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High Rates of Congenital Cytomegalovirus Infection Linked With Maternal HIV Infection Among Neonatal Admissions at a Large Referral Center in Sub-Saharan Africa

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Background. Congenital cytomegalovirus (CMV) infection is the major infectious cause of birth defects and hearing loss globally. There is a growing recognition of the potential clinical impact of congenital CMV infections in high-seroprevalence settings.

Methods. A cross-sectional study of neonatal admissions at a large referral center in sub-Saharan Africa to determine the prevalence of both symptomatic and asymptomatic congenital CMV infection was performed. Real-time polymerase chain reaction was used to screen DNA-extracted sera, urine, and saliva, and an enzyme-linked immunosorbent assay was used to screen serum samples for anti-CMV immunoglobulin M. Multivariate binary logistic regression was used to identify risk factors associated with increased odds of congenital CMV infection.

Results. Congenital CMV was detected in 3.8% (15/395) of neonates. Among these infants, 6 of 15 (40%) presented with jaundice, 1 of whom also had petechiae. Congenital CMV infection was detected in 9 of 79 (11.4%; 95% confidence interval [CI], 6.1%–20.3%) neonates born to human immunodeficiency virus (HIV)–infected mothers, and both maternal HIV (odds ratio [OR], 6.661 [95% CI, 2.126–20.876], $P = .001$) and jaundice (OR, 5.701 [95% CI, 1.776–18.306], $P = .003$) were independently linked with significantly increased odds of congenital CMV infection.

Conclusions. Congenital and early infant CMV infections may have important consequences for child health in sub-Saharan Africa and other high HIV and CMV seroprevalence populations globally.

Keywords. congenital; CMV; HIV; Africa; neonate.

Congenital cytomegalovirus (CMV) infection occurs in 1% of births and is the leading infectious cause of birth defects globally [1]. The most damaging congenital CMV infections arise from maternal primary infections during pregnancy, which can result in mental retardation, and also account for 25% of all cases of hearing loss by 4 years of age [2]. Primary infection during pregnancy, and resultant severe congenital disease, is most common in industrialized countries where seroprevalence is lowest, with white ethnicity, higher socioeconomic status, and lower parity being the most prominent risk factors [3, 4]. Among non-white women of the same ethnic group, seroprevalence was higher in those born in their country of ethnic origin, with family structure and arrangements for childcare likely playing an important role [4].

In sub-Saharan Africa, it is well established that CMV seroprevalence is high among women of childbearing age [5, 6]; thus, the perceived wisdom has been

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that the prevalence or clinical impact of congenital CMV must be low, resulting primarily from maternal reinfections or reactivations [7, 8]. Three studies have evaluated the prevalence of congenital CMV infection in sub-Saharan Africa, giving rates of 1.4%–14% [9–11]. There were important methodological differences between these studies, but even at the lowest estimate, the prevalence of congenital CMV was comparable with that seen in Europe and North America [1]. With respect to outcomes in sub-Saharan Africa, an insufficient number of cases have been followed up, although from 54 cases, there have been 2 documented cases of severe neurological damage and 1 case of hearing loss [9]. One of the studies identified that lower parity, overcrowding, and placental malaria were risk factors linked with congenital CMV infection [11]. There is a growing appreciation of the possible importance of congenital CMV infection in high-seroprevalence populations [12], with large studies in Brazil confirming high rates of congenital CMV infection, linked with hearing loss [13, 14].

CMV infection is a defining opportunistic infection of AIDS progression in children [15], and there is increased prevalence of congenital CMV in children infected with human immunodeficiency virus (HIV) compared with those who are uninfected [16]. Congenital CMV was also more common in HIV-negative children born to HIV-infected mothers not on antiretroviral therapy (ART), compared to those on ART [17]. These US data are of great relevance to sub-Saharan Africa, which is the epicenter of the HIV pandemic, yet the prevalence and clinical impact of congenital and early childhood CMV infections in this region have been little studied.

