We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 2

Human Cytomegalovirus (HCMV) Infection in Sub-Saharan Africa

Matthew Bates, Kunda Musonda and Alimuddin Zumla

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54907

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].

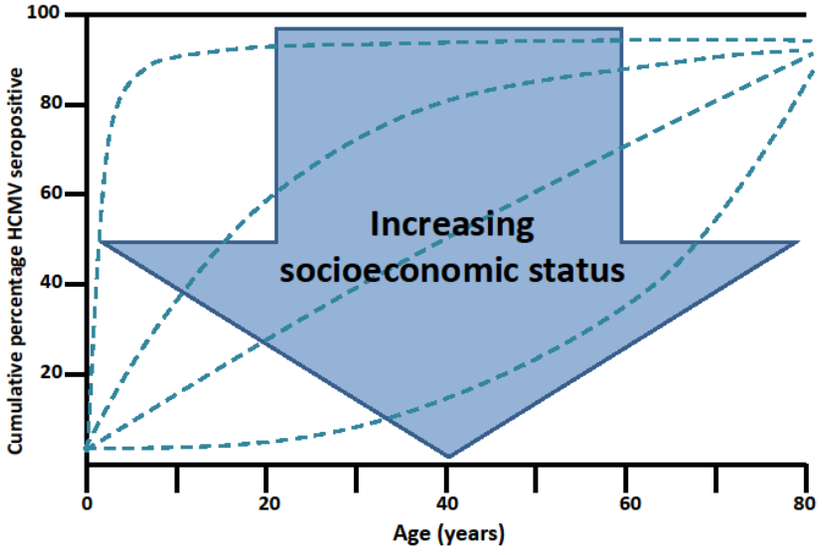

Figure 1. Model for the cumulative prevalence of primary HCMV seroconversion by age with respect to socioeconomic status (SES) groups.

Country (City)	HCMV IgG seroprevalence*	Study population	N=	Assay	Reference
HIV- Adults	**79.3%**				
Nigeria (Ibadan)	55.0%	Adult healthy blood donors	110	Compliment fixation	[22]
Mali (Bamako)	58.0%	Adult healthy HIV-ve blood donors	100	ELISA (Platelia® Sanofi Pasteur)	[23]
Tanzania (Dar Es Salaam)	66.9%	Adult inpatients with STDs (HIV-ve)	158	Passive latex agglutination (CMV-scan card)	[24]
Ghana (Accra)	77.6%	Adult healthy HIV-ve blood donors	3275	ELISA IgG; Diamedix Corporation, USA	[25]
Burkina Faso (Bobo Dioulasso)	82.0%	Adult healthy HIV-ve blood donors	28	ELISA (Platelia® Sanofi Pasteur)	[26]
Ghana (Kumasi)	94.3%	Health Blood Donors	112	Platella TM CMV IgG (Bio-Rad)	[27]
Somalia (Mogadishu)	96%	Healthy adult makes	102	unspecified	[28]
Somalia (Mogadishu)	96%	Adult males attending STD clinic	101	unspecified	[28]
Kenya (Nairobi)	97.0%	Adult healthy blood donors (1.3% HIV+)	400	unspecified	[29]
HIV+ Adults	**80.0%**				
Mali (Bamako)	71.0%	HIV+ Adults	100	ELISA (Platelia® Sanofi Pasteur)	[23]
Tanzania (Dar Es Salaam)	72.3%	Adult inpatients with STDs (HIV+ve)	65	Passive latex agglutination (CMV-scan card)	[24]
Ghana (Kumasi)	92.7%	Asymptomatic HIV+ Adults	55	Platella TM CMV IgG (Bio-Rad)	[27]
Botswana (Gaborone)	96.3%	Asymptomatic HIV+ Adults	43		[30]
AIDS Patients	**81.9%**				
Ghana (Accra)	59.2%	AIDS patients	250	ELISA IgG; Diamedix Corporation, USA	[25]
Mali (Bamako)	89.0%	AIDS patients	100	ELISA (Platelia® Sanofi Pasteur)	[23]
Tanzania (Dar Es Salaam)	90.7%	AIDS patients	43	Passive latex agglutination (CMV-scan card)	[24]
Ghana (Kumasi)	98.3%	AIDS patients	239	Platella TM CMV IgG (Bio-Rad)	[27]
Burkina Faso (Bobo Dioulasso)	100%	AIDS patients	36	ELISA (Platelia® Sanofi Pasteur)	[26]
Pregnant Women	**86.3%**				
Tanzania (Dar Es Salaam)	60.6%	HIV-ve pregnant women	127	Passive latex agglutination (CMV-scan card)	[24]
Tanzania (Dar Es Salaam)	85.7%	HIV+ve pregnant women	14	Passive latex agglutination (CMV-scan card)	[24]
Benin (Cotonou)	97.2%	Pregnant women	211	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[31]
Nigeria (Ibadan)	100%	Pregnant (some not pregnant) women	80	peroxidase enzyme-labelled antigen (ELA)	[5]
South Africa (Johannesburg)	86.4%	Pregnant Women	2160	ELISA (M A Bioproducts, Virginia)	[32]
Children	**88.4%**				
Cameroon (Kumba City)	88.5%	Healthy Children 4-6 years	~100	ELISA (unspecified)	[33]
Cameroon (Kumba City)	98.0%	Healthy Children 11-14 years	~100	ELISA (unspecified)	[33]
Gambia (Banjul)	86.4%	Healthy Children 12 months	178	Immunofluoruescence?	[4]
Mozambique (SE Transvaal)	88.0%	Refugee Children under 5yrs	~100	ELISA (unspecified)	[34]
Mozambique (SE Transvaal)	96.4%	Refugee Children under 11 years	~100	ELISA (unspecified)	[34]
Nigeria (Ibadan)	100%	Newborn Infants	21	peroxidase enzyme-labelled antigen (ELA)	[5]
Zambia (Lusaka)	83%	Healthy 18-month old infants	460	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[3]
Kenya (Nairobi)	100%	HIV-1 infected street children	71	ELISA kit (Murex)	[35]
Tuberculosis studies	**83.0%**				
Nigeria (Ibadan)	50.6%	Non-TB	89	Compliment fixation	[22]
Nigeria (Ibadan)	87.6%	Tuberculosis Patients	161	Compliment fixation	[22]
Burkina Faso (Bobo Dioulasso)	95.0%	TB+ HIV+ve	40	ELISA (Platelia® Sanofi Pasteur)	[26]
Burkina Faso (Bobo Dioulasso)	96.5%	Tuberculosis Patients	80	ELISA (Platelia® Sanofi Pasteur)	[26]
Burkina Faso (Bobo Dioulasso)	97.5%	TB+ HIV-ve	40	ELISA (Platelia® Sanofi Pasteur)	[26]
Other	**95.9%**				
Eritrea (various locations)	94.8%	Various	439	ELISA (unspecified)	[36]
Burundi (Bujumbura)	99.0%	Ophthalmic patients	154	ELISA Enzygnost CMV (Abbott Laboratories, Chicago, IL, USA	[37]

