



ELSEVIER

The Brazilian Journal of
INFECTIOUS DISEASESwww.elsevier.com/locate/bjid

Original article

Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review

Flávia Alves Campos^{a,*}, Gláucia Manzan Queiroz de Andrade^b,
Antônio de Pádua Santos Lanna^c, Bruno Freitas Lage^c,
Maria Vitória Mourão Assumpção^d, Jorge A. Pinto^e

^a Program in Child and Adolescent Health, Universidade Federal de Minas Gerais (UFMG), Pediatrician, Children's Hospital João Paulo II, FHEMIG, Belo Horizonte, MG, Brazil

^b Department of Pediatrics, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

^c School of Medicine, Federal University of Minas Gerais, MG, Brazil

^d Children's Hospital João Paulo II, FHEMIG, MG, Brazil

^e Department of Pediatrics, Pediatric Immunology Division, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

ARTICLE INFO

Article history:

Received 11 January 2014

Accepted 19 May 2014

Available online 8 July 2014

Keywords:

Congenital toxoplasmosis

HIV

Co-infection

ABSTRACT

Introduction: There is a paucity of data on the occurrence of congenital toxoplasmosis in children born to mothers dually infected with HIV and *Toxoplasma gondii*.

Objective: To evaluate aspects of the mother–infant pairs associated with vertical transmission of toxoplasmosis in women co-infected with HIV in a referral center for perinatally acquired infections in Belo Horizonte, Brazil.

Methods: Descriptive study of HIV vertically exposed children, with congenital toxoplasmosis, followed at a referral center (cohort/Belo Horizonte). Prenatal and post-natal variables for the mother–infant pairs were evaluated. A literature review with no filtering for time and language was performed to identify reports of congenital toxoplasmosis in HIV vertically exposed children.

Results: Among 2007 HIV vertically exposed children evaluated in the period from 1998 to 2011, 10 cases of congenital toxoplasmosis were identified (incidence: 0.5%, 95% confidence interval: 0.24–0.91). In searching the literature 22 additional cases in 17 reports were found. Combining the findings of our cohort with other reported cases, 50% (16/32) of congenital toxoplasmosis in HIV vertically exposed children were from Brazil. The cases of congenital toxoplasmosis in HIV vertically exposed children identified in Brazil occurred mainly in the post-Highly Active Antiretroviral Therapy era ($p=0.002$) and presented a lower death rate ($p=0.003$) than those from other countries. In the cohort/Belo Horizonte, HIV infection was identified mainly during gestation; *T. gondii* vertical transmission was observed in pregnant women with $CD4^+ > 500$ cells/mm³ and latent toxoplasmosis. High rates of ocular lesions (87.5%) and central nervous system involvement (70%) were detected.

* Corresponding author at: Universidade Federal de Minas Gerais, Departamento de Pediatria, Av. Alfredo Balena, 190, B. Santa Efigênia, 30130-100 Belo Horizonte, MG, Brazil.

E-mail address: flaviaacampos@yahoo.com.br (F.A. Campos).

<http://dx.doi.org/10.1016/j.bjid.2014.05.008>

1413-8670/© 2014 Elsevier Editora Ltda. Este é um artigo Open Access sob a licença de [CC BY-NC-ND](http://creativecommons.org/licenses/by-nc-nd/4.0/)

Conclusions: The risk of vertical transmission of *T. gondii* in HIV-infected women is low and has been usually associated with maternal immunosuppression and elevated viral load. However, our findings of congenital toxoplasmosis in children born to HIV-infected mothers with latent toxoplasmosis and not immunosuppressed emphasize the need for careful follow-up in these cases.

© 2014 Elsevier Editora Ltda. Este é um artigo Open Access sob a licença de [CC BY-NC-ND](#)

Introduction

Toxoplasma gondii infection has a worldwide occurrence, higher prevalence in tropical countries and is associated with weather conditions, cat population, and local life habits.¹ Classical descriptions include three strains of the parasite: type I is usually associated with acute infection; type II is predominant in immunosuppressed individuals and in human congenital and eye infections; and type III is frequently isolated in animals.² In Brazil, genetic diversity is greater than that in most other countries, and recombinant and atypical genotypes are predominant, usually associated with higher virulence.³⁻⁵

The prevalence of toxoplasmosis among pregnant women in Brazil range from 50% to 80%.⁶ In the metropolitan area of Belo Horizonte, state of Minas Gerais, where the current study was carried out, the seroprevalence is estimated in 60%.⁶ The prevalence of congenital infection is rare in the USA (approximately 0.01%) and higher in some Southern countries of Western Europe (0.01–0.1%).^{1,7} In Brazil, the prevalence is high throughout the country (0.05–0.15%), particularly in Minas Gerais state where it reaches 0.13%.⁸

In HIV-infected patients, most cases of toxoplasmosis result from the reactivation of a latent infection.⁹ In immunocompromised pregnant women with chronic toxoplasmosis, congenital transmission of the parasite probably occurs due to reactivation, with chronic and intermittent parasitemia.¹⁰⁻¹³ Diagnosis in these cases is a challenge, as they are usually associated with low IgG concentration and absence of IgM. For this reason, the protocol proposed by Lebech et al.,¹⁴ which is usually used to diagnose the parasite in the mother–infant pair, does not apply to immunosuppressed pregnant women.

