HHS Public Access

Author manuscript

J Infect Dis. Author manuscript; available in PMC 2017 December 28.

Published in final edited form as:

J Infect Dis. 2016 March 15; 213(6): 891–900. doi:10.1093/infdis/jiv549.

Cytomegalovirus Infection in Human Immunodeficiency Virus (HIV)–Exposed and HIV-Infected Infants: A Systematic Review

Sascha R. Ellington, **Kristie E. N. Clarke**, and **Athena P. Kourtis**

Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

Cytomegalovirus is highly prevalent worldwide and an important opportunistic pathogen in human immunodeficiency virus (HIV)–infected individuals. The effects of cytomegalovirus infection on HIV-exposed infants are poorly understood. We conducted a systematic review to assess the relationship between cytomegalovirus and HIV infections among HIV-exposed infants. Limited evidence suggests that HIV-induced immunosuppression in the mother increases the rate of congenital cytomegalovirus infection, while maternal antiretroviral therapy may reduce it. Limited information exists on the direction of the relationship between cytomegalovirus and HIV transmission among HIV-exposed infants. Only 2 studies have addressed this temporal sequence of events, and they suggest that cytomegalovirus can lead to subsequent HIV infection in HIV-exposed infants. Most evidence suggests that early cytomegalo-virus infection accelerates HIV disease progression in infants. Gaps remain in understanding the role that cytomegalovirus infection plays in HIV-exposed infants. Decreasing cytomegalovirus transmission prenatally and in infancy might further decrease HIV transmission and lead to better health among HIV-exposed infants.

Keywords

cytomegalovirus; HIV; mother-to-child transmission; HIV-exposed infant

Cytomegalovirus (CMV) infection is highly prevalent worldwide. In human immunodeficiency virus (HIV)–infected individuals, CMV is an important pathogen, even though the advent of effective antiretroviral therapy (ART) has made opportunistic infections with CMV less common. CMV seropositivity is still associated with increases in non–AIDS-related events and non–AIDS-related death among HIV-infected individuals [1]. CMV may also play a role in HIV disease progression [2–8].

CMV can be transmitted in utero, during the intrapartum period, and postnatally via breastfeeding, and horizontally, through contaminated secretions such as saliva or urine.

Correspondence: S. R. Ellington, Division of Reproductive Health, Centers for Disease Control and Prevention, MS F74, Chamblee Campus, Bldg 107, Buford Highway, Atlanta, GA 30341 (sellington@cdc.gov).

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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.

Congenital disease can be a source of considerable morbidity, whereas postpartum infection is typically asymptomatic in healthy, full-term infants [9]. However, in resource-limited settings, CMV has been suggested as a cause for morbidity and decreased growth in infants of HIV-infected mothers, even in HIV-uninfected infants [10, 11]. Additionally, symptomatic perinatal CMV infections have been described in infants exposed to but uninfected with HIV (hereafter, “HIV-exposed-uninfected infants”) [12]. This population of infants is increasing in magnitude worldwide because of the successes in decreasing mother-to-child transmission (MTCT) of HIV [13].

CMV has also been hypothesized as a cofactor in the transmission of HIV from mother to child. There are several potential pathways that could mediate such an effect. CMV and HIV can infect the same cell types, with direct coinfection leading to enhanced HIV replication. CMV can also enhance other coreceptor pathways for HIV entry, transactivate viral long terminal repeats, and cause inflammation and immune activation, all of which can enhance HIV replication in vitro [2–8, 14, 15].

While there is evidence of an association of in utero CMV and HIV infections in infants, the temporal sequence of transmission events is not well understood. Whether the burden of infant CMV infection is higher among infants of HIV-infected mothers, particularly in the era of effective ART, is also unclear. In addition, the role of CMV as a cofactor in HIV disease progression during infancy is not well characterized. We conducted a systematic review of the published scientific literature to assess the relationship between CMV and HIV infection in infants.

METHODS

Study Questions

We investigated 5 questions in this systematic review. For each question, the study inclusion criteria are shown.

First, we sought studies that investigated whether HIV-exposed infants are more likely to acquire CMV infection, compared with HIV-unexposed infants. Studies were included if they determined infant CMV infection by 6 months of age and compared CMV infection rates by infant HIV-exposure status.

Second, we searched for studies that considered the effect of prenatal/postnatal antiretroviral exposure on transmission of CMV infection to the HIV-exposed infants. Studies were included if they reported information on maternal ART during pregnancy and/or breastfeeding, determined infant CMV infection status and the timing of infection, and compared infant CMV infection rates by maternal antiretroviral status.

Third, we looked for research that evaluated whether HIV-infected infants are more likely to acquire CMV infection, compared with HIV-exposed-uninfected infants. Studies were included if they determined infant HIV infection status in the first 6 weeks of life, determined infant CMV infection, and compared CMV infection rates by HIV status.

Fourth, we sought studies that addressed whether early CMV infection increases the risk of subsequent MTCT of HIV. Studies were included if they determined infant CMV infection in the first 6 months of life and determined infant HIV infection status and the timing of infection.

