Congenital Cytomegalovirus and HIV Perinatal Transmission

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Background: Congenital cytomegalovirus (CMV) infection (cCMV) is an important cause of hearing loss and cognitive impairment. Prior studies suggest that HIV-exposed children are at higher risk of acquiring cCMV. We assessed the presence, magnitude and risk factors associated with cCMV among infants born to HIV-infected women, who were not receiving antiretrovirals during pregnancy.

Methods: cCMV and urinary CMV load were determined in a cohort of infants born to HIV-infected women not receiving antiretrovirals during pregnancy. Neonatal urines obtained at birth were tested for CMV DNA by qualitative and reflex quantitative real-time polymerase chain reaction.

Results: Urine specimens were available for 992 (58.9%) of 1684 infants; 64 (6.5%) were CMV-positive. Mean CMV load (VL) was 470,276 copies/ml (range: < 200–2,000,000 copies/ml). Among 89 HIV-infected infants, 16 (18%) had cCMV versus 42 (4.9%) of 858 HIV-exposed, uninfected infants ($P < 0.0001$). cCMV was present in 23.2% of infants with *in utero* and 9.1% infants with intrapartum HIV infection ($P < 0.0001$). Rates of cCMV among HIV-infected infants were 4-fold greater (adjusted OR, 4.4; 95% CI: 2.3–8.2) and 6-fold greater among HIV *in utero*–infected infants (adjusted OR, 6; 95% CI: 3–12.1) compared with HIV-exposed, uninfected infants. cCMV was not associated with mode of delivery, gestational age, Apgar scores, 6-month infant mortality, maternal age, race/ethnicity, HIV viral load or CD4 count. Primary cCMV risk factors included infant HIV-infection, particularly *in utero* infection.

Conclusion: High rates of cCMV with high urinary CMV VL were observed in HIV-exposed infants. *In utero* HIV infection appears to be a major risk factor for cCMV in infants whose mothers have not received combination antiretroviral therapy in pregnancy.

Key words: congenital CMV, HIV MTCT, HIV perinatal transmission

(*Pediatr Infect Dis J* 2018;37:1016–1021)

Cytomegalovirus (CMV) is a significant cause of congenital infections worldwide. In the United States and other industrialized countries, congenital CMV (cCMV) affects ≤ 1% of all newborns and accounts for over 40,000 neonatal infections per year.[1,2] In resource-limited countries, where maternal CMV seropositivity rates are higher and there have been limited data on congenital CMV infection (cCMV) rates, the problem of cCMV may be even more widespread.[1,3,4] cCMV's importance and potential clinical sequelae should not be underestimated. Approximately, 10–15% of congenitally infected infants have symptomatic disease that may progress to severe neurodevelopmental delays and sensorineural hearing loss.[1,5–7] Furthermore, approximately 5–17% of asymptomatic congenitally infected infants may also develop clinical findings with later disease progression.[8–10]

Earlier studies have indicated that cCMV may be more common among HIV-exposed infants (2–7%) and among HIV-infected infants (4–26%).[11–15] These findings have particular relevance for

Accepted for publication November 13, 2017.

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Clinical Trials Registration: NCT00099359.

The content, conclusions and opinions expressed in this article are those of the authors and do not necessarily represent those of the National Institutes of Health, the U.S. Department of Health and Human Services or the U.S. Department of State, affiliated universities, programs or companies.

Change of Author Affiliations: Lynne Mofenson, MD, has retired from service at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, but is currently working with the Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC. D. Heather Watts was previously at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, but is currently at the Office of the Global AIDS Coordinator, U.S. Department of State, Washington D.C.

The NICHD HPTN 040 study was supported by NICHD Contract # HHSN267200800001C (NICHD Control # N01-HD-8-0001) and U01 AI047986 (Brazilian AIDS Prevention Trials International Network), NIAID/ NIH. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) U01 AI068632, UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) AI068632. The original parent study was supported in part by Boehringer Ingelheim Pharmaceuticals Inc. and GlaxoSmithKline, on behalf of ViiV Healthcare. Support was also provided by the UCLA Children's Discovery and Innovation Institute through the Harry Winston Fellowship Award, the UCLA AIDS Institute, the UCLA Center for AIDS Research (CFAR) NIH/ NIAID AI02869 and AI28697, and the UCLA Pediatric AIDS Coalition.