In Zambia we have recently shown that CMV seroprevalence is high (83.5%) in healthy 18-month-old infants, and that these early infant CMV infections are linked with impaired physical development and in maternally HIV-exposed children lower psychomotor development [18], although it was not possible to delineate the relative contributions of congenital and early infant CMV infections. In the absence of any baseline data on the prevalence of congenital CMV in Zambia, we chose to first investigate a high morbidity patient group in whom there might be a raised probability of symptomatic congenital CMV. In this study, we evaluate the prevalence of congenital CMV infections, describe the clinical presentation, and identify risk factors among neonates admitted to the neonatal unit at the University Teaching Hospital, Lusaka, Zambia.

METHODS

Ethics Approval

The study was approved by the Biomedical Research Ethics Committee of the University of Zambia School of Medicine, Lusaka. The mothers/guardians of all participants gave written informed consent.

Setting

The study was based on the neonatal unit of the University Teaching Hospital, Zambia's national referral center. The unit has 2 intensive care wards and also a recovery area, and so receives a number of relatively stable neonates in addition to those who require intensive care.

Study Design and Aims

The design was that of a cross-sectional observational study with the aim of determining the prevalence of congenital CMV infection, describing the clinical presentation and identifying associated risk factors. All admitted neonates <3 weeks of age were eligible for inclusion in the study. We defined congenital CMV infection as detection of CMV DNA in any specimen (sera, saliva, or urine), or CMV immunoglobulin M (IgM) in sera, in the first 3 weeks of life. CMV culture facilities were not available at the study site. Whereas detection of CMV IgM alone in neonates is not definitive proof of congenital CMV infection, it was included here for research purposes, in addition to the 3 PCR assays, as there are few data from our region on anti-CMV IgM detection in neonates.

Patient Recruitment

There were a total of 1806 neonatal admissions during the study period (11 November 2012 to 25 April 2013). Our recruitment team approached 1003 mothers during this period. Neonates admitted during the weekend or on bank holidays were not recruited due to limited available resources. Consent was obtained from 395 mothers. At least 1 specimen was collected from each patient (Figure 1). Patient recruitment, clinical evaluation, mother's medical/obstetric history, and sample collection were undertaken by the study pediatrician and a University of Zambia–University College London Medical School research clinical officer.

DNA Extraction

Laboratory analysis was conducted in our dedicated 3-room molecular diagnostics laboratory. DNA from saliva and serum was extracted using the QIAamp DNA Mini Kit, and from urine using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's specifications. Extraction controls were included with every batch of 11 samples. DNA extraction quality was monitored on every 11th sample using a Nanodrop (Thermo Fisher Scientific, Waltham, Massachusetts).

Polymerase Chain Reaction

Samples were tested for presence of CMV DNA by real-time TaqMan polymerase chain reaction (PCR) assay, with a reported sensitivity and specificity of 93.1% and 96.6%, respectively [19]. Real-time PCR was carried out using a Rotor-Gene 6000 (Qiagen). CMV genomic DNA from isolate AD169 (kindly provided by Ursula Gompels, London School of Hygiene and Tropical

