Published in final edited form as:

Pediatr Infect Dis J. 2018 December ; 37(12): 1267–1270. doi:10.1097/INF.0000000000002084.

Is there a Higher Risk of Mother-to-Child Transmission of HIV Among Pregnant Women with Perinatal HIV Infection?

Christopher J. Goodenough, MD, MPH[1], **Kunjal Patel, DSc, MPH**[2], **Russell B. Van Dyke, MD**[3], and **for the Pediatric HIV/AIDS Cohort Study (PHACS)**

[1]University of Texas Health Science Center at Houston, Houston, TX, USA

[2]Department of Epidemiology, Center for Biostatistics in AIDS Research (CBAR), Harvard T.H. Chan School of Public Health, Boston, MA, USA

[3]Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA, USA

Abstract

Cases of mother-to-child-transmission (MTCT) in the PHACS SMARTT study were identified from 2007–2015. Among 2123 births, 9 infants were HIV-infected, giving a MTCT rate of 0.5% (95% CI: 0.3–1.0%). PHIV mothers had a higher MTCT rate (1.1%, 95% CI: 0.3–4.3) than mothers without PHIV (0.4%, 95% CI: 0.2–1.0%), associated with a greater likelihood of detectable viral load at delivery.

Keywords

Human Immunodeficiency virus; pregnant women; perinatal infection; mother to child transmission; children

Introduction

In 2011, PEPFAR released a blueprint for achieving an AIDS-free generation, including the goal of eliminating new HIV infections among children by 2015.[1] While the rate of mother-to-child HIV transmission (MTCT) in the United States (US) has decreased dramatically with maternal combination antiretroviral therapy, elective cesarean when indicated, infant prophylaxis, and formula feeding, MTCT continues to occur.[2] Understanding the maternal

Corresponding author: Christopher J. Goodenough, MD, MPH, Department of Surgery, University of Texas Health Sciences Center – Houston, 6431 Fannin Street, MSB 4.331, Houston, TX 77030. christopher.j.goodenough@uth.tmc.edu; Phone: 978-996-0969.

The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

Author Contributions: All authors meet authorship criteria. Conception and design of the study: Van Dyke, Patel, and Acquisition of data: All authors. Analysis and interpretation of data: All authors
Drafting or revision of manuscript: All authors

Conflict of Interest
Christopher J Goodenough: No conflict
Russell B Van Dyke: No conflict.
Kunjal Patel: No conflict.

and obstetric factors associated with these cases will identify areas of focus for prevention efforts.[2]

In the US between 1988 and 1993, the number of infants infected through MTCT was estimated to be approximately 1630 per year.[3] New perinatal HIV infections (PHIV) have since become a rare event in the US and other resource-rich countries with report rates of MTCT of 2.2% or less.[2,4] The CDC reported that there were 47 infants infected through MTCT in the US in 2014.[5] In resource-rich settings, cases of perinatal HIV transmission are often associated with a failure of identification, treatment, or management of HIV-infected pregnant women, representing missed opportunities for prevention of MTCT. We report the rate of MTCT in the contemporary U.S. perinatal cohort of the Pediatric HIV/AIDS Cohort Study (PHACS) and describe those factors associated with perinatal HIV transmission. We were also particularly interested in our increasing population of pregnant women who themselves have PHIV. With improved perinatal and pediatric HIV care, PHIV-infected girls are now surviving into adolescence, and pregnancy among these women is becoming more common.[6] However, the maternal and infant outcomes of pregnancies among PHIV women are not well described, including the rate of MTCT for pregnant women with PHIV.

Methods

The Surveillance Monitoring of ART Toxicities Study (SMARTT) of PHACS is a US-based prospective cohort study of HIV-infected women and their infants designed to evaluate the safety to the child of *in-utero* exposure to maternal HIV infection and antiretroviral drugs (ARVs).[7] The Dynamic cohort of SMARTT opened in 2007 and enrolls ~250 mother-infant pairs annually at 22 clinical sites in the US including Puerto Rico. HIV-infected pregnant women between 23 weeks gestation and 72 hours following delivery are eligible. Infants determined to be HIV-infected are discontinued from the study. We present the outcomes of all 2123 live births occurring between the start of study enrollment in 2007 and June 30, 2015 (to allow for sufficient follow-up to determine the infection status of the infants).