The authors have no funding or conflicts of interest to disclose.

Prior Presentations: Nielsen-Saines K for the NICHD HPTN 040 Study Team. Increased CMV Co-Infection with *In Utero*-Acquired HIV-1. Oral abstract 2695.8. *2013 Pediatric Academic Society Meetings*. Washington, D.C., May 4–7, 2013.

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ISSN: 0891-3668/18/3710-1016

DOI: 10.1097/INF.0000000000001975

HIV-infected infants, as they are more likely to have symptomatic cCMV, and cCMV may accelerate HIV disease progression.[11,12,14,16,17]

To investigate these issues further, we performed a study using data and specimens from the National Institute of Child Health and Human Development (NICHD) HIV Prevention Trials Network (HPTN) 040 perinatal clinical trial cohort of HIV-exposed infants. The primary objective of this substudy was to determine the rate of CMV coinfection among HIV-exposed infants. Additional secondary objectives included comparing rates of cCMV among HIV-exposed, uninfected and HIV-infected infants (HIV acquired either *in utero* or *intrapartum*), determining predictors of cCMV, and evaluating mortality rates among infants with cCMV.

METHODS

Study Design

This was a substudy of the NICHD HPTN 040 trial, also known as the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT P1043) NICHD/HPTN 040 (or P1043), a phase 3, randomized, open-label, multicenter study that evaluated the efficacy, safety and tolerance of 3 different infant antiretroviral regimens for the prevention of intrapartum HIV transmission to infants born to HIV-infected pregnant women, who had not received antiretroviral drugs during pregnancy.[18] The study enrolled 1684 HIV-infected pregnant women diagnosed with HIV infection at the time of labor and delivery. All women provided written informed consent. Enrollment occurred at multiple sites in Brazil, South Africa, Argentina and the United States. Infants < 32 weeks of gestational age were excluded from the study.

Maternal plasma HIV RNA levels and CD4+ T-lymphocyte subsets were obtained at the time of labor and delivery. The primary endpoint of the parent study was HIV infection status at 3 months of age. Infants were followed until 6 months of age for safety and toxicity monitoring in the parent study.

HIV Diagnosis

HIV DNA polymerase chain reaction (PCR) (Roche Molecular Systems Inc., Basel, Switzerland) was performed on infant blood specimens within 48 hours of birth and at 10–14 days, 4–6 weeks, 3 months and 6 months of age. Repeat HIV DNA PCR testing was performed to confirm a positive result. Diagnosis of infant HIV infection required 2 positive HIV DNA PCR test results on separate specimens. Infants with a positive HIV DNA PCR test result at birth and positive results on repeat testing were classified as having *in utero* HIV infection. Infants with a negative HIV DNA PCR result at birth and a positive HIV DNA PCR result on subsequent testing were classified as having *intrapartum* HIV infection. All HIV-exposed infants, who were enrolled in the study, were exclusively formula fed.

Specimen Collection and CMV Testing

The presence of cCMV was evaluated in NICHD HPTN 040's population of HIV-exposed infants. cCMV and magnitude of urinary viral load was determined in HIV-uninfected, HIV-*in utero* infected and HIV-*intrapartum* infected infants. Stored neonatal urine samples were collected within 48 hours of birth and frozen at – 80°C and stored at study sites. Infant urines were tested by qualitative real-time PCR for CMV DNA (FOCUS Diagnostics CMV Analyte Specific Reagent) with quantification of positive specimens. Infants with detectable CMV in the urine in the first 48 hours of life were diagnosed with cCMV.

Statistical Analysis

χ^2 or Fisher exact tests (when more than 25% of expected cell frequencies were less than 5) was used to compare differences in proportions between cCMV and CMV-uninfected infants.

