Prospective cohort study of children exposed to Hepatitis C virus through a pregnancy screening program

Raquel Borges Pinto, MD[1], **Ana Regina L. Ramos, MD**[1], **Leidy Tovar Padua, MD**[2], **Emma Jane Swayze, MS**[3], **Mary Catherine Cambou, MD**[4], **Maristela Fiorini, MD**[5], **Marineide Melo, MD**[6], **Breno Riegel Santos, MD**[6], **Ivete Cristina Teixeira Canti, MD**[6], **Mara Liane Rieck Silveira, MD**[6], **Maria Inês Gonzalez Solari**[7], **Juliana Ferraz de Correa, MD**[7], **Kara Chew, MD**[4], **Ivana Rosângela dos Santos Varella, MD**[6], **Karin Nielsen-Saines, MD**[4]

[1]Hospital da Criança Conceição, Porto Alegre, RS, Brazil

[2]University of San Diego School of Medicine, University of California, San Diego, CA, USA

[3]Western Michigan University Homer Stryker M.D. School of Medicine Kalamazoo, MI, USA

[4]David Geffen School of Medicine, University of California, Los Angeles, CA, USA

[5]Communicable Disease Surveillance Team, Municipal Health Secretariat of Porto Alegre, RS, Brazil

[6]Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brazil

[7]Central Public Health Laboratory of Rio Grande do Sul, Porto Alegre, RS, Brazil

Abstract

Objectives: Porto Alegre, in south Brazil, has one of the highest Hepatitis C virus (HCV) infections rate in the country (84.4 cases/100,000 in 2018). Prenatal screening of HCV, however, has not been routinely offered.

Methods: We conducted a longitudinal study of pregnant women with HCV and their infants between January 2014 to December 2018. Screening for HCV antibodies was offered to all women delivering at our tertiary institution. HCV RT-PCR was performed if seropositive. Infants were followed prospectively.

Corresponding author: Karin Nielsen-Saines, MD, MPH, Department of Pediatrics, Division of Pediatric Infectious Diseases, Mattel Children's Hospital, David Geffen UCLA School of Medicine, MDCC 22-442 10833 LeConte Avenue, Los Angeles, CA 90095, knielsen@mednet.ucla.edu.

Publisher's Disclaimer: This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest: All authors report no conflicts of interest.

Results: Among 18,953 pregnant women delivering, 17,810 were screened for HCV antibodies (93.9%) with 130 positive results. (HCV seroprevalence 0.7%). HCV RNA was detectable in 57/117 cases (48.7%). HCV viremia was associated with use of injectable drugs (p=0.03), inhaled/ crack drug use (p=0.02), an HCV-seropositive partner, 3 lifetime sexual partners (p=<0.01). Genotype 1 was most prevalent (68%) during pregnancy. Among 43 children with follow-up, 6 (13%) were HCV infected (transmission rate 13.9%); genotype 3 infected 50%. Two infants (33%) cleared infection; mothers had genetic polymorphisms associated with clearance.

Conclusion: HCV vertical transmission was high in our population, with HCV infection during pregnancy being vastly underdiagnosed. Public health efforts must focus on this vulnerable population for disease prevention and early treatment.

Introduction

In 2015, the World Health Organization (WHO) estimated chronic hepatitis C (HCV) affects about 1% of the world population (World Health Organization, 2018). The Brazilian Ministry of Health reported 384,284 HCV cases between 1999 and 2019 (Brasília. DF. Ministry of Health, 2020). Positive infections were identified using one of the following markers: HCV antibodies or HCV RNA. A greater distribution of positive HCV cases was notable in both southeastern (57.7%) and southern (26.7%) regions of Brazil, and rates of HCV among 10 Brazilian capitals exceeded the national average in 2019 (10.8/100,000) (Ministério da Saúde, 2020). Of these cities, Porto Alegre, the southernmost state of Rio Grande do Sul, stands out as having the highest HCV rate (84.4/100,000) (Ministério da Saúde, 2020).

According to a review of 26 CDC-conducted studies, the estimated HCV seroprevalence in pregnant women in the United State (U.S.) is 1.2% (range: 0.1 to 70.8%) (Schillie et al., 2020). The National Center for Health Statistics showed significant increases in HCV-infection among pregnant women and children in the U.S. from 2011 to 2016 (2.6% to 3.6% and 3.6% to 4%, respectively) (Schillie et al., 2018). Universal screening for HCV in pregnant women was recommended by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America in 2018, as well as by the U.S. Preventive Services Task Force in 2020 to promote diagnosis and screening of previously overlooked infections (Ghany et al., 2019, Owens et al., 2020). The CDC also recommends universal screening of pregnant women, except in places where the prevalence of HCV is less than 0.1% (Schillie et al., 2020). In contrast, other entities such as the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the WHO only endorse risk-based screening for HCV (Ministério da Saúde, 2020; Schillie et al., 2020; Hughes et al., 2017). Brazil previously followed a risk-based HCV assessment model, but as of October 2020 has implemented the recommendation of universal HCV triage (Brasília. DF. Ministry of Health, 2020).

In children, mother-to-child transmission (MTCT) is the main mode of HCV acquisition, but mechanisms associated with transmission are still unclear (Mack et al., 2012; Squires et al., 2017). Fortunately, high rates of spontaneous clearance (25-40%), particularly in the first 24 months of age, have been observed in the pediatric population (Mack et al., 2012). Maternal HIV co-infection, especially in untreated individuals, is associated with higher rates of HCV vertical transmission (Benova et al., 2014; Checa et al., 2013). Other potential risk factors contributing to MTCT are elevated maternal viral load, amniocentesis, fetal scalp monitoring during labor, and prolonged rupture of membranes (World Health Organization, 2018; Espinosa et al., 2018; Indolfi et al., 2019).