The factors determining the various clinical manifestations of congenital toxoplasmosis are still poorly known. In fact, there may be a combination of factors, such as the host's genotype and immune status, the parasite tissue load, stage of placental development, and the parasite's own genetic composition.¹⁵⁻¹⁷ In immunosuppressed children co-infected with HIV and *T. gondii*, neurological damage is mainly a result of the toxoplasmosis congenital infection.¹⁸

Given the high prevalence of toxoplasmosis and the presence of more virulent strains of the parasite in Minas Gerais, the difficulty of diagnosing a new infection or reactivation in immunosuppressed pregnant women, and the paucity of studies on congenital toxoplasmosis among children of co-infected mothers, this paper reports a review of the literature and case studies of children with congenital toxoplasmosis that were born to HIV and *T. gondii* co-infected mothers. These

children have been seen at a leading outpatient referral center in Belo Horizonte.

Materials and methods

The study was divided into two parts: a descriptive study of congenital toxoplasmosis in a series of cases in a historical cohort of children vertically exposed to HIV and literature review on congenital toxoplasmosis in infants born to HIV-infected mothers.

Children included in the first part had been in follow-up at the Pediatric Immunology Center, Clinics Hospital, Federal University of Minas Gerais (UFMG), over the last 22 years (1998–2011). All mother–infant pairs are users of the public Brazilian unified health system (SUS) in the Metropolitan Region of Belo Horizonte and other municipalities in the State of Minas Gerais (Southeastern Brazil). The study included all children enrolled in the service that were born to HIV and *T. gondii* co-infected mothers, regardless of the infection stage. The criteria used to diagnose HIV infection and toxoplasmosis in the mothers are described below.

1. HIV infection – positive for anti-HIV-1 and anti-HIV-2 in a screening test and in at least one confirmatory test. This included recommendations by the Centers for Disease Control and Prevention (CDC) and by the Brazilian Ministry of Health.¹⁹
2. *T. gondii* infection – positive anti-*T. gondii* IgG whether or not associated with positive anti-*T. gondii* using enzyme linked immunosorbent assay and indirect immunofluorescence as detection methods. Determining the most likely moment of maternal infection involved: (a) acute infection – pregnant women with seroconversion: maternal IgG- and IgM-specific serologic tests with negative first results and positive second results; (b) undetermined, but probably recent, acute infection in the mothers: positive results for IgG- and IgM-specific serologic tests associated with low IgG avidity; and (c) chronic infection: mothers' seropositive sample before conception or first serologic test carried out during pregnancy with positive IgG and negative IgM results or positive IgG and IgM results, both associated with high-avidity IgG antibodies.¹⁴

The diagnosis of congenital toxoplasmosis and HIV infection in children was performed according to the criteria described below.

1. HIV infection: according to recommendations by the Centers for Disease Control and Prevention (CDC) and by the Brazilian Ministry of Health.¹⁹
2. Congenital infection with *T. gondii*: according to criteria developed by Lebech et al.¹⁴ Present IgM and/or IgA anti-*T. gondii* in the first six months of life, persistently positive IgG anti-*T. gondii* at age of 12 months, or positive IgG associated with positive signs/symptoms and maternal seroconversion during pregnancy. Infection was ruled out in children with negative results for IgG tests in the first year of life, in the absence of anti-parasite treatment, or negative IgG after 1-3 months upon interrupting treatment in the first year of life.¹⁴

The study included all children born to HIV and *T. gondii* co-infected mothers who fulfilled the criteria for the diagnosis of congenital toxoplasmosis, regardless of their HIV status.

Women were considered immunosuppressed if CD4⁺ T lymphocyte were <350 cells/mm³, and with severe immunosuppression if CD4⁺ <200 cells/mm³.¹⁹

In addition to the case studies, an extensive literature review was carried out on Pubmed, Scielo, and Cochrane Library databases. It included materials published until January 2012 and was not filtered for language and time period. The following descriptors were used: *pregnancy AND toxoplasmosis AND HIV*; *congenital toxoplasmosis AND HIV*; *toxoplasmosis AND HIV*.

Both the case studies and literature review targeted the variables related to the pregnant women (prenatal exams, symptomatology, immunosuppression level, and treatment) and to the children (birth conditions, diagnostic methods, symptomatology; anti-parasitic treatment, and case outcome). Information on the study participants was collected using structured questionnaires to capture information from the clinical charts. SPSS (Statistical Package for Social Sciences) version 17.0 was used to store and analyze the database. Description of the clinical and laboratory variables included absolute and relative frequency distribution, medians, and percentiles. For comparisons between proportions Fisher's exact test for small sample population was used. Medians of continuous variables were compared using Kruskal-Wallis' test. Significance level was chosen at 5% ($p < 0.05$).

The current study was approved by UFMG Ethics Committee (approval ETIC 260-03-EX 01/07).

Results

A total of 2007 infants born to HIV-infected mothers were followed-up and systematically tested for toxoplasmosis in the first year of life. Out of this population, 10 children born to nine co-infected mothers were identified with congenital toxoplasmosis. Prenatal information of one of the women who gave birth in 1991 was not available in the database. Most women (7/8) were identified as HIV-infected during pregnancy. Timing of *T. gondii* infection could not be determined based on the analysis of maternal serologic tests. Two pregnant women (2/7) had clinical manifestations of toxoplasmosis, but were not provided specific treatment because the diagnosis was not confirmed upon delivery. One pregnant woman (1/7)

was given sulfamethoxazol and trimethoprim (SMX-TMP) as prophylaxis against pneumocystis during pregnancy, but its use was irregular. A great proportion of clinical manifestations were observed in the cohort/BH: eye and brain damage affected 87.5% and 70.0% of the children, respectively. As in the pregnant women, there was difficulty in diagnosing the disease due to lack of specific IgM and IgA during the first months of life (Table 1).