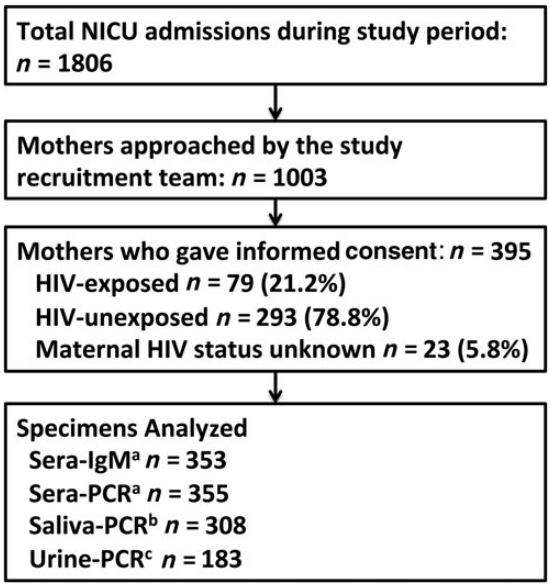

Figure 1. Flow diagram showing patient recruitment and sample collection. [a]Two sera specimens were minimal and used up in DNA extraction for polymerase chain reaction analysis. [b]Saliva collection vials and transport medium were not available at the start of the study. [c]Urine collection proved challenging with patients either being discharged or dying before a sample could be collected. Abbreviations: HIV, human immunodeficiency virus; IgM, immunoglobulin M; NICU, neonatal intensive care unit; PCR, polymerase chain reaction.

Medicine) was used as a positive control. The fidelity of the PCR enzyme and purity of the DNA extraction was also controlled through amplification of the housekeeping gene, β-actin (Table 1), from every 11th sample. Positive, negative (molecular grade water), reagent (no template) and extraction controls were included with each run. Oligonucleotide sequences and cycling conditions for both assays were as indicated (Table 1).

Enzyme-Linked Immunosorbent Assay

Serum collected from the neonates was tested for the presence of anti-CMV IgM using the ETI-CYTOK-M reverse PLUS enzyme-linked immunosorbent assay kit (Diasorin, Seluggia, Italy), according to the manufacturer's instructions. Positive, negative, and cutoff controls were included in all runs, and positive samples were retested to confirm initial positive result.

Statistical Analysis

Data analysis was undertaken using SPSS software, version 21 (IBM SPSS, Armonk, New York). Pearson χ^2test was used to compare congenital CMV prevalence between different specimen types, and also for the comparison of sex, gestational age, maternal HIV status, and neonatal mortality between the study group and the general neonatal inpatient population. Birth weight was compared using Mann-Whitney *U* test. Univariate and multivariate binary logistic regression was used to evaluate risk factors associated with congenital CMV infection.

RESULTS

Characteristics of the Study Population

Our aim was to recruit a representative sample from the inpatient neonatal population and so we collected sex, gestational age, birth weight, maternal HIV status, and mortality data from all admissions during June–July 2013, and compared this with our study group. This analysis does not account for seasonal variation but is a rough indication of the degree to which our sample was representative of the population (Table 2). Mortality data for the population indicate that some infants could not have been recruited onto the study, such as those who died shortly after admission and some who died en route to the neonatal unit. This could explain the underrepresentation of both mortalities and preterm neonates. Recruited neonates may also have received improved care. There was a trend for a selection bias toward male neonates, possibly due to ease of urine collection. The prevalence of maternal HIV infection did not differ significantly between the study group (21.2%) and the general population (20.9%) (Table 2).

Detection and Prevalence of Congenital CMV Infection

In the absence of facilities for culturing CMV, we chose a quadruple strategy defining congenital CMV infection as the

Table 1. Oligonucleotides and Cycling Conditions

Target	Oligo Name	Oligo Sequence (5′-3′)	Cycling Conditions
CMV UL83	UL83F	CAGTCCCGAGACMGTGAGAC	Hold: 95°C, 10 minutes Cycling: 95°C, 10 seconds; 58°C, 20 seconds; 72°C, 1 second (45 cycles)
	UL83R	TGAACATCCCCAGCATCAACG	
	UL83p	[HEX]TGCCACATCTGCTTGCCCGACGC[BHQ]	
β-actin	β-actinF	CACACTGTGCCCATCTACGA	Hold: 94°C, 3 minutes Cycling: 94°C, 20 seconds; 65°C, 50 seconds (45 cycles)
	β-actinR	CTCAGTGAGGATCTTCATGAGGTAGT	
	β-actinp	[FAM]ATGCCCTCCCCCATGCCATCCTGCGT[TAMRA]	

Abbreviation: CMV, Congenital cytomegalovirus.