Inefficient virus transmission to children with perinatal HCV exposure may be explained by immune system defense mechanisms related to human leukocyte antigens (HLA), CD4 lymphocytes, innate immune properties of the placenta, and variations in genes involved in the immune response (Mack et al., 2012; Lapa et al., 2019). In adults, the presence of the C/C genotype in the single nucleotide (SNP) polymorphism rs12979860 and the T/T genotype in the SNP rs8099917 have been associated with both greater spontaneous viral clearance and higher rates of sustained virological response after treatment with pegylated interferon combined with ribavirin (Lapa et al., 2019; Indolfi et al., 2014). Few pediatric studies have investigated the influence of these polymorphisms on HCV viral transmission and spontaneous HCV clearance.

The main objective of this study was to identify the prevalence of HCV in pregnant women in Porto Alegre, Brazil, as well as to compare demographic, behavioral, and biological characteristics of pregnant women with and without detectable HCV RNA. Additionally, we evaluated genotypes and polymorphisms present in HCV-viremic mothers and exposed infants.

Methods

Study Population and Data Sources

The Nossa Senhora da Conceição Hospital, located in Porto Alegre, the capital of Rio Grande do Sul, south Brazil, is a public hospital of medium and high complexity care under the Brazilian Unified Health System (SUS); one of the largest public health systems in the world. The institution is a referral hospital for high-risk pregnancies (Boletim Epidemiológico do Hospital Conceição, 2019).

Study Design and Selection Criteria

A prospective cohort study of pregnant women delivering at Conceição Hospital between January 1, 2014 to December 31, 2018 was conducted. Universal screening for HCV was performed in the hospital maternity ward during the study period. If HCV serology was found to be positive, a quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR) for HCV RNA was performed. Pregnant women with HCV viremia were invited to participate in the study for follow-up of their infants until approximately 36 months after maternal enrollment (Figure 1). The supplementary materials appendix includes information regarding HCV test processing, quantification of viral loads, HCV genotyping, the IL28B

assay, and HCV case definitions utilized throughout the manuscript (Ghany et al., 2020; Mack et al., 2012; Gélinas et al., 2013; Padua et al., 2016).

Statistical Analysis

To calculate the prevalence of HCV in pregnant women, we used a binomial analysis with the calculation of a simple proportion and 95% confidence intervals [CI]. Potential differences between maternal demographic, behavioral, and biological characteristics in women with varying levels of detectable HCV RNA were explored using the Yates or Fisher's Chi-square test. To compare viral load medians, the Mann-Whitney U test was used. Poisson regression was used to determine associations between patient age and detectable HCV viral load. Data was processed and analyzed using the SPSS version 16.0 program. In comparison, a correction with the addition of 0.5 was used with the statistical program Win PEPI 3.60, when the number zero was found in the contingency tables (Abramson et al., 2011).

Results

A total of 17,810 (94%) from18,953 pregnant women delivering at Hospital Nossa Senhora da Conceição between January 2014 and December 2018 were screened for HCV by serology. Of those, 130 women had positive results, demonstrating an HCV seroprevalence of 0.7% (95% CI:0.6%,0.8%). HCV RNA virus load was quantified in 117 (90%) of 130 HCV-seropositive women, with detectable HCV RNA identified in 57 women (48.7%). The median time between date of maternal specimen collection for HCV PCR and date of delivery was 3 days (Q1= −20 days; Q3= 43.5 days). Fifty-one (87.9%) of 58 eligible infants (87.9%), including a pair of twins were exposed to active maternal HCV infection (Prevalence of 0.3%; 95% CI: 0.2% to 0.4%) Since eight of 51 infants (15.7%) were subsequently lost to follow up, the presence of HCV infection was evaluated in 43 (74.1%) of 58 HCV exposed newborns (Figure 2). Six infants (14%) were found to be HCV infected.

Demographic and obstetric characteristics of pregnant women included in our study are shown in Table 1. The median age of the 117 HCV-seropositive women with detectable HCV RNA was 30.7 years (range 16 to 43 years). The majority of the cohort was white (64.1%), obtained an elementary school education (55.6%), and delivered vaginally (55.6%). In addition to HCV, 26 (22.2%) of 117 women were seropositive for HIV. Half (N=13 of 26) of those seropositive for HIV had detectable HCV RNA.. Thirteen women with HCV co-infection (11.1%) were co-infected with syphilis. (Table 1). No women in the study tested positive for concurrent Hepatitis B infection. Compared to those without detectable HCV RNA levels (only seropositive for hepatitis C), pregnant women with detectable HCV RNA were significantly older and more likely to have had multiple pregnancies (p=0.02).

Table 2 demonstrates risk factors associated with maternal HCV exposure in women with either detectable or undetectable HCV RNA levels. Seventy one (65.1%) of 109 pregnant women with available exposure data reported having at least one of the following risk factors (injectable drug use, use of crack/inhalable drugs, surgical treatment, dental treatment, tattoo or piercings, blood transfusions, sexual contact, multiple sexual partners, home contact, occupational contact, or accidental contact with biological material) for HCV transmission.

There was no significant difference in the presence of overall risk factors between women with detectable versus undetectable HCV RNA; 64.2% and 66.1% respectively (p = 0.99). However, we did identify a significant association between specific risk factors including injectable drug use (p=0.03), inhalable/crack drug use (p=0.02), sexual contact with an HCV-seropositive partner (p=0.01), and reports of three or more sexual partners in the group of pregnant women with detectable HCV RNA. In contrast, 57.4% of women with undetectable HCV RNA reported having tattoos or piercings compared to only 37% of women with detectable HCV RNA. Few patients with both detectable and undetectable HCV RNA (approximately 15% in each group) reported a previous blood transfusion (Table 2). No pregnant women in our study had a history of hemodialysis or organ transplants that would increase risk to HCV exposure.