Univariate and multivariable logistic regression analysis was used to examine the relationship of cCMV and HIV infection, demographic/geographic parameters, maternal characteristics and infant mortality. Covariates with a P value of less than 0.15 from univariate models were included in the initial multivariable model selection. All computations were done using SAS software v9.3 (Cary, NC).

Human Subjects

The study was approved by the institutional review boards and national ethics committees at each of the participating study sites.

RESULTS

Rates of Congenital CMV Infection Among HIV-exposed and HIV-infected Infants

Urine specimens were available for 992 (58.9%) of the 1684 infants in the original study. Of these infants, 64 (6.5%) were found to have urines with detectable CMV, with a mean virus load of 470,276 copies/ml (range: < 200–2,000,000 copies/ml). Eleven infants (17.2%) with cCMV had results that were too elevated to quantify (> 2,000,000 copies/ml), whereas approximately 8 (12.5%) had positive but low levels of detectable CMV (< 200 copies/ml). The mean CMV urine virus load was higher for HIV-infected infants (697,698 copies/ml) than that of HIV-uninfected infants (448,897 copies/ml), but these differences were not significant.

Among the 992 infants, 89 (9%) were HIV-infected, 858 (86.6%) were HIV-uninfected and 45 (4.5%) had unknown HIV status because of loss to follow-up or death before 3 months of age (the HIV diagnostic study endpoint) (Table 1). The rates of cCMV were significantly different when evaluated by infant HIV-status (P < 0.0001). The cCMV rate among HIV-infected infants was 18% (n = 16 of 89 infants) compared with only 4.9% (n = 42 of 858 infants) among HIV-exposed, uninfected infants and 13.3% (n = 6 of 45) of infants with unknown HIV status (Table 1). The difference was especially pronounced among HIV *in utero*–infected infants, where 23.2% (n = 13 of 56) had cCMV as opposed to 9.1% (n = 3 of 33) of HIV *intrapartum*-infected infants. Compared with HIV-exposed uninfected infants, the rate of cCMV in HIV-infected infants was more than 4-fold greater (OR, 4.3; 95% CI: 2.3–7.9) with multivariate logistic regression showing similar results adjusted OR (aOR) = 4.4 (95% CI: 2.3–8.2) after adjusting for study site country and maternal/race ethnicity and was almost 6-fold greater among HIV *in utero*–infected infants (OR, 5.9; 95% CI: 2.9–11.8), which was also similar in the adjusted analysis (aOR, 6; 95% CI: 3–12.1) after adjusting for study site country and maternal race/ethnicity (Tables 1, 2).

Deaths among infants ≤ 6 months of age occurred in 21 (2.1%) infants in the cohort with 2 deaths among 64 infants (3.1%) occurring in infants with cCMV (Table 1). Infant mortality was not associated with cCMV. However, further evaluation revealed that HIV-exposed infants who died or were lost to follow-up before the 3-month HIV diagnostic endpoint also appeared to be at increased risk of cCMV (OR, 2.25; 95% CI: 0.98–5.20), although this was marginally significant (P = 0.057).

Other Risk Factors for Congenital CMV Infection

Apart from differences noted in rates of cCMV by infant HIV status and infant HIV mode of acquisition, cCMV rates also differed by geographical location of our study sites (Table 1). Rates of cCMV ranged from 2% to 16.7% from top-enrolling sites in the

TABLE 1. Demographic, Infant Delivery and HIV-related Characteristics by Infant CMV Status (Congenital CMV Infection)