Fifth, we looked for investigations that considered whether infants coinfected with HIV and CMV have faster HIV disease progression during infancy. Studies were included if they included children perinatally infected with HIV who were <1 year old, tested for CMV infection in the first year of life, included at least 1 measure of HIV disease progression as an outcome (including death), and made comparisons by CMV status.

Literature Search

Medline, Embase, CINHAL, CAB Abstracts, Global Health, Web of Science, FedRIP, LILAC (PAHO/WHO), WHOLIS, and the Cochrane Library databases were searched for the following terms: (prenatal OR postnatal OR perinatal OR congenital OR Infant OR fetus OR newborn OR fetal OR baby OR babies) AND (cytomegalovirus OR CMV OR HCMV) AND (HIV OR “human immunodeficiency virus”). Results were limited to studies published in English. No restrictions on publication year were used; the search was last conducted on 30 March 2015.

All abstracts and titles were screened for relevance to each of the 5 review questions. Only publications reporting results from original studies were included. The full text of all relevant articles was reviewed by 2 authors (K. E. A. and A. P. K.) independently, to determine whether they met eligibility criteria for any questions assessed in this systematic review. The third author (S. R. E.) resolved discrepancies. For each included study, the following data were abstracted: (1) objective, (2) study design, (3) population, (4) results, (5) methodologic strengths, and (6) methodologic weaknesses. Fisher exact *P* values were used to compare proportions for studies that did not provide a statistical test or did not specify the statistical test.

RESULTS

The search results yielded 1186 articles. After removing duplicate references and screening titles and abstracts, we reviewed the full text of 102 articles. There were 6 discrepancies resolved by the third reviewer. In total, 19 studies met the eligibility criteria for at least 1 question of the systematic review.

Are HIV-Exposed Infants More Likely to Acquire CMV Infection, Compared With HIV-Unexposed Infants?

Five studies met the eligibility criteria to be included in this assessment [10, 16–19]. A cross-sectional study of neonatal admissions in Zambia examined the prevalence of congenital CMV infection, determined by detection of CMV DNA in saliva, urine, or serum or detection of immunoglobulin M (IgM) antibody in serum in the first 3 weeks of life [17]. Congenital CMV infection was detected in 11.4% (9 of 79; 95% confidence interval [CI], 6.1%–20.3%) of HIV-exposed neonates, compared with 2.1% (6 of 293; 95% CI, .8%–4.6%) of unexposed neonates. Maternal HIV infection was independently associated with an

increased odds of congenital CMV infection, compared with no maternal infection (odds ratio [OR], 6.66; 95% CI, 2.13–20.88; $P = .001$). As this study was not population-based—the point of entry was hospital admission of a sick neonate—results may not be generalizable. An Italian study used CMV-specific polymerase chain reaction (PCR) analysis to examine cord blood obtained using the dried blood spot technique from newborns of women with and those without HIV infection. The study found that 3 of 187 HIV-exposed infants (1.6%) had congenital CMV infection, compared with 0 of 372 infants born to HIV-uninfected women ($P = .04$) [19]. A limitation of this study was that it only tested cord blood samples, which could underestimate CMV prevalence. A study in Zambia found a significant difference in the proportion of infants with high serum CMV DNA loads at 6 months: 6 of 67 HIV-exposed infants (9%), compared with 7 of 235 HIV-unexposed infants (3%), had a CMV DNA load of >50 copies/mL ($P = .044$) [16].

Two other studies yielded different results. A cohort of infants (with or without HIV exposure) recruited into a trial of micro-nutrient-fortified complementary foods in Zambia provided information on rates of CMV infection, as screened by serum CMV DNA at age 6 months [10]. The infants were representative of the region. CMV DNA was detected in the serum of 55 of 120 HIV-exposed infants (45.8%) and 152 of 393 HIV-unexposed infants (38.7%); the difference was not statistically significant. A study from Brazil examined rates of congenital CMV infection among HIV-exposed infants, compared with unexposed infants, from a CMV-immune, low-income population; only 8.7% of HIV-infected mothers had an AIDS-defining condition, and none had late-stage HIV infection [18]. No difference was observed in rates of congenital CMV infection, defined as CMV detection in the urine by PCR or culture by age 15 days, by HIV-exposure status (2.7% vs 2.9% in infant with and those without HIV exposure, respectively). Of interest, perinatal CMV infection (defined as detection of viruria during age 1–3 months) was detected in fewer HIV-exposed infants than HIV-unexposed infants (7.9% vs 39.4%; $P < .001$); most infants (93.9%) in the latter group breastfed, whereas only 5.9% of HIV-exposed infants breastfed.

What Is the Effect of Prenatal/Postnatal Antiretroviral Exposure on Transmission of CMV Infection to HIV-Exposed Infants?