There was a total of 58 infants (1 pair of twins) born to HCV-seropositive mothers with detectable HCV RNA and 60 infants born to HCV-seropositive mothers without detectable HCV RNA levels (N=118 infants, N=117 mothers) (Supplemental Table 1). RNA HCV PCR was performed in early specimens of 51 (87.9%) of 58 exposed infants of whom 43 (84.3%) remained in follow-up. Six of 43 infants were infected with HCV, resulting in an HCV MTCT rate of 13.9% (95% CI: 5.3% to 27.9%). Spontaneous viral clearance occurred in 2 (33.3%) of the 6 children infected with HCV. The description of these cases is detailed in Table 3. Supplemental Table 1 in Appendix B compares the 58 infants of the 57 viremic mothers to the 60 infants of the 60 non-viremic mothers. No significant differences were identified between infants born to mothers with detectable versus undetectable HCV RNA regarding birthweight, gestational age, or HIV infection (Supplemental Table 1). The overall frequency of low birthweight and prematurity in the infants was 16.1% and 14.4% respectively. Although 26 (22%) of 118 newborns were exposed to HIV, only 1(4%) of 26 tested positive for HIV. In this case, the infected infant's mother had detectable HIV RNA close to delivery.

Supplemental Table 2 examines viral markers and host genetic factors of pregnant women and their infants according to HCV MTCT. The median HCV viral load among 57 pregnant women with detectable HCV RNA was 560,554 IU/mL (range=8,040 to 8,375,380 IU/mL; Q1=186,381; Q3=2,045,941). Genotype 1 was most frequently identified in women with detectable HCV RNA levels (39 of 57 women, 68.4%), with 20 cases of subtype 1a, 11 cases of subtype 1b, and 8 cases without a defined subtype. Genotypes 3 and 2 were less common and were present in 14 (24.6%) and 1 (1.7%) of 57 cases, respectively. Genotype results were unavailable in 3 (5.3%) of 57 cases. We also examined maternal factors associated with HCV MTCT in the 43 infants born to mothers with detectable HCV RNA. While 16 of 43 newborns (37.2%) were delivered via cesarean section, half (3 of 6) of the HCV-infected newborns were delivered via cesarean section. HCV-positive infants were also more frequently infected with genotype 3, born to mothers with uncontrolled HCV viral loads greater than 600,000 IU /mL, and born to mothers with an HIV co-infection. However, findings were not statistically significant (Supplemental Table 2). The two infants that achieved HCV viral clearance were born to mothers who had a C/C genotype rs12979860 IL28B and TT genotype rs8099917 (Table 3). Given the small number of infant HCV infections, it was not possible to explore potential associations between maternal/infant IL-28B polymorphisms and spontaneous viral clearance.

Discussion

The HCV seroprevalence of pregnant women in our study was 0.7%. This falls on the higher end of HCV prevalence in pregnant women reported throughout Brazil, ranging from 0.1% to 1.3% (Gardenal et al., 2011; Fernandes et al., 2016; Gomes et al., 2016; Batistão et al., 2017; Barros et al., 2018). We found a subset (0.3%) of pregnant women in our cohort that were not only HCV seropositive, but also had detectable HCV RNA levels around the time of delivery. Rates of detectable HCV viremia in pregnant women in our study are within the range of 0.09% to 2.4% reported in the literature (El-Kamary et al., 2017; Jhaveri et al., 2015; Kopilovi et al., 2015; Orkin et al., 2016). HCV prevalence in pregnant women living in southern Brazil is likely even greater than that reported in our study. Only recently did the Brazilian Ministry of health draft guidelines recommending universal screening for HCV in pregnant women during the first prenatal consultation (Brasília. DF. Ministry of Health, 2020). Self-reported HCV risk assessment is an unreliable measure of true disease prevalence and leaves room for missed diagnostic opportunities.

At an underestimated 13.9%, the rate of HCV MTCT found in our study is notably elevated when compared to transmission rates ranging from 6% to 14% identified in larger prospective studies (Jhaveri et al., 2015; Ceci et al., 2001; Resti et al., 2002). Probable risk factors associated with HCV MTCT include elevated maternal viral load, HIV co-infection, and female gender of the infant (Mack et al., 2012; Benova et al., 2014; Mariné-Barjoan et al., 2007; Ngo-Giang-Huong et al., 2010; Pembrey et al., 2005). No risk factors were associated with HCV transmission in this cohort, likely due to the small number of transmission events noted. Similarly, we were not able to assess the relationship between the presence of IL28B polymorphisms and MTCT as a result of the limited sample size and lack of serial HCV RNA specimens in exposed infants. However, the two infants who eradicated their infection possessed genetic polymorphisms associated with spontaneous clearance.

Previous studies have focused on the relationship between HCV and self-identified Black race. In a cohort study that evaluated the epidemiology of chronic liver diseases, it was observed that chronic HCV infection with or without cirrhosis was more frequent in African Americans compared to other ethnicities (Setiawan et al., 2016). Opposed to other areas in Brazil, the majority of pregnant women in our study self-identified as White. The predominance of White race is unique to southern Brazil and reflects European immigration to this region, where approximately 90% of the population is of European ancestry (Ruiz-Linares et al., 2014). We also found that the majority of women in our study had not completed education beyond elementary school. Lower educational level is consistent with the demographics of patients utilizing free public health systems in Brazil. Characteristics of pregnant women with detectable HCV RNA were older age, multiparity, and history of vaginal delivery. Although previous research has shown an association between HCV seropositivity and concurrent HIV and syphilis co-infections, we did not find a relationship between HIV or syphilis co-infections and the presence of detectable HCV RNA (Yeganeh et al., 2015; Adachi et al., 2018). Further, detectable HCV RNA did not appear to have any effect on HIV disease severity in pregnant women with HIV-coinfections. HIV viral loads and absolute CD4 values were not significantly different in pregnant women with HIV-coinfections with and without detectable HCV RNA. We also looked at the role of

co-infections in HCV MTCT. No transmission events occurred in infants born to VDRL+ mothers, and 2 of 6 transmission events occurred in infants born to HIV co-infected mothers. One of these mothers had detectable HIV RNA and was being treated irregularly, while the other had undetectable HIV RNA and was receiving complete treatment (Table 3). The number of transmission events in our study is too small to make any definite conclusion regarding the association between maternal co-infections and HCV MTCT.

