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The cascade of care to prevent mother-to-child transmission in Rio de Janeiro, Brazil, 1996-2013: improving but still some way to go

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Title Page

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Introduction

HIV mother-to-child-transmission (MTCT) has decreased substantially over the last decades in most parts of the world (1)(2)(3)(4). A transmission rate below 1% has been reported from several cohorts of HIV infected pregnant women(1)(2)(3)(4). Mothers who consistently use combination antiretroviral therapy (cART) during pregnancy, now have mostly undetectable viral load values by the end of pregnancy (5)(6)(7)(8) and measures to prevent perinatal infection during labor and delivery that were previously considered necessary (e.g. elective cesarean section, avoidance of more than four hours of ruptured membranes, or the utility of perinatal intravenous zidovudine (IV ZDV)) are now debated.

In 1995, a program to prevent HIV MTCT in Brazil was launched by the Brazilian Ministry of Health. From then all women should be tested for HIV during pregnancy. HIV infected pregnant women should be referred to a specific clinic where their care and treatment is integrated with antenatal care (ANC). In these centers, women have access to viral load and CD4+ cell count testing and antiretrovirals. Currently, the preferred treatment is ZDV/lamivudine/lopinavir/ritonavir, IV ZDV during labor and delivery, and ZDV syrup for the newborn until 4 weeks of age. Three doses of nevirapine are added, if the mother's viral load before delivery is unknown or above 1000 copies/mL. Since 1999, formula is provided to the newborn during the first 6 months after birth (9). However, flaws in the system are still reported in this as well as in other Prevention of Mother to Child Transmission (PMTCT) programs, and these are important barriers to reaching the aim of an HIV-free generation (10)(11)(12).

Although many obstetricians perceive perinatal HIV infection to be a resolved problem, the pediatric perspective is different: HIV infected children are still being diagnosed in pediatric clinics (13) – and the diagnosis is often only made years after birth. Lack of access to ANC, gaps in HIV testing during pregnancy, or even problems with delivering test results to patients in time for antiretroviral initiation are still barriers in the cascade of care in Brazil, and other middle income countries (11)(4)(14)(15)(16)(12). In this paper, we aimed to describe time trends of the cascade of care of perinatal HIV mother-to-child-transmission prevention in the reference centre for pediatric HIV care in Rio de Janeiro, Brazil. In addition we also describe possible predictors of failure in this cascade.

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Methods

We analyzed data collected at the Instituto de Puericultura e Pediatria Martagao Gesteira (IPPMG) at Universidade Federal do Rio de Janeiro (UFRJ), a tertiary pediatric hospital in Rio de Janeiro. The clinic includes more than 1,000 HIV exposed uninfected (HEU) infants and over 400 HIV-infected children who were ever registered into the cohort. We defined HEU infants as those born to mothers with at least one positive serologic test for HIV before or during pregnancy. In infants who were not breastfed, at least one undetectable viral load measurement 6 weeks after birth or later was required to exclude HIV infection. HIV infection was defined as at least two viral load tests >1000 copies/ml, taken at different times and/or for children above 18 months of age, a positive serologic test. While some children were followed from birth, others presented only later to confirm or refute HIV infection or if symptoms were present. Since IPPMG-UFRJ is one of the first pediatric HIV referral centers in Rio de Janeiro, children from the whole Rio de Janeiro municipality, and even from other areas are followed there.

After the newborns or infants enroll in the clinic, their mothers are counselled not to breastfeed and formula is provided free of charge in the first 6 months of life. All infants born to HIV-infected mothers receive ZDV syrup until four weeks of age, and afterwards cotrimoxazole prophylaxis until the infant has two undetectable viral load measurements. If the children arrived at the center after one year of age, breastfeeding is discontinued, and cotrimoxazole is initiated until the HIV diagnosis is confirmed and the degree of immunosuppression is evaluated. cART is initiated as soon as possible. Viral loads were measured using the Roche Amplicor HIV-1 Monitor test with a detection limit of 400 copies/ml.

