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REVIEW

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Co-Pathogenesis of Human Herpesvirus with HIV In Africa

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Abstract

Human Herpesviruses (HHV's) are ubiquitous in human populations globally, and they cause significant morbidity and mortality. HHV's establish a latent infection that is accompanied by periodic virus reactivation as a result of HIV infections. Further, HIV/AIDS infection in sub-Saharan Africa is perceived to be a significant health concern as it accounts for up to 70% of infectious diseases in the region. Until now, the role played by HHVs is increasingly being recognized. The co-infection of HIV with HHV's changes severity or the natural course of HIV infection which defines the AIDS conditions in HIV infected individuals. Presently, treatment of HIV/AIDS by antiviral drugs targets the clinical manifestations of both HIV and HHVs at their productive stage and boost the immunity of HIV infected individuals, but they are ineffective at eliminating these viruses (HHVs and HIV) from the infected persons. This review focuses on outlining the epidemiology, distribution and role played by HHV's in the pathogenesis of HIV infection in African countries. Additionally, this information is significant in crystallizing and providing an update on recent advancements on HHV's and HIV infections in Africa and possible future directions in this field of research.

Keywords: Human Herpesviruses (HHV's); Human immunodeficiency virus (HIV); Africa; Acquired Immunodeficiency Syndrome (AIDS)

1. Introduction

Worldwide, Human Immunodeficiency Virus (HIV) has been widely studied. The pathogenesis and progression of HIV to Acquired Immunodeficiency Syndrome (AIDS) has been linked and promoted by various biological factors: with the important one being opportunistic infections [1], that are more prevalent in developing countries. Sexually Transmitted Infections (STI's) are among the risk factors that promote HIV transmission. Individuals with both HIV-1 and STI's infections tend to frequently shed more viruses (HIV-1) via genital secretions, thus increasing chances of HIV transmission. Herpes Simplex Virus 2 (HSV-2) is one of the STI's that has been studied extensively as it promotes acquisition, transmission and pathogenesis of HIV infections [2, 3].

Despite the existence of Human Herpesvirus (HHVs) as a latent infection (asymptomatic HSV-2) which can be reactivated as a result of weakened immunity due to HIV infection, other HHVs viruses have been given little attention despite them having a high seroprevalence among human populations; predominantly HIV infected persons [4]. Human Kaposi's sarcoma was one of the earliest HHV's to be identified in HIV infected persons in early 1980s, with a severe clinical manifestation. Sequentially, it was followed by identification of HSV, KS, Burkitt lymphoma and Human cytomegalovirus retinitis which are associated with AIDS condition as part of the report by Center for Disease Control (CDC). However, there exists little data and information on how HHVs infection drives the pathogenesis of HIV progression to AIDS in Sub-Saharan Africa.

2. Literature Search, Methodology & Selection Criteria

In this overview, a literature search with no date restrictions was performed in PubMed and Google scholar, using the key terms HIV in combination with herpesviruses, cytomegalovirus, herpes simplex, immune activation, epidemiology, among others. Only published articles that touch on Africa were considered. We chose recently published to get the true picture of HHV's

co-infection with HIV in Africa. Specifically, we focused on articles published in the past 15 years, but also cited relevant older publications where necessary.

Out of a total of 4426 studies, 4350 were excluded as not relevant. Of the 76 full-length papers retrieved contained the relevant information about the co pathogenesis of HHV with HIV in Africa (Fig. 1).

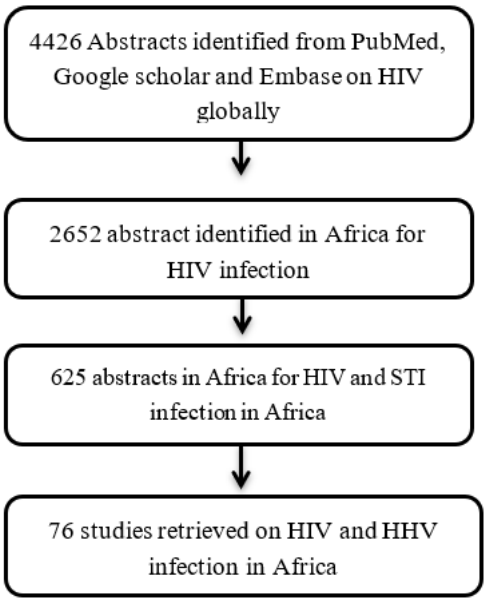

Figure 1: *Flowchart of study selection for inclusion on co pathogenesis of HHV and HIV*

3. History of HIV infection/evolution of HIV infection

In Africa, HIV/AIDS is perceived as the most important sexually transmitted infection of great public health concern. It is estimated to account for up to 70% of the infectious diseases present in the total population, with high morbidity and mortality. Geographically, the pandemic is most experienced in the southern parts of Africa, which is in contrast to the low prevalence rates of HIV infection in North Africa **(Error! Reference source not found.).**

Naturally, the course of HIV infection involves interaction between the virus and the host. Acute HIV infection is subsequently linked to a decrease in CD4 T-cells and an increase in viremia (**Error! Reference source not found.**). Reduction in CD4 T-cells count during the course of infection to less than 200 is defined as clinical AIDS, and in this particular case the viremia will begin to rise again and absolute CD4 count will reduce, which will prompt an increase in the probability to opportunistic infections.