Table 1. Comparison of HCMV seroprevalence in different countries * Percentages in bold are the averages within each group, weighted by study size.

1.1.2. Molecular epidemiology

HCMV has a large genome, predicted to encode at least 165 proteins. This includes hypervariable 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 a tuberculosis and *Pneumocystis jirovecci*, 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 jirovecci* pneumonia and co-infections with both *Pneumocystis jirovecci* and tuberculosis are common in HIV-infected and -exposed infants [60, 61, 105]. In South Africa, HCMV pneumonia was more common than *Pneumocystis jirovecci* 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

http://dx.doi.org/10.5772/54907

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 Jirovecci* 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

This work was supported by the European Commission (grant ADAT-number SANTE/2006/129-131). AZ is grant holder and MB study coordinator. AZ and MB are supported by the European and Developing Countries Clinical Trials Partnership (EDCTP grants REMOX, PANACEA and TB-NEAT), Netherlands; UK Medical Research Council (MRC); UBS Optimus Foundation, Switzerland; University College London Hospitals Comprehensive Biomedical Research Centre (UCLH-CBRC); and the UCLH National Health Service (NHS) Foundation Trust. KM is supported by the Commonwealth Scholarship Commission, U.K.

Author details

Matthew Bates[1,2*], Kunda Musonda[1,2,3] and Alimuddin Zumla[2]

*Address all correspondence to: matthew.bates@ucl.ac.uk

1 UNZA-UCLMS Research and Training Programme and HerpeZ, University of Zambia School of Medicine/University Teaching Hospital, Lusaka, Zambia

2 University College London (UCL) Medical School, Department of Infection, Centre for Infectious Diseases and International Health, Royal Free Hospital, London, UK

3 London School of Hygiene and Tropical Medicine (LSHTM), Department of Infectious Tropical Diseases, Pathogen Molecular Biology Unit, London, UK

References

[1] Booth JC, Hannington G, Bakir TM, Stern H, Kangro H, Griffiths PD, et al. Comparison of enzyme-linked immunosorbent assay, radioimmunoassay, complement fixation, anticomplement immunofluorescence and passive haemagglutination techniques for detecting cytomegalovirus IgG antibody. J Clin Pathol. 1982 Dec;35(12):1345-8.

[2] Booth JC, Kangro HO, Liu KM, el Mohandes L, Tryhorn YS. Discordant results obtained on testing sera from immunocompromised patients for cytomegalovirus IgG by enzyme-linked immunosorbent assay and radioimmunoassay. J Virol Methods. 1989 Oct;26(1):77-89.

[3] Gompels UA, Larke N, Sanz-Ramos M, Bates M, Musonda K, Manno D, et al. Human cytomegalovirus infant infection adversely affects growth and development in maternally HIV-exposed and unexposed infants in Zambia. Clin Infect Dis. 2012 Feb 1;54(3):434-42.

[4] Bello C, Whittle H. Cytomegalovirus infection in Gambian mothers and their babies. J Clin Pathol. 1991 May;44(5):366-9.

[5] Williams JO, Fagbami AH, Omilabu SA. Cytomegalovirus antibodies in Nigeria. Trans R Soc Trop Med Hyg. 1989 Mar-Apr;83(2):260.

[6] Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. Clin Infect Dis. 2006 Nov 1;43(9):1143-51.

[7] Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2010 Jul;20(4):202-13.

[8] Tookey PA, Ades AE, Peckham CS. Cytomegalovirus prevalence in pregnant women: the influence of parity. Arch Dis Child. 1992 Jul;67(7 Spec No):779-83.

[9] Green MS, Cohen D, Slepon R, Robin G, Wiener M. Ethnic and gender differences in the prevalence of anti-cytomegalovirus antibodies among young adults in Israel. Int J Epidemiol. 1993 Aug;22(4):720-3.

[10] Ahlfors K, Ivarsson SA, Johnsson T, Svanberg L. Primary and secondary maternal cytomegalovirus infections and their relation to congenital infection. Analysis of maternal sera. Acta Paediatr Scand. 1982 Jan;71(1):109-13.