We found an association between detectable HCV RNA and prior use of inhalable/crack drugs, sexual contact with an HCV-infected partner, and multiple sexual partners. Intranasal transmission of HCV infection was supported through a study that found the presence of blood and viral HCV RNA in nasal secretions and drug-sniffing equipment among non-injection drug users in New York City (Aaron et al., 2008). In our study, the exposure factor most strongly associated with detectable HCV RNA was sexual contact with an HCV-infected partner. Monogamous relationships are not protective against obtaining a sexually transmitted infection (Terrault et al., 2013). In fact, there are several reasons why people in relationships may be reluctant to disclose infections, including infidelity, cultural stigma, and fear of domestic abuse (Andrade et al., 2015). Conversely, the presence of tattoos was more frequent in HCV-seropositive patients who did not have detectable HCV RNA.

Newborns with HCV exposure have a higher risk of prematurity, low birth weight, and congenital anomalies (Huang et al., 2016; Stokkeland et al., 2017). In a meta-analysis of 7 observational studies, a higher occurrence of intrauterine growth restriction and low birth weight was observed in newborns of mothers with chronic HCV (Huang et al., 2016). We evaluated infant birth outcomes according to the presence of maternal HCV RNA levels and found no significant differences in neonatal characteristics (including birth weight and gestational age) when stratifying by the presence of maternal HCV RNA viremia. This may be due to the fact that HCV RNA levels were not monitored serially throughout pregnancy. HCV infection may impact pregnancy and neonatal outcomes regardless of viremic peaks. In our HCV-seropositive cohort, prematurity was present in 14% of cases and low birth weight was seen in 16% of infants, which is slightly higher than what was noted for the general Brazilian population in 2018 (11% for prematurity and 6% for low birth weight) (Silveira et al., 2017).

With universal prenatal HCV screening, we identified six infants with HCV who received early linkage to care and monitoring that might have otherwise been missed. Challenges with patient follow-up in our study required additional effort from the research team to encourage testing of exposed infants. We actively searched for several children to ensure visit attendance, even involving social services in some cases. Regardless, we were able to follow-up 84.3% of the cohort. The obstacle of patient follow-up is experienced in locations outside of Brazil as well. The Philadelphia Department of Public Health concluded that the vast majority of children exposed to HCV do not undergo routine follow-up (Kuncio et al., 2016). These findings are reinforced in a Tennessee Medicaid study that found HCV testing only occurred in 1 of 4 children perinatally exposed to HCV (Lopata et al., 2020).

Limitations of our study include the small number of HCV transmission events, the relatively modest sample size of HCV-seropositive women, and the difficulties in keeping

this population of infants in follow-up for 36 months. Nevertheless, our study results reinforce the recent recommendation by the Ministry of Health of Brazil regarding the universal screening of HCV in pregnant women (Brasília. DF. Ministry of Health, 2020).

Public health initiatives that focus on HCV screening and follow-up during prenatal care visits are important strategies to prevent MTCT. Universal HCV screening is cost-effective and has the potential to reduce long-term morbidity through linkage to referral and treatment services (Espinosa et al., 2018; Selvapatt et al., 2015; Tasillo et al., 2019; Kushner et al., 2019). During the prenatal period, women are in direct contact with the healthcare system, presenting a crucial opportunity for HCV infection screening and referral for follow-up visits and exposed newborn testing. Our findings emphasize identification of patients at risk and early infant diagnosis must be prioritized, particularly as new treatment modalities for HCV become available to this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

References

Aaron S, McMahon J, Milano Det al.Intranasal transmission of hepatitis C virus: virological and clinical evidence. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2008;47(7):931–934. [PubMed: 18764772]

Abramson JWINPEPI updated: Computer programs for epidemiologists, and their teaching potential. Epidemiologic Perspectives and Innovations. 2011;8.

Adachi K, et al.Combined Evaluation of Sexually Transmitted Infections in HIV-infected Pregnant Women and Infant HIV Transmission. PLoS ONE. 2018;13(1):e0189851. [PubMed: 29304083]

Andrade R, Araújo M, Vieira Let al.Intimate partner violence after the diagnosis of sexually transmitted diseases. Rev Saúde Pública. 2015;49:3. [PubMed: 25741656]

Barros M, Ronchini K, Soares R. Hepatitis B and C in pregnant women attended by a prenatal program in an universitary hospital in Rio de Janeiro, Brazil: Retrospective study of seroprevalence screening. Arq Gastroenterol. 2018;55(3):267–73. [PubMed: 30540090]

Batistão F, Silva H, Schuelter-Trevisol F. Syphilis, HIV and hepatitis B and C serological screening among parturient admitted in the obstetrics center of a hospital in Southern Brazil, 2014–2016. DST - J bras Doenças Sex Transm. 2017;29(3):96–100.

BEHCO-BEHCO Boletim Epidemiológico do Hospital Conceição. Núcleo Hospitalar. 2019;3:2594– 3936.

Benova L, Mohamoud Y, Calvert C, Abu-Raddad L. Vertical transmission of hepatitis C virus: Systematic review and meta-analysis. Clin Infect Dis. 2014;59(6):765–73. [PubMed: 24928290]

Brasília DF. Ministry of Health. Secretariat of Science, Technology, Innovation and Strategic Inputs in Health. Report of Recommendation. Clinical Protocols and Therapeutic Guidelines. Prevention of Vertical Transmission of HIV, Syphilis and Viral Hepatitis. 2020.