Most of the evidence on the frequency of congenital CMV infection among HIV-exposed infants accumulated prior to the combination ART (cART) era [20–22]. However, 5 recent studies shed some light on this question and met the criteria to be included in this review [12, 20, 23–25]. The large French Perinatal Cohort Study showed lower rates of congenital CMV infection in HIV-exposed-uninfected infants in the cART era (1.2%), compared with the pre-cART era (3.5%), particularly if cART began in the first trimester ($P = .004$); among HIV-infected infants, however, rates of congenital CMV infection remained high in the cART era [24]. A study from the United States did not show a change in congenital CMV rate by maternal cART use; most mothers started cART after the first trimester in this study [12]. Consistently, a study of 367 HIV-exposed infants in the United States [23] found that congenital CMV infection was associated with higher maternal HIV load at the start of prenatal care ($P = .02$) and with maternal HIV diagnosis during pregnancy/delivery ($P = .03$); thus, cART would have been started later in pregnancy or not at all in these women. Data from sub-Saharan Africa are limited. A study of 748 newborns of HIV-infected

mothers from South Africa (96% received prenatal antiretrovirals) collected saliva from newborns at a median age of 1 day and tested specimens for CMV via PCR analysis. The study reported a congenital CMV infection rate of 2.9% (22 infants); no association of congenital CMV infection was observed with length or type of maternal antiretroviral prophylaxis. However, low maternal $CD4^+$ T-cell count (<200 cells/μL) during pregnancy was associated with congenital CMV (adjusted OR, 2.9; 95% CI, 1.2–7.3) [25].

Rates of perinatal/early postnatal CMV infection (defined as a positive culture result in the first 6 months of life) were decreased in the cART era, compared with the pre-cART era (8.9% vs 17.9%; $P < .01$) in a US cohort of 414 HIV-exposed infants [12]; maternal ART was associated with a decreased odds of perinatal/early postnatal CMV (OR, 0.21; 95% CI, .07–.63). Furthermore, the likelihood of symptomatic perinatal/early postnatal CMV infection (symptoms included splenomegaly, lymphadenopathy, and hepatomegaly) was increased in infants whose mothers had not received cART, compared with those whose mothers were receiving cART (41% vs 6% of CMV-infected infants; $P < .05$) [12].

The effect of cART on breast milk CMV load was examined among 69 HIV-infected, lactating Malawian women [20]. There was an association between milk HIV-1 RNA and CMV DNA load. However, milk CMV load was similar in women who did and those who did not receive ART in this small sample, leading the authors to postulate that the impact of maternal ART on the magnitude of infant CMV exposure may be limited. Of interest, there was an inverse relationship between milk CMV load and infant growth [20].

Are HIV-Infected Infants More Likely to Acquire CMV Infection, Compared With HIV-Exposed-Uninfected Infants?

Eleven studies met the criteria to be included in this assessment (Table 1) [12, 18, 21–24, 26–30]. Ten of these addressed congenital CMV infection [12, 18, 21–24, 26, 28–30]. One early study in the United States examined data from 154 infants born during 1988–1995 [21]. Congenital CMV infection (defined as infants who tested positive for CMV within 3 weeks of birth) was more common in HIV-infected infants, compared with HIV-exposed-uninfected infants (Table 1). Additionally, the first positive HIV test result was noted to be at an earlier mean age in infants with congenital CMV infection, compared with those without congenital CMV infection (8.8 vs 30.1 days), suggesting a higher frequency of in utero HIV infections among infants with congenital CMV infection, but this difference was not statistically significant ($P = .10$). The large French Perinatal Cohort study tested 4797 HIV-exposed infants for CMV by urine culture in the first 10 days of life (Table 1) [24]. There was a significantly higher prevalence of congenital CMV infection among HIV-infected neonates, compared with HIV-uninfected neonates (Table 1). Similar results were seen in a smaller study of 51 HIV-exposed infants in Kenya [29], as well as in a retrospective case-control analysis of HIV-exposed infants enrolled in a clinical trial comparing long and short durations of maternal and infant use of zidovudine for the prevention of MTCT of HIV in Thailand [28]. Most recently, a subanalysis of data from a study in Malawi revealed that congenital CMV infection was more common among infants with in utero HIV infection, compared with HIV-exposed-uninfected infants (Table 1) [30].

Other studies have not shown significant differences between congenital CMV rates of HIV-infected and HIV-exposed-uninfected neonates, although most had small samples of HIV-infected infants (Table 1) [12, 22, 23, 26].

Of the 6 studies assessing postnatal CMV infection, most found a significantly higher rate of CMV infection in HIV-infected children (Table 1) [12, 18, 22, 26–28]. The study by Chandwani et al was the only one that found no significant difference in postnatal CMV rates by HIV status; however, the *P* value for the comparison was marginally significant (Table 1), and the cumulative infection rate, including congenital CMV infection, was significantly higher in HIV-infected children, compared with HIV-exposed-uninfected children (30% vs 17%; $P = .010$) [26].

Does Early CMV Infection Increase the Risk of Subsequent MTCT of HIV?

While there are several articles describing rates of HIV/CMV coinfection in infants (see the previous subsection), little research has examined whether CMV infection is associated with increased susceptibility to subsequent MTCT of HIV. Two studies met the eligibility criteria for this question; one addressed sequence of perinatal infection events, while the other examined postnatal infection [28, 30].

