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Cytomegalovirus and paediatric HIV infection

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Abstract

Cytomegalovirus (CMV) was among the most common AIDS-defining illnesses prior to the advent of combination antiretroviral therapy (ART). In the ART era, CMV disease remains a significant public health threat among HIV-infected adults and children with delayed HIV diagnosis. CMV co-infection may additionally contribute to accelerated HIV progression, development of inflammation-related comorbidities, immune senescence and developmental deficits. Elimination of CMV would have tremendous public health significance and is an important priority; however, current vaccine strategies are not targeted at HIV-infected individuals. Antivirals active against CMV may be a novel strategy to prevent acquisition and improve outcomes, but haematological side effects are common and necessitate cautious use in pregnant women and infants. Studies in HIV-infected children on ART lag behind adults, and the clinical significance of CMV in this population is not well understood. Furthermore, the effects of CMV in HIV-exposed uninfected (HEU) children need to be clarified to understand whether CMV interventions should also be a priority for this growing population. This review discusses our current understanding of CMV transmission and pathogenesis in HIV-exposed children and highlights unanswered questions for future research.

Keywords: cytomegalovirus, paediatrics, human immunodeficiency virus, HIV-exposed uninfected, pathogenesis

Introduction

Cytomegalovirus (CMV) is associated with severe opportunistic disease during advanced HIV infection, manifesting as retinitis, gastrointestinal disease, pneumonia and central nervous system disease [1]. With the advent of highly active combination antiretroviral therapy (ART), the burden of CMV disease has declined substantially in HIV-infected adults and children [2,3]. However, many individuals, and children in particular, remain at risk due to delayed HIV diagnosis, delayed ART initiation and immune reconstitution inflammatory syndrome (IRIS) [4,5]. Accumulating data in adults suggest CMV co-infection also contributes to accelerated HIV progression and development of non-AIDS-defining comorbidities during ART.

Maternal HIV infection and CMV transmission

Vertical CMV transmission

CMV is transmitted to infants and children via exposure to infected mucosal secretions; CMV is rarely found in the plasma of immunocompetent individuals, but can be detected more frequently in urine [6–8], saliva [7,9], breast milk [10–12], semen [13] and cervicovaginal secretions [8,14,15], and each of these contributes to transmission. Most early infections are maternally acquired, with later infections originating from peers [16]. Following CMV acquisition, infected children shed virus in saliva and urine for years, enabling infection of other family members [7]. CMV seroprevalence varies regionally and is higher in populations with low socioeconomic status [17,18]. In the United States, CMV seroprevalence increases linearly with age, with 36% of 6–11-year-olds, 50% of 30-year-olds and 91% of 80-year-olds infected [19]. In Africa, CMV is acquired earlier, with most infections occurring in infancy [9,20]. High maternal CMV seroprevalence, breastfeeding, premastication of foods and exposure to other infected children contribute to high CMV prevalence in healthy African children.

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CMV transmission in the setting of maternal–child HIV

Longitudinal birth cohorts demonstrate a high risk of both congenital and postnatal CMV transmission in HIV-exposed children (Table 1), with rates increasing along with maternal CMV seroprevalence. The risk of congenital CMV infection ranges from 2.3 to 5.6% in HIV-exposed uninfected infants (HEU) and 4.3 to 29% in HIV-infected infants [21–26].

Perinatal and postnatal CMV transmission also occur at a high rate in both HIV-infected and HEU infants, with 24–90% of children acquiring infection during the first year of life [22,25,26].

Maternal correlates of CMV transmission

In utero CMV transmission is hypothesised to occur secondary to placental infection [27,28]; in the setting of maternal immunosuppression, maternal CMV immune responses are less able to prevent both transmission and congenital disease. Low maternal CD4 cell counts and/or high HIV RNA viral load, and infant HIV infection, are associated with an increased risk of congenital CMV [22,26,29,30].

Exposure to maternal genital secretions may also transmit infection during delivery [14,15]. CMV is commonly detected in cervical and vaginal secretions of both HIV-infected and –uninfected women, with virus detection and levels increasing during late gestation [14,20,31,32] and with increasing progesterone and oestradiol levels [33], or during sexually transmitted infections (STI) [34,35]. In HIV-infected women, cervical CMV shedding is associated with high cervical and plasma HIV RNA levels [32,34,36] and low CD4 T cell counts [32,33]. These data suggest that treatment of genital infections during pregnancy, control of maternal HIV replication, or maternal immune reconstitution may be strategies to decrease cervical CMV shedding and intrapartum transmission. The impact of ART on cervical CMV reactivation is not yet clear; in a cohort of US women there was no difference in cervical CMV shedding between women based on ART use [36].

