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Human Herpesvirus 8 (HHV-8) Genotyping and Genetic Variability in Sub-Saharan Africa Using Peripheral Blood: A Literature Excerpt Compilation

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Abstract

Background: Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), is the etiological agent of Kaposi sarcoma and is highly prevalent in sub-Saharan Africa. Its circulation extends beyond clinically affected individuals to HIV-positive and asymptomatic populations. Molecular characterization based on the ORF-K1 genomic region has revealed substantial genetic diversity and distinct geographic clustering. **Methods:** A literature excerpt compilation was conducted on studies published between January 2015 and March 2025. Relevant articles were identified through searches of PubMed, Scopus, Google Scholar, and ScienceDirect. Studies reporting molecular characterization of Human Herpesvirus 8 (HHV-8) in Sub-Saharan Africa among Kaposi sarcoma patients, HIV-positive individuals, and asymptomatic carriers using peripheral blood, plasma, or peripheral blood mononuclear cells (PBMCs) were included. No systematic screening protocol or meta-analysis was applied. **Results:** HHV-8 genetic diversity was consistently observed across sub-Saharan Africa, showing a geographically structured distribution of viral lineages. East and Central Africa were characterized by a relatively conserved pattern with predominance of genotype B and A5, whereas West Africa exhibited greater heterogeneity with frequent circulation of genotypes B and C. Similar genotype distributions were observed among Kaposi sarcoma patients, HIV-positive individuals, and asymptomatic carriers, supporting widespread community-level circulation independent of clinical status. **Conclusion:** HHV-8 exhibits substantial genetic heterogeneity across sub-Saharan Africa, characterized by a limited number of dominant viral lineages

and regionally structured diversity. Peripheral blood-based molecular studies provide key insights into viral circulation patterns and transmission dynamics across different population groups. However, current evidence remains constrained by heterogeneous study designs and limited geographic coverage. Consequently, further multicenter, standardized molecular studies are needed to better elucidate the relationship between viral genetic diversity, clinical outcomes, and the evolutionary dynamics of HHV-8 in the region.

Keywords

HHV-8, KSHV, HIV, Genetic Diversity, Genotypes, ORF-K1, Phylogenetic Analysis, Sub-Saharan Africa, Kaposi Sarcoma

1. Introduction

Human herpesvirus type 8 (HHV-8), also known as Kaposi Sarcoma-Associated Herpesvirus (KSHV), is the etiological agent of Kaposi Sarcoma, primary effusion lymphoma, and certain forms of multicentric Castleman disease [1]. In sub-Saharan Africa, particularly in East and Central Africa, HHV-8 remains highly endemic and constitutes a major public health concern due to its strong association with HIV/AIDS infection and the high incidence of Kaposi's sarcoma among immunocompromised individuals [2].

Molecular characterization of HHV-8 mainly relies on the analysis of the hypervariable ORF-K1 genomic region, which is widely used for viral genotyping and phylogenetic analysis [3].

Phylogenetic studies conducted over recent years have demonstrated considerable genetic diversity of HHV-8, as well as a geographically specific distribution of viral genotypes across different African regions [4].

In this context, the use of peripheral blood, plasma, or peripheral blood mononuclear cells (PBMCs) as biological specimens has greatly facilitated the development of conventional PCR, real-time PCR, and molecular sequencing techniques for investigating the genetic variability of HHV-8 in several sub-Saharan African countries [3].

The aim of this literature excerpt compilation is to synthesize recent data on HHV-8 genotyping and genetic variability in sub-Saharan Africa, particularly in East, Central, and West Africa, based on molecular studies using peripheral blood-derived specimens. The review includes studies conducted among Kaposi sarcoma patients, HIV-positive individuals, asymptomatic carriers, and mixed populations in order to provide a comprehensive overview of HHV-8 genetic diversity and circulation across different population groups.

2. Materials and Methods

2.1. Study Design

This study is a literature excerpt compilation summarizing published molecular

studies on HHV-8 genetic variability in sub-Saharan Africa between 2015 and 2025. It includes studies conducted among Kaposi sarcoma patients, HIV-positive individuals, asymptomatic carriers, and mixed populations. The aim was to provide a structured qualitative synthesis of available molecular evidence without applying systematic review methodology or meta-analysis.

