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1. Introduction

1.1. HCMV epidemiology in Sub-Saharan Africa

1.1.1. HCMV seroprevalence

There have been over 25 published studies which present HCMV IgG seroprevalence data for sub-Saharan Africa patient groups and cohorts of healthy blood donors (Table 1). Up to eight different serology assays were used and older pre-ELISA methods might have slightly underestimated prevalence [1]. Antibodies to HCMV are generally present in high titres in seropositive individuals, so the use of different assays is unlikely to have had a major effect [2]. Hence, comparing these studies is primarily confounded by the diverse range of patient groups tested. Few studies stratify by age, or they do so using different groupings. Most of the studies use convenience samples, which do not provide accurate population-based estimates of prevalence.

The most striking observation is that HCMV primary infection appears to be endemic in young infants. A population-based study in Zambia of 460 healthy infants showed 83% HCMV seroprevalence by 18 months of age [3](Table 1). This backs up much older studies from the Gambia [4] and Nigeria [5]. This differs from the results of larger studies in the USA (n = 30,000) where HCMV seroprevalence ranges from 36% in 6–11 year-olds to 91% in those over 80 years old. The cumulative incidence of HCMV primary infection was ~1% per year from adolescence [6]. In the USA, non-white ethnicity and lower socioeconomic status (SES) were linked with 10-30 percentage point increases in seroprevalence [7]. A study of over 20,000 women in the U.K attending antenatal clinics found similar results, with increasing parity also being linked
with increased HCMV seroprevalence. This supports the notion that seronegative adult women contract primary HCMV infection from children who are shedding virus [8]. Figure 1 presents a model for cumulative HCMV seroprevalence by age with respect to SES, showing more rapid uptake in low SES communities, and delayed uptake in high SES communities. Conversely an Israeli study found the effect of ethnicity persisted even when corrected for gender, education and SES [9], and high HCMV seroprevalence has been described in populations with high SES groups [10, 11].

Whilst lower SES may be the main driver for endemic infant HCMV primary infection in sub-Saharan Africa, this is not the whole story. What factors, attributable to low SES, facilitate earlier HCMV transmission? HCMV is primarily transmitted through body fluids, being shed in urine, saliva [12, 13] and breast milk [14, 15]. In Nigeria, over-crowding was significantly associated with being HCMV seropositive, but source of drinking water, place of abode and type of toilet facility were not [16]. Some individuals remain seronegative into old age - even in sub-Saharan Africa where most people are infected in infancy. Human genetic variations may block or impair HCMV primary infection, as is seen with the CCR5 Δ32 mutation and HIV [17]. HCMV seronegative individuals have increased longevity, possibly linked with reduced clonal expansion of CD8 T cells and a larger reservoir of circulating naive T cells [18, 19] so early childhood primary infection with HCMV in sub-Saharan Africa may have profound effects. There is evidence linking early HCMV infections in sub-Saharan Africa with impaired physical and mental development [3], analogous to the known developmental CNS defects (hearing loss, mental retardation, cerebral palsy, seizures, chorioretinitis) caused by congenital HCMV infection [20, 21].

Figure 1. Model for the cumulative prevalence of primary HCMV seroconversion by age with respect to socioeconomic status (SES) groups.
### Table 1.
Comparison of HCMV seroprevalence in different countries

* Percentages in bold are the averages within each group, weighted by study size.

<table>
<thead>
<tr>
<th>Country (City)</th>
<th>Study population</th>
<th>N=</th>
<th>Assay</th>
<th>Reference</th>
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<tr>
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<td>Adult healthy blood donors</td>
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1.1.2. Molecular epidemiology