[11] Numazaki K, Fujikawa T, Chiba S. Relationship between seropositivity of husbands and primary cytomegalovirus infection during pregnancy. J Infect Chemother. 2000 Jun;6(2):104-6.

[12] Bello CS. Transmission of cytomegalovirus in the Gambia. West Afr J Med. 1992 Apr-Jun;11(2):140-5.

[13] Butler LM, Neilands TB, Mosam A, Mzolo S, Martin JN. A population-based study of how children are exposed to saliva in KwaZulu-Natal Province, South Africa: implications for the spread of saliva-borne pathogens to children. Trop Med Int Health. 2010 Apr;15(4):442-53.

[14] Jim WT, Shu CH, Chiu NC, Chang JH, Hung HY, Peng CC, et al. High cytomegalovirus load and prolonged virus excretion in breast milk increase risk for viral acquisition by very low birth weight infants. Pediatr Infect Dis J. 2009 Oct;28(10):891-4.

[15] Kerrey BT, Morrow A, Geraghty S, Huey N, Sapsford A, Schleiss MR. Breast milk as a source for acquisition of cytomegalovirus (HCMV) in a

premature infant with sepsis syndrome: detection by real-time PCR. J Clin Virol. 2006 Mar;35(3):313-6.

[16] Oginni FO, Alao OO, Mamman A, Araoye MO, Joseph E. Effect of Demographic Variables on Cytomegalovirus Antibody Seropositivity among Prospective Blood Donors in Jos, Nigeria. Niger Postgrad Med J. 2009 Mar; 16(1):21-4.

[17] Blanpain C, Libert F, Vassart G, Parmentier M. CCR5 and HIV infection. Receptors Channels. 2002;8(1):19-31.

[18] Hadrup SR, Strindhall J, Kollgaard T, Seremet T, Johansson B, Pawelec G, et al. Longitudinal studies of clonally expanded CD8 T cells reveal a repertoire shrinkage predicting mortality and an increased number of dysfunctional cytomegalovirus-specific T cells in the very elderly. J Immunol. 2006 Feb 15;176(4):2645-53.

[19] Khan N, Shariff N, Cobbold M, Bruton R, Ainsworth JA, Sinclair AJ, et al. Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. J Immunol. 2002 Aug 15;169(4):1984-92.

[20] Pass RF. Congenital cytomegalovirus infection and hearing loss. Herpes. 2005 Oct;12(2):50-5.

[21] Pass RF, Fowler KB, Boppana SB, Britt WJ, Stagno S. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. J Clin Virol. 2006 Feb;35(2):216-20.

[22] Olaleye OD, Omilabu SA, Baba SS. Cytomegalovirus infection among tuberculosis patients in a chest hospital in Nigeria. Comp Immunol Microbiol Infect Dis. 1990;13(2):101-6.

[23] Maiga, II, Tounkara A, Coulibaly G, Kouriba B. [Seroprevalence of the human cytomegalovirus among blood donors and AIDS patients in Bamako]. Sante. 2003 Apr-Jun;13(2):117-9.

[24] Mhalu F, Haukenes G. Prevalence of cytomegalovirus antibody in pregnant women, AIDS patients and STD patients in Dar es Salaam. AIDS. 1990 Dec;4(12):1294-5.

[25] Adjei AA, Armah HB, Gbagbo F, Boamah I, Adu-Gyamfi C, Asare I. Seroprevalence of HHV-8, CMV, and EBV among the general population in Ghana, West Africa. BMC Infect Dis. 2008;8:111.

[26] Ledru E, Diagbouga S, Ledru S, Cauchoix B, Yameogo M, Chami D, et al. A study of Toxoplasma and Cytomegalovirus serology in tuberculosis and in HIV-infected patients in Burkina Faso. Acta Trop. 1995 May;59(2): 149-54.

[27] Compston LI, Li C, Sarkodie F, Owusu-Ofori S, Opare-Sem O, Allain JP. Prevalence of persistent and latent viruses in untreated patients infected with HIV-1 from Ghana, West Africa. J Med Virol. 2009 Nov;81(11):1860-8.

[28] Ismail SO, Ahmed HJ, Grillner L, Hederstedt B, Issa A, Bygdeman SM. Sexually transmitted diseases in men in Mogadishu, Somalia. Int J STD AIDS. 1990 Mar;1(2):102-6.

[29] Njeru DG, Mwanda WO, Kitonyi GW, Njagi EC. Prevalence of cytomegalovirus antibodies in blood donors at the National Blood Transfusion Centre, Nairobi. East Afr Med J. 2009 Dec;86(12 Suppl):S58-61.

[30] Wester CW, Bussmann H, Moyo S, Avalos A, Gaolathe T, Ndwapi N, et al. Serological evidence of HIV-associated infection among HIV-1-infected adults in Botswana. Clin Infect Dis. 2006 Dec 15;43(12):1612-5.

[31] Rodier MH, Berthonneau J, Bourgoin A, Giraudeau G, Agius G, Burucoa C, et al. Seroprevalences of Toxoplasma, malaria, rubella, cytomegalovirus, HIV and treponemal infections among pregnant women in Cotonou, Republic of Benin. Acta Trop. 1995 Aug;59(4):271-7.

[32] Schoub BD, Johnson S, McAnerney JM, Blackburn NK, Guidozzi F, Ballot D, et al. Is antenatal screening for rubella and cytomegalovirus justified? S Afr Med J. 1993 Feb;83(2):108-10.

[33] Stroffolini T, Ngatchu T, Chiaramonte M, Giammanco A, Maggio M, Sarzana A, et al. Prevalence of cytomegalovirus seropositivity in an urban childhood population in Cameroon. New Microbiol. 1993 Jan;16(1):83-5.

