

# Human cytomegalovirus (CMV) in Africa: a neglected but important pathogen

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## Abstract

In Africa, human cytomegalovirus (CMV) is an important pathogen in a diverse range of patient groups. Congenital CMV infection is common, and most children undergo primary infection during the first year of life. Preliminary studies suggest that these early primary CMV infections could have population-wide effects on growth and development. In most studies of adults, CMV seroprevalence is close to 100%, but some studies have found that significant minorities of adults are seronegative. CMV is a common cause of pneumonia and meningitis in hospitalised immunosuppressed patient groups, and CMV DNAemia may be an important marker of rapid progression and poor outcomes of HIV infection, despite roll-out of antiretroviral therapy (ART). Diagnosis and treatment of CMV-related disease is broadly neglected in Africa, and no randomised clinical trials of anti-CMV drugs have been conducted to date. Autopsy is rarely performed in Africa, but identifies CMV as a frequent pathogen when it is carried out. Here we review the available literature on CMV in Africa, primarily in adult patients, and discuss this in the context of contemporary understanding of CMV as a human pathogen.

## Introduction

There is growing awareness of the possible importance of human cytomegalovirus (CMV) as a cause or contributory factor in a range of disease conditions in Africa and other developing regions globally. In children, CMV is a common congenital infection the outcomes of which are largely undefined in African populations [1–3]. CMV is also an important cause of pneumonia [4–6] and meningitis [7,8], strongly associated with HIV infection and exposure, and is independently associated with impaired physical development [7,9]. CMV is an important co-infection in HIV-infected adult patient groups, and is associated with increased morbidity and mortality [10,11], yet diagnosis and treatment are broadly unavailable outside selected centres of excellence.

CMV infection in Africa has been overlooked for several reasons. First, there is the perception that most Africans are universally infected with CMV during childhood, and that maternal reactivation or reinfection during pregnancy is less likely than primary infection to cause severe congenital infection [12–14]. However, even in high-income populations, the majority of congenital CMV infections are the result of maternal reactivation or re-infection [15]. Ignoring congenital CMV infection in Africa is therefore shortsighted, and does not consider the possible confounding effects of HIV infection, malnutrition, tuberculosis, and a general higher disease burden. Secondly, CMV disease is an AIDS-defining opportunistic infection [16]. With the roll-out of ART across Africa, it has been assumed that the burden of disease caused by CMV is small and getting smaller [10], and as a result CMV diagnostics and treatment are broadly unavailable outside selected centres of excellence [2,4–6]. Thirdly, there is an assumption that patients in Africa do not receive immunosuppressive therapy that may cause CMV disease, an increasingly obsolete view as access to more advanced treatments and therapies for non-communicable diseases as well as organ transplantation become more available [17,18].

In this review we summarise available data on CMV infections in Africa, from the vast literature of CMV pathogenicity, immunology,

diagnosis and treatment available from studies undertaken in high-income countries.

## Seroprevalence

As for all herpesviruses, the natural host immune response to primary CMV infection does not clear the virus completely, and it persists in a latent or 'non-lytic' state [19]. In lower-income settings, primary infection with CMV generally occurs earlier [9,20–22] than in higher-income settings [23] (although this is not universally true, as high prevalence of CMV IgG has been reported in studies from Finland and Japan [24–26]). Data from the United States have suggested that non-white ethnicity and lower socioeconomic status could be responsible for a 10–30% increase in CMV seroprevalence [27], although ethnic differences should be interpreted with caution: there are no race-associated host genetic polymorphisms known to be linked with earlier acquisition of CMV. Social and environmental factors are the most probable determinants of age of acquisition, and even when seroprevalence differences by ethnicity hold when adjusting for socioeconomic status, such as in an Israeli study [28], it could be socioeconomic status during childhood that is important. For instance, migrants who spent their childhood in sub-Saharan Africa might be more likely to be CMV IgG seropositive, even if social mobility facilitated a rise in socioeconomic status after settling in Israel.