HCMV has a large genome, predicted to encode at least 165 proteins. This includes hyper-variable segments [38-41] containing genes which encode membrane-bound glycoproteins. These are embedded in the virion envelope or presented on the surface of infected cells, making them candidate targets for the host immune response. Most published studies of polymorphisms in these glycoproteins have concentrated on possible associations with and clinical disease or cellular tropism. No compelling connections have been reported in the literature to date, but much of the sequence data is from isolates from Europe, North America and Japan. There is little information regarding HCMV genotypes in Africa. In an early study investigating geographic differences in the frequency of certain HCMV genotypes from immunocompromised patients, they found that the distribution differed between Zimbabwe, Italy and California [42]. This study was limited to UL55 (virion surface glycoprotein gB: involved in cell entry and signaling)[43] which is relatively conserved between strains [40] and not linked with more variable glycoproteins [44]. A study of HCMV strains from 19 Malawian Kaposi’s sarcoma (KS) patients and 58 of their first-degree relatives detected HCMV readily in mouth rinse and urine specimens [45]. Two hypervariable glycoprotein genes were sequenced: gO (UL74) and gN (UL73) involved in promoting focal spread [46, 47] and virion morphogenesis and possible latency associated functions respectively [48, 49]. Studies from Zambia segregate variants of these two glycoproteins into eight linked groups [50, 51]. These studies and others from Africa have found evidence of co-infections with multiple HCMV strains [50, 52] and no evidence for geographic separation. This data contrasts with other herpesviruses such as HHV-6 [53] and KSHV [54]. The high prevalence of co-infections with multiple strains, in a broad range of patients, complicates genotyping studies and attempts to identify disease links with specific glycoprotein genotypes. New techniques combining PCR amplification with RFLP digestion could improve analysis of multiple strains and recombinants in pathological samples [55].

2. HCMV infections and HIV in Sub-Saharan Africa

2.1. General considerations

sub-Saharan Africa is at the epicentre of the HIV pandemic, with 1,900,000 new infections (18.9% children ≤ 14yrs of age) in 2010, and a total of 23.2 million people (13.4% children ≤ 14yrs of age) living with HIV. Progress is slow but new infections are down 16% on 2001, and HIV prevalence has declined in some sub-Saharan African countries. With the roll out of antiretroviral therapy (ART), the numbers of people dying from HIV is also down (30% decrease between 2004 and 2010) [56]. HCMV is an apex opportunistic pathogen, linked with HIV disease progression [57-59], so the HIV pandemic combined with over 80% of primary HCMV infections occurring during infancy, creates a unique environment. Active HCMV infections are common and present as complex co-infections with other viral, bacterial and fungal infections [60, 61]. A broader awareness of the frequency of co-infections and the complex interplay between different pathogens is needed.
2.2. Disease presentations and co-morbidity

The most common presentation of HCMV infection in HIV-infected patients is HCMV pneumonia, where co-infection with other respiratory pathogens such as tuberculosis and Pneumocystis jiroveci, is almost ubiquitous [50, 60]. HCMV is an important HIV co-infection, also linked with a range diseases including meningitis [62], encephalitis [63], psychological disorders [64], malaria [65], various dermatological conditions [66, 67] and those affecting mucosal epithelia [68, 69], hypoadrenalism [70], adrenalitis [71], gastritis [72, 73] and other herpesvirus infections [74]. There has been a huge (possibly disproportionate) focus on HCMV as a cause of HIV-associated retinitis. Globally it has been estimated that 5-25% of AIDS patients will suffer from HCMV retinitis in their lifetime [75] leading to an ‘epidemic of blindness’ [76]. Whilst the cohorts and diagnostic methods vary in different studies, HIV-associated HCMV retinitis is less common in sub-Saharan Africa than elsewhere, seen in just 0-8.5% of adult AIDS patients with ophthalmic conditions [77-83].

2.3. HCMV as a cause of death

It is unclear how much active HCMV infection is contributing to mortality in HIV infected people. One way to address this question is to measure mortality as a primary outcome. For example: a large longitudinal study of HIV infected miners in South Africa associated HCMV viraemia with a three-fold increase in mortality after just 11 months. The affect was weakened when controlling for CD4 T-cell count, WHO stage and HIV viral load– all conditions predictive of mortality [84]. A study of HIV-infected and -exposed Kenyan children found a strong correlation between HIV-1 and HCMV viral loads. Adjusting for maternal immunosuppression and HIV-1 viral load, HCMV viraemia during pregnancy was linked with high risk of death for mothers and infants in the 2 years following delivery [85]. It is difficult to prove that HCMV viraemia is not simply a bystander and is actually involved in pathology. This requires post mortem studies, which are difficult due to cultural factors [86]. Paediatric post mortem studies from sub-Saharan Africa identify HCMV as a common cause of death [87, 88], especially in HIV infected patients [89-91]. There is a need for new post-mortem data, from both prospective studies and routine cases, to better inform on the prevalence of active HCMV as a cause of death, and in particular, to calibrate HCMV viral loads pre-mortem with histopathological evidence of active HCMV infection post-mortem [92].