Maternal and Infant Characteristics	Overall (N = 992) (Column %)	Infant CMV-infected (+cCMV) (N = 64) n (Column %)	Infant CMV-uninfected (-cCMV) (N = 928) n (Column %)	Unadjusted OR (95% CI)	*P* Value
Maternal age (yr)					
Mean [SD]	26.5 [6.2]	26.3 [6.8]	26.5 [6.2]		
Median [min–max]	26 [13–47]	25 [14-41]	26 [13–47]		
13–24	407 (41.0)	31 (48.4)	376 (40.5)	1.14 (0.63–2.04)	0.66
25–29	289 (29.1)	13 (20.3)	276 (29.7)	0.65 (0.32–1.33)	0.24
30 and older	296 (29.8)	20 (31.3)	276 (29.7)	1.00	
Maternal race/ethnicity					
Black	419 (42.2)	26 (40.6)	393 (42.4)	1.35 (0.67–2.73)	0.40
Mixed	316 (31.9)	26 (40.6)	290 (31.3)	1.83 (0.90–3.70)	0.09
White/others	257 (25.9)	12 (18.8)	245 (26.4)	1.00	
Type of delivery					
Cesarean after rupture/timing unknown	130 (13.1)	8 (12.5)	122 (13.2)	0.92 (0.42–2.02)	0.83
Cesarean before rupture	276 (27.8)	17 (26.6)	259 (27.9)	0.92 (0.51–1.66)	0.78
Vaginal	586 (59.1)	39 (60.9)	547 (58.9)	1.00	
Infant gestational age (wk)					
36 or less	92 (9.3)	9 (14.1)	83 (8.9)	1.67 (0.79–3.49)	0.18
37 or more	900 (90.7)	55 (85.9)	845 (91.1)	1.00	
Apgar score at 5 minutes					
0–3	2 (0.2)	0 (0.0)	2 (0.2)	0.0 (0.0- I)	0.99
4–6	3 (0.3)	0 (0.0)	3 (0.4)	0.0 (0.0- I)	0.99
7–10	915 (99.5)	62 (100.0)	853 (99.4)	1.00	
HIV infant status					
Unknown	45 (4.5)	6 (9.4)	39 (4.2)	**3.07 (1.23–7.66)**	**0.02**
Positive	89 (9.0)	16 (25.0)	73 (7.9)	**4.26 (2.28–7.94)**	**< 0.0001**
Negative	858 (86.6)	42 (65.6)	816 (88.0)	1.00	
Infant HIV mode of acquisition					
Unknown	45 (4.5)	6 (9.4)	39 (4.2)	**3.07 (1.23–7.66)**	**0.02**
Intrapartum	33 (3.3)	3 (4.7)	30 (3.2)	1.94 (0.57–6.62)	0.29
In utero	56 (5.7)	13 (20.3)	43 (4.6)	**5.87 (2.94–11.8)**	**< 0.0001**
Negative	858 (86.6)	42 (65.6)	816 (88.0)	1.00	
Infant death					
No	971 (97.9)	62 (96.9)	909 (98.0)	0.65 (0.15–2.85)	0.57
Yes	21 (2.1)	2 (3.1)	19 (2.1)	1.00	
Maternal HIV viral load, copies/mL	—	—	—	1.29 (0.94–1.71)	0.11
Mean [SD]	63,682.2 [212,837]	59,058.3 [107,208]	64,002.1 [218,294]		
Median [min-max]	14,921 [0-3,055,766]	19,181 [195–452,741]	14,578 [0-3,055,766]		
> 100,000	117 (11.8)	8 (12.5)	109 (11.8)	2.06 (0.42–10.0)	0.37
10,000–99,999	459 (46.4)	36 (56.3)	423 (45.7)	2.38 (0.56–10.2)	0.24
1,000–9,999	310 (31.3)	18 (28.1)	292 (31.6)	1.73 (0.39–7.65)	0.47
400–999	45 (4.6)	0 (0.0)	45 (4.9)	0.0 (0.0- Inf)	0.98
0–399	58 (5.9)	2 (3.1)	56 (6.1)	1.00	
Maternal CD4 counts, cells/μL	—	—	—	1.02 (0.94–1.10)	0.71
Mean [SD]	515.3 [303.07]	528.9 [308.01]	514.3 [302.9]		
Median [min–max]	460 [12–2160]	486 [65–1377]	459 [12–2160]		
< 350	335 (34.4)	21 (33.3)	314 (34.5)	0.93 (0.52–1.66)	0.80
350–499	208 (21.4)	13 (20.6)	195 (21.4)	0.92 (0.47–1.82)	0.82
500+	431 (44.3)	29 (46.0)	402 (44.1)	1.00	
Study site					
United States	6 (0.6)	1 (1.6)	5 (0.5)	8.80 (0.77- 100)	0.08
Brazil	851 (85.8)	60 (93.8)	791 (85.2)	**3.34 (1.03–10.8)**	**0.04**
South Africa	135 (13.6)	3 (4.7)	132 (14.2)	1.00	

Bold font indicates values that are statistically significant (p-value <0.05).