We searched PubMed and identified 33 studies that present CMV seroprevalence data from healthy blood donors and patient groups in Africa (Table 1). The pooled prevalence of CMV IgG among HIV-negative adults was 81.8% (range 55–97%). For HIV-infected adults the pooled CMV IgG seroprevalence was lower among those with clinically defined AIDS (81.9%, range 59–100%) than among asymptomatic HIV-infected adults (94.8%, range 71–100%), consistent with the notion of weaker humoral responses associated with AIDS progression [29]. It is also possible that some non-HIV-infected adults are infected but do not mount a measurable IgG response. Among pregnant women seroprevalence mirrored that among healthy blood donors, although the HIV status of participants was not always stated (Table 1).

The number of children screened for CMV IgG was an order of magnitude less than for adults, but pooled seroprevalence was 88.1% (range 80–100%). With this very high seroprevalence in children (Table 1), even in very young infants [9], one would expect

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**Table 1.** Comparison of human CMV seroprevalence in different countries in Africa

Country (City)	HCMV IgG	Study population	N	Assay	Reference
<b>HIV-negative adults</b>		<b>81.8%</b>			
Nigeria (Ibadan)	55.0%	Adult healthy blood donors	110	Complement fixation	[30]
Mali (Bamako)	58.0%	Adult healthy HIV-negative blood donors	100	ELISA (Platelia, Sanofi Pasteur)	[31]
Tanzania (Dar es Salaam)	66.9%	Adult inpatients with STDs (HIV-negative)	158	Passive latex agglutination (CMV-scan card)	[32]
Ghana (Accra)	77.6%	Adult healthy HIV-negative blood donors	3275	ELISA IgG (Diamedix Corporation, USA)	[33]
Burkina Faso (Bobo-Dioulasso)	82.0%	Adult healthy HIV-negative blood donors	28	ELISA (Platelia, Sanofi Pasteur)	[34]
Ghana (Kumasi)	94.3%	Healthy blood donors	112	Platella CMV IgG (Bio-Rad)	[35]
Somalia (Mogadishu)	96.0%	Healthy adult males	102	Unspecified	[36]
Somalia (Mogadishu)	96.0%	Adult males attending STD clinic	101	Unspecified	[36]
Kenya (Nairobi)	97.0%	Adult healthy blood donors (1.3% HIV-positive)	400	Unspecified	[37]
Tunisia (Tunis)	89.0%	Healthy adults	100	CMV IgG CMIA (Abbott Diagnostics)	[38]
Kenya	97.0%	Adult healthy blood donors	395	Not available	[37]
Tunisia (Sfax)	97.0%	Adult healthy blood donors	280	Enzygnost anti-CMV/IgG (Behring)	[39]
<b>HIV-positive adults</b>		<b>94.8%</b>			
Mali (Bamako)	71.0%	HIV-positive adults	100	ELISA (Platelia, Sanofi Pasteur)	[31]
Tanzania (Dar es Salaam)	72.3%	Adult inpatients with STDs (HIV-positive)	65	Passive latex agglutination (CMV-scan card)	[32]
Ghana (Kumasi)	92.7%	Asymptomatic HIV-positive adults	55	Platella CMV IgG (Bio-Rad)	[35]
Botswana (Gaborone)	95.3%	Asymptomatic HIV-positive adults	43		[40]
South Africa (Mopani District, Limpopo)	100.0%	HIV-positive adults, ART naïve, mean CD4 cell count 382±226 cells/μL	405	Serion ELISA classic tests (Virion Serion)	[41]
Tanzania (Mbulu)	100.0%	HIV-positive adults, ART naïve, median baseline CD4 cell count 205 (IQR 79–403) cells/μL	168	CMV IgG CMIA (Abbott Diagnostics)	[42]
Lesotho	100.0%	HIV-positive, on ART	205	CMV IgG CMIA (Abbott Diagnostics)	[43]
Nigeria (Ilorin)	93.9%	Asymptomatic HIV-positive adults	180	IgG ELISA Kit (DIA.PRO, Diagnostic Bioprobes, Italy)	[44]
<b>AIDS patients</b>		<b>81.9%</b>			
Ghana (Accra)	59.2%	AIDS patients	250	ELISA IgG; Diamedix Corporation, USA	[33]
Mali (Bamako)	89.0%	AIDS patients	100	ELISA (Platelia, Sanofi Pasteur)	[31]
Tanzania (Dar es Salaam)	90.7%	AIDS patients	43	Passive latex agglutination (CMV-scan card)	[32]
Ghana (Kumasi)	98.3%	AIDS patients	239	Platella CMV IgG (Bio-Rad)	[35]
Burkina Faso (Bobo-Dioulasso)	100.0%	AIDS patients	36	ELISA (Platelia, Sanofi Pasteur)	[34]
<b>Pregnant women</b>		<b>87.8%</b>			
Tanzania (Dar es Salaam)	60.6%	HIV-negative pregnant women	127	Passive latex agglutination (CMV-scan card)	[32]
Tanzania (Dar es Salaam)	85.7%	HIV-positive pregnant women	14	Passive latex agglutination (CMV-scan card)	[32]
Benin (Cotonou)	97.2%	Pregnant women	211	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[45]
Nigeria (Ibadan)	100.0%	Pregnant and non-pregnant women	80	Peroxidase enzyme-labelled antigen (ELA)	[46]
Nigeria (Kano)	91.1%	Pregnant women	180	CMV IgG ELISA kit (Dialab, Austria)	[47]
South Africa (Johannesburg)	86.4%	Pregnant women	2160	ELISA (M A Bioproducts, Virginia)	[48]
Tunisia	80.9%	Pregnant women	404	CMV IgG CMIA (Abbott Diagnostics)	[49]
Sudan	72.0%	Pregnant women	231	DRG Cytomegalie Virus (CMV) IgG Enzyme Immunoassay Kit	[50]
The Gambia (Sukuta)	100.0%	Pregnant women	169	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[51]
Kenya (Thika)	77.3%	Pregnant women	260	CMV serum immunoglobulin G antibody using a commercial enzyme-linked immunosorbent assay (Wampole; Inverness Medical Professional Diagnostics)	[52]