In total, the bibliographic review retrieved 17 articles with 22 cases of congenital toxoplasmosis in children of co-infected mothers. Four articles reported cross-sectional studies. Congenital toxoplasmosis was rare and associated with maternal immunosuppression during pregnancy.⁷ Only four articles were written by Brazilian researchers reporting six cases altogether^{9,16,20,21} (Table 2).

Comparison of pregnant women and children according to place of origin (Brazil vs. other countries) points to similar characteristics. However, only one Brazilian pregnant woman was diagnosed in the pre-HAART (Highly Active Antiretroviral Therapy) era, which contrasts with the pregnant women from other countries ($p = 0.002$). The group of pregnant women from other countries included twice as many women with CD4⁺ <200 cells/mm³ than the group of Brazilian women, but this difference proved not to be significant. Differences between child mortality rates were found significant between places of origin ($p = 0.003$): 80% of the deaths among children from other countries, out of which 92% had toxoplasmosis diagnosed post-mortem (Tables 3 and 4).

Several cases of vertical toxoplasmosis transmission were observed among the immunosuppressed pregnant women, but this also took place among women with more than 500 CD4⁺ cells (Table 4). In the HIV-infected cohort from Belo Horizonte, the mean absolute CD4⁺ values were higher than that in other settings. This was probably due to the wider variation on CD4⁺ values (36-917 CD4⁺ cells/mm³) (Table 5).

Discussion

The Belo Horizonte cohort (10 children born to 9 women) represents the highest number of children with congenital toxoplasmosis born to HIV and *T. gondii* co-infected mothers that have been reported by a single center. Considering the total cases of children with congenital toxoplasmosis born to co-infected mothers reported in the literature, half of them were from Brazil, with the cohort/BH representing approximately one-third of the total.

Occurrence of congenital toxoplasmosis in children born to HIV and *T. gondii* co-infected mothers is rare, as shown in the cohort/BH and the few cases reported worldwide. The cohort/BH, however, points out the need for investigating *T. gondii* infection systematically to diagnosis congenital toxoplasmosis among newborns that have been exposed to HIV. It also shows that, even in the post-HAART area, children are still at risk of acquiring congenital toxoplasmosis, and it is pertinent to discuss the best approach to co-infected pregnant women and their children. In addition, it contributes to reinforcing the association between vertical *T. gondii* transmission and chronic infection in immunosuppressed women. Additionally, this two-decade long observational study indicates that pregnant women transmitted toxoplasmosis to

Table 1 – Frequency distribution of clinical and laboratory characteristics of children with congenital toxoplasmosis and their HIV/T. gondii co-infected mothers according to the children's place of origin (Metropolitan Area of Belo Horizonte, other regions in Brazil, and other countries).

	Pregnant women					
	Case studies cohort/BH		Literature cases in Brazil		Literature cases worldwide	
	Frequency	%	Frequency	%	Frequency	%
Total number of pregnant women	9		6		15	
Pregnant women diagnosed with infection during pregnancy	7/8	87.5	5/5	100.0	10/13	76.9
Pregnant women with CD4 ⁺ >500 cells/mm ³	1/6	16.6	0/11	9.0	0/9	0.0
CD4 ⁺ <200 cells/mm ³ ^a	2/5	40.0	3/5	60.0	7/9	77.8
Viral load > 100,000 copies/mL ^a	2/4	50.0	1/5	20.0	0/3	0.0
Antiretroviral therapy	5/7	71.5	6/6	100.0	4/8	50.0
SMX-TMP therapy	1/7	14.3	0/2	0.0	2/5	40.0
Toxoplasmosis treatment	0/4	0.0	1/5	20.0	2/11	18.2
Clinic manifestations of toxoplasmosis	2/7	28.5	2/5	40.0	5/12	41.7
IgM+ during pregnancy	1/3	33.3	0/6	0.0	2/10	20.0
Chronic infection	2/2	100.0	5/6	83.3	8/10	80.0
	Children					
	Case studies cohort/BH		Literature cases in Brazil		Literature cases worldwide	
	Frequency	%	Frequency	%	Frequency	%
Total number of children	10		6		16	
Pre-HAART	1/10	10.0	0/6	0.0	11/16	68.75
Term birth	5/9	55.5	3/5	60.0	6/13	46.1
HIV co-infected children	5/9	55.5	3/5	60.0	10/12	83.3
Chorioretinitis	7/8	87.5	4/5	80.0	5/8	62.5
Brain damage	7/10	70.00	2/4	50.0	8/10	80.0
Systemic symptoms of toxoplasmosis	4/4	100.0	2/5	40.0	11/12	91.7
Test for toxoplasmosis in the first quarter	8/10	80.0	6/6	100.0	14/16	87.5
Anti-T. gondii IgM/IgA or PCR + at birth	4/10	40.0	6/6	100.0	7/12	58.3
Result through autopsy	0/2	0.0	1/1	100.0	11/12	91.7
Treatment ^b	8/10	80.0	5/5	100.0	7/10	70.0
Mortality ^c	2/10	20.0	1/4	25.0	12/15	80.0

^a The highest viral load value and the lowest CD4⁺ value were used referring necessarily to a given moment in the pregnancy. The level of 20% of CD4⁺ lymphocytes corresponded to an absolute count at 350 cells/mm³.