A study from Thailand analyzed results of HIV and CMV testing performed on HIV-exposed infants over time from birth through age 18 months. The sequence of infection with CMV and HIV was discernable from the longitudinal data. In utero CMV infection, defined as a positive CMV IgM titer in cord blood or detection of CMV DNA in an infant peripheral blood sample obtained within 10 days of birth. Intrapartum/neonatal CMV infection was defined as CMV-negative cord blood and neonatal peripheral blood samples, with a serum sample positive for CMV IgM or DNA at 6 weeks of age. In utero and perinatal HIV infection were defined as a positive HIV-specific PCR test within 7 days after birth and between 8 days and 1 month after birth, respectively. While congenital CMV infection was associated with intrapartum HIV infection ($P = .03$), perinatal CMV infection was not associated with in utero HIV infection ($P = 1.00$). While not conclusive, this suggests that the timing of CMV infection may be important in determining increased susceptibility to HIV MTCT [28].

A more recent study examined the risk of HIV infection through breastfeeding in Malawian infants with early CMV infection, defined as CMV DNA detection at age 6 months. HIV DNA testing was performed at birth and ages 2, 12, 28, and 48 weeks. Detection of CMV in plasma via PCR analysis at age 6 months was not associated with an increased risk of subsequent HIV acquisition through breastfeeding (hazard ratio [HR], 4.52; 95% CI, .58–35.3), while there was a marginally significant increased risk for the combined outcome of HIV acquisition or infant death (HR, 4.27; 95% CI, .99–18.4) [30]. The study was underpowered to detect a difference in HIV transmission events.

Do HIV/CMV-Coinfected Infants Have Faster HIV Disease Progression During Infancy?

Six articles met eligibility criteria for this question (Table 2) [21, 22, 26, 27, 31, 32]. Although our focus was disease progression during infancy, most studies reported disease progression for longer periods.

Two small, retrospective studies conducted in the United States in the early 1990s assessed the association of CMV coinfection with mortality in HIV-infected infants [27,31].While one study reported a significant association ($P < .05$), the Fisher exact test we conducted yielded a P value of .095, indicating no significant difference (Table 2) [31].The second study also failed to find a statistically significant association (Table 2) [27].In a small prospective cohort study, Gabriel et al reported no difference in survival or HIV disease progression among perinatally HIV-infected children by CMV infection status (Table 2) [32].

Another study of 37 HIV-infected infants found that CMV infection in the first 6 months of life was associated with higher mean p24 antigen concentrations and higher mean $CD8^+$ T-lymphocyte proportion but not with $CD4^+$ T-lymphocyte proportion (Table 2) [26]. A similar study found absolute $CD4^+$ T-lymphocyte counts, $CD4^+$ T-lymphocyte percentage, and ratios of $CD4^+$ to $CD8^+$ T cells were significantly lower in CMV/HIV-coinfected infants, compared with infants without CMV infection (Table 2). Mean survival time for CMV/HIV-coinfected infants was 25 months, compared with 39 months for infants not infected with CMV; this difference was not statistically significant (Table 2) [21].

In 1999, Kovacs et al reported the results of a study that examined the association of CMV infection with HIV disease progression among HIV-infected infants. Infants were recruited from multiple high-risk obstetric clinics in the United States and followed until age 18 months. CMV infection was assessed by urine culture at birth and every 6 months thereafter. Two infants had congenital CMV infection. By age 18 months, infants coinfected with CMV had higher rates of HIV disease progression than infants infected with HIV alone (Table 2). Additionally, CMV infection during the first 18 months more than doubled the risk of HIV disease progression (relative risk, 2.59; 95% CI, 1.13–5.95) [22].

DISCUSSION

This systematic review synthesizes the evidence on the relationship between HIV and CMV infections in infants but also highlights several limitations and gaps in the existing literature. On the question of whether HIV-exposed infants have higher rates of congenital CMV infection, the limited information available suggests that the main determinant may be the mother's level of HIV-induced immunosuppression [10, 16–18]. Most studies in which HIV-infected mothers were not immunosuppressed found no difference in congenital CMV infection rates [10, 18], whereas those with immunosuppressed women found increased congenital CMV infection in HIV-exposed infants. This is biologically plausible, as immunosuppression correlates with CMV shedding in the genital tract of HIV-infected women [14, 17, 29, 33]. Additionally, emerging evidence suggests that maternal ART may decrease the rate of congenital CMV infection [12, 20, 23–25], likely by improving maternal health and immunity, resulting in decreased mucosal shedding of CMV during birth and a reduced incidence of reinfection or disease reactivation. It is more difficult to assess any effects of maternal ART on postnatal CMV transmission, particularly in settings where breastfeeding is practiced, given generally very high rates of CMV transmission via breastfeeding [30, 34, 35]. As an-tiretroviral programs roll out in sub-Saharan Africa and as

more women initiate cART even prior to their pregnancy, studies will need to reevaluate the frequency of congenital, perinatal, and postnatal CMV infection in HIV-exposed infants.

