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Birth Prevalence of Congenital CMV among Infants of HIV-infected Women on Prenatal Antiretroviral Prophylaxis in South Africa

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Summary: There is growing evidence that high maternal HIV seroprevalence could drive an excess burden of congenital CMV. We show for the first time a high prevalence of congenital CMV among HIV-exposed newborns in sub-Saharan Africa, despite universal prenatal antiretroviral prophylaxis.

Abstract

Background

A high rate of congenital CMV has been documented in HIV exposed infants in industrialized settings, both in pre- and post-HAART era. Only limited data on the birth prevalence of congenital CMV among infants of HIV-infected women on prenatal antiretroviral (ARV) prophylaxis are available from sub-Saharan Africa, despite a high prevalence of both infections. We evaluated the prevalence of congenital CMV in HIV-exposed infants in the Western Cape, South Africa.

Methods

HIV-infected mothers were recruited in the immediate postnatal period at a referral maternity hospital between April and October 2012. Maternal and infant clinical data and newborn saliva swabs were collected. Saliva swabs were assayed by real-time PCR for CMV. Data were analyzed using univariate and multivariate logistic regression analyses to determine specific demographic, maternal and newborn characteristics associated with congenital CMV.

Results

CMV was detected in 22/748 newborn saliva swabs (2.9%; 95% CI, 1. 9-4.4%). Overall, 96% of mothers used prenatal ARV prophylaxis (prenatal AZT 43.9%,

HAART 52.1%). Maternal age, gestational age, prematurity (< 37 weeks gestation), type of ARV prophylaxis, length of ARV prophylaxis, birth weight, small for gestational age and infant feeding choice were not significantly different between CMV-infected and uninfected infants. Maternal CD4 count less than 200 cells/μL during pregnancy was independently associated with congenital CMV (aOR 2.9; 95% CI, 1.2-7.3). A negative correlation between CMV viral load in saliva and maternal CD4 count was observed (r = -0.495, n = 22, p = 0.019).

Conclusions

The birth prevalence of congenital CMV was high despite prenatal ARV prophylaxis, and was associated with advanced maternal immunosuppression.

Background

Cytomegalovirus is a leading cause of congenital infections worldwide and a leading non-genetic cause of childhood hearing loss in the post-rubella vaccination era. The birth prevalence of congenital CMV in a population is associated with the proportion of mothers who are seropositive for CMV (1). In developing country settings with near-universal CMV seroimmunity, congenital CMV rates of 1-5% have been reported, compared with rates of 0.6–0.7% in industrialized nations (2-4).

HIV-infected mothers constitute a special subpopulation, in whom an increased frequency of in utero CMV transmission has been consistently documented in countries in Europe and the Americas. The birth prevalence of congenital CMV in these settings ranges from 4-26% among HIV infected newborns, to 1.2-5% in HIV exposed but uninfected (HIV-EU) infants (5-7). Maternal risk factors associated with in utero CMV transmission have not been systematically assessed, although an association with advanced maternal immunosuppression (CD4 <200 cells/μL), both in HIV-infected and uninfected infants, was documented in the French Perinatal Cohort (FPC) (6). HIV-infected and exposed infants who acquire CMV in the first 18 months of life have a higher risk of neurological morbidity (8, 9).

The impact of prenatal antiretroviral (ARV) prophylaxis, either prenatal AZT or highly active antiretroviral therapy (HAART), on congenital CMV transmission in HIV-infected women is unclear. In the FPC, a reduction in congenital CMV transmission rates to 1.2% in the HAART era, from 3.5% in the pre-HAART era, was observed among HIV-EU neonates (6). However, congenital CMV transmission rates remained

constant over time in two consecutive HIV-exposed birth cohorts in the U.S., in spite of increasing use of maternal prenatal HAART (10).

Data on congenital CMV infection among HIV-exposed infants in sub-Saharan Africa is limited. A study in Kenya, conducted on a small sample of infants born to HIV-infected women who used perinatal AZT, reported congenital CMV rates of 29% (n=15) and 6.3% (n=20) in HIV-infected and uninfected newborns, respectively (11). In addition, a recent study of high risk newborns admitted to a referral neonatal unit in Zambia documented a birth prevalence of congenital CMV of 3.8% (15/395) overall, and 11.4% (9/79) in those infants exposed to maternal HIV (12). As the HIV epidemic in sub-Saharan Africa disproportionately affects women of childbearing age, and antenatal HIV seroprevalence rates are stabilizing at alarming proportions in many countries, the sparsity of data on congenital CMV in these populations is concerning (13). We evaluated the prevalence of congenital CMV in a large sample of HIV-exposed newborns in South Africa.