Maternal pregnancy and delivery history, including CD4 and HIV viral load measurements, ARV use, sexually transmitted infections (STI), and type of delivery were abstracted from the medical record. The most complicated ARV regimen used during pregnancy was reported based on the following hierarchy: combination ARV (cARV) with entry/fusion/integrase inhibitors (EI/FI/INSTI) > cARV with protease inhibitors (PI) > cARV with non-nucleoside reverse transcriptase inhibitors (NNRTI) > cARV with only NRTIs > non-cARV. cARV was defined as the use of three or more ARVs. STIs of interest included gonorrhea, Chlamydia, trichomoniasis, syphilis, genital herpes, human papilloma virus, genital warts, and bacterial vaginosis. Maternal route of HIV acquisition, date of first prenatal care visit, and infant HIV status were obtained through chart abstraction or interview.

The rate of MTCT and the 95% confidence interval (CI) were calculated using the Poisson distribution and generalized estimating equations (GEE) to account for mothers with multiple infants on study. The proportion of mothers with a last viral load during pregnancy >1000 copies/mL and last CD4 count during pregnancy <200 cells/mm^3 were compared by mother's route of infection (perinatal vs. horizontal) using similar GEE models. These

factors were not compared by infant infection status due to the small number of infected infants. Maternal demographic, pregnancy and delivery characteristics, and HIV disease status were described by the infection status of the infant as well as the perinatal infection status of the mother.

Results

Included in this analysis are 2123 live-born infants delivered as of June 30, 2015. Of these, 1666 (78%) were subsequently reported to be uninfected (PHEU), 448 (21%) had undetermined HIV-infection status (183 lost-to-follow-up and 265 with indeterminate status at last study visit), and 9 infants were HIV infected, giving a rate of MTCT of 0.5% (95% confidence interval (CI): 0.2–1.0%) among those with defined infection status. (Supplemental Digital Content Table 1). The 9 infected infants were more likely to be female than the PHEU (78% vs. 49%, respectively) while the race and ethnicity of the two groups were similar (67% vs. 63% black/not-Hispanic and 33% vs. 31% Hispanic, respectively). Three of the 9 infected infants were preterm (<37 weeks gestation) and 1 was very preterm (<32 weeks gestation), compared to 19% and 2%, respectively, for PHEU infants.

Characteristics of transmitting and non-transmitting mothers are described in the Supplemental Digital Content Table 1. Their median age at delivery was 24.3 years and 28.5 years, respectively. The transmitting mothers were more likely to have their final viral load during pregnancy >1000 copies/mL (67% vs. 11%) while the proportion with a final CD4 count < 200 cells/mm^3 was similar in the two groups (11% vs. 9%). The proportion of transmitting and non-transmitting mothers with an STI during pregnancy was similar (44% and 42%, respectively).

Of the 2123 mother-infants pairs, 232 (10.9%) included a mother with PHIV (Table 1 and Supplemental Digital Content Table 2). The rate of MTCT was 1.1% (95% CI: 0.3–4.3) among mothers with PHIV and 0.4% (95% CI: 0.2–1.0) among those with horizontally-acquired HIV (HHIV). Mothers with PHIV were significantly more likely to have their final viral load during pregnancy >1000 copies/mL (19% vs. 9%, $p<0.001$) and their final CD4 count < 200 cells/mm^3 (19% vs. 8%, $p<0.001$). They also started prenatal care earlier, started ARVs earlier in pregnancy, were more likely to be receiving ARVs at the time of their first viral load in pregnancy, and received more complex ARV regimens, consistent with long-term use of ARVs.