Inclusion criteria and follow-up

HIV-infected or HEU children followed at the UFRJ clinic between January 1996 and March 2013 were included in the analysis. For each child structured baseline and follow-up questionnaires were completed at first and subsequent visits, respectively. Data on the gestational and perinatal history were extracted from the child's immunization card and the mother's antenatal card. Data on mothers included maternal age, maternal ANC attendance, maternal HIV testing during ANC, whether the mother learned about her HIV infection before, during or after ANC, use of antiretrovirals before and during pregnancy and the results of laboratory tests. In the newborns, data on birth weight, birth length, gestational age at birth, mode of delivery, duration of amniorrhexis, use of antiretrovirals during labor and delivery, use of antiretrovirals during the newborn phase, breastfeeding and duration of breastfeeding were obtained. This information is derived from ANC cards where all details of the pregnancy and delivery are recorded. Children were followed-up in monthly intervals for the first six months, and every three months thereafter. At each visit clinical and laboratory data, and data on antiretrovirals, other treatments, and immunizations were recorded.

The cascade of care on HIV MTCT Prevention

We adapted the cascade of care (12)(15)(16) to the Brazilian health care system and included the following steps: 1. Proportion of mothers attending ANC care among all HEU and HIV positive children; 2. Proportion of mothers with an HIV test done before or during pregnancy among all mothers who went to ANC care; 3. Proportion of mothers receiving any antiretroviral prophylaxis during pregnancy among all mothers diagnosed with HIV before or during pregnancy; 4. Proportion of mothers getting IV ZDV prophylaxis during labor and delivery (L&D) among all women receiving any antiretroviral prophylaxis during pregnancy 5. Proportion of newborns receiving ZDV syrup among all infants whose mothers got IV ZDV prophylaxis during L&D.

Statistical analysis

We used a non-parametric test for trend to compare several characteristics of children at birth and of mothers during pregnancy over three time periods: 1996 to 2000, 2001 to 2006, and 2007 to 2013. The intervals were chosen since guidelines changed at the start of each time period. In 2000/01 formula feeding became available free of charge, and in 2007 universal cART became available.

We used univariable and multivariable logistic regression to evaluate differences between HIV infected and uninfected children in each of the three time periods. Results from regression models were presented as odds ratios with 95% confidence intervals (CI). We included in the final models variables describing ANC (i.e. if the mother went to ANC or not; if she got antiretrovirals during pregnancy), labor and delivery (mode of delivery: non-elective cesarean section, vaginal delivery, and elective cesarean section; if IV ZDV was used during L&D), and neonatal care (if the newborn was breastfed). We did a complete case analysis and an analysis where we imputed missing values of explanatory variables. We created 10 imputed datasets by chained equations and imputed the missing values based on the same variables used in the multivariable analysis and the dependent variable. The fit of the models were assessed by the Hosmer-Lemeshow test.

We also studied factors possibly associated with the completion of the cascade, including as explanatory variables only variables which were not part of the cascade or highly correlated with it (i.e. maternal age, neonatal gender and gestational age at ART initiation). The variables highly correlated with the ones from the cascade were: If the patient was HIV tested during antenatal care, duration of the amniorrhexis, and breastfeeding). Completion of Cascade was defined as in Figure 1 (i.e. participants who followed all the steps stated on the cascade) .

Ethical Issues:

This manuscript was approved by Instituto de Puericultura e Pediatria Martagão Gesteira – UFRJ Ethical Committee.

Results

Overall 989 children were included in the analysis of whom 211 were HIV-infected and 778 HEU. The median (interquartile range [IQR]) age of the mother was 27 (22-31) years. A total of 91 (9.7%) of mothers did not attend ANC. Among those who attended at least one ANC visit, the median gestational age at ANC initiation was 12 weeks (IQR=8-18 weeks). Overall 37% (n=365) of mothers were diagnosed with HIV before pregnancy, 38% (n=378) during and 19% (N=188) after pregnancy. For 161 children, the HIV status of the mother during pregnancy was unknown, and the child was the index case of the family. A total of 162 women breastfed for a median duration of 4 months (IQR=1-15 months). A total of 112 (13%) of the newborns did not receive ZDV syrup, while the remaining received ZDV syrup, and two received nevirapine in addition to ZDV, both were born after 2010.

Trends over time:

The characteristics of antenatal, perinatal, and neonatal care in 989 mother-infant pairs across the three time periods are shown in Table 1. Mothers tended to be older in the latest time period (2007-2013). In this time period, antiretrovirals were initiated earlier. Nevertheless, in women who received antiretrovirals, therapy was not started earlier in 2007-2013, as compared to earlier time periods. Overall, fifty-three women started cART before conception: 2 in the first period, 24 in the second period, and 27 in the third period. ART use during labor and delivery, and the use of ZDV syrup in the newborns increased over time. Higher rates of elective cesarean-section were also observed in the last period, and less infected newborns were followed up in this time period (Table 1). Figure 1 shows that the PMTCT cascade improved substantially in the second and third period compared to the first one.