Table 2. Descriptive Characteristics of the Study Group Compared With the Inpatient Neonatal Population

Characteristic	Study (November 2012–April 2013) No. (%)	Population (June + July 2013) No. (%)	Significance[a] *P* Value
Female sex	161 (41.7)	280 (47.9)	.056
Preterm birth	135 (35.9)	341 (58.5)	<.001
Birth weight, mean (SD)	2.6 (0.9)	2.2 (1.0)	.988[b]
Maternal HIV			
HIV positive	79 (21.2)	112 (20.9)	1
Mortality			
Died	65 (17.1)	321 (55.0)	<.001

Abbreviation: HIV, human immunodeficiency virus; SD, standard deviation.

[a] Pearson χ^2 test unless otherwise indicated.

[b] Mann-Whitney *U* test.

detection of CMV DNA in saliva, urine, or sera, or detection of IgM antibody in sera, in the first 3 weeks postpartum. This strategy helped compensate for the fact that congenital CMV infection does not always involve detectable virus shedding from any one site [20], with a previous study from Gambia showing a very poor correlation between CMV culture results from urine and saliva [9]. We detected congenital CMV infection in 3.8% (15/395) of neonatal admissions (Table 3). The correlation between the 4 different screens was low, with only 3 of 15 cases having >1 positive specimen. Urine gave the greatest yield (4.4% [8/183]), significantly greater than that of saliva (0.97% [3/308], $P = .017$) or serum IgM (0.8% [3/353], $P = .01$) but not significantly greater than that of serum PCR (1.7% [6/355], $P = .062$). A quantification standard to calculate CMV load was not available but by analyzing crude cycle threshold values, median viral loads were comparable between urine and serum samples, and possibly higher in saliva (Table 3).

Table 3. Detection and Prevalence of Congenital Cytomegalovirus Infection

Patient	PCR Saliva[a]	PCR Urine[a]	PCR Sera[a]	IgM Sera	Positives
4	NA	41.4	Negative	Negative	+
5	NA	Negative	Negative	Positive	+
9	NA	26.5	35.8	Negative	++
20	Negative	NA	29.5	Negative	+
23	NA	40.9	Negative	Negative	+
45	Negative	Negative	38.2	Negative	+
100	Negative	NA	Negative	Positive	+
143	Negative	38.2	Negative	Negative	+
227	14.9	Negative	Negative	Negative	+
245	7.7	30.2	40.7	Negative	+++
265	Negative	35.4	36.2	Positive	+++
298	NA	42.2	Negative	Negative	+
340	Negative	NA	37.0	Negative	+
376	38.8	NA	Negative	Negative	+
384	Negative	35.01	Negative	Negative	+
Prevalence	0.97% (3/308)[b]	4.4% (8/183)[b,c,d]	1.7% (6/355)[c]	0.8% (3/353)[d]	NA
Median Ct	14.9	36.8	36.6	NA	NA

Abbreviations: Ct, cycle threshold; IgM, immunoglobulin M; NA, not available; PCR, polymerase chain reaction.

[a] PCR positives indicated by Ct value.

[b] $P = .017$.

[c] $P = .062$.

[d] $P = .01$.

Factors Linked With Congenital CMV Infection

The prevalence of congenital CMV among neonates born to HIV-infected mothers was 11.4% (95% confidence interval [CI], 6.1%–20.3%; 9/79) compared to 2.1% (95% CI, .8%–4.6%; 6/293) in those born to HIV-uninfected mothers (Figure 2 and Table 4). Similarly, the prevalence of congenital CMV among neonates with jaundice was 10.5% (95% CI, 4.4%–22.2%; 6/57), compared to 2.5% (95% CI, 1.2%–5.1%; 8/317) in those without jaundice. Multivariate binary logistic regression confirmed that maternal HIV infection (odds ratio [OR], 6.661 [95% CI, 2.126–20.876], $P = .001$) and neonatal jaundice (OR, 5.701 [95% CI, 1.776–18.306], $P = .003$) were independently associated with significantly increased odds of congenital CMV infection (Table 4). These findings held when the 2 children in whom anti-CMV IgM alone was detected were coded as