[34] Bos P, Steele AD, Peenze I, Aspinall S. Sero-prevalence to hepatitis B and C virus infection in refugees from Mozambique in southern Africa. East Afr Med J. 1995 Feb;72(2):113-5.

[35] Chakraborty R, Rees G, Bourboulia D, Cross AM, Dixon JR, D'Agostino A, et al. Viral coinfections among African children infected with human immunodeficiency virus type 1. Clin Infect Dis. 2003 Apr 1;36(7):922-4.

[36] Ghebrekidan H, Ruden U, Cox S, Wahren B, Grandien M. Prevalence of herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus infections in Eritrea. J Clin Virol. 1999 Jan;12(1):53-64.

[37] Cochereau I, Mlika-Cabanne N, Godinaud P, Niyongabo T, Poste B, Ngayiragije A, et al. AIDS related eye disease in Burundi, Africa. Br J Ophthalmol. 1999 Mar;83(3):339-42.

[38] Murphy E, Yu D, Grimwood J, Schmutz J, Dickson M, Jarvis MA, et al. Coding potential of laboratory and clinical strains of human cytomegalovirus. Proc Natl Acad Sci U S A. 2003 Dec 9;100(25):14976-81.

[39] Davison AJ, Dolan A, Akter P, Addison C, Dargan DJ, Alcendor DJ, et al. The human cytomegalovirus genome revisited: comparison with the chimpanzee cytomegalovirus genome. J Gen Virol. 2003 Jan;84(Pt 1):17-28.

[40] Dolan A, Cunningham C, Hector RD, Hassan-Walker AF, Lee L, Addison C, et al. Genetic content of wild-type human cytomegalovirus. J Gen Virol. 2004 May;85(Pt 5):1301-12.

[41] Qi Y, Mao ZQ, Ruan Q, He R, Ma YP, Sun ZR, et al. Human cytomegalovirus (HCMV) UL139 open reading frame: Sequence variants are clustered into three major genotypes. J Med Virol. 2006 Apr;78(4):517-22.

[42] Zipeto D, Hong C, Gerna G, Zavattoni M, Katzenstein D, Merigan TC, et al. Geographic and demographic differences in the frequency of human cytomegalovirus gB genotypes 1-4 in immunocompromised patients. AIDS Res Hum Retroviruses. 1998 Apr 10;14(6):533-6.

[43] Mocarski ES, Jr; Shenk, T; Pass, R.F. Cytomegaloviruses. In: D.M Knipe PMHea, editor. Fields Virology. 5 ed. Philidelphia: Lippincot, Williams and Wilkins; 2007. p. 2701-72.

[44] Rasmussen L, Geissler A, Winters M. Inter- and intragenic variations complicate the molecular epidemiology of human cytomegalovirus. J Infect Dis. 2003 Mar 1;187(5):809-19.

[45] Beyari MM, Hodgson TA, Kondowe W, Molyneux EM, Scully C, Porter SR, et al. Inter- and intra-person cytomegalovirus infection in Malawian families. J Med Virol. 2005 Apr;75(4):575-82.

[46] Jiang XJ, Adler B, Sampaio KL, Digel M, Jahn G, Ettischer N, et al. UL74 of human cytomegalovirus contributes to virus release by promoting secondary envelopment of virions. J Virol. 2008 Jan 9.

[47] Jiang XJ, Sampaio KL, Ettischer N, Stierhof YD, Jahn G, Kropff B, et al. UL74 of human cytomegalovirus reduces the inhibitory effect of gH-specific and gB-specific antibodies. Arch Virol. 2011 Dec;156(12):2145-55.

[48] Mach M, Osinski K, Kropff B, Schloetzer-Schrehardt U, Krzyzaniak M, Britt W. The carboxy-terminal domain of glycoprotein N of human cytomegalovirus is required for virion morphogenesis. J Virol. 2007 May;81(10):5212-24.

[49] Pignatelli S, Dal Monte P, Rossini G, Camozzi D, Toscano V, Conte R, et al. Latency-associated human cytomegalovirus glycoprotein N genotypes in monocytes from healthy blood donors. Transfusion. 2006 Oct;46(10):1754-62.

[50] Bates M, Monze M, Bima H, Kapambwe M, Kasolo FC, Gompels UA. High human cytomegalovirus loads and diverse linked variable genotypes in both HIV-1 infected and exposed, but uninfected, children in Africa. Virology. 2008 Dec 5;382(1):28-36.

[51] Mattick C, Dewin D, Polley S, Sevilla-Reyes E, Pignatelli S, Rawlinson W, et al. Linkage of human cytomegalovirus glycoprotein gO variant groups identified from worldwide clinical isolates with gN genotypes, implications for disease associations and evidence for N-terminal sites of positive selection. Virology. 2004 Jan 20;318(2):582-97.

[52] Bradley AJ, Kovacs IJ, Gatherer D, Dargan DJ, Alkharsah KR, Chan PK, et al. Genotypic analysis of two hypervariable human cytomegalovirus genes. J Med Virol. 2008 Sep;80(9):1615-23.

[53] Bates M, Monze M, Bima H, Kapambwe M, Clark D, Kasolo FC, et al. Predominant human herpesvirus 6 variant A infant infections in an HIV-1 endemic region of Sub-Saharan Africa. J Med Virol. 2009 May;81(5):779-89.

[54] Kasolo FC, Spinks J, Bima H, Bates M, Gompels UA. Diverse genotypes of Kaposi's sarcoma associated herpesvirus (KSHV) identified in infant blood infections in African childhood-KS and HIV/AIDS endemic region. J Med Virol. 2007 Oct;79(10):1555-61.