All infants of HIV-infected women who had at least 1 available infant urine specimen were tested for CMV. N total differences for specific evaluated risk factors for congenital CMV reflect that data may not be available for every mother-infant pair.

Americas (primarily Brazil but also the United States) but were only 2.1–2.5% in South Africa. Compared with infants in South Africa, HIV-exposed infants in the United States (aOR, 15.6; 95% CI: 1.3–193) and Brazil (aOR, 5.1; 95% CI: 1.4–18.8) had the greatest risk of acquiring cCMV, although it should be noted that the number of U.S. infants was small (N = 7). In contrast, cCMV was not associated with other demographic and obstetric parameters including maternal age, race/ethnicity, mode of delivery, gestational age at delivery or infant Apgar scores. Furthermore, maternal HIV viral load and maternal CD4 count were also not significantly associated with an increased risk of cCMV (Table 1).

DISCUSSION

This study found high rates of congenital CMV infection (cCMV) in HIV-exposed infants, whose mothers were not receiving antiretroviral drugs in pregnancy due to late detection of HIV status resulting from delayed presentation to care. The rates of cCMV

TABLE 2. Adjusted Relationship of cCMV with Potential Risk Factors

Maternal and Infant Risk Factors	Congenital CMV Infection (cCMV)	
	aOR (95% CI)	*P* Value
Infant HIV status		
Unknown	**5.52 (2.03–15.0)**	**0.001**
HIV positive	**4.37 (2.32–8.22)**	**< 0.0001**
HIV negative	1.00	
Infant HIV mode of acquisition		
Unknown	**5.47 (2.01–14.9)**	**0.001**
Infected intrapartum	1.97 (0.56–6.91)	0.29
Infected in utero	**5.98 (2.96–12.1)**	**< 0.0001**
Negative	1.00	
Study site country		
United States	**15.6 (1.26- 193)**	**0.03**
Brazil	**5.14 (1.40–18.8)**	**0.01**
South Africa	1.00	
Maternal race/ethnicity		
Black	1.80 (0.86–3.76)	0.12
Mixed	1.99 (0.96–4.09)	0.06
White/other	1.00	

Bold font indicates values that are statistically significant (p-value <0.05).

were highest among HIV-infected infants, particularly among those with *in utero*–acquired HIV infection.

While CMV is among the most common etiologies of congenital infection worldwide, limited studies of cCMV have been reported from low and middle-income countries, particularly from HIV-infected pregnant women living in Latin America (Brazil) and sub-Saharan Africa (South Africa).[1–4,13,19–23] From studies of healthy pregnant women residing in industrialized nations,[24] we know that cCMV has been estimated to affect less than 1% of all newborn infants,[1,2] whereas studies from Brazil and sub-Saharan Africa have generally suggested higher cCMV rates between 1.1–2.9%[3,4,13] and 1.4–14%,[2,19–23] respectively, in spite of documented high maternal CMV seroprevalence.

Our study provides further evidence demonstrating the extent to which cCMV rates may be elevated among HIV-exposed infants and HIV-infected infants. In our study, cCMV rates for HIV-exposed uninfected infants (4.9%) and HIV-infected infants (18%), particularly for infants that acquired HIV *in utero* (23%), were more than 4–23 times higher than cCMV rates reported among healthy infants in high-income countries (typically ≤ 1%).[1,2] *In utero* HIV infection was the strongest predictor for cCMV (aOR, 6; 95% CI: 3–12.1).