**Table 1.** Continued

Country (City)	HCMV IgG	Study population	N	Assay	Reference
Benin (Tanguiéta)	100.0%	Pregnant women	283	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[53]
Egypt (Ismailia)	100.0%	Pregnant women	546	CMV IgG (DIA.PRO Diagnostic Bioprobes, Italy)	[54]
<b>Children</b>	<b>88.1%</b>				
Cameroon (Kumba City)	88.5%	Healthy children 4–6 years	~100	ELISA (unspecified)	[55]
Cameroon (Kumba City)	98.0%	Healthy children 11–14 years	~100	ELISA (unspecified)	[55]
Gambia (Banjul)	86.4%	Healthy children 12 months	178	Immunofluorescence?	[56]
Gambia (Banjul)	80.4%	Healthy children	138	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[57]
Mozambique (SE Transvaal)	88.0%	Refugee children under 5 years	~100	ELISA (unspecified)	[58]
Mozambique (SE Transvaal)	96.4%	Refugee children under 11 years	~100	ELISA (unspecified)	[58]
Nigeria (Ibadan)	100.0%	Newborn infants	21	Peroxidase enzyme-labelled antigen (ELA)	[46]
Zambia (Lusaka)	83.0%	Healthy 18-month-old infants	460	ETI-CYTOK-G PLUS ELISA (DiaSorin)	[9]
Kenya (Nairobi)	100.0%	HIV-1-infected street children	71	ELISA kit (Murex)	[59]
Egypt	100.0%	Acute lymphoblastic leukaemia	68	ELISA kit (Diagnostic Systems Laboratories, Inc., USA)	[60]
<b>Tuberculosis studies</b>	<b>83.0%</b>				
Nigeria (Ibadan)	50.6%	Non-TB	89	Complement fixation	[30]
Nigeria (Ibadan)	87.6%	Tuberculosis patients	161	Complement fixation	[30]
Burkina Faso (Bobo-Dioulasso)	95.0%	TB-positive, HIV-positive	40	ELISA (Platelia, Sanofi Pasteur)	[34]
Burkina Faso (Bobo-Dioulasso)	96.5%	Tuberculosis patients	80	ELISA (Platelia, Sanofi Pasteur)	[34]
Burkina Faso (Bobo-Dioulasso)	97.5%	TB-positive, HIV-negative	40	ELISA (Platelia, Sanofi Pasteur)	[34]
<b>Other</b>	<b>94.5%</b>				
Eritrea (various locations)	94.8%	Various	439	ELISA (unspecified)	[61]
Burundi (Bujumbura)	99.0%	Ophthalmic patients	154	ELISA Enzygnost CMV (Abbott Laboratories, USA)	[62]
Tunisia	94.9%	HIV-negative adults with haemoglobinopathies	59	CMV IgG CMIA (Abbott Diagnostics)	[38]
Tunisia	77.0%	HIV-negative children with thalassemia or haemophilia	48	CMV IgG CMIA (Abbott Diagnostics)	[38]