Methods

Study population: HIV-exposed newborns were recruited from the postnatal wards of Mowbray Maternity Hospital (MMH), a secondary level referral hospital in the Western Cape Province of South Africa between April and October 2012. MMH serves the local Mowbray area as well as surrounding Midwife Obstetric Units offering subsidized healthcare for pregnant mothers and their babies in the region. Approximately a third of live-born infants (11000/35000) in 2012 in the Metropole West region of the Western Cape were born at MMH. Of the 11,000 babies born at

MMH, approximately 13% are HIV exposed. Approximately 95% of patients seen at MMH do not have access to private health care facilities. Overall, the patient population is representative of the general Western Cape population consisting of approximately 50% mixed race and 50% indigenous black African as well as an increasing number of African migrants/refugees. Maternal HIV status is ascertained prenatally by a rapid HIV test.

Study design and data collection: The study was carried out as an unlinked anonymous cross-sectional survey with convenience sampling. Mothers were eligible for the study if they were known to be HIV-infected, 18 years and older, less than 14 days of delivery, and living in the greater Cape Town area and had given written, informed consent. Eligible mothers were approached during Monday through Friday for participation in the study. Maternal age, CD4 count, date of CD4 count, type of prenatal ARV prophylaxis (none, intrapartum AZT and single dose NVP in labor only, prenatal AZT, HAART) and date of commencement of ARV, infant feeding choice, infant gestational age and birth weight were recorded. Infants with birth weights less than 10th percentile for the gestational age were considered small for gestational age (SGA). A saliva swab in viral transport medium was collected from enrolled newborns; this was done immediately before the next feed in breastfed infants. There were no follow up visits and mothers were not informed of the infant's CMV status.

Testing of samples for CMV: Saliva swabs were stored at -80^{o}C at a regional laboratory in Cape Town. After the completion of study enrollment, samples were shipped to the University of Alabama at Birmingham (UAB) for CMV testing. The

newborn saliva swabs were processed and tested for CMV using a real-time polymerase chain reaction (PCR) assay described previously (14). The PCR positive samples were also tested by the rapid culture method to confirm the PCR result.

Ethical considerations: Ethical approval was obtained from the University of Cape Town (UCT) Health Sciences Faculty Human Research Ethics Committee (HREC), MMH Ethics Committee and the Institutional Review Board for Human Use of UAB. Written informed consent was obtained from HIV-infected mothers prior to enrolling infants in the study.

Statistical analysis: The demographic, maternal and newborn characteristics were compared between CMV-infected and uninfected infants and statistical significance was determined using Chi-Square, Fisher exact test or student T-test as appropriate. Crude odds ratios (ORs) were calculated from 2 x 2 tables to determine the association of various factors with an increased risk for CMV transmission. Logistic regression analyses were performed to determine covariates that were independently associated with intrauterine transmission of CMV. Maternal age, birth weight, gestational age, length of ARV prophylaxis less than 120 days, and CD4 count less than 200 cells/μL were included in the logistic regression model. Adjusted odds ratios (aOR) were calculated and 95% confidence intervals were determined using the parameter estimates and their respective standard errors. All statistical analyses were performed using SPSS v. 21 statistical package (IBM Corp., Armonk, NY, USA).

Results

Subjects and specimens: A total of 833 HIV-infected mothers delivered 831 live-born infants during the study period (April to October 2012) and 757 of those mothers were approached for participation in the study during weekdays, of which 737 mothers consented for participation. An additional 11 babies were enrolled during the training component of the study in March, 2012. Therefore, 90.9% (757/833) of eligible mothers were approached for participation in the study and most women (97.4%, 737/757) agreed to participate. The median (IQR) age at the collection of saliva specimens was 1.0 (1.0 – 2.0) days.

Birth prevalence of congenital CMV: Of the 748 HIV-exposed newborns screened for congenital CMV by real-time PCR of saliva, 22 infants were positive giving a prevalence of 2.9% (95% CI, 1.9 - 4.4%). Twenty of the 22 PCR positive saliva specimens were also positive by rapid culture for CMV.