[55] Grosjean J, Hantz S, Cotin S, Baclet MC, Mengelle C, Trapes L, et al. Direct genotyping of cytomegalovirus envelope glycoproteins from toddler's saliva samples. J Clin Virol. 2009 Dec;46 Suppl 4:S43-8.

[56] WHO. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011. WHO press; 2011.

[57] Kitchen BJ, Engler HD, Gill VJ, Marshall D, Steinberg SM, Pizzo PA, et al. Cytomegalovirus infection in children with human immunodeficiency virus infection. Pediatr Infect Dis J. 1997 Apr;16(4):358-63.

[58] Kovacs A, Schluchter M, Easley K, Demmler G, Shearer W, La Russa P, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. N Engl J Med. 1999 Jul 8;341(2):77-84.

[59] Jeena PM, Coovadia HM, Bhagwanjee S. Prospective, controlled study of the outcome of human immunodeficiency virus-1 antibody-positive children admitted to an intensive care unit. Crit Care Med. 1996 Jun;24(6):963-7.

[60] Chintu C, Mudenda V, Lucas S, Nunn A, Lishimpi K, Maswahu D, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet. 2002 Sep 28;360(9338):985-90.

[61] Rennert WP, Kilner D, Hale M, Stevens G, Stevens W, Crewe-Brown H. Tuberculosis in children dying with HIV-related lung disease: clinical-pathological correlations. Int J Tuberc Lung Dis. 2002 Sep;6(9):806-13.

[62] Kelly MJ, Benjamin LA, Cartwright K, Ajdukiewicz KM, Cohen DB, Menyere M, et al. Epstein-barr virus coinfection in cerebrospinal fluid is

associated with increased mortality in Malawian adults with bacterial meningitis. J Infect Dis. 2011 Jan 1;205(1):106-10.

[63] Bell JE, Lowrie S, Koffi K, Honde M, Andoh J, De Cock KM, et al. The neuropathology of HIV-infected African children in Abidjan, Cote d'Ivoire. J Neuropathol Exp Neurol. 1997 Jun;56(6):686-92.

[64] Tedla Y, Shibre T, Ali O, Tadele G, Woldeamanuel Y, Asrat D, et al. Serum antibodies to Toxoplasma gondii and Herpesvidae family viruses in individuals with schizophrenia and bipolar disorder: a case-control study. Ethiop Med J. 2011 Jul;49(3):211-20.

[65] Harbarth S, Meyer M, Grau GE, Loutan L, Ricou B. Septic Shock due to Cytomegalovirus Infection in Acute Respiratory Distress Syndrome after Falciparum Malaria. J Travel Med. 1997 Sep 1;4(3):148-9.

[66] Grayson W. Recognition of Dual or Multiple Pathology in Skin Biopsies from Patients with HIV/AIDS. Patholog Res Int. 2011;2011:398546.

[67] Ramdial PK, Dlova NC, Sydney C. Cytomegalovirus neuritis in perineal ulcers. J Cutan Pathol. 2002 Aug;29(7):439-44.

[68] Grant HW. Patterns of presentation of human immunodeficiency virus type 1-infected children to the paediatric surgeon. J Pediatr Surg. 1999 Feb;34(2): 251-4.

[69] Contreras A, Falkler WA, Jr., Enwonwu CO, Idigbe EO, Savage KO, Afolabi MB, et al. Human Herpesviridae in acute necrotizing ulcerative gingivitis in children in Nigeria. Oral Microbiol Immunol. 1997 Oct;12(5): 259-65.

[70] Ekpebegh CO, Ogbera AO, Longo-Mbenza B, Blanco-Blanco E, Awotedu A, Oluboyo P. Basal cortisol levels and correlates of hypoadrenalism in patients with human immunodeficiency virus infection. Med Princ Pract. 2011;20(6):525-9.

[71] Unachukwu CN, Uchenna DI, Young EE. Endocrine and metabolic disorders associated with human immune deficiency virus infection. West Afr J Med. 2009 Jan;28(1):3-9.

[72] Harries A. Some clinical aspects of HIV infection in Africa. Afr Health. 1991 Jul;13(5):25-6.

[73] Cooke ML, Goddard EA, Brown RA. Endoscopy findings in HIV-infected children from Sub-Saharan Africa. J Trop Pediatr. 2009 Aug;55(4):238-43.

[74] Meer S, Altini M. Cytomegalovirus co-infection in AIDS-associated oral Kaposi's sarcoma. Adv Dent Res. 2006;19(1):96-8.

[75] Kestelyn PG, Cunningham ET, Jr. HIV/AIDS and blindness. Bull World Health Organ. 2001;79(3):208-13.

[76] Guex-Crosier Y, Telenti A. An epidemic of blindness: a consequence of improved HIV care? Bull World Health Organ. 2001;79(3):181.

[77] Pathai S, Gilbert C, Weiss HA, McNally M, Lawn SD. Differing spectrum of HIV-associated ophthalmic disease among patients starting antiretroviral therapy in India and South Africa. Trop Med Int Health. 2011 Mar;16(3): 356-9.

[78] Emina MO, Odjimogho SE. Ocular problems in HIV and AIDS patients in Nigeria. Optom Vis Sci. 2010 Dec;87(12):979-84.

[79] Nkomazana O, Tshitswana D. Ocular complications of HIV infection in sub-Sahara Africa. Curr HIV/AIDS Rep. 2008 Aug;5(3):120-5.

[80] Kestelyn P. The epidemiology of CMV retinitis in Africa. Ocul Immunol Inflamm. 1999 Dec;7(3-4):173-7.