The majority of studies point to an increased prevalence of congenital CMV infection among HIV-infected neonates, compared with HIV-exposed-uninfected neonates [21, 24, 28, 29]. Similarly, the available evidence indicates a higher frequency of postnatal CMV acquisition among HIV-infected infants, compared with HIV-exposed-uninfected infants [12, 22, 26, 27]. This could be due to a higher degree of immunosuppression in HIV-transmitting mothers, with concomitant increased risk of CMV reactivation, reinfection, and shedding and, thus, an increased risk of CMV transmission to the infant [36]. Additionally, immunosuppression in HIV-infected infants may make them more vulnerable to coinfection.

Only 2 studies were found that could directly assess the question of whether early CMV infection increases the risk of subsequent MTCT of HIV. These 2 studies indicate that congenital CMV infection does increase the risk of subsequent HIV infection for infants during the intrapartum period [28] and postnatally [30]. Even though there is biological plausibility for these findings, more epidemiological evidence is needed to answer this question definitively.

Few studies have assessed the role of early CMV infection on HIV disease progression in infants, and most have small sample sizes and limited power with methodologic differences, making it difficult to directly compare results. Most but not all evidence suggests that early CMV infection accelerates HIV disease progression in infants. However, most included studies were conducted exclusively in the pre-cART era [21, 22, 27, 31, 32]. Of interest, recent, yet unpublished evidence indicates that level of CMV viremia during early life in HIV-infected infants is a predictor of the size of HIV reservoir after cART-induced virologic suppression [37], possibly through coinfection of the same long-lived memory lymphocytes.

A limitation of this review was the inconsistency in specimen type and laboratory methods used for detecting CMV. However, while serological analysis may detect more cases of infant CMV infection, several studies have demonstrated that PCR-based methods for CMV detection are highly correlated with serological testing [38–41]. CMV PCR testing in urine and saliva has very high sensitivity and specificity (>90%), compared with serological testing [38, 41]. Additionally, a recent study assessing the validity of PCR testing in blood found that PCR detected most infant CMV infections [40].

There are remaining gaps in our understanding of the role of CMV in HIV acquisition and health outcomes of HIV-infected infants and HIV-exposed-uninfected infants. Expanded access to maternal cART, starting prior to or early in pregnancy, has many benefits beyond directly decreasing HIV MTCT, including improvements in maternal health and immunity, and decreasing CMV infection risk for the infant. Decreasing CMV transmission prenatally and postnatally might further decrease HIV transmission risk, as well as lead to better health and developmental outcomes among HIV-exposed-uninfected infants. Clinical trials may need to assess methods to further decrease infant CMV exposure while maintaining breastfeeding, which has multiple proven benefits. A trial of valacyclovir starting at 34 weeks of gestation and continuing postnatally for 12 months in mother with HIV and herpes

simplex virus coinfection did not affect postnatal CMV transmission via breastfeeding but modestly decreased cervical CMV shedding [34].Higher doses or novel anti-CMV drugs in the pipeline [42] may offer opportunities to further investigate the effects of inhibition of CMV replication in HIV-infected mothers as a way to further decrease MTCT of both viruses and improve infant survival and health, particularly in resource-limited countries.

Acknowledgments

Financial support. This work was supported by the CDC.

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Table 1

Studies Evaluating Acquisition of Cytomegalovirus (CMV) Infection in Human Immunodeficiency Virus (HIV)–Exposed Infants, by HIV Infection Status

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Exposed Infants/ Children, Outcome Assessed	CMV Detection Method(s)	Statistical Method(s)	Relevant Result(s)	Strength(s)	Weakness(es)
Cooper et al [27], 1992	United States, retrospective cohort study	65 evaluated for postnatal CMV infection	Urine culture and IgG antibody in sera	Fisher exact test was used to compare proportions of infants with and those without postnatal CMV infection, by HIV status	Postnatal CMV infection was more common in HIV-infected children; 25 of 39 HIV-infected infants (64%) infected with CMV as compared to 2 of 26 HIV-exposed, uninfected children (7.7%; $P < .001$)	Longitudinal study design for postnatal results	Congenital CMV status was not determined; timing of HIV infection was unknown, so temporal relationship between HIV and CMV transmission could not be determined for postnatal CMV acquisition
Chandwani et al [26], 1996	United States, 1989–1993, prospective cohort study	260 total: 24 evaluated for congenital CMV infection, and 236 evaluated for postnatal CMV infection	Urine culture	Fisher exact test[a] was used to compare proportions of infants with congenital CMV infection, by HIV status; and those with postnatal CMV infection, by HIV status	Congenital CMV infection was detected in 1 of 5 HIV-infected children (20%) and 0 of 19 HIV- exposed, uninfected infants ($P = .21$); postnatal CMV infection was detected in 39 of 126 HIV-infected children (31%) as compared to 22 of 110 HIV-exposed uninfected children (20%; $P = .07$)	Large sample of HIV-exposed infants evaluated; assessed congenital and postnatal CMV infection; longitudinal study design for postnatal results	Not all children were followed from birth; small sample of HIV- positive infants with congenital CMV infection results (n = 5); timing of HIV infection was unknown, so temporal relationship between HIV and CMV transmission could not be determined for postnatal CMV acquisition
Doyle et al [21], 1996	United States, 1988–1995, retrospective cohort study	154 evaluated for congenital CMV infection	Urine culture or shell vial assay	Fisher exact test was used to compare proportions of infants with and those without congenital CMV infection, by HIV status	Congenital CMV infection was more common in HIV-infected infants (5 of 24 [21%]) as compared to HIV-exposed, uninfected infants (5 of 130 [3.8%]; $P = .008$)	Large sample of HIV-exposed infants evaluated	Small sample of HIV-positive infants with CMV results (n = 24)
Mussi-Pinhata et al [18], 1998	Brazil, 1992–1995, prospective cohort study	128 total: 128 evaluated for congenital CMV	Urine culture	Fisher exact test[a] was used to compare proportions of infants with congenital CMV infection, by HIV status; and those with	0 of 21 HIV-infected infants tested positive for congenital CMV; 3 of 107 HIV-exposed, uninfected infants (2.8%) were infected with	Assessed congenital and postnatal CMV infection; longitudinal	Small sample of HIV-positive infants with CMV results (n = 21); a small proportion of