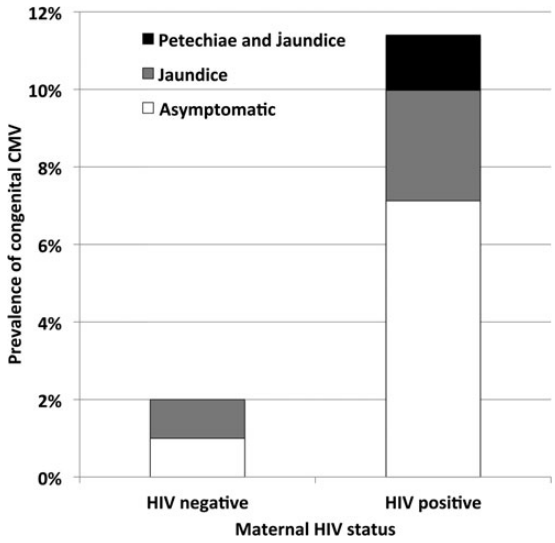

Figure 2. Stacked histogram showing prevalence of congenital cytomegalovirus stratified by maternal human immunodeficiency virus status and indicating symptomatic infections. Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus.

Table 4. Binary Logistic Regression Analysis

Variable	Congenital CMV Proportion (%) [95% CI]	Univariate Analysis OR [95% CI]	*P* value	Multivariate Analysis[a] OR [95% CI]	*P* value
Neonatal factors					
Birth weight, mean (SD)	2.5 (1.1)	0.864 [.489–1.526]	.615	1.341 [.684–2.629]	.393
Sex					
Male	9/225 (4.0%) [2.1%–7.4%]				
Female	6/161 (3.7%) [1.7%–7.9%]	0.929 [.324–2.664]	.891	0.908 [.284–2.902]	.870
Gestational age					
Term	9/241 (3.7%) [1.8%–7.2%]				
Preterm	6/135 (4.4%) [1.8%–9.8%]	1.199 [.417–3.444]	.736	0.715 [.221–2.309]	.575
Jaundice					
No	8/317 (2.5%) [1.2%–5.1%]				
Yes	6/57 (10.5%) [4.4%–22.2%]	4.544 [1.514–13.640]	.007	5.701 [1.776–18.306][b]	.003
Petechiae[c]					
No	13/373 (3.5%) [2.0%–6.0%]				
Yes	1/1 (100%) [5.5%–100%]	Not calculable		Not calculable	
Maternal factors					
Age	27 (25–32)	1.033 [.955–1.118]	.420	0.992 [.902–1.090]	.867
HIV status					
HIV uninfected	6/293 (2.1%) [.8%–4.6%]				
HIV infected	9/79 (11.4%) [6.1%–20.3%]	6.15 [2.119–17.849]	.001	6.661 [2.126–20.876][b]	.001
Education[d]					
None	0/5 (0%) [0%–53.7%]				
Primary	5/106 (4.7%) [1.8%–11.2%]				
Secondary	4/175 (2.3%) [.7%–6.1%]	0.473 [.124–1.8]	.272	0.588 [.148–2.343]	.452
Tertiary	3/49 (6.1%) [1.6%–17.9%]	1.317 [.302–5.748]	.714	1.373 [.225–8.389]	.731
Marital status					
Single	11/316 (3.5%) [1.8%–6.3%]				
Married	1/45 (2.2%) [0.1%–13.2%]	1.587 [.2–12.593]	.662	1.288 [.153–10.843]	.816
Mode of delivery					
SVD	11/277 (4.0%) [2.1%–7.2%]				
Cesarean	4/78 (5.1%) [1.7%–13.3%]	1.307 [.404–4.224]	.655	2.132 [.575–7.905]	.258

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HIV, human immunodeficiency virus; OR, odds ratio; SD, standard deviation; SVD, spontaneous vaginal delivery.

[a] Controlled for the effect of jaundice and maternal HIV status.