Ceci O , Margiotta M, Marello F et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. J Pediatr Gastroenterol Nutr. 2001;33(5):570–5. [PubMed: 11740231]

Checa C, Stoszek S, Quarleri Jet al.Mother-to-Child Transmission of Hepatitis C Virus (HCV) Among HIV/HCV-Coinfected Women. J Pediatric Infect Dis Soc. 2013;2(2).

El-Kamary S, Hashem M, Saleh Det al.Reliability of risk-based screening for hepatitis C virus infection among pregnant women in Egypt. J Infect. 2015;70(5):512–9. [PubMed: 25623176]

Espinosa C, Jhaveri R, Barritt A. Unique Challenges of Hepatitis C in Infants, Children, and Adolescents. Clinical Therapeutics. Excerpta Medica Inc. 2018;40:1299–307.

Fernandes C da S, Alves M de M, de Souza M, Machado G, Couto G, Evangelista R. Prevalence of hepatitis B and C seropositivity in pregnant women. Rev da Esc Enferm. 2014;48(1):89–96.

Gardenal R, Figueiró-Filho E, Luf J, de Paula G, Vidal F, Neto P, et al.Hepatite C e gestação: Análise de fatores associados à transmissão vertical. Rev Soc Bras Med Trop. 2011;44(1):43–7. [PubMed: 21340407]

Gélinas J, Fabre T, Willems Pet al.IL28B SNP screening and distribution in the French Canadian population using a rapid PCR-based test. Immunogenetics. 2013;65(6):397–403. [PubMed: 23455512]

Ghany M, Morgan T. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology. 2020;71(2):686–721. [PubMed: 31816111]

Gomes Filho C, Macedo Filho J, Minuzzi A, Gomes M, Luquetti A. Detecção de doenças transmissíveis em gestantes no estado de Goiás: O teste da mamãe. Rev Patol Trop. 2016;45(4):369.

Huang Q, Hang L, Zhong M, Gao Y, Luo M, Yu Y. Maternal HCV infection is associated with intrauterine fetal growth disturbance A meta-analysis of observational studies. Med (United States). 2016;95(35).

Hughes B, Page C, Kuller J. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol. 2017;217(5):B2–12.

Indolfi G, Azzari C, Resti M. Polymorphisms in the IFNL3/IL28B gene and hepatitis C: From adults to children. World Journal of Gastroenterology. WJG Press. 2014;20:9245–52. [PubMed: 25071317]

Indolfi G, Easterbrook P, Dusheiko Get al.Hepatitis C virus infection in children and adolescents. The Lancet Gastroenterology and Hepatology. Elsevier Ltd. 2019;4:477–87. [PubMed: 30982721]

Jhaveri R, Hashem M, El-Kamary Set al.Hepatitis C virus (HCV) vertical transmission in 12-month-old infants born to HCV-infected women and assessment of maternal risk factors. Open Forum Infectious Diseases. 2015;2.

Kopilovi B, Poljak M, Seme K, Klavs I. Hepatitis C virus infection among pregnant women in Slovenia: study on 31,849 samples obtained in four screening rounds during 1999, 2003, 2009 and 2013. Euro Surveill. 2015;20(22):21144. [PubMed: 26062646]

Kuncio D, Newbern E, Juhnson Cet al.Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women. Clinical Infectious Diseases. 2016: 980–5. [PubMed: 26797211]

Kushner T, Chappell C, Kim A. Testing for Hepatitis C in Pregnancy: the Time Has Come for Routine Rather than Risk-Based. Current Hepatology Reports. 2019;18:206–15. [PubMed: 31890461]

Lapa D, Garbuglia A, Capobianchi M, Del Porto P. Hepatitis C Virus Genetic Variability, Human Immune Response, and Genome Polymorphisms: Which Is the Interplay?Cells. 2019;8(4):305.

Lopata S, McNeer E, Dudley Jet al.Hepatitis C testing among perinatally exposed infants. Pediatrics. 2020;145(3).

Mack C, Gonzalez-Peralta R, Gupta Net al.NASPGHAN Practice guidelines: Diagnosis and management of hepatitis c infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54:838–55. [PubMed: 22487950]

Mariné-Barjoan E, Berrébi A, Giordanengo Vet al.HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? AIDS2007;21(13):1811–1815. [PubMed: 17690581]

Ministério da Saúde. Boletim hepatites Virais Ministério da Saúde [Internet], 2020 [Available from: www.aids.gov.br

Ngo-Giang-Huong N, Jourdaina G, Sirirungsi W, Decker Let al.Human immunodeficiency virus-hepatitis C virus co-infection in pregnant women and perinatal transmission to infants in Thailand. Int J Infect Dis. 2010;14(7).

Orkin C, Jeffery-Smith A, Foster G, Tong C. Retrospective hepatitis C seroprevalence screening in the antenatal setting- should we be creening antenatal women?BMJ Open. 2016;6:e010661.

Owens D, Davidson K, Krist Aet al.Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2020;323:970–5. [PubMed: 32119076]

Padua L, Jhaveri R. Hepatitis C Mother-to-Child Transmission [Internet], 2016. Available from: http://neoreviews.aappublications.org/

Pembrey L, Newell M, Tovo Pet al.The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol. 2005;43(3):515–25. [PubMed: 16144064]

Resti M , Azzari C, Galli L et al. Italian Study Group on Mother-to-Infant Hepatitis C Virus Transmission. Maternal drug use is a preeminent risk factor for mother-to-child hepatitis C virus transmission: results from a multicenter study of 1372 mother-infant pairs. J Infect Dis. 2002;185(5):567–72. [PubMed: 11865412]

Ruiz-Linares A, Adhikari K, Acuña-Alonzo Vet al.Admixture in Latin America: geographic structure, phenotypic diversity and self-perception of ancestry based on 7,342 individuals. PLoS Genet2014;10(9):e1004572. [PubMed: 25254375]

Schillie S, Canary L, Koneru Aet al.Hepatitis C Virus in Women of Childbearing Age, Pregnant Women, and Children. Am J Prev Med. 2018111;55(5):633—41. [PubMed: 30342628]

Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm reports Morb Mortal Wkly report Recomm reports. 2020;69(2):1–17.