Discussion

Our observed rate of MTCT of 0.5% is among the lowest reported among large cohorts of infected mothers. We acknowledge that our study population represents a select group of women who were managed at research sites and were receiving care at the time of study enrollment. Hence, they should represent the best possible outcomes.

We found that the rate of MTCT among women with PHIV was nearly 3 times that of those with HHIV. Many perinatally-infected individuals are reaching reproductive age, and, as we found, perinatally-infected mothers are more likely to have detectable viral loads and lower

CD4+ counts than HHIV mothers.[6] In addition, youth with PHIV have a high prevalence of resistant virus.[8] Thus, it is important to recognize that this emerging at-risk population, with lifelong HIV infection and prolonged use of ART, present with more advanced HIV disease and their care may be complicated by poor retention in care, poor ART adherence and ARV-resistant virus.

Advances in antiretroviral therapy and management of HIV-infected pregnant women have resulted in a declining rate of MTCT. A recent report from the state of Nevada demonstrated a significant decrease in the MTCT rate after implementation of an integrated program to prevent MTCT.[9] Their program focused on evaluating current practices and identifying gaps in performance, which were addressed with specific interventions designed to increase access to prenatal care, receipt of prenatal and perinatal ARVs, and appropriate use of cesarean section. As a result of these interventions, the MTCT rate decreased from 23% to 0%. These results suggest that MTCT can be eliminated in resource-rich countries with the identification of populations at increased risk of transmission and addressing interventions to prevent transmission.[10]

Cases of MTCT represent missed opportunities for prevention. A recent report of 27 cases of MTCT found that only 3 mothers had an undetectable HIV-1 viral load at delivery.[11] In our cohort, maternal viral load >1000 copies/mL at delivery was the principal risk factor for MTCT and was more than twice as likely among those with PHIV. This highlights the importance of achieving virologic suppression during pregnancy.[12] Pregnant women with PHIV warrant particular attention to achieve HIV viral load suppression and maintenance of CD4+ counts through the early initiation of ARVs during pregnancy and reinforcing adherence to ARVs.

A limitation of this study is that 448 infants (21%) had unknown HIV infection status. Assuming that the MTCT rate was the same for those with unknown status as for those with known status, then the overall MTCT rate would remain 0.5% (11/2123). The MTCT rate by maternal route of infection in unlikely to differ between those with and without known infant infection status.

In conclusion, we report an overall MTCT rate of 0.5%. The rate of MTCT may be higher among pregnant women with PHIV, due in part to a greater likelihood of having a detectable viral load at delivery, the strongest predictor of transmission.[12] Efforts to decrease rates of transmission should focus on viral suppression during pregnancy, and women with PHIV warrant particular attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National

Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigators: Kenneth Rich, Ellen Chadwick; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2015, in alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; **Baylor College of Medicine**: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris; **Bronx Lebanon Hospital Center:** Murli Purswani, Emma Stuard, Anna Cintron; **Children's Diagnostic & Treatment Center**: Ana Puga, Dia Cooley, Patricia A. Garvie, James Blood; **New York University School of Medicine**: William Borkowsky, Sandra Deygoo,Marsha Vasserman; **Rutgers - New Jersey Medical School:** Arry Dieudonne, Linda Bettica; **St. Jude Children's Research Hospital**: Katherine Knapp, Kim Allison, Megan Wilkins; **San Juan Hospital/Department of Pediatrics:** Midnela Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; **SUNY Downstate Medical Center**: Stephan Kohlhoff, Ava Dennie, Susan Bewley; **Tulane University School of Medicine**: Russell Van Dyke, Karen Craig, Patricia Sirois; **University of Alabama, Birmingham**: Marilyn Crain, Paige Hickman, Dan Marullo; **University of California, San Diego**: Stephen A. Spector, Kim Norris, Sharon Nichols; **University of Colorado, Denver:** Elizabeth McFarland, Carrie Chambers, Jenna Wallace, Emily Barr; **University of Florida, Center for HIV/AIDS Research, Education and Service:** Mobeen Rathore, Kristi Stowers, Saniyyah Mahmoudi, Ann Usitalo; **University of Illinois, Chicago:** Karen Hayani, Kenneth Rich, Lourdes Richardson, Renee Smith; **University of Miami:** Gwendolyn Scott, Sady Dominguez, Anai Cuadra; **University of Southern California:** Toni Frederick, Mariam Davtyan, Guadalupe Morales-Avendano; **University of Puerto Rico School of Medicine, Medical Science Campus**: Zoe M. Rodriguez, Ibet Heyer, Nydia Scalley Trifilio.

