



# The Emergence of HHV-8 Infection among HIV-positive Individuals Residing in Bali, Indonesia

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## Abstract

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**BACKGROUND:** Human herpesvirus 8 (HHV-8) is considered as the etiological agent of Kaposi's sarcoma (KS). In people living with human immunodeficiency virus (HIV) (PLHIV), KS defines acquired immunodeficiency syndrome (AIDS). The previous study found that HIV-positive individuals were more likely to be HHV-8 seropositive than HIV-negative individuals. Reports regarding the presence of HHV-8 and HIV coinfection in Indonesia are severely limited.

**AIM:** This study aimed to identify HHV-8 infection among HIV-positive individuals in Bali, Indonesia.

**METHODS:** Forty-three plasma samples were collected from 16 antiretroviral therapy (ART) naive and 27 ART-experienced individuals residing in Buleleng Regency, Bali, Indonesia. Detection of HHV-8 antigen was performed using enzyme-linked immunosorbent assay method. The Fisher's exact test and the Spearman correlation test would be used to analyzed data accordingly.

**RESULTS:** Seven samples (7/43, 16.3%), one of ART-naive individual (1/16, 6.25%) and six of ART-experienced individuals (6/27, 22.2%), were tested positive for HHV-8 antigen. HHV-8 infection was correlated neither to sex ( $p = 1.000$ ) and age ( $p = 0.716$ ), nor to ART status ( $p = 0.178$ ) and length of ART ( $p = 0.465$ ).

**CONCLUSION:** This study indicates the emergence of HHV-8 infection among HIV-positive individuals residing in Bali, Indonesia. Sufficient diagnosis of HHV-8 should be considered for all HIV-positive individuals to deliver appropriate treatment. Extensive researches are suggested to be conducted in more regions of Indonesia to determine the magnitude of HHV-8 infection among HIV-positive individuals.

## Introduction

Human herpesvirus 8 (HHV-8) is a gammaherpesvirus, which capable of infecting several cell types, specifically the B and T lymphocyte. *In vitro* replication of the viruses occurs in lymphoblastoid cells, but some lytic infections might occur in epithelial and fibroblasts. HHV-8 is also known as Kaposi's sarcoma (KS) associated herpesvirus (KSHV), an etiological agent of all types of KS [1]. KS is a low-grade vascular tumor, which remains as one of the most common acquired immunodeficiency syndrome (AIDS)-defining malignancies [2].

Human immunodeficiency virus (HIV) infection is known to aggravate HHV-8 replication; thus, HIV infection is an important risk factor for the development of KS. HIV-associated KS usually arises in infected individuals with low CD4 T-cell counts. In people living with HIV (PLHIV), antiretroviral therapy (ART) is considered as a key treatment to address HIV-8 coinfection due to its effectiveness in suppressing HIV replication. ART is known to greatly reduce the incidence of HIV-associated KS [2].

Seroprevalence of HHV-8 in both HIV-positive and negative individuals has been studied in 32 countries of sub-Saharan Africa, North and South America, Europe, Asia, and Australia. It is found that HIV-positive individuals were more likely to be HHV-8 seropositive than HIV-negative individuals [3]. In Indonesia, data regarding HHV-8 infection in HIV-positive individuals are severely limited. The previous study conducted in East Java indicates the emergence of HHV-8 and HIV coinfection among Indonesian PLHIV [4]. However, no further data regarding HHV-8 and HIV coinfection in other Indonesian region. This research aimed to identify the emergence of HHV-8 infection among HIV-positive individuals residing Bali, Indonesia; thus more information regarding HHV-8 and HIV coinfection in Indonesia can be obtained.

## Methods

### Sample collection and HHV-8 antigen detection

This study employed a cross-sectional design. Ethical approval for this research was obtained from

the Ethics and Law Committee of Universitas Airlangga Hospital (Ethical approval no. 033/KEH/2016). Participants were recruited using non-random sampling method, in which only eligible and consented individuals were enrolled. Informed consent was obtained from all study participants before sample collection. Forty-three plasma samples were collected from HIV-positive individuals in the General Hospital of Buleleng Regency, Bali, Indonesia. Detection of HHV-8 antigen was performed by subjecting the plasma samples to sandwich enzyme-linked immunosorbent assay test (Abbexa, Cambridge, UK). HHV-8 antigen in the sample would be interpreted as positive if the optical density (OD) value of sample is equal or more than the cutoff value. If the OD value of the sample is less than cutoff value, it would be considered as negative. Cutoff value was determined by the following equation: OD value of negative control +0.15.

### Statistical analysis

Statistical analysis were performed with a minimum significance level of  $p = 0.05$ . Correlation between sex and HHV-8 infection status was analyzed using Fisher's exact test, while correlation between age, ART status, and length of ART toward HHV-status was analyzed using Spearman correlation.

## Results

Forty-three patients enrolled in this study were comprised of 16 ART-naïve and 27 ART-experienced individuals. About 24 (55.8%) participants were male. In regards to age, participants were predominantly within 30–39 years old group. Among ART-experienced individuals, 18 participants (66.7%) were receiving ART for more than 6 months. Demographic and clinical information of the participants is presented in Table 1.