^b Every treatment for toxoplasmosis was included in the analysis, provided that it was carried out in the first year of life.

^c Death was considered for those cases reported up to the last day of research or date of publication.

their children even when they did not have severe immunosuppression or kept absolute CD4⁺ values within normal limits.

A recent study has estimated the prevalence of congenital toxoplasmosis at 0.13% in the general population in the state of Minas Gerais, one infected child in every 770 live births.⁸ Considering this estimate and the number of HIV-exposed children followed up in the cohort/BH ($n=2007$), the expected estimate before this study was two or three children with congenital toxoplasmosis. Therefore, 10 infected children, as identified in the present study, represent a prevalence that is at least three times higher than expected in newborns of HIV-uninfected pregnant women. Since the Brazilian environment is favorable to *T. gondii* infection, HIV infection still occurs among mothers in reproductive age, and as congenital toxoplasmosis manifests somewhat later in the newborns'

lives, these cases might have been underestimated in our country.

In the present study we were not able to ascertain the risk of toxoplasmosis transmission among co-infected pregnant women. The European Collaborative Study has estimated it to be lower than 4.2%.²² This study, carried out in the pre-HAART era 1985–1999, included 1058 children born to 981 European HIV-infected women estimated maternal prevalence of toxoplasmosis of 42.6%, based on specific IgG detection in infants tested before their third month of age. They did not differentiate acute from chronic *T. gondii* infection and reported that only 18% of the mothers had CD4⁺ lymphocyte count below 200 cells/mm³ at delivery, and 137 children had documented HIV perinatal infection. Other international studies predicted this risk, and the European AIDS surveillance system has reported toxoplasmosis occurrence in only

Table 2 – Distribution of studies on children with congenital toxoplasmosis born to HIV and *T. gondii* co-infected mothers, according to year and place.

Author/place	Publication year	Type of study	Number of cases	Results
Cohen-Addad et al., ²⁹ USA	1988	Case report	1	1 co-infected newborn: HIV, <i>T. gondii</i> , and CMV
Mitchell et al., ³⁰ USA	1990	Case report	4	3 co-infected newborns: HIV and <i>T. gondii</i> ; 1 co-infected newborn: HIV, <i>T. gondii</i> , and CMV
Medlock et al., ³¹ USA	1990	Case report	1	1 newborn with toxoplasmosis
Velin et al., ³² France	1991	Case report	1	1 co-infected newborn: HIV and <i>T. gondii</i>
O'Donohoe et al., ³³ UK	1991	Case report	1	1 co-infected newborn: HIV, <i>T. gondii</i> , CMV, and Hep. B
Taccone et al., ³⁴ Italy	1992	Case report	1	1 co-infected newborn: HIV and <i>T. gondii</i>
Escribano Subias et al., ³⁵ Spain	1993	Case report	1	1 co-infected newborn: HIV and <i>T. gondii</i>
Marty et al., ¹² France	1994	Case report	1	1 therapeutic abortion because of toxoplasmosis
Minkoff et al., ⁷ USA	1997	Prospective cross-sectional study	1 ^a	1 newborn with toxoplasmosis
Marty et al., ¹⁰ France	2002	Case report	1	1 fetal death because of toxoplasmosis
Bachmeyer et al., ¹¹ France	2006	Case report	1	1 newborn with toxoplasmosis
Cruz et al., ¹⁶ Brazil	2007	Cross-sectional study	1 ^b	1 newborn with toxoplasmosis
Fernandes et al., ⁹ Brazil	2009	Case report	1	1 co-infected newborn: HIV and <i>T. gondii</i>
Lago et al., ²¹ Brazil	2009	Prospective cross-sectional study	1 ^c	1 co-infected newborn: HIV and <i>T. gondii</i>
Azevedo et al., ²⁰ Brazil	2010	Cross-sectional study	3 ^d	1 fetal death, 1 newborn with toxoplasmosis, 1 co-infected newborn HIV and <i>T. gondii</i>
Caby et al., ³⁶ France	2010	Case report	1	1 fetal death
Tan et al., ²⁶ Canada	2010	Case report	1	1 co-infected newborn: HIV, <i>T. gondii</i> , and CMV
Case studies (cohort/BH), Brazil	2012	Case report	10	5 co-infected newborns: HIV and <i>T. gondii</i>

^a One case out of 121 HIV-exposed children of mothers with IgG+ during pregnancy.
^b One case out of 767 HIV-exposed children monitored from 1996 through 2007.
^c One case out of 103 HIV-exposed children of mothers with IgG+ during pregnancy.
^d One case out of 113 HIV-exposed children monitored from 1998 onwards.