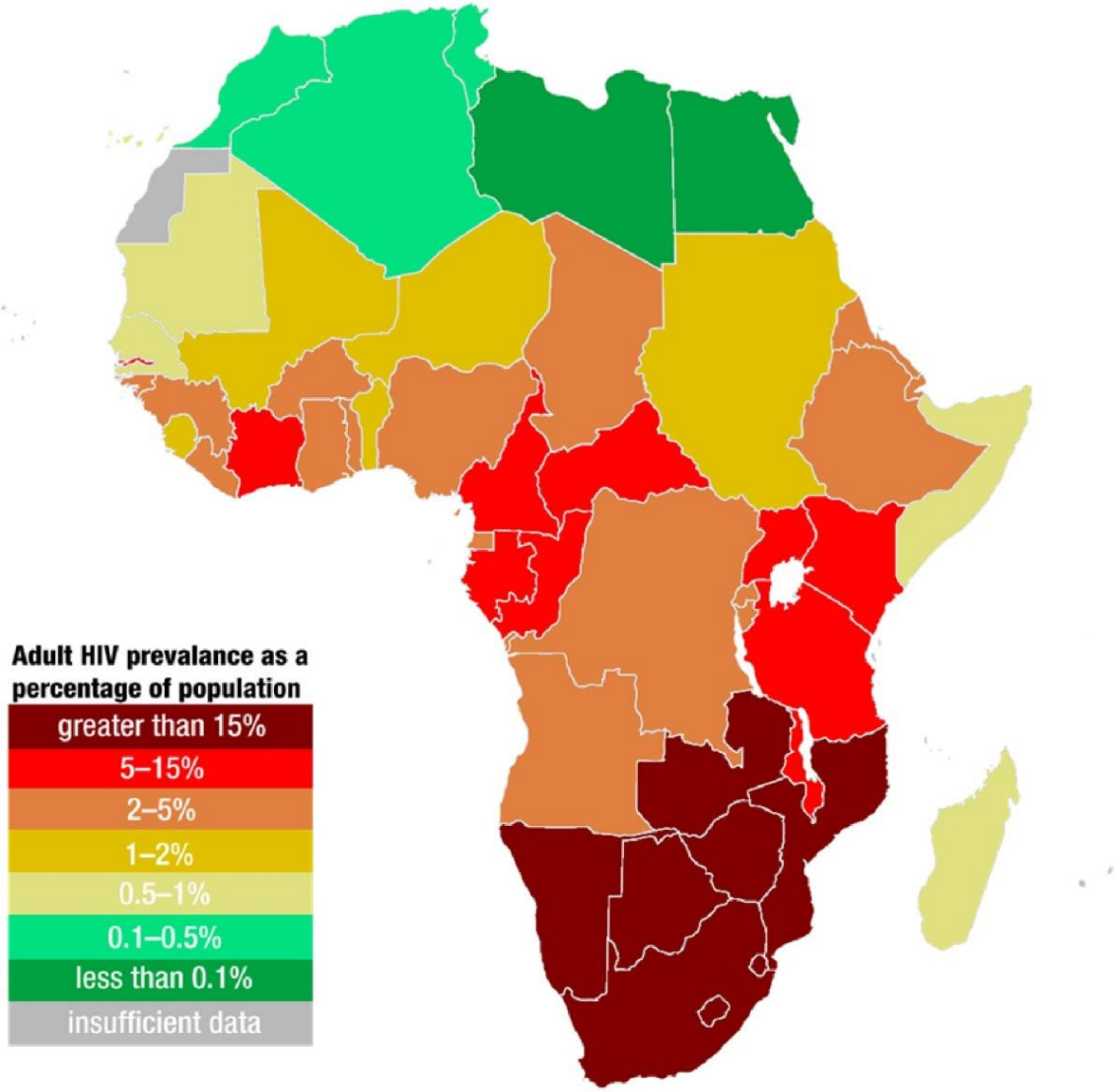

Figure 1: *Prevalence of HIV infection as distributed in different African countries [5]*

Overall, the HIV infection disrupts the state of equilibrium between host and HHVs leading to its reactivation from latency, with rapid replications of the virus [6]. This state starts to define AIDS condition in HIV infected individuals. Lately, the interaction of HIV and HHVs are increasingly being recognized but, taxonomically there exists no correlation between co-infection of *Retroviridae* and *Herpesviridae* members.