[81] Beare NA, Kublin JG, Lewis DK, Schijffelen MJ, Peters RP, Joaki G, et al. Ocular disease in patients with tuberculosis and HIV presenting with fever in Africa. Br J Ophthalmol. 2002 Oct;86(10):1076-9.

[82] Balo KP, Amoussou YP, Bechetoille A, Mihluedo H, Djagnikpo PA, Akpandja SM, et al. [Cytomegalovirus retinitis and ocular complications in AIDS patients in Togo]. J Fr Ophtalmol. 1999 Dec;22(10):1042-6.

[83] Nirwoth JP, Hall AB, Lewallen S. Prevalence of cytomegalovirus retinitis in Tanzanians with low CD4 levels. Br J Ophthalmol. 2010 Apr;95(4):460-2.

[84] Fielding K, Koba A, Grant AD, Charalambous S, Day J, Spak C, et al. Cytomegalovirus viremia as a risk factor for mortality prior to antiretroviral therapy among HIV-infected gold miners in South Africa. PLoS One. 2011;6(10):e25571.

[85] Slyker JA, Lohman-Payne BL, John-Stewart GC, Maleche-Obimbo E, Emery S, Richardson B, et al. Acute cytomegalovirus infection in Kenyan HIV-infected infants. Aids. 2009 Oct 23;23(16):2173-81.

[86] Lishimpi K, Chintu C, Lucas S, Mudenda V, Kaluwaji J, Story A, et al. Necropsies in African children: consent dilemmas for parents and guardians. Arch Dis Child. 2001 Jun;84(6):463-7.

[87] Cox JA, Lukande RL, Lucas S, Nelson AM, Van Marck E, Colebunders R. Autopsy causes of death in HIV-positive individuals in Sub-Saharan Africa and correlation with clinical diagnoses. AIDS Rev. 2010 Oct-Dec;12(4):183-94.

[88] Martinson NA, Karstaedt A, Venter WD, Omar T, King P, Mbengo T, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. Aids. 2007 Oct 1;21(15):2043-50.

[89] Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. Arch Dis Child. 1997 Feb;76(2):124-8.

[90] Jeena PM, Coovadia HM, Chrystal V. Pneumocystis carinii and cytomegalovirus infections in severely ill, HIV-infected African infants. Ann Trop Paediatr. 1996 Dec;16(4):361-8.

[91] Beadsworth MB, Cohen D, Ratcliffe L, Jenkins N, Taylor W, Campbell F, et al. Autopsies in HIV: still identifying missed diagnoses. Int J STD AIDS. 2009 Feb;20(2):84-6.

[92] Mudenda V, Lucas S, Shibemba A, O'Grady J, Bates M, Kapata N, et al. Tuberculosis and Tuberculosis/HIV/AIDS-Associated Mortality in Africa: The Urgent Need to Expand and Invest in Routine and Research Autopsies. J Infect Dis. 2012 Mar 23.

[93] WHO. World Health Statistics. 2010.

[94] Gray DM, Zar HJ. Community-acquired pneumonia in HIV-infected children: a global perspective. Curr Opin Pulm Med. 2010 May;16(3):208-16.

[95] Preidis GA, McCollum ED, Mwansambo C, Kazembe PN, Schutze GE, Kline MW. Pneumonia and malnutrition are highly predictive of mortality among African children hospitalized with human immunodeficiency virus infection or exposure in the era of antiretroviral therapy. J Pediatr. Sep; 159(3):484-9.

[96] McNally LM, Jeena PM, Gajee K, Thula SA, Sturm AW, Cassol S, et al. Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. Lancet. 2007 Apr 28;369(9571):1440-51.

[97] Enarson PM, Gie RP, Enarson DA, Mwansambo C, Graham SM. Impact of HIV on standard case management for severe pneumonia in children. Expert Rev Respir Med. 2010 Apr;4(2):211-20.

[98] Nantanda R, Hildenwall H, Peterson S, Kaddu-Mulindwa D, Kalyesubula I, Tumwine JK. Bacterial aetiology and outcome in children with severe pneumonia in Uganda. Ann Trop Paediatr. 2008 Dec;28(4):253-60.

[99] Rabie H, de Boer A, van den Bos S, Cotton MF, Kling S, Goussard P. Children with human immunodeficiency virus infection admitted to a paediatric intensive care unit in South Africa. J Trop Pediatr. 2007 Aug; 53(4):270-3.

[100] Jeena P. The role of HIV infection in acute respiratory infections among children in Sub-Saharan Africa. Int J Tuberc Lung Dis. 2005 Jul;9(7):708-15.

[101] Pillay T, Adhikari M, Mokili J, Moodley D, Connolly C, Doorasamy T, et al. Severe, rapidly progressive human immunodeficiency virus type 1 disease in newborns with coinfections. Pediatr Infect Dis J. 2001 Apr;20(4): 404-10.

[102] Delport SD, Brisley T. Aetiology and outcome of severe community-acquired pneumonia in children admitted to a paediatric intensive care unit. S Afr Med J. 2002 Nov;92(11):907-11.

[103] Punpanich W, Groome M, Muhe L, Qazi SA, Madhi SA. Systematic review on the etiology and antibiotic treatment of pneumonia in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2011 Oct; 30(10):e192-202.

[104] Ruffini DD, Madhi SA. The high burden of Pneumocystis carinii pneumonia in African HIV-1-infected children hospitalized for severe pneumonia. AIDS. 2002 Jan 4;16(1):105-12.

[105] Graham SM. Impact of HIV on childhood respiratory illness: differences between developing and developed countries. Pediatr Pulmonol. 2003 Dec; 36(6):462-8.