2.2. Data Sources and Search Strategy

A structured literature search was performed in PubMed, Scopus, Google Scholar, and ScienceDirect to identify studies published between January 2015 and March 2025, with the final search conducted on March 31, 2025. The search strategy combined keywords related to Human Herpesvirus 8 (HHV-8), Kaposi sarcoma-associated herpesvirus (KSHV), genotyping, genetic variability, ORF-K1, phylogenetic analysis, peripheral blood, plasma, PBMCs, and sub-Saharan Africa.

The search syntax included Boolean combinations of terms such as:

"Human Herpesvirus 8" OR "HHV-8" OR "Kaposi Sarcoma-associated Herpesvirus" OR "KSHV" AND "genotyping" OR "genetic variability" OR "phylogenetic analysis" AND "ORF-K1" AND "Kaposi sarcoma" AND "peripheral blood" OR "plasma" OR "PBMCs" AND "Africa" OR "sub-Saharan Africa".

Only English-language publications were included. In addition, the reference lists of eligible studies were manually screened to identify further relevant articles. The literature selection process followed a structured screening approach based on predefined eligibility criteria.

2.3. Study Selection Process

A total of 14 records were identified through database searching and manual screening. After removal of duplicates, titles and abstracts were screened for relevance. Nine studies were excluded at this stage due to failure to meet the inclusion criteria. Full-text assessment was then performed on the remaining studies, resulting in the inclusion of five studies in the literature excerpt compilation.

The selection process is summarized as follows:

- Records identified: 14
- Included after screening: 5
- Excluded: 9

Geographically, the included studies comprised:

- East Africa: 0 study
- Central Africa: 2 studies
- West Africa: 1 study
- Multicountry studies: 2 studies

2.4. Inclusion Criteria

Studies were included if they:

- Reported molecular analysis of HHV-8
- Studies were conducted in sub-Saharan Africa

- Used blood-derived specimens (peripheral blood, plasma, or PBMCs)
- Performed genotyping or phylogenetic analysis targeting ORF-K1
- Applied PCR, nested PCR, sequencing, or related molecular techniques

2.5. Exclusion Criteria

Studies were excluded if they:

- Were non-molecular in design
- Did not use blood-derived specimens
- Were reviews, editorials, case reports, or conference abstracts
- Did not provide HHV-8 genotyping or phylogenetic data

2.6. Data Extraction

A standardized data extraction approach was used. For each included study, the following variables were collected: author and year, country or region, study population, specimen type, molecular techniques used, target gene (ORF-K1), and reported HHV-8 lineages.

2.7. Study Quality Considerations

As this study is a literature excerpt compilation, no formal risk-of-bias assessment tool was applied. However, included studies were descriptively appraised with attention to study design, population characteristics, and molecular methodologies to ensure interpretative consistency.

3. Results

The geographical distribution of the included studies is summarized in Table 1. Overall, five studies were included in the literature excerpt compilation, comprising two studies from Central Africa, one from West Africa, and two multicountry investigations, while no eligible studies from East Africa met the inclusion criteria (Table 1).

Table 1. Distribution of included studies by African region and corresponding authors.

Region	Countries Represented	Studies (Authors, Year)	Number of Studies
East Africa	Kenya, Uganda, Tanzania	-	0
Central Africa	Gabon, Cameroon, Central African Republic	[5] [6]	1 1
West Africa	Senegal, The Gambia, Togo, Côte d'Ivoire	[1]	1
Multicountry/Continental Studies	Multiple African Countries	[4] [2]	1 1
Total	-	-	**5**

4. Discussion

- HHV-8 Genetic Diversity across Sub-Saharan Africa

The present review highlights substantial genetic diversity of Human Herpesvirus 8 (HHV-8) across sub-Saharan Africa, characterized by the predominance of a limited number of viral lineages alongside the consistent presence of less frequent variants. This pattern suggests a structured but not fully resolved phylogeographic organization of HHV-8 in the region, likely shaped by long-term endemic circulation and local transmission networks rather than recent introductions alone.

The studies summarized (Table 2) highlight the genetic diversity of HHV-8 in sub-Saharan Africa based on blood-derived specimens. ORF-K1 remains the main target used for genotyping, showing the predominance of genotype B, with variable detection of A5, C, and recombinant variants across regions. Differences in populations, specimens, and molecular methods should be considered when comparing genotype distributions between studies.

Table 2. Summary of studies reporting HHV-8 genotyping and genetic variability in sub-Saharan Africa using blood-derived specimens.

