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HIV-1 mother-to-child transmission and drug resistance among Brazilian pregnant women with high access to diagnosis and prophylactic measures

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ABSTRACT

Background: A high-coverage public health prenatal program (70,000 women/year) from central western Brazil/Goias State has represented a unique opportunity for the early diagnosis of HIV-1 and implementation of strategies to prevent mother-to-child transmission (MTCT).
Objectives: To investigate MTCT among a prospective cohort of HIV-1 infected mothers/exposed infants.
Study design: 142 mothers/their 149 infants (2008–2010) were investigated regarding maternal viral load, CD4$^+$cell counts, HIV-1 *pol* sequences; infants' HIV-1 RNA tests (30/120days), sequential anti-HIV-1/2 serology. HIV-1 subtypes were assigned by REGA. Transmitted drug resistance was identified by the Calibrated Population Resistance tool, secondary resistance by Stanford HIV-1 Drug Resistance/International AIDS Society databases.
Results: Mothers (median age = 24 years; 25/142 adolescents) were diagnosed during prenatal care (2008–2010) or previously (1994–2007). Recent cases were younger, mostly asymptomatic. Undetectable viremia and MTCT prophylaxis predominated in formerly diagnosed mothers. Recent cases had higher subtype C prevalence. One naive patient had transmitted resistance; ten antiretroviral-experienced patients had secondary resistance: 6 from MTCT prophylaxis, 4 under HAART. Late disclosure of diagnosis, vaginal delivery, breastfeeding, lack of oral zidovudine were observed in the three MTCT cases (3/149; 2.01%). Two of three infected infants harbored subtype C; infected infants/mothers did not have drug resistance mutations. Two of the transmitting-mothers had viremia <1000 copies/ml. Among exposed-uninfected infants the median time to seroreversion was 12 months.
Conclusions: In this study delayed disclosure of diagnosis, partial/no preventive measures, drug resistance among asymptomatic women under prophylaxis and MTCT in low viremic mothers raise concerns. The expansion of subtype C infection corroborates surveillance of HIV-1 diversity in this region.
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1. Background

HIV-1 mother-to-child-transmission (MTCT) is a multifactorial event in which high maternal viral load, low CD4$^+$ cell counts, mode of delivery, antiretroviral (ARV) therapy and prematurity play a role.[1] Preventive strategies including prophylactic or therapeutic ARV use, cesarian section and breastfeeding proscription can reduce MTCT from 25% up to 1%.[2,3] However, ARV treatment can promote the selection and transmission of resistant mutants and compromise prevention.[4,5]

Brazil was the first developing country to implement a countrywide public health program to prevent HIV-1 MTCT, however it still occurs.[6,7] Routine prenatal HIV-1 screening represents a unique circumstance for the early diagnosis and prevention of MTCT. Nevertheless, missing opportunities can jeopardize preventive measures.[8]

In Goias State, central western Brazil, a special public health prenatal program ("Program for the Protection of Pregnant Women/PPPW") implemented in 2003 screens ~70,000 pregnant women/year from ~240 municipalities. Serological screening includes HIV-1, hepatitis B/C, Human T-Lymphotropic-Virus, syphilis, toxoplasmosis, rubella, Chagas' disease and

Abbreviations: HIV-1, human immunodeficiency virus type 1; MTCT, mother-to-child transmission; ARV, antiretroviral; PPPW, Program for the Protection of Pregnant Women; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse-transcriptase inhibitors; NNRTI, nonnucleoside reverse-transcriptase; PI, inhibitor protease; PR, protease; RT, reverse transcriptase; cDNA, complementary DNA; CPR, Calibrated Population Resistance Tool; IAS-USA, International AIDS Society-USA; CI, confidence Interval; AZT, zidovudine; MDR, multidrugresistant.

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Cytomegalovirus. A survey among 28,561 pregnant women from this regional Program showed an HIV-1 prevalence of 0.09% (95% CI 0.06%–0.14%).[9] A recent report by the Ministry of Health showed important regional differences in the rate of HIV-1 MTCT in Brazil: highest rate in southern (5.8%) and lowest rate (1%) in central western region.[7]

2. Objectives

This prospective study among pairs of HIV-1 infected mothers and exposed infants from central western Brazil describes MTCT and related factors (prophylaxis, resistance mutations). HIV-1 subtypes and seroreversion in exposed-uninfected children are also reported.

3. Study design

3.1. Patients

During the study period (June/2008–June/2010), 146,897 pregnant women were screened by the PPPW/"Institute of Diagnoses and Prevention/IDP/APAE", Goiania/Goias). Around 70% (148/198) of confirmed cases of HIV-1 infection were enrolled. This cohort included both recently and formerly diagnosed women as prenatal screening includes all pregnant women, regardless of previous HIV-1 diagnosis. Enrollment occurred any time during pregnancy or up to 30 days postpartum. Mother–infant pairs were prospectively followed up (one year) at the main regional public hospital for HIV-1 care (Anuar Auad Hospital, HAA/HDT/SUS). Epidemiological data were collected in standardized forms; clinical, obstetric data were obtained from medical records. This research protocol was approved by the institutional review board ("Comite de Etica e Pesquisa HAA/HDT/SUS", protocol #003/2008). All women provided informed consent for themselves and their newborns.