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Exposed Infants/ Children, Outcome Assessed	CMV Detection Method(s)	Statistical Method(s)	Relevant Result(s)	Strength(s)	Weakness(es)
		infection, and 125 evaluated for perinatal CMV infection		perinatal CMV infection, by HIV status	CMV congenitally (P = 1.00); perinatal CMV infection frequency was higher among HIV-infected infants as compared to uninfected infants (4 of 21 [19%] vs 4 of 104 [3.8%]; P = .027)	study design for postnatal CMV results	HIV-positive mothers breastfed, and results were not provided by breastfeeding status; timing of HIV infection was unknown, so temporal relationship between HIV and CMV transmission could not be determined for postnatal CMV acquisition
Kovacs et al [22], 1999	United States, prospective cohort study	440 total: 247 evaluated for congenital CMV infection; no. evaluated for postnatal CMV infection not provided	Urine culture or shell vial assay and CMV IgG and IgM antibody testing	Fisher exact test[a] was used to compare proportions of infants with and those without congenital CMV infection, by HIV status; Weibull model was used to calculate rates of CMV infection at age 6 mo, fitted separately for HIV-infected infants and HIV-exposed, uninfected infants	Congenital CMV infection frequency did not differ by infant HIV status: 2 of 47 HIV- infected infants (4.3%) had CMV infection as compared to 9 of 200 HIV-exposed uninfected infants (4.5%; P = 1.00); CMV infection at age 6 mo was more common in HIV-infected infants as compared to uninfected infants (39.9% vs 15.3%; P = .001), continuing through age 4 y at end of study	Longitudinal study design for postnatal results; assessed congenital and postnatal CMV infection	Postnatal CMV infection data were not provided separately, and only cumulative CMV infection was reported; timing of HIV infection was unknown, so temporal relationship between HIV and CMV transmission could not be determined for postnatal CMV acquisition
Guibert et al [24], 2009	France, 1993–2004, prospective cohort study	4797 evaluated for congenital CMV infection	Urine culture	Fisher exact test was used to compare proportions of infants with and those without congenital CMV infection, by HIV status	Congenital CMV infection was detected in 13 of 126 HIV- infected infants (10.3%) as compared to 94 of 4302 HIV- exposed uninfected infants (2.2%; P < .001)	Large sample of HIV-exposed infants evaluated	No postnatal CMV testing was conducted
Slyker et al [29], 2009	Kenya, 1999–2005 prospective cohort study	51 evaluated for congenital CMV infection	CMV DNA PCR on cord blood samples for congenital CMV testing	Fisher exact test was used to compare proportions of infants with and those without congenital CMV infection, by HIV status	Congenital CMV infection was more common in HIV-infected infants: 29% (4 of 14) of HIV- infected newborns had CMV infection compared to 2.7% (1 of 37) of HIV-exposed		Small sample of HIV-positive infants with congenital CMV results (n = 14); CMV status was assessed postnatally, but