Author	Year	Country/Region	Population	Specimen	Method	Target Gene	Number of Strains Analyzed	Genotype Frequency (%)					Main Findings
								B	A5	C	F	Recombinant/ Others	
[6]	2015	Multiple African Countries	Mixed	PBMCs	PCR and Sequencing	ORF-K1	46	52.2	26.1	15.2	4.3	2.2	Demonstrated substantial HHV-8 genetic variability and distinct phylogenetic clustering across African regions
[1]	2018	West Africa	Mixed	PBMCs	PCR, Sequencing	ORF-K1	48	50.0	29.2	16.7	2.1	2.0	Confirmed circulation of genotypes B and C in Western African populations
[2]	2021	Sub-Saharan Africa	Mixed	Blood-Derived Samples	Sequencing Analysis	ORF-K1	110	42.7	29.1	15.5	4.5	8.2	Updated geographical distribution of HHV-8 genotypes across Sub-Saharan Africa
[4]	2022	Multiple African Countries	Mixed	Viral DNA	Whole Genome Sequencing	ORF-K1	88	38.6	26.2	15.9	6.8	12.6	Identified two major African evolutionary lineages and evidence of viral diversification

Continued

[5]	2021	Central Africa (Gabon)	Mixed	Whole Blood/ PBMCs	PCR and Sequencing	ORF-K1	31	77.4	19.4	-	3.2	High HHV-8 prevalence in rural Gabon, strong predominance of genotype B, First detection of genotype F, absence of genotype C

Country-level analyses generally support regional molecular patterns, although important gaps and inconsistencies remain across studies. In Central Africa, reports from Gabon indicate the circulation of multiple viral lineages among both Kaposi sarcoma patients and rural populations [5], suggesting community-wide dissemination beyond clinical settings. Similar observations from Cameroon and the Central African Republic, where closely related viral variants dominate, may reflect stable endemic transmission with limited viral replacement over time [6]. However, the relatively small number of studies and limited sampling depth in these settings restrict strong generalizations.

In West Africa, studies from Senegal, The Gambia, Côte d'Ivoire, and Togo demonstrate a higher degree of genetic heterogeneity with co-circulation of multiple viral lineages [1]. This increased diversity may reflect either multiple introduction events, higher recombination dynamics, or undersampling of structured subpopulations. However, the lack of standardized sequencing approaches across studies limits the direct comparability of these findings.

A large multicountry investigation also confirmed widespread circulation of genetically diverse HHV-8 lineages among HIV-positive individuals and Kaposi sarcoma patients [2], reinforcing the concept that viral diversity is not restricted to specific clinical groups or localized epidemics but is broadly distributed across sub-Saharan Africa.

Overall, while these observations support distinct regional patterns, the evidence base remains uneven, and conclusions are constrained by heterogeneity in sampling design, geographic coverage, and molecular resolution.

- Consistency of Findings by Specimen Type and Genomic Target

A major interpretative limitation is the heterogeneity of biological specimens and genomic targets across studies. Most available data rely on ORF-K1-based genotyping, which, while highly informative for phylogenetic discrimination, captures only a fragment of the viral genome and may not fully represent whole-genome evolutionary dynamics. The reliance on a single genomic marker introduces potential bias toward lineage classification based on a hypervariable region, which may exaggerate apparent diversity in some contexts.

Studies using whole blood, plasma, or peripheral blood mononuclear cells (PBMCs) remain limited, and direct comparative analyses are scarce. Consequently, it remains unclear whether observed lineage distributions are fully stable across compartments or influenced by differences in viral load, latency status, or cell-associ-

ated persistence. The absence of standardized multi-compartment sampling across studies represents a critical gap in the current literature.

Similarly, the predominance of ORF-K1 as the principal target restricts broader genomic interpretation. Without complementary genomic regions, the extent to which observed patterns reflect whole-genome evolution versus localized sequence variation remains uncertain.

- Evolutionary Mechanisms Driving HHV-8 Diversification

The genetic diversification of HHV-8 in sub-Saharan Africa reflects a complex interplay of long-term co-evolution, host immune pressure, and historical population dynamics. The strong variability observed within ORF-K1, particularly in the VR1 and VR2 regions, is consistent with positive selection pressures driven by host immune responses [3]. However, the extent to which this variability translates into functionally relevant phenotypic differences remains incompletely understood.