[b] Disregarding the 2 immunoglobulin M–positive cases that were negative by polymerase chain reaction, adjusted ORs were 6.768 [95% CI, 1.994–22.967], $P = .002$, for maternal HIV infection and 5.281 [95% CI, 1.517–18.387], $P = .009$, for jaundice.

[c] There was only 1 neonate with petechiae.

[d] Maternal education was analyzed with "primary" as the reference category. The 5 mothers with no formal education were excluded from the analysis.

negative (Table 4). Just 1 neonate presented with petechiae, and this was also 1 of the 15 cases of congenital CMV; hence, petechiae was more prevalent among congenital CMV cases than among noncongenital CMV cases (0% vs 7.1%, $P = .037$; data not shown). From partial data we did not see any link between congenital CMV and hemoglobin level, platelet count, aspartate aminotransferase, or alanine aminotransferase (data not shown).

Symptomatic Congenital CMV Infection and Mortality

The mortality rate of our study group was 17.1%. Maternal HIV infection and preterm birth were independently linked with mortality (data not shown), but congenital CMV infection was not linked with significantly increased odds of death (OR, 1.818 [95% CI, .560–5.899], $P = .319$; data not shown). Four of 15 (26.7%) neonates with congenital CMV died, compared with 61 of 366 (16.7%) of neonates without congenital CMV ($P = .242$, Fisher exact test). Six neonates with congenital CMV (40%) were admitted with a clinical presentation suggestive of symptomatic congenital CMV infection: 5 cases of jaundice and 1 case of jaundice with petechiae. Two of the neonates with jaundice died. The first was a term baby admitted with respiratory distress syndrome born to an HIV-negative mother. The second was a preterm baby of 1.5 kg, admitted due to prematurity and grunting, born to an HIV-infected mother. The remaining 9 neonates with congenital CMV, who did not present with symptoms, were admitted for a range of reasons including prematurity, respiratory distress, birth asphyxia, suspected sepsis, meconium aspiration, and macrosomia, none of which was linked with an increase in the odds of congenital CMV infection (data not shown).

DISCUSSION

There are 3 key findings from this study: (1) There was a high prevalence (3.8%) of congenital CMV on our neonatal unit; (2) symptoms associated with symptomatic congenital CMV were observed in up to 40% of cases, linked with mortality; and (3) this is the first demonstration of a strong association between maternal HIV infection and congenital CMV infection in a high HIV and CMV seroprevalence population in sub-Saharan Africa.

In Zambia, early infant CMV infections have been linked with impaired physical development and, in HIV-exposed children, impaired psychomotor development [18], although the degree to which congenital transmission of CMV might have contributed to these effects was not determined. With no baseline data on the prevalence of congenital CMV in Zambia, we chose to screen a high morbidity/high mortality inpatient group, to get the first indication of prevalence, to assess whether congenital CMV could cause symptomatic disease in this setting, and to identify risk factors linked with congenital CMV of possible use in the design of broader population-based studies.

We define congenital CMV as detection of viral DNA in infant saliva, urine, or sera, or detection of anti-CMV IgM in infant sera. Detection of IgM alone is not considered definitive proof of CMV infection, with false-positive results arising from cross-reactivity with other pathogens (regretfully, we did not have sufficient resources to screen for other congenital and neonatal infections) and false-negative results due to very young and/or immunocompromised neonates not mounting a detectable response to infection [21, 22]. For these reasons, the true prevalence of congenital CMV infection in our study group is most accurately represented by our PCR results (up to 4.4% in urine). Although our study group was not representative of the population, a prevalence ranging from 1% to 5% is confluent with the findings of 3 previous population-based studies assessing congenital CMV prevalence in sub-Saharan Africa. The first was from the Ivory Coast and dates back to 1978, where CMV was cultured from the urine of 1.4% (n = 2032) of healthy neonates in the first 12 hours postpartum [10]; 1.4% is a likely underestimate of the true prevalence in accordance with the current accepted definition of congenital CMV, which is the detection of virus within 3 weeks postpartum. There are then 2 studies on the prevalence of congenital CMV from Gambia The first, in 1991, cultured CMV from either the urine or saliva from 14% of healthy neonates (n = 184), with a strong discordance between saliva and urine detection, suggesting that screening just 1 specimen type might result in underestimates of prevalence [9]. Importantly, this study documented developmental defects and neurological damage in congenitally infected neonates. The second Gambian study detected CMV by PCR in the urine of 5.4% of healthy infants (n = 741) [11]. This study performed 1 year of follow-up, documenting more frequent health complaints in congenitally infected children, but did not identify any neurological deficits.