Apart from 2 exceptions in smaller studies,[19,25] the cCMV rates among HIV-exposed, uninfected infants in our substudy were higher than those seen in the majority of other published studies ranging from 2.2% to 4.6% among studies of HIV-exposed infants in the United States, France, South Africa, Brazil and Thailand.[11,13–16,26–30] Among HIV-infected infants, cCMV rates correlated with those reported in other studies, which typically ranged from 4.3% to 21%;[11,12,14,16,29] but included some studies with rates as low as 0%[13] and others with rates as high as 26–29%.[31,32]

Our study was designed to clearly discern between HIV *in utero* and *intrapartum* infections, because the primary objective of the parent study was to evaluate the use of postnatal antiretroviral prophylaxis in the prevention of *intrapartum* HIV transmission. Postpartum HIV or CMV transmission by breast milk was not of concern as formula feeding was an entry criterion for study participation. This distinction in the timing of HIV transmission in a large cohort of HIV-exposed infants allowed us to further explore potential associations between different transplacental infections, in this case HIV and CMV, which is a unique feature of our study.

Based on prior epidemiologic studies from Brazil and sub-Saharan Africa, it is presumed that the majority of women in our substudy were CMV seropositive and demonstrated either CMV reinfection during pregnancy or reactivation, given the risk factors of pregnancy-induced maternal immunosuppression, especially in the third trimester, and immunosuppression from undiagnosed and untreated HIV.[26] One potential explanation for the relatively high rates of cCMV in our cohort of HIV-exposed uninfected and HIV-infected infants may be that women were not diagnosed with HIV until the time of labor and delivery and were not on highly active antiretroviral treatment (HAART) during pregnancy. Some studies have suggested that the use of HAART by pregnant HIV-infected women may reduce cCMV rates among their HIV-exposed infants by improving their immune status during pregnancy.[11,26–28,31]

The findings of our study also provide additional evidence highlighting the complex interrelationship "synergism" dynamics of HIV and CMV, suggesting that infection with one of these viruses may be a risk factor for infection with the other.[12,19,29,33,34] Both CMV and HIV have the ability to infect similar cells;[12,34–36] *in vitro* studies have demonstrated that both viruses have the capability to stimulate gene expression and viral replication in the other.[12,14,33–35,37–39] Other studies have also found that CMV may facilitate susceptibility to HIV infection by augmenting expression of Fc receptors, enhancing production of cytokines and other cellular products and activating sentinel players such as T cells and monocytes.[12,33,39,40] As with HIV and CMV, transplacental passage of 1 pathogen may facilitate passage of other concurrent pathogens, which has also been suggested for HIV and *Treponema pallidum* or even HIV and *Toxoplasma gondii*.[34,41–45] For instance, in NICHD HPTN 040, we saw a higher rate of congenital syphilis infection overall and also among *in utero* HIV-infected infants.[45]

While HIV infection in infants is a risk factor for cCMV, other predictors such as lower maternal CD4 count (particularly < 200 cells/mm^3)[11,27] and younger maternal age were not associated with an increased risk of cCMV in our study, although there have been a reported associations in other studies.[11] It is possible that younger maternal age (potentially associated with a higher likelihood of CMV primary infection) may not play a significant role in settings like ours, where CMV reactivation or reinfection are likely responsible for CMV transmission. In addition, while prior studies have suggested high rates of infant death with cCMV (nearly 27%), infant mortality was low in our study, and cCMV was not associated with an increased risk for infant death.[12,14,16,19]

Limitations

A major strength of our study was the relatively large sample size of HIV-exposed infants evaluated for cCMV compared with other studies, even though it was restricted to mother-infant pairs from our NICHD/HPTN 040 parent study[18] with available infant urines for specimen analysis; some sites were unable to collect urine specimens. Due to the lack of a comparison group of pregnant women without HIV, we could not evaluate cCMV rates in the general population and their risk factors for cCMV. Thus, our findings related to cCMV are only specific to infants born to HIV-infected pregnant women, who were not on HAART during pregnancy because of a late HIV diagnosis. In addition, because this was a secondary analysis, information on perinatal/postnatal CMV infection and symptomatic cCMV in infants with regard to rates of chorioretinitis, brain calcifications, microcephaly, other central nervous system anomalies or hearing loss were not collected and is beyond the scope of this study.