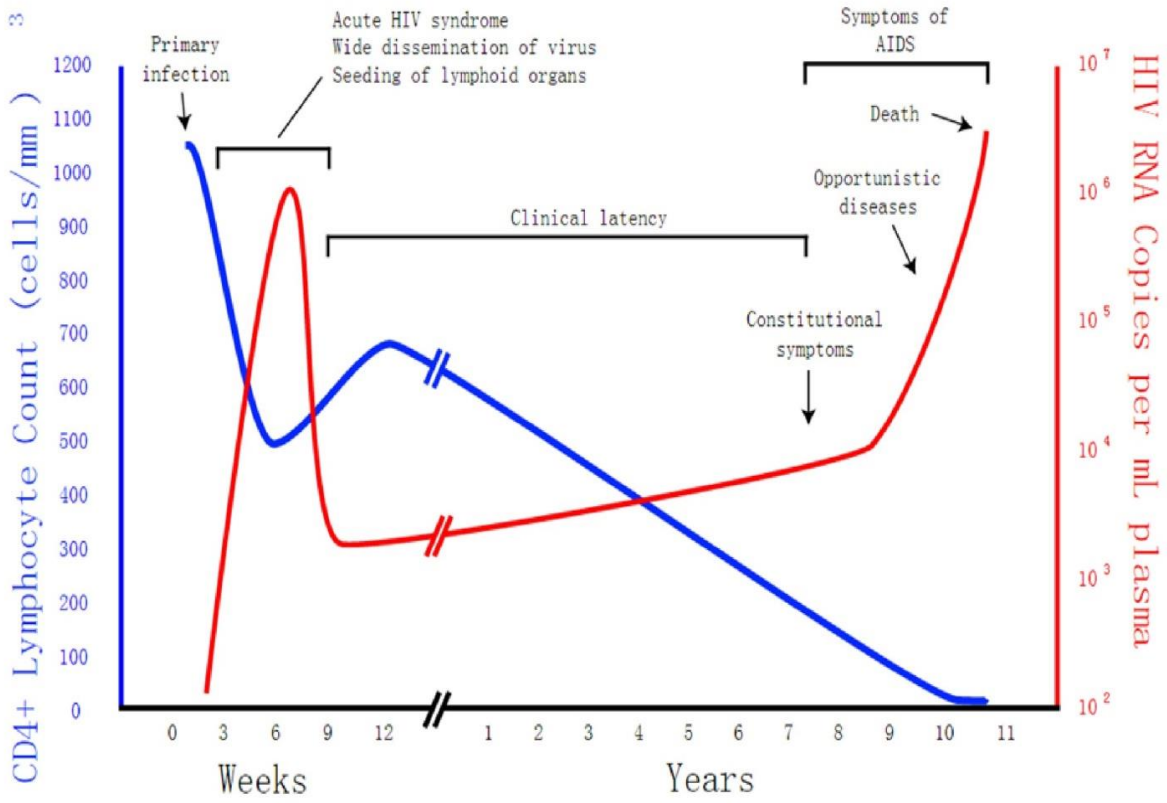

Figure 2: *Effects of HIV viremia on CD4 T cells among AIDS patients [5]*

4. Epidemiology and clinical manifestation of HHV's co-infection with HIV

4.1 Herpes simplex virus (HSV)

Herpes Simplex Viruses are divided into two: HSV 1 and HSV 2. These two viruses share a homology of about 80% similarities and cause infections to millions of people worldwide. Their

infection results in morbidity and mortality in advanced stages of HIV infection. Manifested symptoms are genital ulcers, esophagitis, meningoencephalitis, hepatitis, pneumonia, retinal necrosis and other disseminated infection [7].

Globally, HSV-1 and HSV-2 infections are becoming a public health concern. Seroprevalence of HSV-1 ranges from 70-100% and 6-50% for HSV-2 respectively [8]. However, both HIV and HSV-2 are transmitted via sexual route; this is evident from previous work which reported that the acquisition of HIV is up to four-fold among HSV-2 infected persons [9]. HSV-2 prevalence varies in Africa, with the highest infection reported in major African cities [8]. In males, the reported rates of HSV-2 prevalence range from 5.9% in South Africa to 33.76% in Uganda (**Error! Reference source not found.**), while in females the prevalence rate were 1.4% in Zimbabwe (Harare), 5.11% in Nigeria (Enugu State), 20.7% in Manyara and Singida, Tanzania, 33.3% in Ibadan, Nigeria, 36.6% in Umlazi, South Africa, 61.1% in Lokoja, Nigeria and 65% in Durban South Africa. Also, current studies conducted in the general population reported 11% of HSV-2 cases in rural settings in South Africa, 26.6% in Kisumu and 35% in Nairobi, Kenya (**Error! Reference source not found.**). Active HSV-2 infections are symptomatic and it involves a high concentration of activated CD4 positive T-cells, which are the main target by HIV in the genitalia infected with HSV-2 (genital ulcer) which ruptures the mucosa layer thus interfering with its integrity resulting to the entry of HIV [10].

Table 1: Co-infection studies of Herpes simplex virus (HSV) with HIV

Subjects	Countries (City/Town)	Participant Group	Age (Years)	Study Findings	Reference
	South Africa (Umlazi.)	615 pregnant women	>18 years	HIV and HSV-2 positive rate were 36.6% and 8.3%. HIV-1 positive women were 1.5 and 2.5 times more likely to test positive for HSV-2	[11]

Female	Nigeria (Lokoja)	250 pregnant women	15-35 years	HIV and HSV were detected in 2.4% and 100% respectively and all were in the 2nd trimester of gestation, and co-infection rate was 2.4%.	[12]
	Uganda (Kampala)	1,027 women	>14 years	They was an association between HSV-2 and HIV among alcoholic women	[13]
	South Africa (Soweto)	390 women enrolled	18-40 years	Seroprevalence of HSV-2 was 58.7%; HIV co-infected with HSV was 22.6%. Reactivation of HSV-2 is common among pregnant HIV positive women in South Africa	[14]
	Nigeria (Enugu State)	180 females attending antenatal clinic	NA	The co-infection rate was 5.11% between HSV2 with HIV. HSV-2 increases the risk of HIV infection.	[15]
	Zimbabwe (Harare)	301 adolescents	NA	Seroprevalence of HIV-1 was 46%, of which 1.4% was HSV-2. Skin disease (HSV-2) was a prominent clinical feature amongst HIV-infected adolescents	[16]
	Tanzania (Manyara & Singida)	1,377 pregnant women	15-49 years	Prevalence of HSV-2 was 20.7% among HIV expectant women	[17]
	Tanzania (Northwestern)	821 Female workers who are HSV seropositive	16-35 years	HIV infection incidence was 4.27 per 100 person-years. HSV therapy decreases the incidence of infection with HIV	[18]