The broad discordance between specimen type (urine vs saliva vs serum samples) and assay type (serum PCR vs serum IgM) in our study and previous research [9] suggests that sites of viral shedding may vary, possibly influenced by time or frequency of maternal viral shedding during pregnancy, and that detection in 1 specimen alone should be considered a minimum estimate [20]. Future studies should screen multiple specimens until the long-term clinical impact of congenital CMV infections in sub-Saharan Africa is better understood. Our molecular analysis was undertaken in a dedicated molecular diagnostics suite, with rigorous controls, and we are confident that positive results indicate the detection of CMV DNA. To what degree they represent active infections that might be causing pathology requires larger longitudinal studies.

We observed symptoms possibly indicative of symptomatic congenital CMV infection in 40% (6/15) of cases, possibly

higher than studies from industrialized countries where clearly defined symptomatic infection is seen in 10%–15% of congenitally infected neonates [12], likely because we recruited admitted neonates. Two of the symptomatic patients died, with a point mortality rate of 33% (2/6). Taking into account the gross underrepresentation of early neonatal deaths in our cohort, it is possible that we did not capture some additional congenital CMV-associated deaths, which may occur in 9% of symptomatic cases in low-seroprevalence (CMV and HIV) settings [1]. This may also explain why we did not document other common symptoms such as neurological abnormalities, low birth weight, and hepatosplenomegaly [17]. The degree to which our results may inform on prevalence among healthy neonates cannot be determined, but even by the lowest estimates, our data and those from previous population-based studies in sub-Saharan Africa [9–11] suggest rates of congenital CMV infection at least as high as those seen in low-seroprevalence populations in industrialized countries, with isolated cases of neurological disease and hearing loss.

Studies from the United States have demonstrated that CMV shedding in the genital tract of HIV-infected women, and in the cervical fluid and peripheral blood mononuclear cells of pregnant HIV-infected women, correlates strongly with reduced CD4 [23, 24] and raised HIV load [25]. Immune suppression in HIV-infected pregnant women likely leads to increased incidence of reinfection or reactivation, or prolonged CMV viral shedding, lengthening the opportunity for congenital transmission. Other US studies have shown higher prevalence [15, 16, 26] and poorer outcomes [15] due to congenital CMV infection in HIV-infected and/or -exposed children and higher prevalence of congenital CMV in children born to HIV-infected mothers who have not initiated ART [17]. A study from Kenya detected CMV shedding in the genital tract of 59% of HIV-infected women [27], yet congenital CMV in the context of maternal HIV infection has not been previously studied in sub-Saharan Africa.

Here we show for the first time in the region that maternal HIV infection is strongly associated with congenital CMV infection, which is detectable in up to 10% of children born to HIV-infected mothers. The entry point for our study was admission of the neonate; hence, we did not test mothers antenatally and cannot determine the degree to which congenital infections were due to maternal reactivations or reinfections with multiple strains. HIV-exposed infants are known to suffer physical and mental developmental delay [28, 29], which in Zambia has been linked with CMV infection [18]. Importantly, the relationship between CMV and HIV appears to be bidirectional, with data from Thailand showing that congenital and postnatal CMV infections are strong independent correlates of mother-to-child transmission of HIV [30]. Congenital and/or early infant CMV infections may be an important contributing factor to mother-to-child transmission of HIV and developmental delay in HIV-infected and exposed African children, which must be investigated further through sufficiently powered longitudinal case-controlled studies.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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