The standard highly active-antiretroviral-therapy/HAART regimen used for MTCT prophylaxis/treatment consisted of two NRTIs: zidovudine (ZDV)/3TC–Combivir® and one PI (LPV/ritonavir-boosted–Kaletra®).[10]

3.2. Immunological and virological profiles

The classification into asymptomatic/symptomatic was defined at diagnosis according to CDC AIDS-defining conditions. $CD4^+$ cell counts (FACSCalibur, Becton & Dickson, San Jose, CA, USA), HIV-1 RNA tests (Amplicor HIV-1 Monitor test, version 1.5; Roche, USA) were performed in maternal samples (last trimester-30 days postpartum) and in infants (30, 120 days of life). MTCT diagnosis was based on two positive HIV-1 RNA tests in samples collected after 30 days of life. Two negative HIV-1 RNA tests (30/120 days of life) excluded MTCT. Exposed-uninfected newborns were monitored by anti-HIV-1/2 IgG ELISA (Wiener Laboratories, Argentina) each 3–4 months throughout the first 12 months or until seroreversion.

3.3. HIV-1 subtypes and resistance analysis in pol gene

Plasma RNA (mothers/infected newborns) was extracted, retrotranscribed into complementary DNA (cDNA) and the entire HIV-1 protease (PR) and reverse transcriptase (RT) fragment (~750-bp) were amplified by nested polymerase chain reaction followed by direct sequencing, as described.[11] HIV-1 subtypes were identified using REGA tool version 2.0.[12]

Transmitted drug resistance was identified by the Calibrated Population Resistance tool[13] secondary drug resistance by the Stanford Surveillance Drug Resistance Mutation/International AIDS Society-USA (IAS-USA) major mutation list (Accessed: August/2011). GenBank accession numbers of the generated sequences are JN114115, JN114116,

Table 1
Main epidemiological, clinical and MTCT prophylaxis characteristics among newly diagnosed mothers for HIV-1 infection and mothers diagnosed before index pregnancy.

Variable	Recently diagnosed mothers ($n=65$)	Formerly diagnosed mothers ($n=77$)	P
Age at diagnosis (years)			
Median (range)	25 (15–39)	23 (14–36)	0.04
Clinical status at diagnosis n/N (%)			
Asymptomatic (HIV)	56/62[a] (90.3.0)	54/76[b] (71.1)	0.04
Symptomatic (AIDS)	06/62 (9.7)	22/76 (28.9)	
$CD4^+$ cell counts (cells/mm^3)[A]			
Median (range)	543 (162-1418)[c]	499 (91–1931)[d]	0.21
Plasma viral load[A] **(copies/mL)**			
Median (n)	19,826 (35)	5836 (27)	0.007
Range	492–750,000	455- 312,349	
Undetectable n (%)	22/57[e] (38.6)	43/70[f] (61.4)	0.01
ARV during pregnancy[A] **n (%)**			
1st or 2nd trimester	38 (58.5)	56 (72.7)	0.04
3rd trimester	14 (21.5)	08 (10.4)	
No ARV	13 (20.0)	13 (16.9)	
Maternal IV ZDV during labor[A] **n/N (%)**			
Yes	56/62[g] (90.3)	72/75[h] (96.0)	0.16
No	06/62 (9.7)	03/75 (4.0)	
Mode of delivery[A]			
Cesarian section n/N (%)	43/65 (66.1)	63/77 (81.8)	0.05
Vaginal n/N (%)	22/65 (33.9)	14/77 (18.2)	
HIV-1 Subtypes in pol[B] **n/N (%)**			
B	25/40 (62.5)	29/43 (67.5)	0.40
BF1	04/40 (10.0)	09/43 (20.9)	0.14
C	09/40 (22.5)	02/43 (4.6)	0.02
F1	02/40 (5.0)	02/43 (4.6)	0.66
CB	00 (0.0)	01/43 (2.3)	0.51

The P values were determined by Fisher's exact test, Mann–Whitney or Spearman test, as appropriate [CI 95% ($p<0.05$)]; ARV = Antiretroviral; ZDV = zidovudine; Missing data: $a=03$, $b=01$; $c=08$; $d=06$; $e=08$; $f=07$; $g=03$; $h=2$.

[A] Spearman tests considering: ARV therapy as covariate to compare $CD4^+$ T cell counts and viral loads for the two groups ($r=0.11$; $r=0.24$, respectively); time of diagnosis as a covariate to compare prophylaxis, maternal intravenous ZDV use during labor and mode of delivery ($r=-0.25$; $r=0.22$; $r=0.16$, respectively).

[B] Not amplified = 59.

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