**Table 1: Characteristics of HIV-positive patients and HHV-8 antigen status**

Characteristic	n	HHV-8 antigen negative (%)	HHV-8 antigen positive (%)	p-value*
Sex				1.000
Male	24	20 (83.3)	4 (16.7)	
Female	19	16 (84.2)	3 (15.8)	
Age (years)				0.716
20–29	13	11 (84.6)	2 (15.4)	
30–39	19	15 (78.9)	4 (21.1)	
40–49	10	9 (90)	1 (10)	
50–59	1	1 (100)	0 (0)	
ART status				0.178
Naïve	16	15 (93.75)	1 (6.25)	
Treated	27	21 (77.8)	6 (22.2)	
Length of ART				0.465
0 month	16	15 (93.3)	1 (6.7)	
≤6 months	9	6 (66.7)	3 (33.3)	
>6 months	18	15 (83.3)	3 (16.7)	
Total samples	43	36 (83.7)	7 (16.3)	

\*Significant if  $p < 0.05$ .

Seven samples (16.3%) were tested positive for HHV-8 antigen, including one (6.25%)

of ART-naïve individuals and six (22.2%) of ART-experienced individuals. HHV-8 infection was correlated neither to sex ( $p = 1.000$ ) and age ( $p = 0.716$ ), nor to ART status ( $p = 0.178$ ) and length of ART ( $p = 0.465$ ) (Table 1).

## Discussion

This study found the presence of HHV-8 antigen among 16.3% HIV-positive individuals residing in Bali, Indonesia. It is similar to the previous study in Surabaya and Tulungagung, East Java, Indonesia, which identified HHV-8 antigen among 14.5% HIV-positive individuals [4]. These results confirm the emergence of HHV-8 and HIV coinfection in Indonesia, which might need more comprehensive diagnosis to further identify KS.

The emergence of HHV-8 infection in HIV-positive patients was varied geographically. A study in Malaysia, India, Sri Lanka, Thailand, Trinidad, Jamaica, and the United States found a low seroprevalence of HHV-8 in both healthy and HIV-positive individuals. The low seroprevalence might correlate with the fact that hardly any HIV-related KS has been reported in those countries. In contrast, high HHV-8 seroprevalence in both healthy and HIV-positive individuals was found in African countries, including Ghana, Uganda, and Zambia [5].

Another studies in other region of Africa revealed that the prevalence of HHV-8 infection in HIV-positive individuals was 20.1% in Zimbabwe, 16.7% in South Africa, 62% in Nigeria, and 70% in Cameroon [6], [7], [8]. In North America and Europe, the prevalence of HHV-8 infection among HIV-infected individuals can be as low as 15%, up to 91% in HIV-related KS individuals [9], [10], [11]. In South America, especially in Brazil, the prevalence of HHV-8 infection in HIV-infected individuals can be as low as 13.9%, to 80% in individuals with KS [12], [13], [14]. In the Asian region, 22.2% of HIV-positive individuals in Xinjiang, China were HHV-8 seropositive [15], while 12% of HIV-positive homosexual men in Thailand, 16% heterosexual men, and 9% intravenous drug users were tested positive for HHV-8 antigen [16].

Four of 24 men (16.7%) and three of 19 women (15.8%) in this study were tested positive for HHV-8. There was no significant difference between HHV-8 infection in men and women ( $p = 1.000$ ), which also presented in several other studies [17], [18]. Thus, appropriate diagnosis of HHV-8 infection in HIV-positive individuals should be performed equally in both male and female patient.

In regards to age, we found no correlation between patient's age and HHV-8 positivity ( $p = 0.716$ ).

The correlation between age and HHV-8 positivity is inconclusive. A study indicated no correlation between age and HHV-8 positivity [13]. Other studies found positive correlation between HHV-8 seropositivity and age [17], [19]. while on the contrary, a study in North India found that HHV-8 seroprevalence was decreasing in older individuals [20]. With these contradicting evidence, it is worth to be taken into consideration that HHV-8 infection might be present despite the age of HIV-positive individuals.

We identified 1 ART-naive (6.25%) and 6 ART-experienced (22.2%) individuals with HHV-8 infection. We observed no correlation between ART status ( $p = 0.178$ ) and length of ART ( $p = 0.465$ ), which is consistent with the previous study [21]. A meta-analysis performed by Rohner *et al.* also found no evidence regarding the correlation of pre-ART and ART period with HHV-8 and HIV coinfection [3]. HIV infection aggravates HHV-8 replication; thus, sufficient suppression of HIV replication using ART is considered as a key treatment to address the HHV-8 coinfection. Lower incidence of HIV-associated KS in the era of highly active ART is greatly attributed to the effectiveness of available ART [2]. Recent study reported high prevalence of HIV transmitted drug resistance and moderate prevalence of acquired drug resistance among PLHIV residing in Buleleng, Bali, Indonesia. Drug resistance reduces the effectiveness of ART in suppressing HIV replication [22], [23]. This issue should be taken into consideration to delivered appropriate treatment in both ART-naive and ART-experienced individuals, especially when HHV-8 infection present. Failure to achieve HIV viral suppression using ART might lead to clinical progression of HHV-8 infection into KS [2].

This study has limitation. In regards to sample size, another study with bigger sample size might be needed to better determine the magnitude of HHV-8 and HIV coinfection in Bali, Indonesia. In regards to strength of the study, since no prior research addressing the same issue, this study could deliver information regarding the presence of HHV-8 and HIV coinfection in Bali, Indonesia.

## Conclusion

This study indicates the emergence of HHV-8 infection among HIV-positive individuals residing in Bali, Indonesia. No correlation found between HHV-8 infection with sex, age, ART status, and length of ART; thus, sufficient diagnosis of HHV-8 should be considered for all HIV-positive individuals to deliver appropriate treatment. Extensive researches are suggested to be conducted in more regions of Indonesia to determine the magnitude of HHV-8 infection among HIV-positive individuals.

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