25 of the 1762 (1.4%) cases of vertically HIV-infected children reported until late 1994. Nevertheless, it is unknown whether such cases were due to congenital or acquired infection. Unfortunately, these surveillance systems do not include seroreverting children born to HIV positive mothers, which prevent the assessment of the risk of toxoplasmosis transmission among these co-infected pregnant women.²² Minkoff et al.⁷ indicated a rate of 3.7% of vertical *Toxoplasma* transmission among HIV-infected women, but transmission could take place in up to 33% of the cases if the women are severely immunocompromised. However, the low prevalence of toxoplasmosis in the sample of pregnant women (20%) and the small sample size limited the study impact. Although there are three prospective studies from Brazil, not enough data are available to determine the risk of transmission.^{16,20,21}

A prospective study was carried out in the state of Rio Grande do Sul, located in southern Brazil, from 2002 through 2005, following up 121 HIV and *T. gondii* co-infected pregnant women, to investigate the serologic profile of co-infected pregnant women and the risk of transmission of

congenital toxoplasmosis. One child was identified with congenital toxoplasmosis, who, according to the authors, was born to a mother that had acquired the infection during pregnancy and did not present either high IgG concentration levels or IgM antibodies. The study also compared the IgG anti-*T. gondii* concentration level among the co-infected pregnant women and 1624 HIV negative pregnant women. The authors concluded that high *T. gondii*-specific IgG concentration levels were much more frequent among HIV infected pregnant women, but without statistical significance; high concentration, therefore, was not associated with an increased risk of mother–fetus transmission of toxoplasmosis.²¹ Another study followed up 767 HIV-exposed children in the city of Rio de Janeiro, Brazil, from 1996 through 2007. Only one child had congenital toxoplasmosis, and 74% of the mothers had serological evidences of IgG anti-*Toxoplasma* during pregnancy.¹⁶ A third study, also in Rio de Janeiro, describes three children with congenital toxoplasmosis out of the 113 HIV-exposed children. In the sample, 70% of the pregnant women had serological (IgG positive) evidence of *T. gondii* infection during pregnancy.²⁰ A

Table 3 – Frequency distribution of pregnancy characteristics of HIV/*T. gondii* co-infected mothers of children with congenital toxoplasmosis, according to the children's place of origin (Metropolitan Area of Belo Horizonte, other regions in Brazil, and other countries).

Variable	Cases				p value
	Brazilian		Worldwide		
	Frequency	%	Frequency	%	
Total number 15					
<i>Exposure to HIV</i>					
Pre-HAART	1/15	6.6	10/15	66.7	0.002
HIV identification during pregnancy	12/13	92.3	10/13	76.9	0.593
Antiretroviral therapy	11/13	84.6	4/8	50.0	0.146
SMX-TMP therapy	1/9	11.1	2/5	40.0	0.505
<i>Immune response to HIV</i>					
CD4 ⁺ < 200 cells/mm ³	4/10	40.0	7/9	77.7	0.115
Viral load > 100,000 copies/mL ^a	3/9	33.3	0/3	0.0	0.509
<i>Monitoring for toxoplasmosis</i>					
Eye damage	1/3	33.3	0/0	0.0	–
Systemic symptoms	4/12	33.3	5/12	41.6	1.000
IgM+ during pregnancy	1/9	11.1	2/10	20.0	1.000
Treatment for toxoplasmosis	1/9	11.1	2/11	18.1	1.000
Chronic infection	7/8	87.5	8/10	80.0	1.000

^a The highest viral load value and the lowest CD4⁺ value were used referring necessarily to a given moment in the pregnancy.

fourth study, also carried out in Rio de Janeiro (1996–2001), consisted of a cohort of 227 HIV-infected pregnant women, and found a prevalence of chronic *T. gondii* infection among 71.4% of them.^{23,24} Five children of this cohort were infected with HIV, but no case of congenital toxoplasmosis was diagnosed. The women with CD4⁺ < 200 cells/mm³ were provided with SMX-TMP three times a week during pregnancy.²⁴ This

prophylactic regimen was used for pneumocystis prevention, but may have contributed to preventing reactivation of latent toxoplasmosis, which may have accounted for a rare occurrence of vertical transmission.²⁵

Altogether, these data call for caution in interpreting the estimate of 4% risk of vertical toxoplasmosis transmission in co-infected pregnant women that has been reported in the

Table 4 – Comparison between Brazilian and international cases according to children's characteristics.

Variable	Cases				p value
	Brazilian		Worldwide		
	Frequency	%	Frequency	%	
Total number 16					
<i>Birth conditions</i>					
Term birth	8/14	57.1	6/13	46.1	0.706
<i>Exposure to HIV</i>					
Pre-HAART era (1995)	1/16	6.25	11/16	68.75	0.001
HIV-co-infected children	8/14	57.1	10/12	83.3	0.216
CD4 ⁺ < 200 cells/mm ³	0/4	0	1/5	20.0	1.000
<i>Toxoplasmosis manifestations</i>					
Eye damage	11/13	84.6	5/8	62.5	0.325
Brain damage	9/14	64.2	8/10	80.0	0.653
Systemic symptoms	6/9	66.6	11/12	91.6	0.272
<i>Monitoring for toxoplasmosis</i>					
Tests in the first quarter	14/16	87.5	14/6	87.5	1.000
IgM or IgA or PCR + in the first quarter of life	10/16	62.5	7/12	58.3	1.000
Autopsy	1/3	33.3	11/12	91.6	0.081
<i>Outcome</i>					
Treatment for toxoplasmosis ^b	13/15	86.6	7/10	70.0	0.358
Death ^c	3/14	21.4	12/15	80.0	0.003

^b Every treatment for toxoplasmosis was included in the analysis, provided that it was carried out in the first year of life.