General population	Kenya (Kisumu)	1,106 participants	16-34 years	Prevalence was 26.6%, and incidences of HIV/HSV was high in females	[19]
	South Africa (Mopani district)	46 participants	>18 years	HSV-1 DNA was detected in 11 % and HIV infection was detected in 86%. There is an association between HSV-1 infection and keratitis in HIV infected person	[20]
	South Africa (Kwa Zulu Natal)	2,675 students	15-18 years	HSV-2 prevalence was 2.6% in males and 10.7% female. This poses a high risk for HIV infection which was at 1.4%	[21]
	Kenya (Nairobi)	19,840 participants	15-64 years	35% were infected with HSV-2, 81% of HIV-infected persons were co-infected with HSV-2.	[22]

Abbreviation: *HSV, human herpes simplex virus; HIV, Human immune deficiency virus, NA, not applicable*

The high rates of HIV infection (70%) in Africa has been attributed to the high prevalence of HSV-2 infection [8]. In teenager girls aged between 15 to 19 years, the prevalence rate of HSV-2 was estimated to be at 28% as compared to other STI's whereas its seroprevalence in individuals living with HIV was high with more than 90% infected [20, 21]. In Africa, the number of genital herpes cases caused by HSV-1 is not yet fully established.

4.2 Varicella Zoster Virus (VZV)

Varicella Zoster Virus (VZV) is a member of alphaherpesviruses subfamily that is associated with two distinct conditions; chickenpox in children and shingles/herpes zoster (HZ) in adults. VZV infections are ubiquitous worldwide, primary infection of VZV among children results in benign diseases with symptoms ranging from fever to a pruritic vesicular rash. Sometimes it can be

accompanied by the following complications: a skin infection caused by bacteria, encephalitis and pneumonia. While in immunosuppressed individuals (HIV/AIDS) it is associated with significant morbidity and mortality [11].

Reactivation of VZV causes HZ which are painful vesicular rashes distributed in dermatome. The most common complication of HZ is post-herpetic neuralgia and uvetis which affects the eyes and can lead to blindness when it occurs. In certain cases, the clinical presentation of VZV might not be rashes [26], nor neurological complication. The epidemiological reports for VZV infections in Africa show that elderly and HIV infected persons as the most affected [26].

HIV infected persons have a greater chance (12-17 folds) of acquiring HZ in Africa thus, the probability of getting HZ is high. Were et al. reported a seroprevalence rate of VZV (23.6%) among HIV positive children with malignancy and severe malnutrition in Kenya [27]. According to the previous investigation, VZV prevalence varies significantly in African countries: HIV infected women in Rwanda had a prevalence rate of 12.5% for VZV infections with a strong correlation between HIV infection and shingles. However, in Tanzania, the prevalence of HZ in women was 3.2% which was associated with a low CD4 count among HIV patients. Furthermore, the prevalence rate of VZV infection general population varies in different countries; 2.3% of patients in Johannesburg, South Africa had HZ, 5% in Dar es salaam, Tanzania and 11% of VZV DNA proportion in a rural setting in South Africa (**Error! Reference source not found.**). The study conducted in Zambia, among HIV positive patient with CNS infection reported VZV as the fourth most common viral infection and its fatality rate is very high [28]. On comparison, the investigation on viral meningitis in Malawi reported more than half of the patients tested positive for HIV, but, detected with no VZV co-infection [29]. Compston et al., reported that HIV infection were associated with VZV seropositive, and dysfunction of the immunity whereby it results to a slight increase in replication of VZV, this boost VZV antibodies leading to its higher seroprevalence [30].

Table 2: Co-infection studies of Varicella Zoster Virus (VZV) with HIV

Subjects	Countries (City/Town)	Participant Group	Age (Years)	Study Findings	References
Children	Kenya (Nairobi)	147 Children with malignancies, severe malnutrition	1-12 years	Seroprevalence of VZV antibodies was 23.6% among children with HIV	[27]
Female	Rwanda (Kigali)	710 HIV-infected women enrolled in RWISA	>15 years	VZV prevalence was 12.5%. There was a strong association between shingle and HIV infection in women	[31]
General population	South Africa (Mopani district)	46 HIV positive persons	>18 years	VZV DNA proportion was detected in 11%. There was an association between the high prevalence of VZV and HIV positive patients	[20]
	South Africa (Johannesburg)	15,025 HIV positive patients	NA	Only 2.3% of patients had herpes zoster and with low CD4 counts	[32]
	South Africa (Cape town),	102 patients	NA	There is no association between HIV and VZO. The CD4 level was less than 200	[33]

Abbreviation: *VZV, varicella zoster virus; HIV, human immune deficiency virus; HZ, herpes zoster; VZO, varicella zoster opthalmicus; RWISA, Rwanda Women's Interassociation Study Assessment; NA, not applicable*

4.3 Epstein Barr Virus (EBV)

Epstein-Barr virus (EBV) is a gammaherpesvirus which is spread widely in human populations. The first case of EBV infection was isolated from a patient with Burkitt lymphoma in Africa in

1963 [34]. EBV has co-evolved over time in different hosts and it persists in latent stage for the entire lifetime.

Few reports show that EBV and HIV co-infection influence each other mutually in disease progression. Virological findings show a higher circulation and replication of EBV in oropharyngeal secretions in AIDS patients. Serologically, asymptomatic EBV infections have been shown to reactivate and persist in HIV infected individuals [35]. Clinical pathology of EBV infections has been associated with several lesions in AIDS patients, such as oral hairy leukoplakia [36] in adults, lymphocytic interstitial pneumonitis and leomycosarcorma in children and lymphoid neoplasm in central nervous system affecting both children and adults [37].

EBV infection is the most prevalent herpesvirus among immunocompromised persons, and the virus is usually activated to become an oncogene. The infection is detected early in life among HIV positive children in Africa, with the prevalence ranging from 2% in Harare - Zimbabwe, 66% in Kampala - Uganda and 79% in Nairobi - Kenya (**Error! Reference source not found.**). AIDS infection plays a vital role in reactivation of EBV infection and ungoverned lymphoproliferation in HIV infected persons [38].