Selvapatt N, Ward T, Bailey Het al.Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. J Hepatol. 2015;63(4):797–804. [PubMed: 26024832]

Setiawan V, Stram D, Porcel Jet al.Prevalence of chronic liver disease and cirrhosis by underlying cause in underlying cause in understudied ethnic groups: the Multiethnic cohort. Hepatology2016;64:1969–1977. [PubMed: 27301913]

Silveira M, Victora C, Bernardo L, da Silva B, Matijasevich A, Barros F. Low birthweight and preterm birth: trends and inequalities in four population-based birth cohorts in Pelotas, Brazil, 1982–2015. International Journal of Epidemiology. 2018;48: i46–i53.

Squires J, Balistreri W. Hepatitis C virus infection in children and adolescents. Hepatol Commun. 2017;1(2):87–98. [PubMed: 29404447]

Stokkeland K, Ludvigsson J, Hultcrantz Ret al.Pregnancy outcome in more than 5000 births to women with viral hepatitis: a population-based cohort study in Sweden. Eur J Epidemiol. 2017;32(7):617–25. [PubMed: 28550648]

Tasillo A, Eftekhari Yazdi G, Nolen Set al.Short-Term Effects and Long-Term Cost-Effectiveness of Universal Hepatitis C Testing in Prenatal Care. Obstet Gynecol. 2019;133(2):289–300. [PubMed: 30633134]

Terrault N, Dodge J, Murphy Eet al.Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. Hepatology. 2013;57(3):881–9. [PubMed: 23175457]

World Health Organization. WHO guidelines. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. [Available from: 2018. https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1]

Yeganeh N, Watts H, Camarca Met al.Syphilis in HIV-infected mothers and infants: results from the NICHD/HPTN 040 study. Pediatr Infect Dis J. 2015;34:3.

Highlights:

- Risk-based HCV screening in pregnant women contribute to missed diagnoses of HCV.

- Inhaled drug use, HCV+ partnerships, 3 lifetime partners linked to HCV viremia.

- Infant clearance of HCV is associated with maternal genetic polymorphisms.

- Close follow-up of HCV pregnant women is imperative in Latin America.
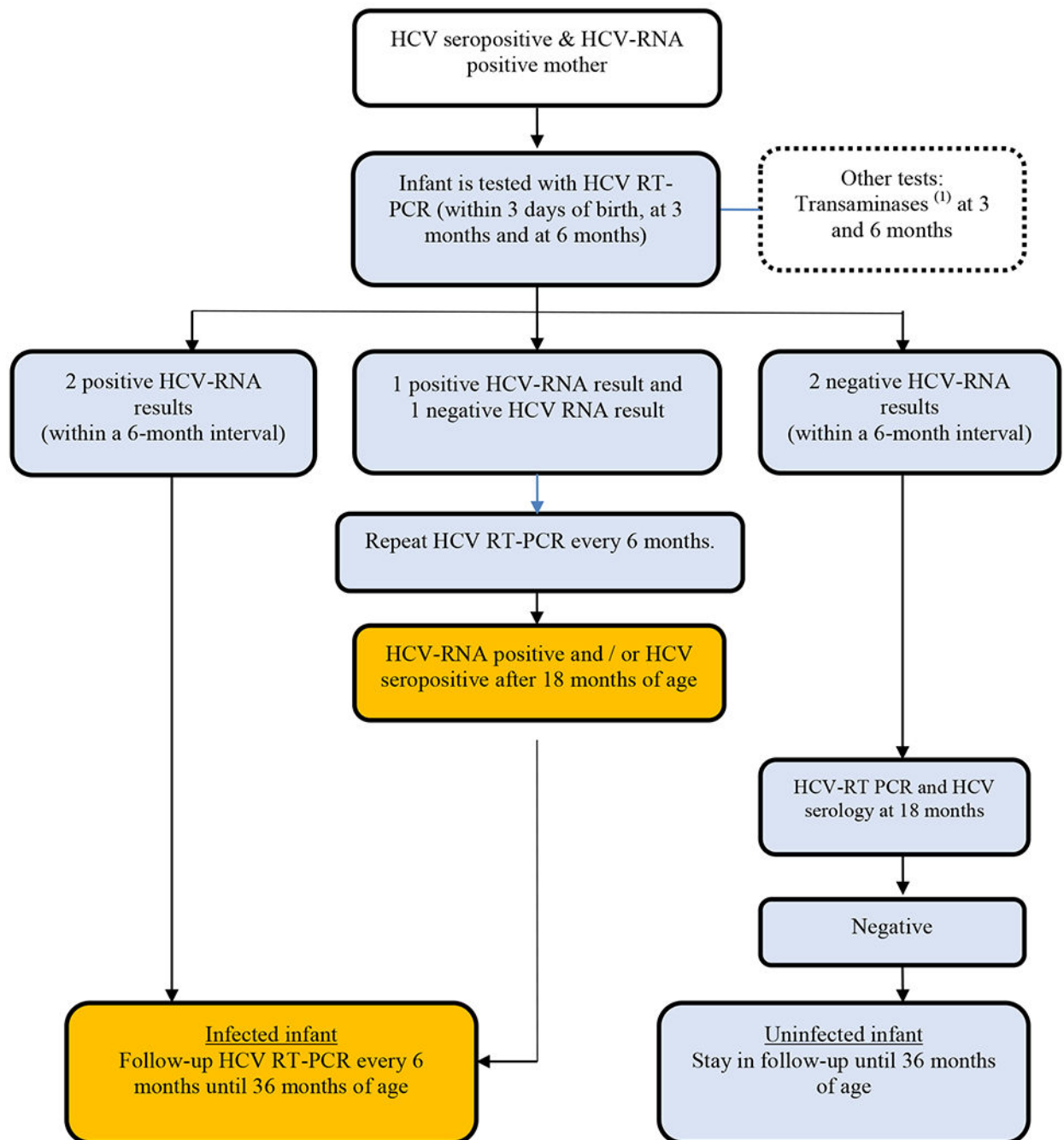
Figure 1. Algorithm for the evaluation of HCV-exposed infants

Schema of laboratory assessments performed during the follow-up of infants exposed to HCV.