^c Death was considered for those cases reported up to the last day of research or date of publication.

Table 5 – Comparison of the lowest absolute values of T CD4⁺ lymphocytes (cells/mm³) during the pregnancy of HIV and *T. gondii* co-infected women and their children with congenital toxoplasmosis, according to place of origin.

Place of origin of co-infected mothers and children with congenital toxoplasmosis	n	Mean	SD	Median	P25	P50	P75
Cohort/BH	5/9	325.60	348.66	208.00	82.50	208.00	627.50
Cases in other regions in Brazil	5/6	197.40	110.83	171.00	100.00	171.00	308.00
Cases in other countries	9/15	152.89	151.84	100.00	42.00	100.00	263.50

Kruskal-Wallis test – $p = 0.437$.

literature, as the population under scrutiny is heterogeneous. This risk can be higher among co-infected women with HIV and chronic *T. gondii* infection when they have severe immunosuppression. Another factor that may affect vertical transmission is the use of antimicrobials as a prophylactic measure against pneumocystis by immunosuppressed pregnant women.^{11,25}

The finding of just one child born of the cohort/BH in the pre-HAART area may be explained by the developments at the specialized outpatient referral center over time: only recently has it introduced standards for reportable cases, follow-up protocols, and systematic performance of serologic tests among pregnant women at risk. These developments also explain the difference between national and international death rates. The systematic study of toxoplasmosis in newborns in Minas Gerais allowed for diagnosing the disease regardless of evident clinical damage.

Several challenges exist to diagnosing congenital transmission of the infection building on its clinical markers. Unfortunately, the Lebech et al.¹⁴ criteria used to diagnose toxoplasmosis in pregnant women and children do not include cases of immunosuppression. Clinical manifestations that might prompt suspicions of infection are usually absent or belated; 80–90% are asymptomatic at birth, regardless of the co-infection. Tan et al. have reported a case of a co-infected newborn that reputedly had negative results for tomography of the skull and fundoscopy, and could not be diagnosed with toxoplasmosis before the 50th day of life. This case underscores the difficulty of diagnosing congenital toxoplasmosis among HIV-co-infected individuals and the need for repeating diagnostic tests and even empiric therapy, because clinical and radiographic abnormalities may be identified belatedly and the results may be negative in the first serological tests.²⁶ Explanations for this may be: intrauterine exposure to the SMX-TMP used as a prophylaxis by the mother; disappearance of anti-*T. gondii* IgM during fetal life and its non-detection at birth; and the possibility of several congenital co-infections that might share overlapping clinical features, such as CMV. Another explanation is that simultaneous HIV infection may contribute to failed IgG immunologic response to *T. gondii*.²⁶

For laboratory diagnosis of toxoplasmosis, increased antibody concentrations can be found in the cases of reactivations in HIV infected individuals, including pregnant women with CD4⁺ > 200 cells/mm³. In primo-infection, paradoxically, humoral response may be reduced against the recently introduced antigens.²⁰ Reinfection by different strains may not lead to specific IgM seroconversion.¹¹ Avidity of IgG antibodies, if carried out at the beginning of the pregnancy,

may be useful in assessing the risk of vertical transmission, since they differentiate a recently acquired infection from an old infection.¹⁶ It is not prudent to diagnose fetal infection through parasite DNA detection in amniotic liquid because of the risk of infecting the fetus with HIV during the procedure on co-infected pregnant women.²⁶ These results pose difficulties in dealing with suspected cases of toxoplasmosis and implementing treatment measures aimed at the newborn. Therefore, to increase sensitivity to confirm suspected cases among newborns, physicians should perform IgG, IgM, and IgA specific tests in the immediate postnatal period. Initial negative results should imply repeating the tests. Parasite DNA tests through PCR of the children's blood or cerebro-spinal fluid sample may contribute to an accurate diagnosis.

Several authors advise that all infants born to HIV seropositive mothers should be tested for congenital infections. Physicians should not miss the opportunity to treat children from their birth or even during their intrauterine life (in recommended cases).^{20,26} No consensus exists in relation to toxoplasmosis prophylaxis during the prenatal period. Some authors contend that anti-*T. gondii* IgG positive women with CD4⁺ < 100 cells/mm³ should be given an antimicrobial prophylaxis during pregnancy to reduce the risk of transmitting the parasite to the fetus. They further argue that this procedure may also be appropriate for non-HIV-infected patients that are highly immunocompromised for other reasons.⁷ An article by Marty et al. suggests that chemoprophylaxis with SMX-TMP associated with antiretroviral treatment should be provided to HIV and toxoplasmosis seropositive pregnant women when they have CD4⁺ < 200 cells/mm³ and high viral load.^{10,25} Other studies suggest that the risk of maternal-fetal transmission is not sufficiently high to justify routine anti-toxoplasmosis chemoprophylaxis in HIV-infected pregnant women, but they nevertheless emphasize the need for further research on the matter.²² As the risk of maternal-fetal transmission is not well known, particularly in countries like Brazil, which have high rates of *T. gondii* seroprevalence, the current obstetrical tendency of not prescribing anti-toxoplasmosis chemoprophylaxis to chronically infected women is understandable.²⁰

It is recommended that specific treatment against *Toxoplasma* be initiated in HIV and toxoplasmosis co-infected children for one year, after which secondary prophylaxis should be provided. In Brazil, the recommendation is to hold back on secondary chemoprophylaxis until two consecutive assessments prove that CD4⁺ lymphocyte is higher than 15%.⁹

Although the small sample size is a limitation of this study, it is important to emphasize that this is a cohort of two

decades with systematic investigation of toxoplasmosis in infants born to HIV infected mothers, which allowed identification of vertical transmission in HIV infected pregnant women with chronic toxoplasmosis. Incompleteness of study variables is a common bias encountered in retrospective studies. This limitation was minimized in the present study by the existence of standardized clinical forms used for the follow-up of both cohorts.