Adapted from [2]. Percentages in bold are the averages within each group, weighted by study size. CMIA, chemiluminescent microparticle immunoassay

seroprevalence among adults to be consistently close to 100%. It is therefore surprising that a significant minority of adults in many studies are CMV IgG negative. Our pooled analysis of CMV IgG seroprevalence is limited by the lack of data on confounding variables and the use of different CMV IgG assays in different studies, but CMV IgG is considered to be a readily detectable biomarker, with many of the assays cited used routinely in the transplant setting to define the CMV exposure of donor and recipient. As detection of pathogen-specific IgG is the very backbone of diagnostic programmes for HIV, malaria and many other common infections, it seems unlikely, with the exception of HIV-infected individuals, that the reason is impaired humoral response to CMV, which is known for high immunogenicity. Therefore, it cannot be excluded that seronegative adults are protected from CMV infection in some unknown way. Possible explanations include socioeconomic and host genetic factors. Studying the host genetics of CMV-seronegative African adults may identify novel markers of protection. Recently, Japanese researchers found that the polymorphism Thr72Ala in NKG2D, a leptin-like receptor expressed by NK cells, might be associated with symptomatic congenital CMV infection [63]. Host polymorphisms in mice have also been associated with differential pathogenicity to HSV-1 [64], but there is currently no evidence of a host polymorphism in humans that results in a sufficiently

rapid innate immune response that prevents establishment of humoral immunity to herpesviruses.

### CMV infections in African children

A detailed discussion of this topic is planned for a later issue of the *Journal of Virus Eradication*. For this reason, we only summarise here. CMV is important in African children for two reasons. First, congenital CMV infection appears to be highly prevalent [65–67] despite pre-existing maternal immunity, and is strongly associated with maternal HIV infection [68]. The longitudinal outcomes of congenital CMV infection (cCMV) in Africa have not been thoroughly studied, but cases of sensorineural hearing loss and sudden infant death have been documented [56]. There is an emerging consensus that cCMV, along with other congenital and neonatal infections, is an under-appreciated cause of morbidity and mortality in African children [69]. Secondly, most African children are infected with CMV early in infancy irrespective of HIV infection or exposure [5,9,70,71], which is distinctly different from higher-income settings where primary infection with CMV generally occurs much later. Traditionally cCMV has been defined as detection of CMV within 3 weeks postpartum, but in Africa many infants undergo non-congenital primary CMV infection soon after this cut-off [5], and preliminary studies suggest these early infant

non-congenital infections could also be associated with developmental sequelae. CMV shedding in African infants is associated with vertical transmission of HIV [71], and these early infant non-congenital CMV infections are independently associated with impaired physical development, and among HIV-exposed children, impaired psychomotor development [9]. CMV pneumonia is the most prevalent acute disease presentation [72], strongly associated with HIV infection [4–6]. CMV is also a probable cause of meningitis and gastrointestinal infection in African children, with or without accompanying bacterial infection [7,73], but routine diagnosis and treatment is broadly unavailable.