Multicountry studies reporting multiple lineages and recombinant forms [4] suggest that recombination may play a non-negligible role in HHV-8 evolution. Nevertheless, the frequency and epidemiological significance of recombination events remain uncertain due to limited whole-genome sequencing data. As a result, evolutionary interpretations should be considered provisional rather than definitive.

Although long-term endemic circulation in sub-Saharan Africa is a plausible hypothesis, it cannot be confirmed solely from current phylogenetic data. The absence of time-resolved molecular data further limits the ability to reconstruct precise evolutionary trajectories.

- Genotype Distribution and Clinical Associations

Importantly, observed associations reported in isolated studies may be confounded by host factors, particularly HIV status, immune suppression level, and co-infections, rather than reflecting intrinsic viral pathogenic differences (**Table 2**). Consequently, any proposed genotype-disease relationship remains speculative and requires validation through well-designed longitudinal studies.

- Implications for Kaposi Sarcoma Pathogenesis

The genetic diversity of HHV-8, particularly within ORF-K1, may influence viral-host interactions relevant to Kaposi's sarcoma pathogenesis. ORF-K1-mediated modulation of signaling pathways involved in angiogenesis, apoptosis, and cellular proliferation provides a biological rationale for potential variability in pathogenic outcomes [3]. However, direct evidence linking specific viral lineages to functional differences in oncogenic potential remains limited.

The detection of recombinant strains in multicountry analyses further suggests ongoing viral evolution, which could theoretically contribute to phenotypic variability. Nevertheless, the absence of experimental validation and functional assays prevents definitive conclusions regarding causality. Thus, the role of HHV-8 genetic diversity in Kaposi's sarcoma pathogenesis should be considered supportive but not determinative.

- Impact of HIV Co-Infection on HHV-8 Diversity

HIV co-infection is a major driver of HHV-8 epidemiology and likely contributes indirectly to observed genetic diversity. Immunosuppression enhances viral replication and shedding, increasing transmission efficiency and sustaining circulation within high-risk populations. However, whether HIV directly influences viral evolution or merely amplifies existing diversity remains unclear.

Although antiretroviral therapy partially restores immune function, persistent viral reservoirs and incomplete immune reconstitution may allow continued HHV-8 persistence and transmission. This sustained viral circulation likely contributes to the maintenance of multiple co-existing lineages across sub-Saharan Africa.

- Limitations of the Review

This review has several limitations. First, the number of available studies on HHV-8 genotyping across sub-Saharan Africa was relatively limited, particularly in East Africa, where few molecular epidemiological studies have been conducted. This limited evidence base restricts robust regional comparisons and may introduce geographical bias in the interpretation of viral diversity patterns.

Second, the included studies were heterogeneous in terms of study populations, comprising Kaposi sarcoma patients, HIV-positive individuals, asymptomatic carriers, and mixed cohorts. This heterogeneity limits the ability to disentangle host-related effects from true viral evolutionary differences and introduces variability in observed findings.

Third, methodological differences in PCR protocols, sequencing strategies, and phylogenetic inference methods may have influenced lineage assignment and reduced comparability across studies. The absence of standardized molecular workflows remains a major constraint for cross-study integration.

5. Conclusions

HHV-8 exhibits substantial genetic diversity across East, Central, and West Africa. Studies based on peripheral blood samples consistently indicate the predominance of a limited number of viral lineages, particularly in Central and East Africa. Molecular analyses targeting the ORF-K1 gene have significantly advanced the understanding of the virus's epidemiology and phylogenetic evolution within sub-Saharan Africa.

However, the current evidence is limited by the absence of stratified synthesis according to specimen type and genomic target. Most available data derive from ORF-K1-based analyses, meaning that overall interpretations largely reflect this genomic region. Furthermore, the scarcity of studies using whole blood, plasma, and peripheral blood mononuclear cells (PBMCs) limits a robust evaluation of the consistency of viral lineage distribution across different biological matrices, thereby constraining comparative interpretation.

Strengthening molecular biology infrastructure and expanding sequencing capacity remain essential to improve HHV-8 epidemiological surveillance and to enhance monitoring of Kaposi's sarcoma across African countries.

Author Contributions

Kahasha, P.M. was the principal investigator and contributed to all stages of the research, manuscript drafting and revision. He was the corresponding author. Bulakali, R.C. contributed to the co-supervision of the study. Mukadi, B.K. contributed to the supervision and direction of the research. Marbaix, E. contributed to the critical review and revision of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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