Infants infected with EBV acquire HIV infection earlier in life as compared to uninfected ones, and the peak of EBV viremia and severe symptoms in affected infancy might lead to hospitalization. The low socio-economic levels in Africa contribute to the high prevalence of EBV infection and the acquisition of maternal HIV infection [35].

According to previous investigations conducted in African population from 2008, the prevalence rate of EBV were; 7.1% in Burkina Faso (Ouagadougou), 11% in Lilongwe, Malawi, 53% in Blantyre, Malawi, 90% in Lusaka - Zambia and 100% in a rural setting in South Africa (**Error! Reference source not found.**). The introduction and use of HAART has led to a significant decrease in HIV viral load and subsequent decrease in all types of EBV infections: a situation that

impedes the development of AIDS-related lymphoma [39]. Currently, there exists insufficient data about lymphoproliferative diseases associated with EBV infections. For instance, in Cape Town, South Africa, it is documented that less than 2% of treated lymphoma is a result of HIV infection [40].

Table 3: Co-infection studies of Epstein Barr Virus (EBV) with HIV

Subjects	Countries (City/Town)	Participant Group	Age (years)	Study Findings	References
Children	Uganda (Kampala)	213 HIV-1-infected children	0-18 years	Prevalence of EBV (66%) was detected among children, EBV DNA levels were higher in children with an HIV-1 RNA load of > 3 log10 copies/mL	[39]
	Zimbabwe (Harare)	257 HIV-infected infants	<6weeks	HIV-infected infants had EBV co-infection was 2%. Congenital EBV was at 7% while postnatal EBV was 4%	[41]
	Kenya (Nairobi)	127 infants born to HIV-infected women	0-1year	Majority of HIV-infected infants had detectable EBV DNA for >3 months (79%).	[42]
	Malawi (Blantyre)	148 paediatrics in an oncology unit	<15 years	EBV and HIV act jointly in the pathogenesis of Burkitt lymphoma	[43]
General population	Burkina Faso (Ouagadougou)	238 HIV-positive patients	NA	EBV infection rate was 7.1%. The infection was high in a patient with >500 CD4 count	[44]

	Zambia (Lusaka)	147 adult patients	NA	Seroprevalence of EBV was over 90%. There was an association between EBV EA and HIV infection.	[45]
	South Africa (Mopani District)	405 HIV-infected individuals	14-49 years	Seroprevalence of EBV was 100%. CD4 cell count was negatively associated with EBV and IgG titres	[46]
	Malawi (Lilongwe)	31 patients	2-51 years	11% of study participants were detected with classical Hodgkin lymphoma. Most cases were EBV associated and one-third of adults being HIV positive.	[47]
	Malawi (Blantyre)	149 adults with bacterial meningitis	16-79 years	EBV was found in the CSF (53%). This was strongly associated with HIV seropositivity.	[48]

Abbreviation: *EBV, Epstein Barr virus; EA early antigen; HIV, Human immune deficiency virus; CSF, cerebral spinal fluid; NA not applicable*

4.4 Human Cytomegalovirus (HCMV)

Human Cytomegalovirus (HCMV) is a member of beta herpesvirus which is ubiquitous in nature. Globally, the HCMV seroprevalence rate ranges from 40 to 100% with low prevalence in developed countries [49] and high prevalence in developing countries. HCMV is widely recognized as an opportunistic pathogen amongst immunocompromised persons, particularly in HIV positive patients and those undergoing organ transplants

There are high incidences of co-infection between HIV and HCMV; however, the clinical manifestations have been minimized with the introduction of HAART. Furthermore, there is a complex interaction between these two chronic viral co-infections, which pose a greater risk in

the vulnerable population such as children and immunosuppressed adults. In Africa, HCMV and HIV are endemic in infants and children; prompting an increased viral co-infection in utero during the early days of their lives [41].

Both HCMV and HIV have similar modes of transmission which include sexual contacts and blood transfusions. In Africa, poor nutrition, overcrowding, living conditions [50] and co-infection with other herpesviruses [51] are linked to increased HCMV seroprevalence. A cohort study done in West Africa shows increased seropositivity of HCMV among HIV infected persons as compared to uninfected individuals [30]. Current studies in Africa show that HCMV infection might be a risk factor in the transmission of HIV: a study conducted in Kwa Zulu Natal, South Africa, showed an independent association between HCMV in breast milk and postnatal mother to child transmission of HIV [52].

The prevalence of HCMV varies significantly in the African population. The existing data are inadequate in a few countries, but conducted studies in children reported a prevalence ranging from 2.9% in South Africa [53], 3.8% in Zambia [54], 66% in Nairobi, Kenya and 79% in Harare, Zimbabwe (**Error! Reference source not found.**). An estimated two-thirds of infants show serological evidence of HCMV by three months, and 85% by the age of one year [55]. Among breastfeeding HIV positive mothers in Kwa Zulu Natal in South Africa, there is an increased shedding of HCMV in breast milk as reported by Viljoen et al. Another study conducted in Uganda (Rakai) reported the HCMV prevalence rate of 78% in HIV positive women (**Error! Reference source not found.**). HCMV infections are virtually universal in the general population, and the co-infection rate of HCMV with HIV in Africa ranges from 5.9% for HCMV retinitis in Ghana (Cape Coast Teaching Hospital), 10% Malawi (Blantyre), 11.1% in Kwara State, Nigeria and 100% in rural settings of South Africa (**Error! Reference source not found.**).