Factors associated with CMV transmission: Overall, 96% of mothers used prenatal ARV prophylaxis (prenatal AZT 43.9%, HAART 52.1%). The median (IQR) length of ARV prophylaxis was 130 (95-165) days for the women receiving prenatal AZT (n=327) and 167 (101-829) days for the group on HAART (n=390). Of the 746 mothers with known CD4 counts, the timing of CD4 counts was available for 731 mothers. Of those, 721 mothers had CD4 counts obtained during the first or second trimesters of pregnancy at a median of 18 (IQR 13-24) weeks gestation, and the remaining 10 women had CD4 counts obtained prior to conception at a median of 29

(IQR 12-40) weeks preconception. Maternal age, gestational age, prematurity (< 37 weeks gestation), type of ARV prophylaxis, length of ARV prophylaxis, birth weight, small for gestational age and infant feeding choice were not significantly different between CMV-infected and uninfected infants (Table 1). Significantly more mothers with CD4 counts less than 200 cells/μL had babies with congenital CMV (8/126, 6.3%) compared to mothers with CD4 counts greater than 200 cells/μL (14/620, 2.3%, p = 0.01) (Table 1). A significant association between maternal CD4 counts and intrauterine transmission of CMV was observed when the data were analyzed using Chi square for trend (p<0.005). Ten of the 475 (2.1%) infants born to mothers with CD4 count >300 cells/μL had congenital CMV, whereas 4/145 (2.8%), and 8/126 (6.3%) with maternal CD4 counts between 200 and 300 cells/μL, and <200 cells/μL, respectively had congenital CMV (Figure 1). As shown in Table 2, maternal CD4 count less than 200 cells/μL was the only factor that was independently associated with the risk for congenital CMV (aOR 2.9; 95% CI, 1.2 - 7.3).

Viral load: The geometric mean saliva CMV viral load among infected infants was 776.3 copies/ml (95% CI 234.4 – 2570.4 copies/ml). A negative correlation between CMV viral load in saliva and maternal CD4 counts was observed, r = -0.495, n = 22, p = 0.019 (Figure 2).

Discussion

We evaluated the prevalence of congenital CMV among infants born to HIV-infected mothers in the Western Cape. This is the first study to document congenital CMV prevalence among a large sample of HIV-exposed infants in sub-Saharan Africa, and

the first report of congenital CMV in South Africa. Despite universal maternal ARV prophylaxis, the prevalence of congenital CMV in this study was high compared to the rate in the general population documented in newborn CMV screening studies in the U.S., Europe and South America (1, 15). In addition, the overall rate of congenital CMV in this study was consistent with that reported for HIV-EU infants in these countries (6, 7, 10).

We observed a significantly higher prevalence of congenital CMV among infants of mothers whose CD4 count during pregnancy was lower than 200 cells/μL. On logistic regression analysis, this was the only factor independently associated with congenital CMV in the study population. Maternal immunosuppression close to delivery was also reported as an independent predictor of congenital CMV in the FPC (6). In addition, we found an inverse relationship between various categories of maternal CD4 count and congenital CMV infection prevalence, further supporting the role of maternal immunity in CMV transmission (Figure 1). A similar, although non-significant, trend was recently documented in HIV-EU newborns of mothers on antenatal antiretroviral therapy in the U.S.(7). In mothers with CD4 counts >200 cells/μL, the rate of congenital CMV infection in our study remained elevated in relation to populations with high CMV seroimmunity (2, 15).

The mechanisms by which maternal immunosuppression is linked to congenital CMV transmission in HIV exposed newborns have not been elucidated. HIV-infected individuals are often CMV seropositive, therefore it is plausible that impaired maternal immunity could lead to more frequent reactivation or re-infection with CMV, or higher levels of CMV viremia (16). HIV viremia during pregnancy, prior to the

initiation of antiretroviral therapy, or as a result of incomplete virological suppression in mothers on treatment, could mediate congenital CMV transmission by potentiating CMV replication (17), or leading to vertical transmission of HIV (18). Although low rates of mother-to-child transmission (MTCT) of HIV (2-3%) have been reported in the era of prenatal ARV prophylaxis in South Africa (19), ongoing HIV transmission could be sufficient to drive an excess risk of congenital CMV among HIV-exposed infants (5, 6). As maternal CD4 count could reflect the ability to control CMV infection, the level of maternal HIV viremia and the risk of MTCT of HIV, it may be a good overall predictor of congenital CMV transmission in HIV-infected women.