(1) If an infant had detectable HCV RT-PCR results, transaminases were requested every 6 months up to 3 years of age.
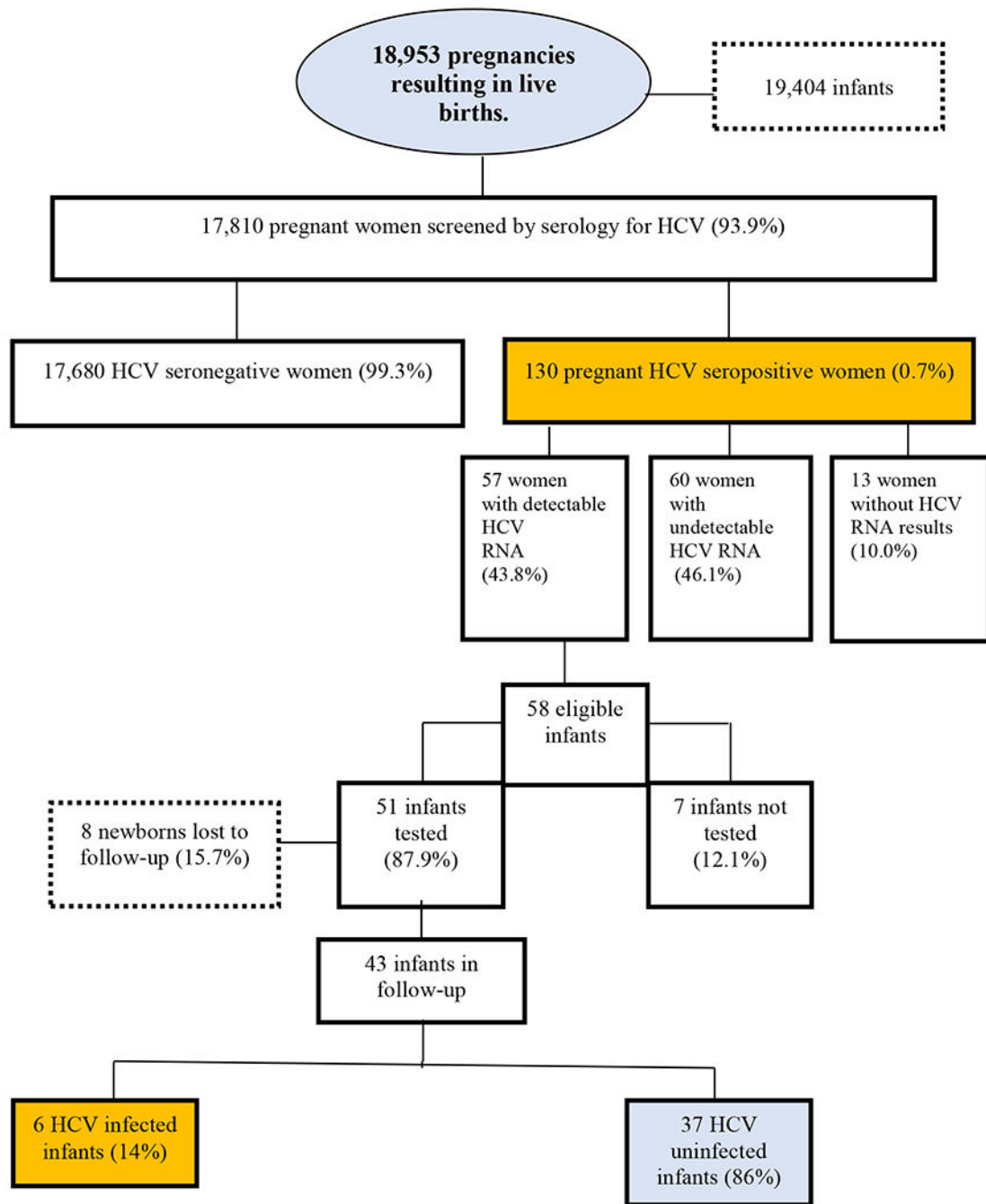
Figure 2. Patient selection flow chart

HCV screening at delivery between January 2014 to December 2018. (n=18,953 pregnancies and 19,404 live newborns)

(1) One twin pregnancy included in 58 eligible infants born to 57 unique HCV-seropositive mothers.

Table 1:

Demographic and obstetric characteristics of pregnant women with detectable versus undetectable HCV RNA

N=117	Total	Pregnant women with detectable HCV RNA	Pregnant women with undetectable HCV RNA	RR (95%CI)	p
	N (%)	N (%)	N (%)		
	117	57 (48.7)	60 (51.3)		
Age median (IQR) [1]	30.0 (16.0, 43.0)	32.0 (16.0, 43.0)	29.0 (16.0, 43.0)	1.04 (1.01,1.07)	**0.02**
Race					
White	75 (64.1)	37 (64.9)	38 (63.3)	1.04 (0.70,1.53)	1.00
Education					
Elementary School Level	65 (55.6)	33 (57.9)	32 (53.3)	1.10 (0.75,1.60)	0.71
Gravida					
Primigravida	25 (21.4)	7 (12.3)	18 (30.0)	0.52 (0.27,1.00)	**0.02**
Type of Delivery					
Vaginal	65 (55.6)	37 (64.9)	28 (46.7)	1.48 (0.99, 2.22)	0.05
Co-infections					
Syphilis	13 (11.1)	5 (8.8)	8 (13.3)	0.77 (0.38,1.57)	0.56
HIV	26 (22.2)	13 (22.8)	13 (21.7)	1.03 (0.67,1.60)	1.00
	N=26	N=13	N=13		
Detectable HIV viral load (> 40 copies /ml)[2]	13 (50.0)	7 (53.8)	6 (46.2)	0.86 (0.40,1.86)	1.00
CD4> 200 cells /μl	24 (92.3)	12 (92.3)	12 (92.3)	1.00 (0.24,4.23)	1.00

[1] Results expressed as mean ± standard deviation (amplitude). Poisson regression was used to compare means between groups.