Table 4: Co-infection studies of Human Cytomegalovirus (HCMV) with HIV

Subject	Countries (City/Town)	Participant Group	Age (Years)	Study Findings	References
Children	Malawi (Lilongwe)	410 HIV infected children	3 months to 15 years	HCMV IgG was most prevalence (in 73% of children <1 year, and 100% in all other groups). 3.3% of the patients were HCMV IgM positive. HCMV infection occurs early in life among children initiating ART.	[56]
	Zambia (Lusaka)	303 pediatric inpatients	3 weeks to 2 years	Prevalence of HCMV was 3.8% and it was independently associated with HIV infection	[54]
	South Africa (western cape province)	425 HIV infants	2 months to 5 months	HCMV prevalence was 2.9% infected infants peaks at 3-4 months of age	[53]
	Kenya (Nairobi)	141 infants born to an HIV infected mother	<1 year	Prevalence of HCMV was 66% among infants in the valacyclovir placebo arm	[57]
	Zimbabwe (Harare)	257 ARV-naïve HIV-infected infants	<6weeks	HCMV IgG positive was 79% by age 6 weeks and there is no association with mortality	[41]
	Kenya (Nairobi)	474 HIV (+) infants from HIV (+) mother	0 to 1year	HCMV induces T cell activation which results in the rapid progression of HIV infection	[58]

Female	South Africa (Kwa Zulu Natal)	124 HIV positive mother and their infants	NA	HCMV is associated with increased shedding of HIV in milk	[52]
	Uganda (Rakai)	96 women co-infected with HIV.	>20 years	HCMV DNA was 78.0% women, higher HIV viral load before ART initiation, and younger age were associated with HCMV shedding	[59]
General population	Nigeria (Kwara state)	360 consented HIV-1 patients	1 to 70 years	Detection of anti-CMV IgM and IgG antibodies positive were 11.7% and 73.6%, respectively. There was an association between HCMV infection and HAART recipient	[60]
	Nigeria (Kwara state)	180 consented HIV-1 seropositive patients	16 to 56 years	11.1% of HIV-1 seropositive subjects were positive for anti-CMV IgM antibody while 93.9% were positive for anti-CMV IgG antibody. HIV-1 seropositive patients had active HCMV infection	[61]
	South Africa (Mopani district)	405 HIV positive person	>18 years	100% of HCMV IgG which negatively associated with CD4 counts	[46]
	Malawi (Blantyre)	149 adults with bacterial meningitis	16 to 79 years	HCMV DNA proportion was detected (10%) HIV-positive patients (median CD4 count, 121 cells/mm3	[48]

Abbreviation: *HCMV, human cytomegalovirus; HIV, human immune deficiency virus; (+), positive; ART, antiretroviral therapy, HAART, highly active antiretroviral therapy; NA, not applicable.*

According to previous studies conducted in African countries, there was a strong correlation between high HIV viral load and HCMV [62]. This scenario can be explained by the influence of HIV infection on HCMV viremia, whereby symptomatic HCMV is a result of high concentration of HIV-p-24 antigen, but these have not yet been fully confirmed [63]. They play a vital role in the activation of pro-viral latent HIV DNA in different molecular ways; the HCMV IE-2 gene interferes with gene expression of HIV within the same cell [64], also infection causes cytokine release cells, whereby the latent pro-viral HIV is activated via signal transduction [65]. Cellular activation of HCMV contributes to the pathogenesis of HIV by depletion of T cells through apoptosis which induces the cell death [58].

Recently, the increased use of HAART has decreased the reactivation of HCMV infection which initially used to be a co-factor for HIV progression to AIDS. A study carried out by Fowotade et al., among HIV individuals co-infected with HCMV was reported to be greater than 90%, but with the introduction of HAART, it led to a decrease in HCMV reactivation among individuals at risk of HIV infection [61].

4.5 Human Herpes Virus 6 (HHV-6)

Human Herpesvirus 6 (HHV-6) belong to beta herpesvirus subfamily; the first HHV-6 case was isolated from peripheral blood lymphocytes of a patient with lymphoproliferative disease in 1986 [66]. HHV-6 has two distinct variants; HHV-6A and -6B, it causes *Roseala infantum* in children below two years. The prevalence rate ranges from 65% to 100% in children below one year [67, 68]. There is no significant difference between HHV-6 infection and ethnic groups from the same geographical region. Although, an exceptional case has been reported in Morocco where the seroprevalence rate was at 20% [69]. Africa, in general, has a high prevalence rate of HHV 6 (86-100%) which is acquired early in life. Reactivation of HHV-6 in adults is due to immunosuppression brought by other human diseases particularly AIDS in Africa (**Error! Reference source not found.**).

Table 5: Co-infection studies of HHV-6, HHV-7 and HHV-8 with HIV

Subjects	Countries (Cities/Towns)	Participant Group	Age (years)	Study Findings	References
Children	Zambia (Lusaka)	303 paediatrics	3 weeks to 2 years	HHV-6B DNAemia was 20.5% and HHV-6A was 0.3% and there was no association with HIV infection, HHV-7 DNAemia was not associated with HIV	[70]
Female	South Africa (Gauteng province)	1,740 pregnant women attending antenatal clinic	NA	KSHV seroprevalence was very high (45%) and nearly double that of HIV infection (23%). HIV was strongly associated with increased risk for KSHV seropositivity	[71]
General population	Burkina Faso (Ouagadougou)	238 HIV-positive patients	16-79 years	HHV-6 prevalence was 7.1%, the infection was high in a patient with >500 CD4 count and HAART treatment does not affect the virus	[44]
	Cameroon (Yaoundé)	316 cases	NA	Prevalence of KS was 2.2% in HIV-infected patients. The CD4 counts were < 200 cells/mm3	[72]
	Malawi (Kamuzu)	42 HIV-positive patients with MCD	NA	Concurrent Kaposi Sarcoma was present for MCD patient. There was an association between HIV infection and MCD	[47]
	Uganda (TASO clinics)	5,972 HIV positive individuals	26-39 years	There was a non-significant increase in mean annual prevalence trend for Kaposis's sarcoma in HIV patients.	[73]