3. HCMV pneumonia in HIV infected children

Pneumonia is the most common cause of death in children <5 yrs of age globally, accounting for 18% of all deaths [93]. In sub-Saharan Africa, pneumonia is the leading cause of death in HIV-infected and -exposed children [94-97]. Across the region antibiotics are cheap and widely available, yet pneumonia is still a major cause of paediatric mortality. This is likely in part due to antibiotic resistance [98], but also several viral pathogens cause lower respiratory tract infections and remain undiagnosed and untreated.
HCMV pneumonia is very common in HIV-infected and –exposed in sub-Saharan Africa [99, 100] and is associated with rapid progression of HIV disease [101] and death [102-104]. A seminal post mortem study in 264 Zambian children who died of respiratory disease identified classical HCMV inclusions in the lung tissue of up to 22% of HIV-infected cases [60], and then follow-up molecular work found high loads of HCMV were virtually ubiquitous in the lung tissue of HIV-infected paediatric respiratory deaths [50]. HCMV pneumonia is virtually impossible to distinguish clinically from Pneumocystis jiroveci pneumonia and co-infections with both Pneumocystis jiroveci and tuberculosis are common in HIV-infected and -exposed infants [60, 61, 105]. In South Africa, HCMV pneumonia was more common than Pneumocystis jiroveci pneumonia and other viral pneumonias in HIV-infected children [106], and was histologically confirmed in 72% of HIV-infected and ventilated infant mortalities with severe pneumonia. The authors recommend empiric use of ganciclovir or other anti-HCMV drugs in HIV-infected children with severe pneumonia who are not responding to co-trimoxazole [107].

4. HCMV Congenital Infection in sub-Saharan Africa

Congenital HCMV is generally defined by the detection of viral DNA and/or IgM antibody in infant sera within the first 3 weeks post-partum [108]. It is a damaging infection initiated by either primary or reactivated infection in the mother during pregnancy, although congenital HCMV infections transmitted from mothers with pre-existing immunity can be less severe [109]. Congenital HCMV is the major viral cause of mental and physical disability in children, infecting 0.2-2.2% of newborns [110, 111]. Around 7-11% of infected foetuses are then born with symptoms [112, 113], with a neonatal mortality rate of 20-30% [114, 115]. Of those congenitally infected (both symptomatic and asymptomatic), up to 28% will develop late sequelae [116]. Symptoms include growth retardation, hepatosplenomegaly, jaundice, pneumonia, gastrointestinal, and neurological disease such as sensorineural hearing loss, mental retardation, chorioretinitis, seizures [117] and cerebral palsy [118].

Congenital HCMV infection was considered rare in populations with high adult seroprevalence [33]. A study of 2032 newborn infants in the Ivory Coast cultured HCMV from urine and showed congenital HCMV infection in 1.4% of all births [119]. In sub-Saharan Africa, congenital HCMV largely reflects maternal reactivations or re-infections, which may not result in severe disease in the child [109]. However, a few studies from the region suggest congenital HCMV maybe a significant cause of morbidity and mortality. A study from Zambia associated HCMV antibody titres above 1:1024 with still births [120]. HCMV IgM antibodies were detected in 24% of 99 newborn babies who were jaundiced, died within a few days of birth or showed gross congenital abnormalities [121]. Cervical shedding of HCMV is very common in HIV-infected women, and is readily detected in amniotic fluid collected at C-section [122, 123]. A Gambian study found the prevalence of congenital CMV among healthy neonates was 5.4%, at least 2-fold higher than reported in industrialized countries. Congenitally infected children were more often first born babies, more frequently born in crowded compounds and active placental malaria was more prevalent. During the first year of follow up, mothers of congenitally infected children reported more health complaints for their child [124]. Recently
a study from Zambia has shown that HCMV seroprevalence in 18 month old infants is linked with impaired growth and mental development [3]. There is a need for more prospective studies to investigate the clinical significance of congenital HCMV infections in sub-Saharan Africa.