### CMV and HIV-infected African adults

Before effective antiretroviral therapy was available, CMV end-organ disease was a common complication of HIV infection in industrialised countries, mainly occurring in patients with CD4 T cell counts <50 cells/ $\mu$ L [74]. However, after introduction of combination ART, CMV disease became a rare complication in this setting [75]. In Africa, access to ART is improving [76], but HIV-associated tuberculosis and bacterial pneumonia continue to be leading causes of death [72,77]. The role of CMV comorbidity in these patient groups is largely unknown, as diagnostic testing for CMV is not routinely performed.

### CMV retinitis

Retinitis is the most common manifestation of CMV disease in HIV-infected patients in Western countries [78], and this has led to a body of work investigating CMV retinitis in developing countries. In a systematic review of HIV-infected individuals in Africa (18 studies, 4325 patients), the prevalence of CMV retinitis was 2.2% (95% CI: 1.3–3.1%), significantly lower than in Asia [79]. One reason for this difference may be lower CD4 T cell counts on starting ART in Asia compared to Africa [80]. However, a study comparing the prevalence of CMV retinitis in India and South Africa found retinitis to be significantly less common in South Africa, even after controlling for differences in ART use [81]. In Africa, widespread pre-existing CMV immunity from infancy may contribute to different prevalence of CMV retinitis in African adults compared to adults coming from lower CMV seroprevalence settings. It is unknown whether there are any genetic factors that might influence different levels of CMV retinitis between African and Asian populations.

### CMV extraocular disease and autopsy

In contrast to CMV retinitis, which can be diagnosed by ophthalmoscopy, confirmatory diagnosis of extraocular CMV disease generally requires histopathological examination of biopsy or post mortem specimens, procedures that are not widely available in Africa. Whilst molecular diagnostic tests to detect CMV DNA are now commonly used in the research setting [6,7,42], detection of DNA in most clinical specimens does not automatically indicate disease and need for treatment and there is still insufficient data to define reliable viral load cut-offs for most patient groups [5].

Several research studies from Africa indicate that CMV may be an important pathogen in patients with suspected acute neurological disease. A study of meningitis in an HIV-Infected Ugandan cohort detected CMV in the cerebrospinal fluid (CSF) in 7% of patients, frequently in combination with other pathogens [82]. In Malawi, CMV was detected in the CSF in 14% (2/14) of HIV-infected patients with aseptic meningitis [83]. In this study, confirmed bacterial or fungal meningitis cases were not screened for viruses, but a later study from the same research group, found CMV in the CSF of 10% (11/115) of HIV-infected patients with bacterial meningitis [8]. This study also showed a significant

association between dual EBV/CMV infection and mortality, with dual herpesvirus infection possibly eliciting greater CSF inflammation than mono-infection. A study from a tertiary care centre in Zambia found CMV in the CSF of 6% of HIV-infected adults with symptoms suggestive of CNS opportunistic disease, frequently in combination with other pathogens [84]. Together, these four studies indicate that CMV is detectable in the CSF of a minority of HIV-infected individuals with suspected meningitis or CNS opportunistic disease, and is associated with poor outcome. In resource-rich settings, CMV is not generally recognised as a cause of isolated meningitis in HIV-infected adults, but is established as a cause of encephalitis, myelitis, polyradiculopathy and peripheral neuropathy. However, the above studies do not reveal sufficient data to conclude whether detection of CMV DNA in the CSF is a feature of any of these diverse neurological manifestations. Imaging studies, either magnetic resonance imaging (MRI) or computer tomography (CT), have value in the diagnosis of encephalitis and myelitis, but are not affordable or available to most patients living with HIV in Africa.