[106] Zampoli M, Morrow B, Hsiao NY, Whitelaw A, Zar HJ. Prevalence and outcome of cytomegalovirus-associated pneumonia in relation to human immunodeficiency virus infection. Pediatr Infect Dis J. 2010 May;30(5):413-7.

[107] Goussard P, Kling S, Gie RP, Nel ED, Heyns L, Rossouw GJ, et al. CMV pneumonia in HIV-infected ventilated infants. Pediatr Pulmonol. 2010 Jul; 45(7):650-5.

[108] Mosca F, Pugni L. Cytomegalovirus infection: the state of the art. J Chemother. 2007 Oct;19 Suppl 2:46-8.

[109] Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med. 1992 Mar 5;326(10):663-7.

[110] Barbi M, Binda S, Caroppo S, Calvario A, Germinario C, Bozzi A, et al. Multicity Italian study of congenital cytomegalovirus infection. Pediatr Infect Dis J. 2006 Feb;25(2):156-9.

[111] Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. Jama. 1986 Oct 10;256(14):1904-8.

[112] Griffiths PD, Walter S. Cytomegalovirus. Curr Opin Infect Dis. 2005 Jun; 18(3):241-5.

[113] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007 Jul-Aug;17(4):253-76.

[114] Gaytant MA, Steegers EA, Semmekrot BA, Merkus HM, Galama JM. Congenital cytomegalovirus infection: review of the epidemiology and outcome. Obstet Gynecol Surv. 2002 Apr;57(4):245-56.

[115] Ross DS, Dollard SC, Victor M, Sumartojo E, Cannon MJ. The epidemiology and prevention of congenital cytomegalovirus infection and disease: activities of the Centers for Disease Control and Prevention Workgroup. J Womens Health (Larchmt). 2006 Apr;15(3):224-9.

[116] Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med. 2005 Sep 29;353(13):1350-62.

[117] Stagno S, Pass RF, Reynolds DW, Moore MA, Nahmias AJ, Alford CA. Comparative study of diagnostic procedures for congenital cytomegalovirus infection. Pediatrics. 1980 Feb;65(2):251-7.

[118] Gibson CS, MacLennan AH, Goldwater PN, Haan EA, Priest K, Dekker GA. Neurotropic viruses and cerebral palsy: population based case-control study. BMJ. 2006 Jan 14;332(7533):76-80.

[119] Schopfer K, Lauber E, Krech U. Congenital cytomegalovirus infection in newborn infants of mothers infected before pregnancy. Arch Dis Child. 1978 Jul;53(7):536-9.

[120] Watts TE, Larsen SA, Brown ST. A case-control study of stillbirths at a teaching hospital in Zambia, 1979-80: serological investigations for selected infectious agents. Bull World Health Organ. 1984;62(5):803-8.

[121] Bos P, Steele D, Alexander J. Prevalence of antibodies to rubella, herpes simplex 2 and cytomegalovirus in pregnant women and in neonates at Ga-Rankuwa. Cent Afr J Med. 1995 Jan;41(1):14-7.

[122] Mostad SB, Kreiss JK, Ryncarz A, Chohan B, Mandaliya K, Ndinya-Achola J, et al. Cervical shedding of herpes simplex virus and cytomegalovirus throughout the menstrual cycle in women infected with human immunodeficiency virus type 1. Am J Obstet Gynecol. 2000 Oct;183(4):948-55.

[123] Mohlala BK, Tucker TJ, Besser MJ, Williamson C, Yeats J, Smit L, et al. Investigation of HIV in amniotic fluid from HIV-infected pregnant women at full term. J Infect Dis. 2005 Aug 1;192(3):488-91.

[124] van der Sande MA, Kaye S, Miles DJ, Waight P, Jeffries DJ, Ojuola OO, et al. Risk factors for and clinical outcome of congenital cytomegalovirus infection in a peri-urban West-African birth cohort. PLoS One. 2007;2(6):e492.

[125] Gerna G, Lilleri D, Furione M, Baldanti F. Management of human cytomegalovirus infection in transplantation: validation of virologic cut-offs for preemptive therapy and immunological cut-offs for protection. New Microbiol. 2011 Jul;34(3):229-54.

[126] Brantsaeter AB, Holberg-Petersen M, Jeansson S, Goplen AK, Bruun JN. CMV quantitative PCR in the diagnosis of CMV disease in patients with HIV-infection - a retrospective autopsy based study. BMC Infect Dis. 2007;7:127.

[127] Erhabor O, Adias TC. From whole blood to component therapy: the economic, supply/demand need for implementation of component therapy in Sub-Saharan Africa. Transfus Clin Biol. 2011 Dec;18(5-6):516-26.

[128] Adler MW. Antiretrovirals for developing world. Lancet. 1998 Jan 24;351(9098):232.

[129] Kober K, Van Damme W. Scaling up access to antiretroviral treatment in southern Africa: who will do the job? Lancet. 2004 Jul 3-9;364(9428):103-7.

[130] Lynch S, Ford N, van Cutsem G, Bygrave H, Janssens B, Decroo T, et al. Public health. Getting HIV treatment to the most people. Science. 2012 Jul 20;337(6092):298-300.

[131] Sharland M, Luck S, Griffiths P, Cotton M. Antiviral therapy of CMV disease in children. Adv Exp Med Biol. 2010;697:243-60.

[132] Mphahlele MJ, Mda S. Immunising the HIV-infected child: A view from Sub-Saharan Africa. Vaccine. 2012 Sep 7;30 Suppl 3:C61-5.

[133] Janaszek W, Gay NJ, Gut W. Measles vaccine efficacy during an epidemic in 1998 in the highly vaccinated population of Poland. Vaccine. 2003 Jan 17;21(5-6):473-8.