Funding

This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

References

1. [Accessed March 3, 2016] PEPFAR blueprint: Creating an AIDS-free generation. The Office of the Global AIDS Coordinator. 2012. http://www.pepfar.gov/documents/organization/201386.pdf
2. Whitmore SK, Taylor AW, Espinoza L, Shouse RL, Lampe MA, Nesheim S. Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. Pediatrics. 2012; 129(1):e74–81. [PubMed: 22144694]
3. Davis SF, Byers RH Jr, Lindegren ML, Caldwell MB, Karon JM, Gwinn M. Prevalence and incidence of vertically acquired HIV infection in the United States. Jama. 1995; 274(12):952–955. [PubMed: 7674525]
4. Peters H, Francis K, Sconza R, et al. UK Mother-to-Child HIV Transmission Rates Continue to Decline: 2012–2014. Clin Infect Dis. 2017; 64(4):527–528. [PubMed: 28174911]
5. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2015. HIV Surveillance Supplemental Report. 2017; 22 [Accessed October 18, 2017]
6. Munjal I, Dobroszycki J, Fakioglu E, et al. Impact of HIV-1 infection and pregnancy on maternal health: comparison between perinatally and behaviorally infected young women. Adolescent health, medicine and therapeutics. 2013; 4:51–58.

7. Griner R, Williams PL, Read JS, et al. In utero and postnatal exposure to antiretrovirals among HIV-exposed but uninfected children in the United States. AIDS Patient Care STDS. 2011; 25(7):385–394. [PubMed: 21992592]

8. Van Dyke RB, Patel K, Kagan RM, et al. Antiretroviral Drug Resistance Among Children and Youth in the United States With Perinatal HIV. Clin Infect Dis. 2016

9. Ezeanolue EE, Pharr JR, Hunt A, Patel D, Jackson D. Why are Children Still Being Infected with HIV? Impact of an Integrated Public Health and Clinical Practice Intervention on Mother-to-Child HIV Transmission in Las Vegas, Nevada, 2007–2012. Annals of medical and health sciences research. 2015; 5(4):253–259. [PubMed: 26229713]

10. Nesheim S, Taylor A, Lampe MA, et al. A Framework for Elimination of Perinatal Transmission of HIV in the United States. Pediatrics. 2012; 130(4):738–744. [PubMed: 22945404]

11. Camacho-Gonzalez AF, Kingbo MH, Boylan A, Eckard AR, Chahroudi A, Chakraborty R. Missed opportunities for prevention of mother-to-child transmission in the United States. Aids. 2015; 29(12):1511–1515. [PubMed: 26244391]

12. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. Aids. 2014; 28(7):1049–1057. [PubMed: 24566097]