The authors of this study underscore the importance of diagnosis and treating toxoplasmosis in the prenatal period, along with HIV monitoring during the entire pregnancy. Immunodepression, even when mild, may contribute to the transmission of latent infections to the newborn, and this could be averted with appropriate treatment. Immunocompromised women should be tested for toxoplasma and cytomegalovirus infection in multiple occasions throughout their pregnancy. Successful cases have shown that adequate measures preserve the mothers' health and avoid fetus infection in this scenario.^{23,27,28}

Conclusion

To date, the general risk of maternal-fetal transmission of *Toxoplasma infection* is deemed to be low among HIV-infected women, even when their CD4⁺ lymphocyte counts are very low (<200 cells/mL). However, the cohort/BH had a higher number of cases of congenital toxoplasmosis than expected among children born to co-infected mothers. Despite the discrepancy, these data should be interpreted with caution, due to the heterogeneity of the population under scrutiny, classification biases that hinder association between transmission and acute or chronic *T. gondii* infection, insufficient sample sizes to detect cases of the disease, and the paucity of prospective studies monitoring the mother/child duo.

This risk is also estimated to be low in countries with a high prevalence of toxoplasmosis, such as Brazil, and associated with the mothers' severe immunodeficiency (CD4⁺ < 200 cells/mm³) and high viral load. However, the occurrence of the disease among asymptomatic pregnant women with latent toxoplasmosis and CD4⁺ within normal limits underscores the need for careful monitoring of both mother and child in these cases. Further studies are needed to determine the effect of chemoprophylaxis on the transmission rates. The authors recommend that toxoplasmosis tests be carried out in all infants born to HIV-seropositive mothers.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

- Remington JS, McLeod R, Wilson CB, Desmonts G. Toxoplasmosis. In: Remington JS, Klein J, Wilson CB, Baker CJ, editors. Infectious disease of the fetus and newborn infant. 6th ed. Philadelphia: Elsevier Saunders; 2011. p. 918-1041.
- Ajzenberg D, Cogné N, Paris L, et al. Genotype of 86 *Toxoplasma gondii* isolates associated with human congenital toxoplasmosis: and correlation with clinical findings. *J Infect Dis.* 2002;186:684-9.
- Saeij JP, Boyle JP, Boothroyd JC. Differences among the three major strains of *Toxoplasma gondii* and their specific interactions with the infected host. *Trends Parasitol.* 2005;21:476-81.
- Vaudaux JD, Muccioli C, James ER, et al. Identification of an atypical strain of *Toxoplasma gondii* as the cause of a waterborne outbreak of toxoplasmosis in Santa Isabel do Ivaí, Brazil. *J Infect Dis.* 2010;202:1226-33.
- Ajzenberg D, Bañuls AL, Su C, et al. Genetic diversity: clonality and sexuality in *Toxoplasma gondii*. *Int J Parasitol.* 2004;34:1185-96.
- Carellos EVM, Andrade GMQ, Aguiar RALP. Avaliação da aplicação do protocolo de triagem pré-natal para toxoplasmose em Belo Horizonte, Minas Gerais, Brasil: estudo transversal em puérperas de duas maternidades. *Cad Saúde Pública.* 2008;24:391-401.
- Minkoff H, Remington JS, Holman S, Ramirez R, Goodwin S, Landesman S. Vertical transmission of toxoplasma by human immunodeficiency virus-infected women. *Am J Obstet Gynecol.* 1997;176:555-9.
- Vasconcelos-Santos DV, Azevedo DOM, Campos WR, et al. Congenital toxoplasmosis in southeastern Brazil: results of early ophthalmologic examination of a large cohort of neonates. *Ophthalmology.* 2009;116:2199-205.
- Fernandes RC, Vasconcelos VP, Araújo LC, Medina-Acosta E. Vertical transmission of HIV and toxoplasma by reactivation in a chronically infected woman. *Braz J Infect Dis.* 2009;13:70-1.
- Marty P, Bongain A, Loiseau S, et al. Lethal congenital toxoplasmosis resulting from reactivation of toxoplasmosis in a pregnant HIV-positive patient. *Presse Med.* 2002;31:1558.
- Bachmeyer C, Mouchnino G, Thulliez P, Blum L. Congenital toxoplasmosis from an HIV-infected woman as a result of reactivation. *J Infect.* 2006;52:e55-7.
- Marty P, Bongain A, Rahal A, et al. Prenatal diagnosis of severe fetal toxoplasmosis as a result of toxoplasmic reactivation in an HIV-1 seropositive woman. *Prenat Diagn.* 1994;14:414-5.
- Hassl A, Tuma W. Toxoplasmosis diagnosis in pregnant women infected with human immunodeficiency virus I. *Pediatr Infect Dis J.* 1995;14:1016-7.
- Lebech M, Joynson DH, Seitz HM, et al. Classification system and case definitions of *Toxoplasma gondii* infection in immunocompetent pregnant women and their congenitally infected offspring. European Research Network on Congenital Toxoplasmosis. *Eur J Clin Microbiol Infect Dis.* 1996;15:799-805.
- Sibley LD, Howe DK. Genetic basis of pathogenicity in toxoplasmosis. *Curr Top Microbiol Immunol.* 1996;219:3-15.
- Cruz ML, Cardoso CA, Saavedra MC, Santos ED, Melino T. Congenital toxoplasmosis infection in an infant born to an HIV-1-infected mother. *Braz J Infect Dis.* 2007;11:610-1.
- Howe DK, Summers BC, Sibley LD. Acute virulence in mice is associated with markers on chromosome VIII in *Toxoplasma gondii*. *Infect Immun.* 1996;64:5193-8.
- Abrams EJ. Opportunistic infections and other clinical manifestations of HIV disease in children. *Pediatr Clin North Am.* 2000;47:79-108.
- Recomendações para profilaxia de Transmissão Vertical do HIV e Terapia Antiretroviral em Gestantes: manual de bolso. Brasília: Ministério da Saúde SdVeS, Programa Nacional de DST e Aids; 2010. p. 172.
- Azevedo KM, Setúbal S, Lopes VG, Camacho LA, Oliveira SA. Congenital toxoplasmosis transmitted by human immunodeficiency-virus infected women. *Braz J Infect Dis.* 2010;14:186-9.
- Lago EG, Conrado GS, Piccoli CS, Carvalho RL, Bender AL. *Toxoplasma gondii* antibody profile in HIV-infected pregnant