Nearly all CMV-seropositive HIV-uninfected women also have detectable CMV DNA in their breast milk, with a smaller proportion having recoverable infectious virus [11,37,38]. CMV can be detected in colostrum [20], and isolated from both cellular and cell-free milk components [38]. In HIV-uninfected women, breast milk CMV levels peak at 4–6 weeks postpartum, then decline

Table 1. CMV transmission rates in HIV-exposed birth cohorts

Reference	Population	ART or PMTCT	CMV transmission rates
Doyle 1996 [21]	1988–1995 USA, 30 HIV+ and 171 HEU	None	HIV+ 21% cCMV
			HEU 3.8% cCMV
Kovacs 1999 [22]	1990–1994 USA, 75 HIV+, 365 HEU in P^2C^2 HIV study	None	HIV+ 4.3% cCMV, ~52% CMV+ at 1 year
			HEU 4.5% cCMV, ~24% CMV+ at 1 year
Guibert 2009 [23]	1993–2004 France, 4797 HIV-exposed infants in ANRS Cohort	ART & PMTCT use increasing over time	HIV+ 10% cCMV
			HEU 5.6% cCMV
			HEU 1997–1998: 3.5% cCMV
			HEU 2003–2004: 1.2% cCMV
Gumbo 2014 [24]	1997–2001 Zimbabwe, 257 HIV+ infants in ZVITAMBO	None	HIV+ 11% cCMV
			HIV+ 79% CMV+ at 6 weeks
Slyker 2009 [25]	1999–2003 Kenya, 44 HIV+, 20 HEU	Short course antenatal ZDV	HIV+ 29% cCMV
			HEU 2.7% cCMV
			Overall, ~90% CMV+ at 3 months
Chang 2015 [26]	2004–2010 Malawi, 492 infants born to HIV-infected mothers in BAN trial	Three different short-course PMTCT regimens	HIV+ 10% cCMV
			HEU 2.3% cCMV
			Overall 79% CMV+ by 48 weeks
Meyer 2014 [67]	2009–2010, Malawi, 69 HIV-exposed infants	Variable PMTCT & ART, NVP for mother and neonate	Overall 4% cCMV
Mwaanza 2014 [127]	2012–2013 Zambia, 79 infants of HIV+ mothers admitted to neonatal unit	Not reported	Overall 11% cCMV

This list is not comprehensive, but illustrates population differences between high and low CMV-prevalence regions (USA and Africa), between HIV-infected and HEU infants, and potential time trends related to increasing use of ART/PMTCT.
cCMV: congenital CMV infection; HEU: HIV exposed uninfected; HIV+: HIV infected; PMTCT: prophylaxis for prevention of mother-to-child HIV transmission; ZDV: zidovudine; NVP: nevirapine; sdNVP: single-dose nevirapine.

rapidly [39,40]. In contrast, HIV-infected women experience high levels of CMV DNA in breast milk, which can persist for 6 months or more [32,41]. Breast milk is a major route of CMV transmission in both HIV-uninfected [37,42,43] and HIV-infected women [44], with breast milk CMV DNA levels strongly correlating with transmission risk [32]. High HIV RNA levels in breast milk and plasma, and low CD4 percentage, are associated with higher breast milk CMV levels [29,32,41]. In a cohort of Kenyan HIV-infected women, randomised to feed their infants via breast milk or formula, breastfeeding conferred a 60% increased risk of CMV transmission, independent of infant HIV infection, and 40% of CMV transmissions were estimated to have occurred via nursing [44].

Non-perinatal/non-breast milk transmissions, presumably via saliva or urine, also constitute a large proportion of CMV infections in HIV-exposed infants. In the formula-fed Kenyan infants, 69% acquired CMV before they were 1 year old, and most were late transmissions not attributed to *in utero*/intrapartum transmission (67% in the HEU infants and 55% in the HIV-infected infants) [44]. These infections probably occurred via exposure to saliva or urine. Low CD4 T cell counts are associated with salivary CMV shedding [45], suggesting that maternal ART could also reduce transmission via this route.