Differences of care between HIV infected and HEU children:

The characteristics of HIV infected and HEU children were remarkably different as shown in (Table 2). The rate of mothers´ HIV infection diagnosis before or during pregnancy was higher in non-infected group, and even higher considering the last period of observation. In particular, mothers of the HIV non-infected group were exposed to more HIV transmission preventive measures as elective cesarean section, use of antiretrovirals during pregnancy, labor and delivery. The mothers of HIV infected children were more likely to not received antiretrovirals during pregnancy (some of them were not even diagnosed with HIV before delivery). Overall seven mothers (35%) of HIV infected infants used ZDV monotherapy during pregnancy, 4 (20%) used a dual therapy, one used a non-nucleoside reverse transcriptase inhibitors (NNRTI) based cART regimen and 8 (40%) a protease inhibitor (PI) based cART regimen.

The preventive measures to HIV MTCT were very effective, as we observed their frequency differences between HIV infected and non-infected group (Table 2). However, we had 20 HIV infections which occurred despite the mothers´ use of ART. All these mothers also used ZDV IV during labor, and all newborns took ZDV syrup. The possible main potential risk factor in these children was the advanced gestational age at cART initiation: all started cART at 27 weeks or later. Five mothers had more than 4 hours of ruptured membranes, five delivered vaginally, ten by emergency/non-elective cesarean-section, and five by elective cesarean-section. Three mothers breastfed.

In the 778 HEU infants, 149 (19%) mothers used ZDV during pregnancy, 77 (10%) used dual-therapy; 87 (11%) used an NNRTI-based cART regimen, 277 (35%) used a PI-based, and 8 (1%) used both an NNRTI and PI-based cART regimen. In 180 (23%) HEU this information was not available.

Table 3 shows differences between HIV infected and HEU children from the logistic regression over time, for the model with and without imputation of missing values. In both models, many more children were HIV positive in 1996-2000 as compared to the two later time periods. Even after adjusting for mode of delivery and the use of ART during pregnancy, use of antiretrovirals during labor and delivery was associated with a reduced risk of children being HIV positive.

In the analysis where completion of the cascade was the outcome, earlier initiation of antenatal care was the only variable which was associated with the outcome. The average gestational age at the first antenatal visit was 13 weeks in those who completed the cascade versus 16 weeks in those who did not ($p<0.01$).

Discussion

The gaps in the PMTCT cascade decreased substantially over time, and not surprisingly fewer children were HIV infected in later time periods. However, the cascade of care remained similar between the second (2001-2006) and the third (2007-2013) time period, and even in children who did not get infected, several gaps were identified after 17 years of a well-structured program. Lack of ANC care and no or delayed initiation of antiretrovirals during pregnancy were the main problems identified in HIV infected children. The presence of risk factors which are typically associated with an increased risk of HIV vertical transmission (such as lack of HIV testing during pregnancy (5)(6)(7)(8) and breastfeeding) decreased over time, but some of these risk factors were still present in the latest time period.

Several recent studies found that some perinatal interventions which were often deemed necessary to prevent MTCT (such as IV ZDV during labor and delivery, elective cesarean section, or avoidance of more than 4 hours of ruptured membranes) may not be important any more (5)(6)(17)(8). However, our findings suggest that these findings cannot be extrapolated to Rio de Janeiro and possibly other settings with gaps in the PMTCT cascade. Even after adjusting for mode of delivery, and the use of antiretrovirals during pregnancy, children of mothers who did not use antiretrovirals during labor and delivery were more likely to be HIV positive. In our study elective cesarean section and vaginal delivery were associated with a lower probability of being HIV infected as compared to non-elective cesarean section in the second time period. In contrast a European clinical trial described that the HIV transmission risk from vaginal delivery and non-elective cesarean section were the same, but higher than for elective cesarean section (18). Another recent study demonstrated that for women with a viral load value <1000 copies/mL, the HIV transmission risk for vaginal delivery or elective cesarean section are the same (19). We believe that our results reflect the safety of elective cesarean sections in HIV infected patients and the low frequency of vaginal deliveries in Brazil (20). Consequently, the vaginal deliveries in our population probably represent non-complicated vaginal deliveries, with shorter labor and amniorrhexis.