CONCLUSION

HIV-exposed infants are at significant risk for acquiring cCMV during pregnancy. HIV-infected infants, particularly those

who acquired HIV *in utero*, are at greatest risk for congenital CMV. CMV screening is an important component of a comprehensive evaluation needed for HIV-exposed infants, particularly among those born to women not on antiretrovirals during pregnancy.

ACKNOWLEDGMENTS

In addition to the authors, members of the NICHD/HPTN 040/PACTG 1043 protocol team include the following: Argentina, Buenos Aires- Foundation for Maternal and Infant Health (FUNDASAMIN): Edgardo Szyld, Silvia Marzo. Brazil, Belo Horizonte-Federal University of Minas Gerais: Flavia Faleiro Ferreira, Fabiana Kakehasi. Porto Alegre-Hospital Nossa Senhora da Conceicao: Rita Lira. Porto Alegre-Hospital Femina: Carla Franceschini de Fraga, Rita Lira. Porto Alegre-Irmandade da Santa Casa de Misericordia de Porto Alegre: Debora Fernandes Coelho, Alberto Sanseverino, Luis Carlos Ribeiro. Rio de Janeiro-Hospital dos Servidores do Estado: M. Leticia Santos Cruz, Ezequias Martins, Jacqueline Anita de Menezes, Luisa Andrea Torres Salgado. Rio de Janeiro-Hospital Geral de Nova Iguaçu: Ana Valeria Cordovil, Andréa Gouveia, Priscila Mazzucanti, Jorge Eurico Ribeiro. Ribeirao Preto -Universidade de Sao Paulo: Geraldo Duarte, Adriana Aparecida Tiraboschi Barbaro, Carolina Sales Vieira. Sao Paulo-Universidade Federal de Sao Paulo: Regina Succi. South Africa, Capetown-Stellenbosch University and Tygerberg Hospital: Mark Cotton, Jeanne Louw, Elke Maritz. Johannesburg-Perinatal HIV Research Unit, University of Witwatersrand and Chris Hani Baragwanath Hospital: Sarita Lalsab, Shini Legoete, James Alasdair McIntyre, Mandisa Nyati. United States, Baltimore-Johns Hopkins University: Allison Agwu, Jean Anderson, Joan Bess, Jonathan Ellen, Todd Noletto, Nancy Hutton. Gainesville-Shands Hospital: Carol Delany, Robert M. Lawrence. Jacksonville-University of Florida: Chas Griggs, Mobeen Rathore, Kathleen Thoma, Michelle Tucker. Long Beach- Miller Childrens Hospital: Audra Deveikis, Susan Marks. Newark-University Medical and Dental School of NJ: Linda Bettica, James M. Oleske. San Juan City-San Juan City Hospital: Midnela Acevedo Flores, Elvia Pérez. Oswaldo Cruz Foundation, Rio de Janeiro (FIOCRUZ): Ronaldo I. Moreira, Marilia Santini de Oliveira, Monica Derrico, Valéria Ribeiro, Thiago Torres e FIOTEC (Fundação para o Desenvolvimento Científico e Tecnológico). University of California-Davis: Ruth Dickover. Westat, Inc.: James Bethel, Emmanuel Aluko, Yolanda Bertucci, Jennifer Bryant, Patty Chen, Barbara Driver, Ruby Duston, Adriana Ferreira, Priya Guyadeen, Sarah Howell, Marsha Johnson, Linda Kaufman, Naomi Leshabane, Lilya Meyerson, Rita Patel, Lubima Petrova, Georgine Price, Susan Raitt, Scott Watson, Yiling Xu, Eunice Yu. Other protocol team members included Jennifer Read from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Elizabeth Smith and Sheryl Zwerski from the National Institute of Allergy and Infectious Diseases (NIAID). The authors thank the patients and their families who enrolled in this trial. We would like to acknowledge laboratory personnel who conducted all of the urine specimen preparation and shipment, Mary Ann Hausner and Jessica Liu. We also thank Marita McDonough and Lauren Petrella from Boehringer Ingelheim Pharmaceuticals and Helen Watson from GlaxoSmithKline (on behalf of ViiV Healthcare) for assistance with the donation of study drugs from their respective companies for the conduct of the parent study.

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