	Togo (Lome)	157 patients	NA	The average CD4-cell count was 226±168 cells/mm are associated with a high prevalence of AIDs-related Kaposi's sarcoma	[74]
	South Africa (Johannesburg)	404 HIV-infected treatment-naïve adults	>18 years	The prevalence of KSHV was estimated at 48%. KSHV DNA was 11% in participants. KSHV viremia but not KSHV seropositivity may be associated with markers of advanced HIV disease.	[75]
	South Africa (Kwa Zulu Natal)	701 KS patients on antiviral treatment	NA	Anti-retroviral treatment (ART) improves the care of AIDS-associated KS	[76]
	Tanzania (Dar es salaam)	150 HIV positive patients	NA	Kaposi's sarcoma was detected in 3% of the patients. There was an association between KSHV and HIV infection	[77]
	Nigeria (Jos)	48 HIV positive patients	NA	AIDS-KS patients had lower levels of viral load (29,347 copies/mL) together with low CD4 counts	[78]

Abbreviation: *HHV-7, human herpesvirus 6; HHV-7, Human herpesvirus 7; KS, Kaposi's Sarcoma; KSHV, Kaposi's Sarcoma-associated herpes virus; MCD, Multicentric Castleman disease; HIV, Human immune deficiency virus; ART, antiretroviral therapy; TASO, The Aids Support Organization*

In recent studies, the association of disease progression of HIV and HHV-6 is not clear. Moreover, there exists little information regarding the co-infection of the two viruses in Africa, the work by Tembo et al in Zambia reported a prevalence rate of 20.5% for HHV-6B and HHV-6A at 0.3% in 2015 respectively among the pediatric population (Table 5), similar studies were also conducted

among HIV patients which reported HHV-6B prevalence rate of 7.1% in Burkina Faso by Lassina et al., in 2017 (**Error! Reference source not found.**). HIV infection reactivates HHV-6 infection resulting to a high viral load in lymph nodes, and viremia which is disseminated later to other parts of the body followed by active CNS infection, retinitis and pneumocystis which leads to death due to immune suppression as a result of AIDS [67]. These findings provide some evidence on how HHV 6 promotes the pathogenesis and progression of HIV to AIDS [79].

4.6 Human Herpes virus 7 (HHV-7)

Human Herpes virus 7 (HHV-7) is a beta-herpes virus that was discovered in 1990 [80]. It is distinguished from HHV-6 by their mode of replication. Similar to other HHVs, it establishes latency in infected cells of T lymphocytes where it remains in an asymptomatic state with viral shedding in saliva. HHV-7 infection has been reported in a few cases of Exanthema subitum in children, and also CNS disorder has been linked with primary infection of HHV-7 [67].

There is inadequate information regarding HHV-7 prevalence, immunology and pathogenesis of HIV/AIDS infection. Previous studies report an age range between 18 months to 3 years as the most commonly affected age group by HHV-7. For instance, in the United States, more than 90% of the populations show evidence of HHV-7 infection at the age of 5 years. Also, very low prevalence has been reported in other developed nation such as Belgium, Japan and Australia while high prevalence has been noted in less developed countries such as South Africa [81]. Among immunosuppressed persons with AIDS: HHV-7 causes dermatological manifestations, ulcers and herpetic retinal infections. There exists little information on the role of HHV-7 in AIDS progression in Africa. Notably, a study conducted in Zambia among paediatrics population reported that there was no association between HHV-7 and HIV infection **(**Error! Reference source not found.**)**

4.7 Human herpes virus 8 (HHV-8)

Human herpes virus 8 (HHV-8), also known as Kaposi's Sarcoma Associated Herpesvirus (KSHV), is a gamma herpes virus that is ubiquitous in nature and that causes Kaposi's sarcoma (KS), primary effusion B-cell lymphoma, lymph proliferative disorder and multicentric Castleman's disease. KS malignancy is one of the major AIDs defining infections present in HIV patients [82]. Primary infection of HHV-8 in immunocompromised persons and post-transplantation individuals is more aggressive with broad clinical features ranging from fever, rashes, bone marrow failure, pancytopenia, lymphadenopathy to more widespread visceral, muscular or nodular skin lesions [83].

The prevalence of HHV-8 varies depending on geographical location; endemic or non-endemic regions. HHV-8 is geographically categorized into 3 based on low seroprevalence with a range of <5% which is common in USA, Europe and Asia; intermediate seroprevalence which ranges from 5%–20%, which is greater than Mediterranean, Caribbean, Eastern Europe, and the Middle East; and high seroprevalence ≥50%, which is frequent in Africa and Brazilian Amazon regions. The seroprevalence of HHV-8 increases with age and by adulthood, the majority of the individuals would have seroconverted [84].

Previous work on HHV-8 prevalence in Africa reported that most of the children develop HHV-8 antibodies before attaining the age of 13 years. The hypothesis behind this high seroprevalence rate is as a result of the presence of the virus in the region for a long period with unknown co-factors that increases its transmission. Despite this high prevalence, only a small percentage develops KS [85].