Table 1

Maternal and Infant Characteristics by Maternal Route of HIV Acquisition

Characteristic	Total (N=2123)	PHIV+ (N=232)	HHIV+ (N=1646)	Missing (N=245)
Maternal age at delivery (years), Median (IQR)	28.4 (23.8, 33.1)	23.0 (20.5, 27.3)	29.3 (24.9, 33.7)	27.5 (23.0, 33.2)
Missing, N (%)	81 (4)	13 (6)	62 (4)	6 (2)
Trimester of first prenatal care visit				
1	1039 (49)	144 (62)	877 (53)	18 (7)
2	447 (21)	53 (23)	378 (23)	16 (7)
3	55 (3)	3 (1)	47 (3)	5 (2)
No prenatal care/Missing	582 (27)	32 (14)	344 (21)	206 (84)
1st viral load (copies/mL) during pregnancy				
>1000 copies/mL, N (%)	1034 (49)	115 (50)	784 (48)	135 (55)
On ARVs at measure, N (%)	1060 (50)	153 (66)	800 (49)	107 (44)
Missing VL, N (%)	34 (2)	1 (0)	21 (1)	12 (5)
Missing ARV at time of VL, N (%)	42 (2)	5 (2)	33 (2)	4 (2)
Last viral load (copies/mL) during pregnancy				
>1000 copies/mL, N (%)	241 (11)	45 (19)	153 (9)	43 (18)
On ARVs at measure, N (%)	1994 (94)	221 (95)	1554 (94)	219 (89)
Missing, N (%)	34 (2)	1 (0)	21 (1)	12 (5)
Missing ARV at time of VL, N (%)	42 (2)	5 (2)	33 (2)	4 (2)
1st CD4 (cells/mm^3) during pregnancy				
<200, N (%)	282 (13)	51 (22)	192 (12)	39 (16)
200–350, N (%)	458 (22)	49 (21)	347 (21)	62 (25)
351–500, N (%)	436 (21)	44 (19)	340 (21)	52 (21)
>500, N (%)	901 (42)	85 (37)	737 (45)	79 (32)
Missing, N (%)	44 (2)	3 (1)	28 (2)	13 (5)
Last CD4 (cells/mm^3) during pregnancy				
<200, N (%)	208 (10)	45 (19)	130 (8)	33 (13)
200-350, N (%)	358 (17)	47 (20)	271 (16)	40 (16)

Characteristic	Total (N=2123)	PHIV+ (N=232)	HHIV+ (N=1646)	Missing (N=245)
351–500, N (%)	526 (25)	43 (19)	419 (25)	64 (26)
>500, N (%)	985 (46)	94 (41)	796 (48)	95 (39)
Missing, N (%)	44 (2)	3 (1)	28 (2)	13 (5)
ARV regimen during pregnancy, N (%)				
None	23 (1)	3 (1)	15 (1)	5 (2)
Non-cART	12 (1)	3 (1)	6 (0)	3 (1)
cART with only NRTIs	157 (7)	6 (3)	122 (7)	29 (12)
cART with NNRTI	160 (8)	15 (6)	140 (9)	5 (2)
cART with PI	1509 (71)	152 (66)	1173 (71)	184 (75)
cART with EI/FI/INSTI	215 (10)	48 (21)	156 (9)	11 (4)
Missing	47 (2)	5 (2)	34 (2)	8 (3)
Gestational age starting ARV, (weeks) Median (IQR)	11.9 (0, 18.9)	0 (0, 15.0)	11.9 (0, 18.7)	15.6 (4.4, 22.7)
Duration of ARV use during pregnancy (weeks), Median (IQR)	25.7 (18.3, 36.7)	33.0 (22.1, 37.7)	25.6 (18.7, 36.7)	21.1 (14.4, 31.1)
Infant HIV infection status, N (%)				
PHIV+	9 (0.4)	2 (0.9)	6 (0.4)	1 (0.4)
PHEU	1666 (78)	184 (79)	1392 (85)	90 (37)
Indeterminate	448 (21)	46 (20)	248 (15)	154 (63)
Rate of MTCT among those with known outcome (%, 95% CI)[1]	0.5 (0.3, 1.0)	1.1 (0.3, 4.3)	0.4 (0.2, 1.0)	1.1 (0.2, 7.7)

[1] Confidence intervals calculated using generalized estimating equations (GEE) to account for mothers with multiple infants on study.

PHIV+: perinatally HIV-infected, HHIV+: horizontally HIV-infected, PHEU: perinatally HIV-exposed and uninfected, ARV: antiretroviral drug, cART: combination antiretroviral regimen, EI: entry inhibitor, FI: fusion inhibitor, INSTI: integrase inhibitor, PI: protease inhibitor, NNRTI: nucleoside reverse transcriptase inhibitor, NRTI: nucleoside/tide reverse transcriptase inhibitor.