5. HCMV diagnosis and treatment in Sub-Saharan Africa

One of the greatest challenges for HCMV diagnosis in this region is to differentiate clinically active from sub-clinical infection. Serological tests for HCMV IgM are useful for diagnosing primary infections in infants, particularly congenital infections in neonates, but the majority of the disease burden is caused by re-activation or re-infections in immunocompromised patients. Detection of the virus itself was traditionally achieved using culture-based methods. These are time-consuming and require well-trained staff and a well-serviced diagnostic laboratory. Moreover, HCMV culture is not very sensitive. For these reasons, quantitative DNA-based molecular diagnostics are now commonly used to detect active HCMV infections. The required infrastructure is becoming commonly available at tertiary and secondary referral centres across sub-Saharan Africa, often donated by international research projects. However, low-level HCMV reactivations are common in a wide range of patients, linked with reduced immune surveillance due to other infections, illness or malnutrition.

Most studies of HCMV viral loads with respect to disease outcomes are in the transplant field, where viral loads within the range of $10^4$ to $10^6$ copies/ml whole blood have been suggested to be indicative of active disease, depending on the specific patient group [125]. An autopsy study found that a cut off of $10^4$ copies/ml whole blood, gave a specificity and positive predictive value of 100% for HCMV disease, making the commercial assay used (COBAS AMPLICOR CMV Monitor test - Roche) better for ‘ruling in’, than ‘ruling out’ [126]. There is a need for prospective studies in sub-Saharan Africa to monitor HCMV viral loads in patients with HIV-associated pneumonia, and infants with congenital HCMV infection, the two major HCMV disease groups in the region – although there are also transplant recipients in sub-Saharan Africa [127]. HCMV is shed in high loads in both urine and saliva (non-invasive specimens ideal for low income settings) and detection of virus DNA in these specimens should be evaluated versus viraemia, as potentially useful markers of active disease.

Several drugs are licensed for the treatment of HCMV infections, although they are expensive and broadly unavailable in sub-Saharan Africa. At some tertiary referral centres in South Africa, intravenous ganciclovir is used to treat HCMV pneumonia in HIV-infected and -exposed children failing antibiotic or anti-mycobacterial therapy. Decisions are largely consultant-led but two descriptive studies have reported dramatic reductions in mortality due to ganciclovir [106, 107]. Readers are advised to look up the latest guidelines on treatment of HCMV and to check the correct doses, side effects and dosing schedules. In South African centres, PCR or culture-proven HCMV disease is typically treated with 5mg/kg intravenously every 12hrs for 14-21 days, and then daily maintenance therapy at 5mg/kg [94]. But there is an
urgent need for further descriptive studies to identify patients for treatment. Randomized controlled clinical trials are needed to evaluate safety and efficacy.

The introduction of expensive antiviral treatments in low income settings is always problematic; Ethics review boards may state that it is unethical to trial antiviral drugs which are unaffordable and inaccessible to the majority of the affected patients. The path to new treatments has to start somewhere, and as scientists we favour evidence as the basis for action. The case of CD4 testing and antiretroviral therapy has proven that resources can be mobilized from a range of stake holders, including governments, NGOs and private enterprise [128-130]. A second ethical dilemma is that if the drug is being used successfully in South Africa to treat HIV-associated HCMV pneumonia, is it ethical for Ganciclovir trials to administer placebos? When answering such ethical questions we should note that HCMV affects a broad range of patient groups across sub-Saharan Africa, including congenitally infected neonates, HIV infected infants, children and adults causing pneumonia, specific organ disease (eg. retinitis, encephalitis, gastritis) and disseminated infection. Furthermore, malnutrition and co-infection with other common pathogens (Malaria, Tuberculosis, *Pneumocystis jiroveci* etc.) are prevalent. For this diverse patient group, the evidence base for the optimal dose, duration and route of administration is poor [131].