- women and the risk of congenital toxoplasmosis. *Eur J Clin Microbiol Infect Dis*. 2009;28:345-51.
22. European Collaborative Study and Research Network on Congenital Toxoplasmosis. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. *Eur J Obstet Gynecol Reprod Biol*. 1996;68:93-6.
 23. Nogueira SA, Guedes AL, Machado ES, et al. Toxoplasmic encephalitis in an HIV infected pregnant woman: successful outcome for both mother and child. *Braz J Infect Dis*. 2002;6:201-5.
 24. Nogueira SA, Machado ES, Costa TP, et al., editors. Prevalência de co-infecções numa coorte de gestantes infectadas pelo HIV no Rio de Janeiro. Abstracts da IV Conferência Internacional sobre infecção pelo HIV em mulheres e crianças; Rio de Janeiro, 11 e 12 de Abril de 2002.
 25. Derouin F, Jacqz-Aigrain E, Thulliez P, Couvreur J, Lepout C. Cotrimoxazole for prenatal treatment of congenital toxoplasmosis? *Parasitol Today*. 2000;16:254-6.
 26. Tan DH, Asztalos E, Douglas D, Read S, Bitnun A. Congenital transmission of human immunodeficiency virus: cytomegalovirus, and toxoplasmosis in a premature infant. *Pediatr Infect Dis J*. 2009;28:1129-31.
 27. Hedriana HL, Mitchell JL, Brown GM, Williams SB. Normal fetal outcome in a pregnancy with central nervous system toxoplasmosis and human immunodeficiency virus infection. A case report. *J Reprod Med*. 1993;38:747-50.
 28. D'Offizi G, Topino S, Anzidei G, Frigiotti D, Narciso P. Primary *Toxoplasma gondii* infection in a pregnant human immunodeficiency virus-infected woman. *Pediatr Infect Dis J*. 2002;21:981-2.
 29. Cohen-Addad NE, Joshi VV, Sharer LR, Epstein LG, Gubitosi TA, Oleske JM. Congenital acquired immunodeficiency syndrome and congenital toxoplasmosis: pathologic support for a chronology of events. *J Perinatol*. 1988;8:328-31.
 30. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. *Pediatr Infect Dis J*. 1990;9:512-8.
 31. Medlock MD, Tilleli JT, Pearl GS. Congenital cardiac toxoplasmosis in a newborn with acquired immunodeficiency syndrome. *Pediatr Infect Dis J*. 1990;9:129-32.
 32. Velin P, Dupont D, Barbot D, Baechler-Sadoul E, Marty P, Gillet JY. Double mother-fetus HIV-1 and toxoplasma contamination. *Presse Med*. 1991;20:960.
 33. O'Donohoe JM, Brueton MJ, Holliman RE. Concurrent congenital human immunodeficiency virus infection and toxoplasmosis. *Pediatr Infect Dis J*. 1991;10:627-8.
 34. Taccone A, Fondelli MP, Ferrea G, Marzoli A. An unusual CT presentation of congenital cerebral toxoplasmosis in an 8 month-old boy with AIDS. *Pediatr Radiol*. 1992;22:68-9.
 35. Escribano Subias J, Bilbao Sustacha J, Balaguer Santamaría A, Bofarull Bosch JM. Congenital toxoplasmosis in a newborn infant with AIDS. *An Esp Pediatr*. 1993;39:349-50.
 36. Caby F, Lemerrier D, Coulomb A, et al. Fetal death as a result of placental immune reconstitution inflammatory syndrome. *J Infect*. 2010;61:185-8.