Immunological determinants of CMV transmission

The high rate of CMV infection in healthy infants, high rate of recurrent infection in infected individuals, and near ubiquity of CMV seroprevalence in some populations demonstrates the exemplary ability of CMV to subvert host immune responses. A comprehensive review of our current knowledge of CMV immunity is beyond the scope of this article, but has been recently discussed in the context of congenital infection by Schleiss *et al.* [46] and summarised in the context of HIV by Adland *et al.* [47]. HIV induces dysregulation of virtually every aspect of the innate and adaptive immune systems, and undoubtedly compromises containment of maternal CMV at mucosal sites relevant to transmission. Additionally, on the infant side, HIV infection [48], and even HIV exposure in the absence of acquisition of infection [49], leads to abnormalities in innate and adaptive immune responses that may enable earlier CMV acquisition and impaired CMV containment.

Maternal CMV antibodies offer only limited protection against transmission. Maternal preconceptional humoral immunity reduces the risk of *in utero* CMV transmission and symptomatic CMV disease [50]; however, reinfection with a new CMV variant can occur, and may also lead to symptomatic disease [51]. Maternal CMV neutralising antibodies are efficiently transferred across the placenta [52], but do not appear to offer substantial protection from postpartum CMV infection in the first months of life [53]. Rather, higher maternal CMV-specific IgG plasma levels were associated with increased mucosal CMV shedding and a higher risk of earlier CMV transmission in a longitudinal study of Gambian women and their infants [20]; in this cohort there was also no association between breast milk CMV IgG or IgA levels, or infant cord blood IgG levels, and infant CMV infection risk. HIV infection alters B cell function [54], and could compromise the level or avidity of CMV-specific responses. In HIV-infected individuals, CMV-specific antibody responses are elevated in comparison to HIV-uninfected individuals, but functional deficits may contribute to CMV retinitis and end-organ disease [55,56]. Maternal ART improves CMV antibody levels concurrent to decreasing CMV viraemia [57], but the extent to which humoral immune responses are normalised is unknown.

Table 2. Adverse health outcomes associated with CMV infection in HIV-exposed children

Category	Children affected	Health outcomes
HIV acquisition	HEU	Increased risk of *in utero* or breast milk-acquired HIV infection
Opportunistic CMV disease	HIV+ with low CD4 percent or cell count	Retinitis, pneumonia, gastrointestinal and central nervous system disease in children with delayed HIV diagnosis/ART
HIV disease progression	HIV+	Increased immune activation, increased systemic inflammation, accelerated HIV disease progression
HIV persistence	HIV+	Larger HIV reservoirs
Non-communicable diseases	HIV+	Increased risk of atherosclerosis, cardiovascular and neurovascular diseases related to chronic inflammation
Infectious morbidity	HIV+, HEU	Increased risk of infectious diseases secondary to CMV-induced immunomodulation and acquisition of immune risk phenotype
Immune reconstitution	HIV+ starting ART	Immune reconstitution inflammatory syndrome, impaired restoration of naïve CD4 T cells
Hearing loss	HIV+, HEU	Sensorineural hearing loss secondary to cCMV
Neurocognitive development	HIV+, HEU	Reduced cognitive, motor abilities secondary to cCMV
Growth	HIV+, HEU	Impaired growth and recovery following ART
Altered vaccine responses	HIV+, HEU	Reduced immune responses to some vaccines, modified by age
Immune risk phenotype	HIV+	Immunosenescence, accelerated 'immune ageing'

HEU: HIV-exposed uninfected; cCMV: congenital CMV.

T cell responses play an important role in the containment of CMV infection [46,58] and are compromised by both pregnancy and HIV infection. HIV-specific CD4 and CD8 T cells are found in the cervix and breast milk, and CMV-specific T cells similarly contribute to suppression of mucosal CMV replication at these sites. HIV-specific CD8 T cell responses in breast milk are associated with protection of infants from breast milk HIV transmission [59]; CMV-specific effector CD8 T cells are also found in milk [60] and semen [61], and could play a similar role in modulating CMV transmission.

