) during the considered pregnancy, 1 (1.1%) after the pregnancy, and 15 (16.3%) did not have this information in their records. ART during pregnancy occurred in 85 (92.4%) cases; 5

women did not have it (4.3%), and 3 (3.3%) did not have such information. As for intravenous ART intrapartum, 54 (58.7%) mothers had it, 2 (2.2%) did not, and 36 (39.1%) did not have this information in their records.

The ART regimen used by the women during pregnancy was comprised of AZT/3TC e LPV/r for 70 (76.1%) mothers, TDF/3TC and LPV/r for 4 (4.3%), another regimen for 9 (9.8%), and unknown regimen for 9. As for the type of delivery, 29 (31.5%) had vaginal delivery, 56 (60.9%) had a cesarean, and 7 (7.6%) were unknown. The gestational age at birth was less than 37 weeks (preterm) in 9 (9.8%) children, 60 (65.2%) were born at term ( $\geq 37$  weeks), and 23 (25.8%) were unknown.

**Table 1.** Maternal-fetal characteristics of the 92 children exposed to HIV born in 2015 in Goiás and being followed in HDT/HAA

CHARACTERISTICS	n	%
<b>Child gender</b>		
Male	46	50.0
Female	46	50.0
<b>Maternal age</b>		
≤ 20 years old	7	7.6
> 20 years old	63	68.5
Unknown	22	23.9
<b>Number of pregnancies</b>		
1 <sup>st</sup> pregnancy	15	16.3
> 1 pregnancy	62	67.4
Unknown	15	16.3
<b>Moment of maternal HIV diagnosis</b>		
Before pregnancy	35	38.0
During pregnancy	41	44.6
After pregnancy	1	1.1
Unknown	15	16.3
<b>ART during pregnancy</b>		
Yes	85	92.4
No	5	4.3
Unknown	3	3.3
<b>Intravenous ART intrapartum</b>		
Yes	54	58.7
No	2	2.2
Unknown	36	39.1
<b>Type of ART regimen during pregnancy</b>		
AZT/3TC + LPV/r	70	76.1
TDF/3TC + LPV/r	4	4.3
Another regimen	9	9.8
Unknown	9	9.8
<b>Type of delivery</b>		
Vaginal	29	31.5
Cesarean	56	60.9
Unknown	7	7.6
<b>Gestational age</b>		
Preterm, < 37 weeks	9	9.8
Term, ≥ 37 weeks	60	65.2
Unknown	23	25.8
<b>Weight at birth</b>		
≥ 2,500 g	70	76.1
≥ 2,000 and < 2,500 g	10	10.9
< 2,000 g	7	7.6
Unknown	5	5.4
<b>Breastfeeding</b>		
Yes	1	1.1
No	57	62.0
Unknown	34	37.0
<b>Newborn prophylaxis</b>		
Yes	81	88.0
No	2	2.2
Unknown	9	9.8
<b>HIV infection in the child</b>		
Infected	4	4.3
Not infected	88	95.7
<b>Seroreversion age in the child</b>		
12 to 18 months of age	37	40.2
> 18 months of age	29	31.5
Unknown	26	28.3

HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy; AZT: Zidovudine; 3TC: Lamivudine; LPV: Lopinavir; r: Ritonavir

The weight at birth was 2,500 g or more for 70 (76.1%) children, between 2,000 and 2,500 g for 10 (10.9%), less than 2,000 g for 7 (7.6%), and 5 (5.4%) did not have this information. The prophylaxis for the newborn was administered in 81 (88%) cases, 2 (2.2%) newborns did not receive it, and 9 (9.8%) did not have this information in their records.

As for the seroreversion age, 37 children (40.2%) had it between 12 and 18 months of age, while 29 (31.5%) had it after 18 months of age, and this information was

unknown in 26 (28.3%) children. Finally, infection by HIV occurred in 4 children (4.3%), while 88 (95.7%) were not infected, according to the DHHS guideline.