6. Effect of HCMV on vaccine efficacy and immune senescence in Sub-Saharan Africa

Infant vaccination programmes are a central component of national paediatric disease prevention strategies in sub-Saharan Africa [132], but they are less effective than equivalent programmes in high income populations. For example: The efficacy of live attenuated measles virus vaccine in Europe and North America is over 90% [133-135] whereas in West Africa it is below 70% [136-138]. This could be partly due to the higher infectious disease burden in sub-Saharan Africa, which may affect antibody [139, 140] and cytokine [141] responses to vaccination, and also reduced vaccine performance in HIV-infected children [132]. With 3.1 million children living with HIV/AIDS across the region [56], vaccine safety and efficacy must be independently assessed in this significant and vulnerable patient group. HIV-infected children can generally seroconvert in response to both live-attenuated and inactivated/subunit vaccines, but the immune response is generally weaker with lower antibody levels and seroprotection rates in HIV-infected children [142-144]. The weaker immune response in HIV-infected children could be due to defective antigen presentation, defective B-cell priming or impaired differentiation into memory cells, impaired primary response due to low CD4, loss of protective antibodies or loss of immunological memory of T and B cells after priming [143].

Most HIV-infected children in sub-Saharan Africa will also be infected with HCMV, which encodes over thirty genes with potential immunomodulatory functions. These genes may affect classical and non-classical major histocompatibility complex (MHC) protein function, leukocyte migration and activation, cytokine responses and host cell susceptibility to apoptosis [43]. HCMV can infect and initiate gene expression in an extraordinarily broad range of cell
types, although IE gene transcripts have not been detected in T- or B-lymphocytes [145, 146]. Despite this, HCMV influences cell-mediated immunity. T-cell populations in HCMV-infected infants in the Gambia showed higher levels of differentiation [147, 148] and similar HCMV-induced differentiation in elderly non-African populations is associated with depleted naive T-cell populations and impaired vaccine responses [149]. HCMV infection is also associated with a decline in naive T cells and impaired T-cell reconstitution in HIV infected adults initiating HAART [150]. But naive T-cell populations appear unaffected by HCMV infection in African children, and infection was not linked with impaired T-cell responses to measles virus vaccination [151], with HCMV activated T-helpers possibly improving measles antibody response [152]. A study in older African children, found that HIV-negative Malawian teenagers had a lower percentage of naïve T cells, higher memory T and higher CD28- memory T-cells, compared to age-matched UK teenagers. Whilst all of the adolescents tested in Malawi were seropositive for HCMV, seroprevalence was just 36% in the UK group, and was associated with a reduced percentage of naïve T cells and an increased percentage of CD28- memory T cells in the periphery [153].

Whilst more evidence is required, these studies suggest early infant infection with HCMV, and maybe a general higher burden of infectious disease, contribute to a more rapid ageing of the immune system in sub-Saharan Africa. Whilst access to anti-HCMV drugs would likely significantly reduce morbidity and mortality in acute HCMV infections, such as congenitally infected infants or HIV/AIDS patients with pneumonia or disseminated HCMV, the implications of a successful HCMV vaccine have potentially far-reaching benefits across the region. Future studies evaluating vaccine efficacy in sub-Saharan Africa should stratify by HCMV serostatus, and where facilities permit, include work on HCMV genotypes and flow cytometric analysis to further characterise the effect of infant HCMV infection on immunity.

7. Summary

In sub-Saharan Africa, HCMV infection is endemic in young infants where it is linked with impaired physical and mental development [3], giving the infection a unique epidemiology across the region, with a potentially broad-reaching impact on the health of southern African populations. Studies conducted in sub-Saharan Africa and elsewhere, have shown that HCMV is a serious cause or morbidity and mortality, in both immunocompromised groups and congenitally infected children. In a region where 23.2 million people are living with HIV and most of the population are infected with HCMV in infancy [124], more prospective studies are required to better characterise the impact of HCMV in sub-Saharan Africa. This will lay the foundations for future clinical trials of anti-HCMV drugs in patient sub-sets in whom there is strong evidence that they might be effective. Drugs such as ganciclovir are already used in South Africa as life-saving treatment for HIV-infected children with severe pneumonia that is not responsive to antibiotic or anti-mycobacterial therapy. Furthermore, the clinical impact and importance of HCMV infections in sub-Saharan Africa may increase over the next decade for several reasons: Wider access to ART is resulting in increasing numbers of older HIV infected patients; Cancer incidence is forecast to increase by 32% across sub-Saharan Africa
between 2010 and 2020 [154]; The number of transplant recipients is also set to increase, as the capacity of tertiary care centres develops and improves.

Acknowledgements

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References