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Exposed Infants/ Children, Outcome Assessed	CMV Detection Method(s)	Statistical Method(s)	Relevant Result(s)	Strength(s)	Weakness(es)
					uninfected newborns (P = .02)		results were not provided separately; only cumulative percentage with CMV infection was reported
Duryea et al [23], 2010	United States, 1997–2005, retrospective cohort study	333 evaluated for congenital CMV infection	Urine culture	Fisher exact test[a] was used to compare proportions of infants with and those without congenital CMV infection, by HIV status	No differences in congenital CMV infection frequency, by HIV status: 0 of 4 HIV-infected infants had CMV infection as compared to 10 of 329 HIV- exposed uninfected infants (3%; P = 1.00)	Large sample of HIV-exposed infants evaluated	Small sample of HIV-positive infants with CMV results (n = 4); no postnatal CMV testing conducted
Khamduang et al [28], 2011	Thailand, 1997– 2001, retrospective case-control study	293 total: HIV-infected infants were matched to HIV-exposed uninfected infants, by maternal HIV RNA level; 231 evaluated for congenital CMV infection, and 181 evaluated for postnatal CMV infection	Plasma or serum screened at age 18 mo for CMV IgG antibody; if positive, PBMCs tested with CMV DNA PCR	Exact conditional logistic regression was used to compare proportions of infants with congenital CMV infection, by in utero HIV status; proportions of those with congenital CMV infection, by overall HIV infection status; and overall CMV infection frequency (including congenital), by overall HIV status	Among infants with in utero HIV results, 7 of 27 HIV-infected infants (26%) had congenital CMV infection as compared to 3 of 58 HIV-exposed uninfected infants (5%; P = .01); among all infants with HIV results, 10 of 71 HIV-infected infants (14%) had congenital CMV infection as compared to 5 of 160 HIV- exposed uninfected infants (3%; P = .009); among all infants with HIV results, overall CMV infection was more common in HIV-infected infants as compared to HIV-exposed uninfected infants (84% vs 63%, respectively; P < .001)	Large sample of HIV-infected infants with CMV results; assessed congenital and postnatal CMV infection; infant HIV infection status determined for in utero and intrapartum periods; inferences can be drawn about the temporal relationship between HIV and CMV transmission	Timing of CMV infection was not determined for 26% of HIV-infected infants and 18% of HIV-exposed, uninfected infants with CMV infection
Frederick et al [12], 2012	United States, 1988–2006, prospective cohort study	414 total: 248 evaluated for congenital CMV infection, and 393 evaluated for postnatal CMV infection	Urine and oral swab culture	Fisher exact test[a] was used to compare proportions of infants with congenital CMV infection, by HIV status; and those with perinatal/early postnatal CMV infection, by HIV status	Congenital CMV results did not differ by infant HIV status: 1 of 21 HIV-infected infants (4.8%) had CMV infection as compared to 8 of 227 HIV- exposed uninfected infants (3.5%; P = .77); perinatal/early postnatal CMV infection was more prevalent in HIV-infected infants (9 of 32	Large sample of HIV-exposed infants evaluated; assessed congenital and postnatal CMV infection; longitudinal study design	Small sample of HIV-positive infants with CMV results (n = 21 for congenital outcome and n = 32 perinatal/early postnatal outcome); timing of HIV infection was unknown, so

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Reference, Publication Year	Study Site, Period, Design	No. of HIV-Exposed Infants/ Children, Outcome Assessed	CMV Detection Method(s)	Statistical Method(s)	Relevant Result(s)	Strength(s)	Weakness(es)
					[28.1%]) as compared to HIV-uninfected infants (43 of 361 [11.9%]; $P < .01$).	for postnatal results	temporal relationship between HIV and CMV transmission could not be determined for postnatal CMV acquisition
Chang et al [30], 2015	Malawi, 2004–2010, retrospective cohort study	272 evaluated for congenital CMV infection	CMV DNA PCR on plasma and PBMCs	Fisher exact test was used to compare proportions of infants with and those without congenital CMV infection, by HIV status	Congenital CMV infection was more common among HIV- infected infants (3 of 30 [10%]) as compared to HIV-exposed uninfected infants (8 of 242 [2.3%]; $P = .049$, after adjustment for missing data)	Large sample of HIV-exposed infants evaluated	Postnatal CMV testing was conducted but only among HIV-exposed uninfected infants

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction.

[a] Calculated by authors of this systematic review, using data abstracted from the article.

J Infect Dis. Author manuscript; available in PMC 2017 December 28.

Table 2

Studies Evaluating the Effect of Early Cytomegalovirus (CMV) Infection on Human Immunodeficiency Virus (HIV) Disease Progression Among Infants Perinatally Infected With HIV

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Infected Infants Followed	Statistical Method(s)	Disease Progression Result(s)	Strength(s)	Weakness(es)
Frenkel et al [31], 1990	United States, 1983–1990, retrospective cohort study	24 HIV-infected infants aged 0–39 mo at the time of referral	None described; Fisher exact test[a] was used to compare proportions of infants who died, by CMV status	11 HIV-infected children (46%) were coinfected with CMV; 7 of 11 CMV-coinfected children (64%) died as compared to 3 of 13 CMV-negative children (23%); authors reported that the difference was statistically significant ($P < .05$), but $P = .095$ by the Fisher exact test	Longitudinal study among HIV-infected children	Small sample of HIV-positive infants with CMV results; not all children were followed from birth; included CMV infections acquired after age 1 y
Cooper et al [27], 1992	United States, retrospective cohort study	39 HIV-infected infants (38 infected perinatally and 1 child infected via blood transfusion in the first week of life)	Fisher exact test was used to compare proportions of infants who died, by CMV status	25 (64%) HIV-infected children were coinfected with CMV; CMV disease was identified in 5 children all of whom acquired CMV in the first year of life; 6 of 25 coinfected children (24%) died as compared to 1 of 14 children (7.1%) infected with HIV alone ($P = .39$)	Longitudinal study design	Small sample of HIV-positive infants with CMV results (n = 39); timing of CMV infection was unknown; 60% of CMV-coinfected infants (15) were CMV positive within first y of life, but results were not stratified by age at CMV infection
Chandwani et al [26], 1996	United States, 1989–1993, prospective cohort study	37 HIV-infected infants tested for CMV infection by age 6 mo	Analysis of covariance was used to evaluate age- adjusted differences in quantitative variables	11 HIV-infected infants (30%) were coinfected with CMV in the first 6 mo of life, of whom 5 (45%) developed symptomatic disease, with 4 of these 5 dying within 10 mo of diagnosis; mean p24 antigen concentrations were higher in CMV-coinfected infants as compared to CMV uninfected infants (313 pg/mL vs 212 pg/mL; $P = .04$) at age 6 mo; mean $CD8^+$ T-lymphocyte proportion was significantly higher among CMV- coinfected infants as compared to CMV- uninfected infants (34% vs 24%; $P = .03$) at age 6 mo; mean $CD4^+$ T-lymphocyte proportion was not different by CMV status (30% vs 31%; $P = .85$) at age 6 mo	Longitudinal study	Small sample of HIV-positive infants with CMV results within first year of life (n = 37); survival data were not provided for CMV-negative infants; incident CMV could not be assessed