The impact of maternal ART on CMV transmission

WHO Option B+, which entails lifelong maternal ART for all HIV-infected pregnant women, is being adopted as the standard of care in many countries, and is likely to have a downstream impact on CMV transmission. The association between maternal immunosuppression/HIV viral load and CMV transmission risk suggests ART is likely to reduce the risk of congenital CMV transmission and delay postpartum transmission; however, current data are primarily limited to women who have received a short course of ART for prevention of mother-to-child transmission (PMTCT), or who only recently initiated ART. Short-course maternal ART did not have a significant effect on congenital CMV risk in two studies [62,63]. However, Guibert and colleagues noted a decreasing risk of congenital CMV in HIV-exposed infants with increasing maternal ART use over time in France [23]. In a US cohort, antenatal ART was associated with a lower risk of peripartum and early postnatal infection [63], and in two other studies earlier ART initiation during pregnancy was associated with reduced risk of infant congenital infection [29,64]. ART alone decreases blood CMV levels in the absence of anti-CMV therapy [65,66], and maternal immune restoration is also expected to reduce viral shedding in compartments relevant to transmission. However, the few reports to date have not found a significant effect of ART on breast milk [67] or cervical CMV levels [36]. Gianella *et al.* found a paradoxical increase in vaginal CMV shedding during the 2–4-month period after starting ART [68], and hypothesised transient inflammation during immune restoration could increase CMV replication. Studies involving women on long-term ART will be needed to determine the impact maternal ART will have on maternal CMV shedding and transmission.

CMV and HIV transmission

CMV may also facilitate HIV acquisition [26,41,64]. In the BAN study, infant CMV DNA detection at 24 weeks of life was associated with a 2.5-fold higher risk of death or HIV acquisition between 24 and 48 weeks [26]. In a South African cohort, breast milk CMV levels were positively associated with an increased risk of postpartum HIV transmission, after adjusting for maternal plasma or breast milk HIV RNA [41]; the authors speculated that CMV-induced immune activation could potentially recruit HIV-infected cells, induce HIV reactivation in infected breast milk cells, or contribute to localised immunosuppression facilitating HIV replication. Stimulation of cord blood mononuclear cells with CMV increased expression of CCR5, suggesting an additional mechanism by which CMV might increase susceptibility to HIV [69].

The impact of CMV co-infection on morbidity and mortality of HIV-exposed children

CMV-related morbidity in HIV-infected adults

CMV was among the most frequent AIDS-defining conditions in the pre-ART era [1]. Additionally, in the absence of severe immunosuppression, CMV co-infection has been associated with an increased risk of death, immune activation, HIV disease progression and non-AIDS-related morbidities. A report from the ICONA cohort of >6000 HIV-infected adults found that CMV co-infection was associated with a 53% increased risk of developing a severe non-AIDS defining event or non-AIDS related death over 15 years of follow-up [70]. CMV co-infection was also independently associated with a 2.27-fold increased risk of cardiovascular or cerebrovascular disease, but was not associated with non-AIDS-related malignancies or non-vascular neurological disease. These data suggest that CMV may contribute to diverse non-infectious inflammatory pathologies.

CMV co-infection and outcomes in HIV-infected children

In HIV-infected children with severe immunosuppression, CMV has been associated with retinitis, pneumonitis, hepatitis, enteritis, oesophagitis and encephalopathy [22,71–73] (Table 2). In an early ART-naïve cohort from the US, CMV-co-infected children were found to have a 2.5-fold increased risk of death or AIDS-defining criteria, a 2.5-fold increased risk of meeting CDC Category 3 criteria

and a 2.9-fold increased risk of HIV-associated encephalopathy [22]. Other cohorts similarly reported trends for earlier mortality during CMV co-infection, with symptomatic CMV disease present in many children [21,71]. The risk for CMV disease in HIV-infected children may be related to CMV viraemia. In healthy and HIV-infected adults, detection of CMV DNA in plasma is rare unless the CD4 cell count is <200 cells/mm^3 [32,74]. In contrast, HIV-infected infants experience prolonged and often high-level (>1000 CMV DNA copies/mL) CMV viraemia that can last for 2 or more years and correlates with the level of HIV RNA in plasma [25]. Plasma CMV DNA viral load is an independent predictor of mortality in HIV-infected adults and children, and high levels are also predictive of CMV disease [71,75–77]. The duration of CMV viraemia, and long-term relevance of prolonged viraemia in HIV-infected children, are unknown because few research studies follow children beyond 2 years.

A small number of studies has assessed the impact of CMV infection on disease and mortality in children receiving modern ART. In 424 HIV-exposed Malawian children, Chang *et al*. found infants with detectable CMV DNA in plasma at 24 weeks had a four-fold higher risk of subsequent mortality or HIV infection [26]. The high rate of congenital CMV associated with infant HIV suggests that long-term hearing and neurodevelopmental sequelae in these children are also likely (Table 2). In the PACTG 366 cohort, no association was found between CMV infection and neurocognitive development using a battery of tests [78]. A definitive understanding of the impact of CMV on long-term clinical outcomes will require extended follow-up of birth cohorts to discriminate the potentially differential effects of congenital and postpartum-acquired CMV.