In our study, recommended treatment guidelines were often not followed in mother-infant pairs. For patients with low viral load values during labor and delivery, vaginal delivery is recommended in many countries including Brazil (6)(7)(8)(9). In our study, the use of cART during pregnancy increased over time and probably more women reached low viral load values during labor and delivery in recent years. However vaginal delivery did not become more frequent over time. This is in contrast to an European study which reported an increase in vaginal deliveries from 17% to 52% after European countries issued guidelines recommending vaginal deliveries for women who presented with viral load <400 copies/mL. However, the authors stated that there are still missed opportunities for vaginal deliveries in this population, and they also still observed 7% of preterm deliveries (21). Unfortunately viral load values were in general not recorded in our data and values were only available for the minority of the children.

Although Brazilian guidelines recommended an intensified infant antiretroviral regimen since September 2012 (adding nevirapine syrup to ZDV if the mother presented in L&D without antiretroviral treatment during pregnancy) (9), this recommendation was followed in only two of the 94 HEU children who were born since then, demonstrating again the gap between a public health policy decision and implementation.

WHO launched the Option B+ PMTCT recommendation for HIV-infected pregnant women in 2013 prior to a randomized trial demonstrating reduced MTCT with cART compared to dual therapy in women with high CD4 counts (22)(23) (24). According to these recommendations, pregnant women should start cART as soon as they know they are HIV-infected, and continue treatment for the rest of their lives (22). Our data suggest that not Option B+, but universal testing would be needed that women are diagnosed before or early in pregnancy and could start antiretrovirals in time. Indeed, among infants infected despite maternal cART, all mothers started cART late in pregnancy. Rapid initiation of cART in HIV infected pregnant women is also challenging. Pregnant women often have gastrointestinal symptoms during the first trimester, which can be aggravated by antiretroviral therapy initiation. The time to understand and accept the HIV diagnosis is short, and stigma and fear of side effects may prevent women from initiating lifelong therapy. Consequetly, diagnosis and treatment initiation before pregnancy would resolve this barrier (25).

Strengths and limitations

This study has several strengths: it included data from a large number of HEU and HIV infected children that were systematically collected during an extended time period of 17 years. The children were followed at a reference center, which is located in Rio de Janeiro, the second largest city in Brazil. The center not only covers the Rio de Janeiro Municipality, but several surrounding cities in Brazil. Since our data were collected from the perspective of pediatricians, we were able to identify possible flaws in the system, which can often not be detected from the perspective of obstetricians. Many Brazilian studies, which reported very low MTCT rates, reflect the latter perspective: they included mainly women who had access to ANC, and good quality of antenatal care (13)(14).

The study has also a number of limitations. Although the data from this study were derived from a large reference center, this is a single center cohort study and results may therefore not be generalizable to Brazil or other settings. Although we compared two different groups (i.e. HIV infected and HEU children), all children and mothers came from the same reference area and the socioeconomic background was similar. We included only children who were born after 1995, because by this year the HIV PMTC Program in Rio de Janeiro was implemented, and all women had theoretically access to care.

The fact that more children were infected in the second time period compared to the third period may seem surprising, since the cascade of care did not change substantially over these periods. We tried to study which factors may be responsible for this seemingly discrepant result by doing an additional analysis where "cascade completion" was the outcome. The only significant variable was gestational age at ANC initiation. However, although the difference of 3 weeks (13 vs 16 weeks) was statistically significant, it's clinical relevance is questionable. It is instead more likely, that the more frequent use of HAART in the latter time period (Table 1) may explain this difference, but due to the limited sample size we were not able to formally test for this.

As in many other observational cohort studies, some covariables were missing. However, the multivariable analysis was based on 86% of all data, and the results from the multiple imputation were similar (Table 3). We did not have information on some factors which are possibly associated with MTCT, including education or literacy, HIV status of the partner and possible associated stigma, or adherence to antiretrovirals.

In conclusion, we identified the lack of access to HIV diagnosis and treatment as major gaps in the PMTCT cascade. Similar gaps were also identified in other studies from low and middle-income countries (15)(10)(16). In the future, studies that describe the characteristics of the individuals who did not complete the cascade, and that identify possible barriers to its completion must be pursued, and locally adapted interventions must be developed which will allow us to reach an HIV-free generation.

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