[134] Lynn TV, Beller M, Funk EA, Middaugh JP, Ritter D, Rota PA, et al. Incremental effectiveness of 2 doses of measles-containing vaccine compared with 1 dose among high school students during an outbreak. J Infect Dis. 2004 May 1;189 Suppl 1:S86-90.

[135] Vitek CR, Aduddell M, Brinton MJ, Hoffman RE, Redd SC. Increased protections during a measles outbreak of children previously vaccinated with a second dose of measles-mumps-rubella vaccine. Pediatr Infect Dis J. 1999 Jul;18(7):620-3.

[136] Aaby P, Knudsen K, Jensen TG, Tharup J, Poulsen A, Sodemann M, et al. Measles incidence, vaccine efficacy, and mortality in two urban Afri-

can areas with high vaccination coverage. J Infect Dis. 1990 Nov;162(5): 1043-8.

[137] Cisse B, Aaby P, Simondon F, Samb B, Soumare M, Whittle H. Role of schools in the transmission of measles in rural Senegal: implications for measles control in developing countries. Am J Epidemiol. 1999 Feb 15;149(4):295-301.

[138] Malfait P, Jataou IM, Jollet MC, Margot A, De Benoist AC, Moren A. Measles epidemic in the urban community of Niamey: transmission patterns, vaccine efficacy and immunization strategies, Niger, 1990 to 1991. Pediatr Infect Dis J. 1994 Jan;13(1):38-45.

[139] Usen S, Milligan P, Ethevenaux C, Greenwood B, Mulholland K. Effect of fever on the serum antibody response of Gambian children to Haemophilus influenzae type b conjugate vaccine. Pediatr Infect Dis J. 2000 May; 19(5):444-9.

[140] Williamson WA, Greenwood BM. Impairment of the immune response to vaccination after acute malaria. Lancet. 1978 Jun 24;1(8078):1328-9.

[141] Lalor MK, Floyd S, Gorak-Stolinska P, Ben-Smith A, Weir RE, Smith SG, et al. BCG vaccination induces different cytokine profiles following infant BCG vaccination in the UK and Malawi. J Infect Dis. 2011 Oct 1;204(7): 1075-85.

[142] Botha MH, Dochez C. Introducing human papillomavirus vaccines into the health system in South Africa. Vaccine. 2012 Sep 7;30 Suppl 3:C28-34.

[143] Moss WJ, Clements CJ, Halsey NA. Immunization of children at risk of infection with human immunodeficiency virus. Bull World Health Organ. 2003;81(1):61-70.

[144] Simani OE, Leroux-Roels G, Francois G, Burnett RJ, Meheus A, Mphahlele MJ. Reduced detection and levels of protective antibodies to hepatitis B vaccine in under 2-year-old HIV positive South African children at a paediatric outpatient clinic. Vaccine. 2009 Jan 1;27(1):146-51.

[145] Sinzger C, Digel M, Jahn G. Cytomegalovirus cell tropism. Curr Top Microbiol Immunol. 2008;325:63-83.

[146] Sinzger C, Grefte A, Plachter B, Gouw AS, The TH, Jahn G. Fibroblasts, epithelial cells, endothelial cells and smooth muscle cells are major targets of human cytomegalovirus infection in lung and gastrointestinal tissues. J Gen Virol. 1995 Apr;76 (Pt 4):741-50.

[147] Miles DJ, van der Sande M, Jeffries D, Kaye S, Ismaili J, Ojuola O, et al. Cytomegalovirus infection in Gambian infants leads to profound CD8 T-cell differentiation. J Virol. 2007 Jun;81(11):5766-76.

[148] Miles DJ, van der Sande M, Jeffries D, Kaye S, Ojuola O, Sanneh M, et al. Maintenance of large subpopulations of differentiated CD8 T-cells two years after cytomegalovirus infection in Gambian infants. PLoS One. 2008;3(8):e2905.

[149] Trzonkowski P, Mysliwska J, Szmit E, Wieckiewicz J, Lukaszuk K, Brydak LB, et al. Association between cytomegalovirus infection, enhanced proinflammatory response and low level of anti-hemagglutinins during the anti-influenza vaccination--an impact of immunosenescence. Vaccine. 2003 Sep 8;21(25-26):3826-36.

[150] Appay V, Fastenackels S, Katlama C, Ait-Mohand H, Schneider L, Guihot A, et al. Old age and anti-cytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients. AIDS. 2011 Sep 24;25(15):1813-22.

[151] Miles DJ, Sanneh M, Holder B, Crozier S, Nyamweya S, Touray ES, et al. Cytomegalovirus infection induces T-cell differentiation without impairing antigen-specific responses in Gambian infants. Immunology. 2008 Jul; 124(3):388-400.

[152] Holder B, Miles DJ, Kaye S, Crozier S, Mohammed NI, Duah NO, et al. Epstein-Barr virus but not cytomegalovirus is associated with reduced vaccine antibody responses in Gambian infants. PLoS One. 2010;5(11):e14013.

[153] Ben-Smith A, Gorak-Stolinska P, Floyd S, Weir RE, Lalor MK, Mvula H, et al. Differences between naive and memory T cell phenotype in Malawian and UK adolescents: a role for Cytomegalovirus? BMC Infect Dis. 2008;8:139.

[154] Ferlay J SH, Bray F, Forman D, Mathers C,, DM P. Cancer Incidence and Mortality Worldwide. GLOBOCAN 2008 v1.2; 2008 [updated 2008; cited 2012 24th August]; Available from: http://globocan.iarc.fr/.

IntechOpen