Mechanisms by which CMV contributes to HIV pathogenesis

As Griffiths reports, CMV and HIV can interact directly in a number of ways that can facilitate replication of both viruses [79]. HIV RNA and CMV DNA viral loads are correlated in plasma, breast milk and cervix of co-infected women [30,32]. The two viruses infect a number of shared cell types and could interact directly through transactivation, through secretion of cytokines that reactivate provirus, or by increasing the HIV tropism through CMV's expression of receptor analogues or formation of pseudoviruses [79].

Persistent immune activation is a hallmark of HIV infection and its pathogenesis, and may be augmented by CMV. Acute CMV infection leads to an expansion of highly differentiated [80–82] and activated (CD38+, HLA-DR+, CD95+, Bcl-2^{low}) T cells [80,83], and the frequency of activated CD8+ T cells is reduced in both blood [84] and semen [61] following treatment with valganciclovir. Activation and expansion of CD4 T cells during acute CMV infection could expand the pool of target cells for HIV, leading to higher viral loads and perhaps larger viral reservoirs. Consistent with this hypothesis, Gianella found higher HIV proviral loads in the peripheral blood mononuclear cells (PBMC) of men who had detectable CMV DNA in semen or PBMC [85]. In a cohort of early ART-treated infants from South Africa (CHER Study), higher plasma CMV DNA levels at baseline were associated with increased HIV viral reservoir size after 2 years of ART [86]. CMV infection also induces expression of IL-6 [87], a cytokine associated with mortality in HIV-infected individuals. CMV IgG levels were associated with IL-6 and also soluble CD14+ levels in the plasma of CMV-co-infected women [88], suggesting that CMV may increase gut microbial translocation and persistent monocyte activation. Via this mechanism, CMV could contribute to comorbidities associated with persistent inflammation [89–91]. Non-communicable diseases associated with HIV, including metabolic, cardiovascular and renal disease are unstudied in African paediatric HIV cohorts to date, but are likely to increase in public health significance with increasing longevity of children on ART.

CMV may also affect susceptibility to other infections via immunomodulatory effects, which foster its own persistence but may also affect susceptibility to other infections [58]. CMV may increase or decrease responses to vaccination, depending on the type of antigen and the age of the host [92–94]. In the Swedish OCTO and NONA studies, CMV was associated with an immunological phenotype in the elderly, which is characterised by expansion of CD28-CD57+ CD8+ T cells and a low CD4:CD8 ratio, and is predictive of mortality and reduced cellular immune responses [95–97]. In HIV/CMV co-infected subjects, HIV-induced immunosenescence may synergise with CMV to further compromise immune responsiveness [98].

ART and immune reconstitution in children

Healthy neonates with congenital CMV infection can generate high-level, adult-like CMV-specific CD8 T cell responses [99,100]. However, the infant CD4 T cell response to CMV is qualitatively different in young children compared to adults; differences include a lower frequency of CMV-specific CD4 T cells, a decreased capacity to generate CMV-specific IFN-γ CD4 T cells and a lower production of IL-2 [100–102]. These immunological differences may enable prolonged viral replication and leave infants especially susceptible to CMV disease in the setting of HIV. The extent to which early infant ART improves CMV containment is not yet clear; however, in adults ART alone is often sufficient to promote CMV viraemia control [65,66]. IFN-γ-secreting CMV-specific CD4 and CD8 T cells, and proliferating CMV-specific CD4 T cells, are readily detectable at high frequencies in children with HIV infection, and persist following ART and HIV suppression [103–106]. This is in contrast to the reduction in HIV-specific T cell responses that occurs during ART, and suggests ongoing re-stimulation of CMV-specific T cells. In the ACTG366 cohort, CMV-negative children recovered their naïve and terminally differentiated CD8 T cell populations more quickly than CMV-infected children, suggesting that co-infection could impair immunological restoration of the T cell compartment when starting ART [107].