A diagnosis of CMV disease is rarely made *antemortem* in poorly resourced African hospitals, as affordable diagnostics and treatment for CMV have not been developed. Even in industrialised countries, the diagnosis of CMV disease is often first made at autopsy [85], in which the detection of classic owl's eye inclusions is indicative of active CMV disease. However, autopsies are rarely performed in Africa, as they require infrastructure and expertise that is unavailable outside of major referral hospitals [72]. In addition, there is also strong cultural opposition to mutilation of the deceased [86]. A review of African autopsy studies from 2010 identified nine complete autopsy studies that included HIV-infected cadavers, and found CMV disease in 4–18% of these [87]. A similar review focusing on lung pathology gave a pooled prevalence of 7.5% (68/902) for CMV pneumonitis in HIV-infected adult cadavers [72]. An autopsy study from Cote d'Ivoire (pre-ART) found CMV disease to be the cause of death in 2% of patients with HIV-1 compared with 18% of patients with HIV-2, possibly because of longer survival with a low CD4 cell count in HIV-2-infected individuals [88].

A study from South Africa among HIV-infected ART-naïve gold miners found that mortality increased with higher CMV DNAemia (>1000 copies/mL vs no viraemia) with an adjusted hazard ratio of 3.7 [89]. An association between CMV DNAemia and risk of dying was also found in a study from Tanzania among adults initiating ART, where baseline CMV DNAemia (>200 copies/mL in dried blood spots) was an independent risk factor for death with an adjusted hazard ratio of 5.0 [42]. Among South African patients in intensive care, CMV DNAemia (>1000 copies/mL) was associated with a greater risk of mortality (hazard ratio: 3.5) [11].

### CMV in non-HIV-infected immunosuppressed adults

CMV may reactivate and cause severe disease after solid organ and bone marrow transplantation [90,91]. Organ transplantation is a rare procedure in most African countries, but in general CMV represents a similar challenge to that in most other countries, except that CMV mismatch is less common due to high seroprevalence in the population [90,91]. Patients with inflammatory bowel disease (IBD) are also at risk of complications from CMV infection [92]. In a study from Egypt, evidence of CMV disease was found in 35% of cases with steroid refractory colitis [93]. This indicates that CMV may play a role in at least certain populations with IBD in Africa where this disease is diagnosed and treated. As healthcare services in Africa improve, and more advanced treatment is offered, the burden of CMV infection and disease is also likely to escalate.

## Diagnostic and therapeutic challenges

Globally, CMV DNA appears to be a biomarker of morbidity and mortality in a range of patient groups [94], and this has also been found in Africa. Uncontrolled data from South Africa indicate that for severely ill patients ganciclovir therapy could be life-saving [4,11], yet to date there have been no randomised controlled trials of anti-CMV drugs in Africa. Of critical importance is the high cost of ganciclovir and valganciclovir, and the perception that competing priorities are more important. The development of new [95] or cheaper generic CMV drugs and repurposing of available medicines [96] are steps in the right direction, but treatment will only become more available to low-income patient groups if trials are undertaken and if they demonstrate sufficient impact. When designing therapeutic trials for CMV, the method of diagnosis, and even the definition of CMV disease, present several challenges. The traditional gold standard of histopathological observation of ‘owl’s eye’ inclusions in diseased tissue requires invasive sampling (e.g. pulmonary or gastrointestinal biopsy), and is an unlikely criterion for use in clinical trials in Africa. Culture techniques have been used to study CMV in Africa, from urine, saliva or respiratory specimens [5,56], but more recent studies have used molecular diagnostics. Large-scale investment in HIV and TB programmes, along with other research activities, means that PCR platforms are widely available at large teaching hospitals across Africa, the most probable sites for anti-CMV drug trials. Standardised commercial CMV PCR assays offer a quantitative measure of the CMV load, facilitating reliable inter-site and inter-study comparisons. In South Africa, intravenous ganciclovir is used at several centres to treat infants with culture- or PCR-confirmed CMV pneumonitis [4–6], but decisions are consultant-led and dosing informed by studies from Western countries in transplant patients. Ganciclovir is associated with a range of haematological adverse events, especially neutropenia, and could be toxic in young infants with fragile immune systems. Some researchers have proposed diagnosing CMV in community-based studies, such as those designed to investigate interactions between cCMV and early infant CMV infections and developmental outcomes or vertical transmission of HIV. Several groups have explored the use of dried blood spots (DBS), which can be easily stored and transported to research centres for CMV analysis [42,97,98].