CMV transmission rates in this study did not differ between mothers using prenatal AZT prophylaxis and mothers on HAART. A lack of association between type of prenatal ARV prophylaxis and prevalence of congenital CMV was previously documented in cohorts of HIV-exposed infants in the U.S. and Europe (6, 10).

Maternal CD4 count correlated inversely with CMV viral load in saliva of newborns with congenital CMV. This suggests that impaired maternal immunity may have resulted not only in increased CMV transmission to the fetus but also increased CMV virus replication in infected fetuses (Figure 2).

There are several limitations to this study. The background prevalence of congenital CMV in the general population and in the pre-ARV era in South Africa is not known. Therefore, it is not possible to determine whether the birth prevalence we observed is higher than expected for the general population, or to delineate the impact of maternal ARV prophylaxis on congenital CMV prevalence. The anonymous unlinked

design of this study precluded ascertainment of infants' HIV infection status, and clinical and follow-up assessments of CMV-infected infants. In addition, maternal viral load data were not routinely available, and thus not collected. Both maternal HIV viral load and infant HIV infection are possible mediators or confounders of the relationships we observed between congenital CMV transmission and maternal CD4 count, as well duration of AZT prophylaxis. Furthermore, maternal prenatal CD4 counts were only obtained at the start of ARV prophylaxis and serial measurements were not available making it difficult to assess maternal immune status later in pregnancy. The absence of demographic characteristics, such as race, education, and socioeconomic status, which could also have played a role in intrauterine CMV transmission was an additional limitation. Although the storage of specimens for several months prior to testing may have affected the saliva real-time PCR results, this is unlikely as the specimens were kept frozen at -80^{o}C for the study duration, and shipped on dry ice. Storage of specimens could have affected the results of the rapid culture assay, and this could explain the failure to culture two of the PCR positive specimens. On the other hand, the results from our ongoing multicenter CMV screening study suggest that saliva real-time PCR assay is more sensitive than the rapid culture (20), which could be the basis for the discrepant culture and PCR results. Although it is not possible to exclude breast milk contamination of samples, this is unlikely given that our specimen collection method allowed an interval of at least one to two hours between infants' last exposure to breast milk and saliva swab collection.

The link between maternal CD4 count and congenital CMV transmission, shown here and in upper income countries, suggests that early initiation of combination

antiretroviral therapy in HIV infected women of child-bearing age, prior to becoming immunocompromised, could lower the risk of congenital CMV in their infants. This has important implications for countries with high maternal HIV prevalence.

In South Africa, intensification of the adult HIV program in recent years (21) can be expected to continue to reduce the rates of immunosuppression among women prior to conception. In addition, recent implementation of WHO option B guidelines for prevention of MTCT (PMTCT) will impact pregnant women across all CD4 count categories. Therefore, the birth prevalence of congenital CMV in HIV-exposed infants in this population should be reevaluated, while the transmission rate in HIV-uninfected mothers should also be determined. In addition, systematic studies are needed to investigate the risk factors, including immunological and virological markers, associated with congenital CMV transmission in settings with a high burden of HIV. Furthermore, the burden of congenital CMV-induced hearing loss in this population, as well as the impact of congenital CMV infection on morbidity, growth and development in HIV-exposed infants, should be evaluated. Finally, the validity of saliva real-time PCR for newborn CMV screening in populations where breastfeeding is common should be formally assessed.

In summary, the findings of our study demonstrate a high rate of congenital CMV in the era of prenatal antiretroviral therapy in this South African population of HIV exposed newborns, and an association of CMV transmission with advanced maternal immunosuppression.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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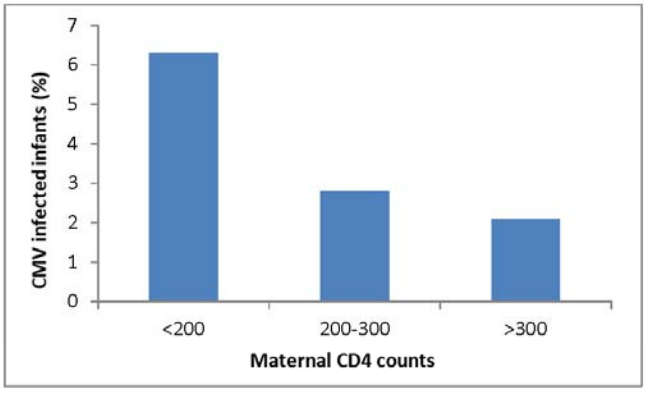
Figure Legends

Figure 1. The proportion of HIV-exposed infants with congenital CMV infection according to maternal CD4 counts was analyzed using Chi square for trend analysis ($p<0.005$). Ten of the 475 (2.1%) infants born to mothers with CD4 count >300 cells/μL had congenital CMV, whereas 4/145 (2.8%), and 8/126 (6.3%) with maternal CD4 counts between 200 and 300 cells/μL, and <200 cells/μL, respectively had congenital CMV.