CMV co-infection and outcomes in HIV-exposed uninfected children

The relevance of CMV to HIV-exposed uninfected children (HEU) is currently unknown. The population of HEU is growing rapidly and it is thus critically important to establish whether CMV compromises outcomes in this population. As noted above, rates of congenital CMV are higher in HEU infants compared to unexposed children. Congenital CMV infection confers a high risk of sensorineural hearing loss (SNHL); Fowler *et al*. found that 18% of children experienced delayed onset hearing loss with a median age of detection of 24 months, and 23% of children experienced fluctuating SNHL [108]. The risk of SNHL in congenitally infected children born to mothers with CMV immunity is similar to those born to mothers with primary CMV infection [109], and it is thus likely that a significant proportion of HEU children with congenital CMV infection will experience significant hearing impairments. HEU infants often experience prolonged viraemia following primary CMV infection [25]. There is some evidence that the risk of hearing loss may be increased with higher levels of CMV replication; in HIV-unexposed children with congenital CMV, a low CMV viral load in blood or urine correlates with protection against SNHL in asymptomatic children [110,111].

Current data regarding the impact of postnatally acquired CMV on growth and developmental outcomes in HEU children are

extremely limited. A study in 120 Zambian children born to HIV-infected mothers found that CMV DNA detection in serum at 6 months of age was associated with lower length-for-age Z score at 18 months, and that CMV infection at 18 months of age was associated with lower head circumference Z score and lower Bayley psychomotor development index at 18 months [112]; however, the impact of CMV independent from infant HIV infection is unclear. A report from Malawi found higher levels of CMV DNA in breast milk were associated with lower length- and weight-for-age Z scores at 6 months in HEU infants [67]. A separate cohort of Malawian children found no association between CMV viraemia at 24 weeks and growth in HIV-exposed children [26]. To date, there have been no long-term birth cohorts examining the impact of CMV on development in HIV-exposed children, and these are urgently needed to understand interventional priorities.

Interventional challenges and concluding remarks

As noted above, improved access and efficacy of ART and PMTCT may have population effects on CMV transmission, and further research is urgently needed to understand whether ART alone will reverse some of the disease trends associated with CMV in HIV-exposed children. Preventing CMV presents unique challenges in this population. Interrupting early CMV acquisition would require establishment of protective immunity within the first days or weeks of life. Vaccine development currently aims to prevent primary CMV infection in pregnant women and downstream congenital CMV disease [113]. However, this strategy does not address the need to prevent *in utero* transmission in HIV-infected women where seroprevalence nears 100%. In a recent trial, hyperimmune globulin in pregnant women with primary CMV infection was not found to have a significant impact on rates of congenital CMV infection or neonatal disease [114]. Innovative vaccination strategies to boost maternal pre-existing immunity to CMV warrant exploration, as these could potentially reduce the risk of recurrent CMV infection during pregnancy, or improve the clinical outcome in HIV-exposed infants.

Antiviral therapy aimed at reducing maternal CMV shedding at sites relevant to transmission, or by giving prophylaxis to the infant, is an alternative approach to reduce CMV transmission. Although effective at preventing or reducing the severity of disease in both transplant recipients and congenitally infected infants, all currently licensed drugs with activity against CMV have haematological side effects or toxicities [115] that warrant cautionary use in pregnant women and infants. Among children with symptomatic congenital CMV infection, randomisation to intravenous ganciclovir or oral valganciclovir significantly improved hearing and neurodevelopmental outcomes [116–118]. Oral valganciclovir had better tolerability than intravenous ganciclovir, with a lower risk of neutropenia (~20% *vs* 63%, respectively) [116,117]. However, as the author of these studies notes, the risk/benefit balance of presumptive treatment for children with *asymptomatic* congenital CMV is unclear. Neutropenia is also common during ART initiation in adults and children with HIV [119,120], and also among HEU infants exposed to PMTCT [121]; hence additional considerations are necessary when evaluating the risks and benefits of CMV suppression in HIV-exposed infants. Whether maternal antiviral therapy could reduce the risk of CMV transmission is also unclear; valaciclovir given at standard dosing for HSV-2 suppression moderately reduced cervical CMV reactivation in HIV-infected women but had no impact on maternal breast milk CMV levels or CMV transmission risk [122]. Additionally, novel compounds are currently in clinical trials with improved safety profiles and high activity against CMV (such as maribavir [123], brincidofovir (CMX-001) [124] and letermovir [125]); the efficacy of these drugs remains to be determined [126] and clinical trials are ongoing, but these agents could be attractive candidates for trials to prevent CMV transmission or disease in HIV infected women and their children.

Conflicts of interest

None to declare.

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