The equatorial region of Africa is endemic with KS amid high progression of HHV-8, thus its termed as the KS belt. This was recognized before the HIV era [86]. The belt runs from the coastal region of Cameroon via northeast of Democratic Republic of Congo into the Rift Valley region of Malawi, Uganda, Tanzania and Zambia [87]. Important to note, a continuous incidence increase

of KS has been observed in these regions as a result of HIV infection. Previous investigative studies reported HHV-8 as a co-factor in the progression of HIV to AIDS in most African countries; this was seen in 45% of women in Gauteng province, South Africa, while in the general population, the prevalence rate was 2.2% in Yaoundé, Cameroon to 48% in Johannesburg, South Africa (**Error! Reference source not found.**). However, the seroprevalence of HHV-8 in Africa tends to increase with age from childhood to adulthood. With the introduction of antiretroviral therapy, the KS incidence is being controlled in sub-Saharan Africa.

In Africa, HHVs infection is considered to be the most common opportunistic infections among HIV infected persons despite the use of high acquired antiretroviral therapy (HAART). Figure 3 indicates a summary of the geographical distribution of HHVs infection discussed earlier.

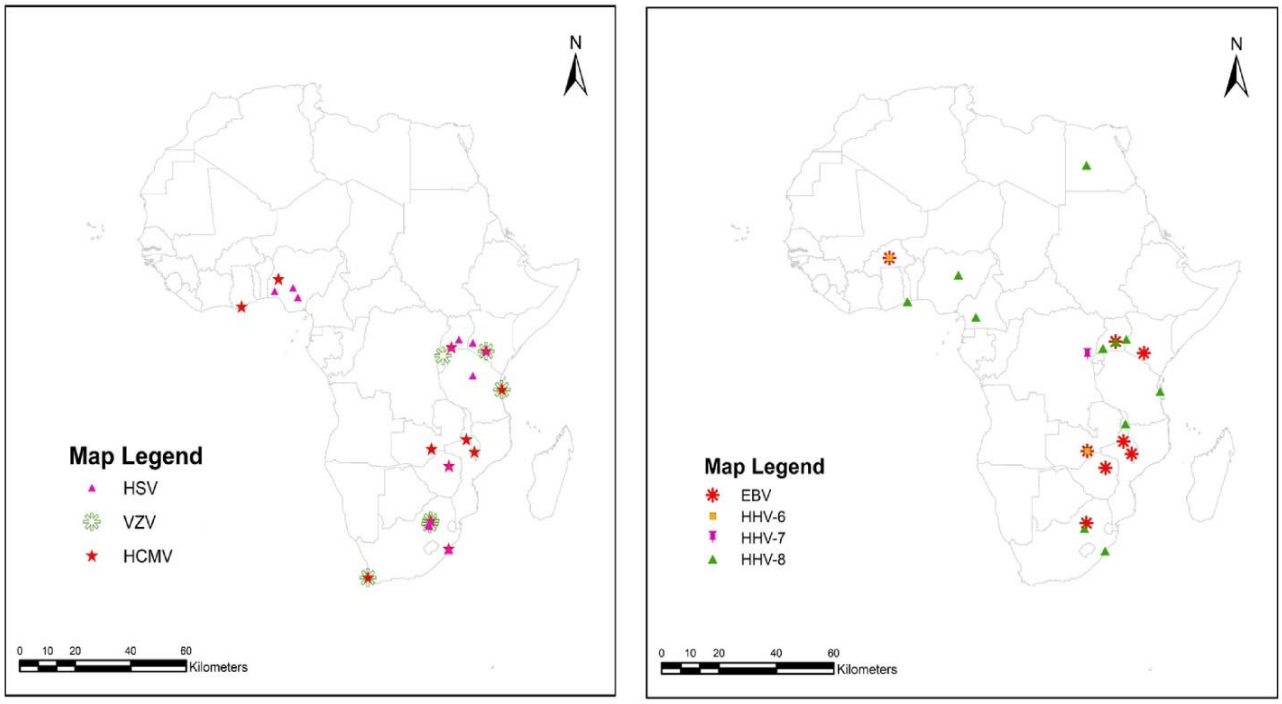

Figure 3: Geographical distribution of HHVs infection in Africa

5. Conclusion

HHVs play a vital role in HIV progression to AIDS in Africa. However, screening and treatment of subclinical HHVs infection are advantageous to individuals with HIV infection. HSV infections promote the acquisition and progression of HIV to AIDS with a broad range of HSV related diseases. Treatment of HSV suppresses HIV infection by delaying its progression to AIDS. Chickenpox in children and HZ in adult remains a major concern even after the introduction of antiretroviral therapy, due to the complications arising from vaccination against HZ that might lead to liver complications. HCMV viremia is significant as it can be used to predict HIV progression to AIDS by comparing the CD4 T lymphocyte count in HIV positive persons to ascertain the pathogenesis of HIV to AIDS. Majority of the human population in Africa with HIV are seropositive with HCMV that leads to rapid exhaustion of HAART and reduction of CD4 cell count, giving rising to HCMV diseases. Apart from HSV, VZV, HCMV and HHV-8 that have been involved to play a role in the pathogenesis of HIV to AIDS, other HHVs such as EBV, HHV-6, and HHV-7 have inadequate information in regards to their direct involvement in HIV pathogenesis to AIDS in Africa, although they are associated with malignancy which plays a role in HIV progression to AIDS despite the use of HAART. Many questions still remain unanswered on molecular interaction and their role in which they play in HIV progression to AIDS despite the use of antiviral therapy, a lot of work need to be done at the clinical level to understand the mechanism of interaction between HHVs and HIV.

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