Figure 2. Scatterplot summarizing the relationship between maternal CD4 count and infant saliva CMV viral load. There was a negative correlation between the two variables, $r = -0.495$, $n = 22$, $p = 0.019$.



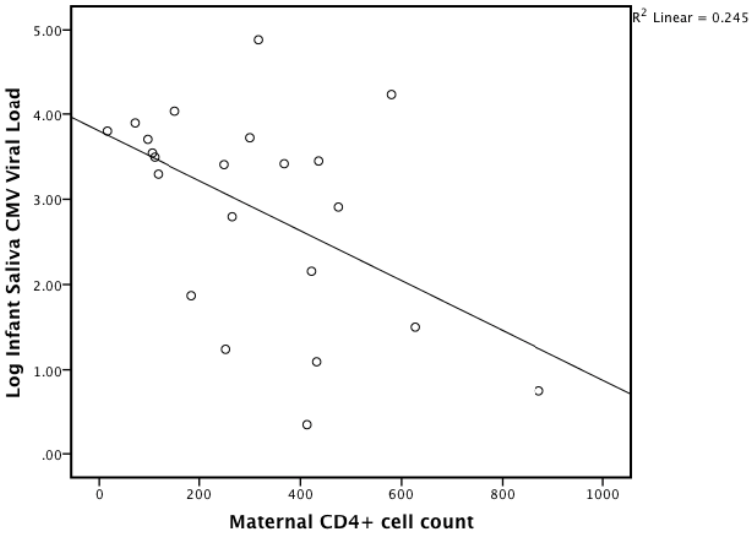


Table 1. Comparison of demographic, maternal and newborn characteristics between CMV-infected and uninfected newborns exposed to HIV. Abbreviation: Intrapartum AZT/sdNVP: intrapartum zidovudine with single dose nevirapine

Finding	CMV infected infants (n=22)	CMV uninfected infants (n=726)	OR (95%CI)	P value
	Mean ± SD			
Maternal age	27.1 ± 5.1	28.5 ± 5.3	0.95 (0.9-1.0)	0.23
Length of ARV prophylaxis (days)	344 ± 526	383 ± 652	0.99 (0.9-1.0)	0.78
Maternal CD4 count	312 ± 211	395 ± 205	0.99 (0.9-1.0)	0.06
Gestational age (weeks)	36.8 ± 2.7	37.5 ± 1.8	0.86 (0.7-1.0)	0.25
Birth weight (kg)	2.8 ± 0.7	3.0 ± 0.6	0.99 (0.9-1.0)	0.06
	Positive (%)			
Type of ARV prophylaxis				0.89
None	1 (4.5)	15 (2.1)		
Intrapartum AZT/sdNVP	0 (0)	10 (1.4)		
Prenatal AZT	9 (40.9)	319 (43.9)		
HAART	12 (54.5)	378 (52.1)		
Length of ARV prophylaxis <120 days	11 (50)	262 (36)	1.8 (0.8-4.4)	0.18
Maternal CD4 count <200	8 (36.4)	118 (16.3)	2.9 (1.2-7.0)	0.01
Prematurity (<37 weeks)	5 (22.7)	104 (17)	1.7 (0.6-4.6)	0.35
Small for gestational age	2 (9.1)	67 (9.3)	1.0 (0.2-4.4)	0.98
Infant feeding choice				0.69
Breastfeeding	14 (63.6)	476 (65.6)		
Formula	7 (31.8)	236 (32.5)		

Table 2. Logistic regression analysis to determine risk factors for congenital CMV infection in HIV-exposed infants

Risk factor	aOR (95% CI)	P value
Maternal age	0.93 (0.8 - 1.0)	0.14
Birth weight	0.99 (0.9 - 1.0)	0.41
Gestational age	0.86 (0.7 - 1.1)	0.52
Maternal CD4 count <200	2.9 (1.2 - 7.3)	0.02
Length of ARV prophylaxis <120 days	1.6 (0.7 - 3.9)	0.29