Reference, Publication Year	Study Site, Period, Design	No. of HIV-Infected Infants Followed	Statistical Method(s)	Disease Progression Result(s)	Strength(s)	Weakness(es)
Doyle et al [21], 1996	United States, 1988–1995, retrospective cohort study	24 HIV-infected infants tested for CMV during age ≤2 mo	Student *t* test was used to analyze quantitative variables; Kaplan–Meier method was used to compare survival, by CMV status	6 HIV-infected infants (25%) acquired CMV infection during age ≤2 mo; mean absolute $CD4^+$ T-lymphocyte count was significantly lower for CMV-coinfected infants as compared to CMV-negative infants (643 vs 1590 cells/m^3; $P = .004$) at age 6 mo; mean $CD4^+$ T-lymphocytes proportion was significantly lower for CMV-coinfected infants as compared to CMV-negative infants (16 vs 30%; $P = .04$) at age 6 mo; mean ratios of $CD4^+$ to $CD8^+$ T lymphocytes were significantly lower for CMV-coinfected infants as compared to CMV-negative infants (0.48 vs 1.26; $P = .04$) at age 6 mo; mean survival time for HIV-positive infants coinfected with CMV was 25 mo, while mean survival time for CMV-negative was 39 mo ($P = .088$)	Longitudinal study focused on congenital CMV infection	Small sample of HIV-positive infants with CMV results
Kovacs et al [22], 1999	United States, prospective cohort study	75 HIV-infected infants	Kaplan–Meier method was used to compare survival, by CMV status; a generalized Wilcoxon test was used to compare overall incidence	40 of 75 HIV-infected infants (53%) were coinfected with CMV by age 18 mo; by age 18 mo, coinfected infants had higher rates of HIV disease progression[b] (70% vs 30%; $P = .001$); coinfected infants had higher rates of CDC class C symptoms or death (53% vs 22%; $P = .008$); cumulative 18-month death rate was 5.0% for coinfected infants as compared to 0% for infants without CMV-infection, this difference increased with age (27.5% vs 0% at 3 y and 30% vs 9% at 4 y; $P = .06$)	Longitudinal study design for postnatal results; assessed congenital and postnatal CMV infection	Results not provided for CMV status by age 12 mo
Gabriel et al [32], 2007	Spain, 1987–2002, prospective cohort study	81 infants infected with HIV during age ≤12 mo	An actuarial method and log- rank test were used to compare survival curves, by CMV status; Student *t* test was used to compare quantitative variables	16 HIV-infected infants (20%) were coinfected with CMV; there was no difference in death, by CMV status, at age 2 y (20% of coinfected infants as compared to 24% of CMV-negative infants); mean absolute $CD4^+$ T- lymphocyte counts were the same in CMV-coinfected infants and CMV- uninfected infants (1464 vs 1770 cells/m^3; $P = .46$) at age 1 y; mean $CD4^+$ T-lymphocyte percentage was the same in CMV-coinfected infants and CMV-uninfected infants (28.7 vs 29.6%; $P = .85$) at age 1 y; mean ratios of $CD4^+$ to $CD8^+$ T lymphocytes were the same for CMV-coinfected infants and CMV- negative infants (1.07 vs 1.4; $P = .32$) at age 1 y; mean HIV load was higher in CMV-negative, HIV-infected infants as compared to coinfected infants (549 343 vs 6523; $P = .02$)	Longitudinal study among HIV-infected children	Counts for deaths not provided; statistical comparisons in survival analyses were not clear

Abbreviation: CDC, Centers for Disease Control and Prevention.

[a] Calculated by authors of this systematic review, using data abstracted from the article.

[b] Defined as the presence of CDC-defined class C symptoms, CD4 <750 cells/μL at 1 year of age, or CD4 < 500 cells/μL at 18 months of age.