In Table 2, there is a bivariate analysis of the HIV MTCT risk related to the maternal-fetal characteristics. The proper antiretroviral prophylaxis was a statistically significant variable, contributing as a protective factor for the HIV MTCT (OR: 0.02 [0.00-0.56]; CI 95%;  $p = 0.04$ ). The use of ART during pregnancy, as the other variables, were not statistically significant.

**Table 2.** HIV Mother-to-Child Transmission risk related to the maternal-fetal characteristics.

	HIV MTCT			
	Yes	No	OR (CI 95%)	<i>p</i>
<b>Moment of maternal HIV diagnosis</b>				
Before/During pregnancy	3	73		
After pregnancy	0	1	0.96 (0.91 – 1.00)	0.48
<b>ART during pregnancy</b>				
Yes	4	81		
No	0	4	0.95 (0.90 – 0.99)	0.41
<b>Type of delivery</b>				
Vaginal	0	29		
Cesarean	4	52	1.07 (1.00 – 1.16)	0.09
<b>ART regimen</b>				
AZT/3TC + LPV/r	3	67		
TDF/3TC + LPV/r	0	4	0.96 (0.91 – 1.01)	0.42
<b>Gestational age</b>				
Preterm	0	9		
Term	2	58	1.03 (0.98 – 1.08)	0.38
<b>Weight at birth</b>				
< 2,000 g	2	78		
≥ 2,000 g	1	6	0.15 (0.01 – 1.95)	0.12
<b>Breastfeeding</b>				
Yes	0	1		
No	2	55	1.03 (0.98 – 1.08)	0.48
<b>Newborn prophylaxis</b>				
Yes	2	79		
No	1	1	0.02 (0.00 – 0.56)	0.04

MTCT: Mother-to-child transmission; HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy; AZT: Zidovudine; 3TC: Lamivudine; LPV: Lopinavir; r: Ritonavir.

## DISCUSSION

In our study, the HIV MTCT rate in exposed children born in 2015 in Goiás and being followed in HDT was of 4.34%. This rate is lower compared to certain rates of other Brazilian regions, such as the 6.6% rate found in a cohort study performed in the state of Amazonas between 1999 and 2011<sup>11</sup>, and also lower than some developed countries' rates, such as the 6% rate found in a cohort study performed in the University of Texas from 2000 to

2007<sup>7</sup> – as in the United States the estimated incidence of perinatal HIV infection in 2013 was of 1.8 per thousand inhabitants, with a 96% decrease in the HIV MTCT rate between 1992 and 2013<sup>12</sup>.

It is important to remark that in the state of Goiás the reduction of the HIV MTCT rate is improving: it was estimated to be of 27.8% between 1995 and 2001<sup>9</sup>, and then of 2.0% between 2008 and 2010<sup>13</sup>, which represents an unexpected enhancement. Also, the frequency of 92.4% of ART during pregnancy observed in our study can be

considered high when compared to the frequency of 34% previously observed<sup>9</sup>, which may correspond to a better access to ART.

As for the antiretroviral prophylaxis for the newborn, we found that it is a statistically significant variable (OR: 0.02 [0.00-0.56]; CI 95%;  $p = 0.04$ ). This result agrees with other studies<sup>11</sup>, including the Pediatric AIDS Clinical Trials Group 1043 (PACTG-1043)<sup>14</sup>, which demonstrated a 50% reduction in the HIV MTCT rate with proper antiretroviral prophylaxis.

A limitation of our study is the number of participants, which may be considered small. Also, being a retrospective study, it cannot establish causality. On the other hand, it should be observed that, since 2012, there was no new published research in Goiás concerning its HIV

MTCT. In addition, our study reinforces even more how necessary it is to administer prophylaxis for the newborn as preventive measure for the HIV MTCT.

We conclude that the HIV mother-to-child transmission rate remains high among children born in Goiás in 2015, thus it is a challenge to reduce this rate in the next years so to meet the goal of less than 2% indicated by the 2017 Guide for Certification of HIV Elimination<sup>6</sup>. Among the strategic measures adopted to achieve this goal, the main ones are the salvaging of patients with loss of follow-up and the reinforcement of proper use of antiretroviral prophylaxis to the newborn.

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