[2] Results expressed as median (Q1; Q3) (amplitude).

Table 2:

Risk factors for maternal HCV exposure in HCV RNA positive and negative groups

N=117	Total	Pregnant women with detectable HCV RNA	Pregnant women with undetectable HCV RNA	RR (95%CI)	p
	N (%)	N (%)	N (%)		
	109	53	56		
Presence of HCV exposure risk factors	71 (65.1)	34 (64.2)	37 (66.1)	0.96 (0.64,1.43)	0.99
Injectable drugs	28/107 (26.2)	19/53 (35.8)	9/54 (16.7)	1.58 (1.10,2.26)	**0.03**
Acupuncture [1]	2/107 (1.9)	0/53 (0.0)	2/54 (3.7)	0.21 (0.01,4.30)	0.50
Inhalable / crack drugs	14/107 (13.1)	11/53 (20.8)	3/54 (5.6)	1.74 (1.22,2.48)	**0.02**
UDI[1]	3/107 (2.8)	3/53 (5.7)	0/54 (0.0)	6.75 (0.36,127.6)	0.12
Surgical treatment	45/106 (42.5)	18/52 (34.6)	27/54 (50.0)	0.72 (0.47,1.09)	0.16
Dental treatment	50/107 (46.7)	21/53 (39.6)	29/54 (53.7)	0.75 (0.50,1.11)	0.21
Tattoo or piercing	51/108 (47.2)	20/54 (37,0)	31/54 (57.4)	0.66 (0.44,0.98)	0.05
Blood transfusion	16/108 (14.8)	8/53 (15.1)	8/55 (14.5)	1.02 (0.60,1.74)	1.00
Sexual contact	13/91 (14.3)	11/43 (25.6)	2/48 (4.2)	2.06 (1.45,2.93)	**0.01**
3 sexual partners	35/106 (33.0)	25/53 (47.2)	10/53 (18.9)	1.81 (1.27,2.59)	**0.01**
Household contact	12/93 (12.9)	8/45 (17.8)	4/48 (8.3)	1.46 (0.92 – 2,32)	0.22
Occupational contact	4/92 (4.3)	3/45 (6.7)	1/47 (2.1)	1.57 (0.86 – 2,88)	0.36
Accident with biological material	2/104 (1.9)	1/50 (2.0)	1/54 (1.9)	1.04 (0.26 – 4,22)	1.00

[1] IDU = injecting drug use. Agresti correction was used to compare the groups (WinPepiversion 11.5).

Table 3:

HCV Mother-to--child transmission cases according to maternal and neonatal factors

N=6	Case A	Case B	Case C[1]	Case D	Case E	Case F
Maternal factors						
Date of delivery	08/01/2014	01/09/2016	12/14/2016	12/11/2015	01/09/2018	11/21/2018
Type of delivery	Vaginal	Vaginal	Cesarean	Cesarean	Vaginal	Cesarean
HCV viral load at delivery	2,108,206	28,744	2,053,219	31,422	4,836,313	690,433
Genotype	3	3	1a	1a	1a	3
Interleukin 28B RS 129/RS 809	CC/TT	CC/TT	TT/GG	Not done	Not done	Not done
Use of inhaled drugs or crack	Yes	No	Yes	No	No	No
Injection drug use	No	No	No	Yes	No	No
HBsAg	Non-reagent	Non-reagent	Non-reagent	Non-reagent	Non-reagent	Non-reagent
Anti-HIV	Non-reagent	Non-reagent	Reagent	Reagent	Non-reagent	Non-reagent
HIV viral load (cop/mL)	Not Infected	Not Infected	Not Infected	1,383	Not Infected	Not Infected
RPR	Non-reagent	Non-reagent	Non-reagent	Non-reagent	Non-reagent	Non-reagent
Neonatal factors						
Classification	Transient viremia	Transient viremia	Infected	Infected	Infected	Infected
Sex	F	M	M	F	M	F
Gestational age (months)	39	41	37,6	39	39	38
Birthweight (grams)	2,905	3,860	4,290	2,970	3,500	3,645
First detectable HCV viral load units	3,638,534	20,140	53,871	31,422	107	87,974
Age at collection of the first detectable HCV VL (months)	7	12	5	34	0	84
Age of spontaneous clearance (months)	35	18	NA	NA	NA	NA
Genotype	NA	NA	1b	1a	1a	3
Interleukin 28B rs12979860 / rs8099917	CC/TT	CT/TT	CT/GT	Not done	Not done	Not done
HCV serology (age in months)	Non-reagent (13.0)	Non-reagent (18.6)	Reagent (26.6)	Reagent (38.4)	Reagent (26.0)	Reagent (23.0)
Maximum ALT (age, months) [2]	21 (12)	31 (14)	344 (4)	88 (4)	53 (25)	32 (3)

[1] Mother with active TB infection, child received prophylactic isoniazid up to 3 months of life.

[2] Reference values: ALT (alanine transaminase) upper limit - Boys <60; Girls <55 (55)

NA = not applicable; VL=viral load

[*] Mother being treated for HIV but with irregular adherence