## Immunology

CMV is highly immunogenic and, more than the other human herpesviruses, appears to be inextricably linked to the ageing of the immune system. Establishment of chronic CMV infection leads to a clonal expansion of differentiated CMV-specific CD8+ T cells, which in older adults can account for up to 20% of the T cell repertoire [99]. Due to the dominance of CMV as a target for cell-mediated immunity, and the fact that primary CMV infection is ubiquitous in African children, some researchers have sought to study T cell responses to CMV, to gain insight into the development of immunity in African infants that might inform on vaccination strategies. Seminal studies from the Gambia used tetramer staining to show that even in young infants, primary CMV infection was followed by a rapid clonal expansion of differentiated CMV-specific CD8+ T cells [100], which persisted for at least 2 years after primary infection [57]. Even the overall CD8+ T cell population (which could have included T cells for other CMV antigens) acquired the same differentiated phenotype after CMV primary infection [100]. Conversely, CMV-specific CD4+ T cell responses do not appear to be so important for the control of CMV infection in the same infant population [57]. A study from Malawi compared CD4+ and CD8+ T cell phenotypes between HIV-1-negative Malawian and UK teenagers. All ( $n=59$ ) Malawian

participants were CMV IgG seropositive, compared with 36% (21/58) of UK teenagers. Malawian teenagers had a lower proportion of naïve T cells and a higher proportion of memory T cells compared with age-matched UK teenagers. Similarly, within the UK teenagers, those who were CMV seropositive had reduced proportions of naïve and increased memory T cells [101]. CMV appears to be a driving component of this earlier ageing of the immune system in African children, within the context of higher exposure to a range of pathogens in high disease-burden settings.

A study that included adults and children from Tanzania replicated some of these findings, and also showed that among adults, increased IFN- $\gamma$  and MIP-1 $\beta$  production by CMV-specific CD4+ T cells was linked independently to active TB infection [102]. There are strong parallels between CMV and TB: They both establish life-long latency, both reactivate upon immune suppression, both cause acute disease in a broad range of tissues, and both are associated with immune reconstitution inflammatory syndrome (IRIS) in patients initiating ART [103]. A recent study in HIV-infected adults from South Africa found that after ART, the recovery of pathogen-specific T cells is relative to their memory phenotype before treatment: for example, TB-specific T cells (which are generally less differentiated) have a higher replenishment capacity than those for CMV (which are generally more differentiated) [104].

## Conclusions

CMV is emerging as an important pathogen in African populations, both as an acute cause of disease, and also as a more general marker for poor outcomes, in children and immunosuppressed patients. There is a need for greater implementation of diagnostic tests and clinical trials for treatment of acute CMV disease in patient groups such as HIV-infected or exposed children with CMV pneumonia, and in HIV-infected adults with evidence of active CMV infection or disease. Furthermore, for a range of clinical trials, vaccination and immunology studies focused on African patients with HIV or TB, investigators should consider the possible confounding effects of CMV infection and incorporate viral load testing into their protocols if appropriate.

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