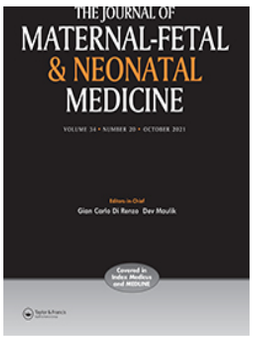

The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

Low prevalence of human gammaherpesvirus 8 (HHV-8) infection among HIV-infected pregnant women in Rio De Janeiro, Brazil

Amanda de O. Lopes, Lyana R. P. Lima, Tania R. Tozetto-Mendoza, Katrini G. Martinelli, Mariza G. Morgado, José H. Pilotto & Vanessa S. de Paula

To cite this article: Amanda de O. Lopes, Lyana R. P. Lima, Tania R. Tozetto-Mendoza, Katrini G. Martinelli, Mariza G. Morgado, José H. Pilotto & Vanessa S. de Paula (2021) Low prevalence of human gammaherpesvirus 8 (HHV-8) infection among HIV-infected pregnant women in Rio De Janeiro, Brazil, The Journal of Maternal-Fetal & Neonatal Medicine, 34:20, 3458-3461, DOI: 10.1080/14767058.2019.1685967

To link to this article: https://doi.org/10.1080/14767058.2019.1685967

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2021, VOL. 34, NO. 20, 3458–3461
https://doi.org/10.1080/14767058.2019.1685967

Taylor & Francis
Taylor & Francis Group

SHORT REPORT

Low prevalence of human gammaherpesvirus 8 (HHV-8) infection among HIV-infected pregnant women in Rio De Janeiro, Brazil

Amanda de O. Lopes[a], Lyana R. P. Lima[a], Tania R. Tozetto-Mendoza[b], Katrini G. Martinelli[c], Mariza G. Morgado[d], José H. Pilotto[d,e] and Vanessa S. de Paula[a]

[a]Laboratório de Virologia Molecular, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio De Janeiro, Brazil; [b]Laboratório de Virologia, LIM52, Instituto de Medicina Tropical de São Paulo, Universidade de São Paulo, São Paulo, Brazil; [c]Departamento de Medicina Social, Universidade Federal do Espírito Santo, Espírito Santo, Brazil; [d]Laboratório de AIDS e Imunologia Molecular, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; [e]Hospital Geral de Nova Iguaçu, Rio de Janeiro, Brazil

ABSTRACT

Pregnant women coinfected with the human immunodeficiency virus (HIV) and human gammaherpesvirus 8 (HHV-8) are at higher risk of Kaposi's sarcoma development, increased viral load, and vertical transmission of these viruses. A total of 131 pregnant women infected with HIV were examined for antibodies against HHV-8 latency-associated nuclear antigen (LANA) and lytic antigens using immunofluorescence assays. The presence of HHV-8 DNA was confirmed using real-time polymerase chain reaction (qPCR) and nested PCR. Overall, 0.8% (1/131) of the patients contained antibodies to HHV-8 LANA and lytic antigens, and no HHV-8 DNA was detected. This study, including a small population of HIV-infected pregnant women in Brazil, indicates a low prevalence of HHV-8 seropositivity and absence of active infection in this group. However, a potential role of HHV-8 in the increased transmission and pathogenic activity of HIV in pregnant women is suggested. Attention should be given to the emergence of HHV-8 infection in this population group in order to avoid comorbidities and transmission of HIV.

ARTICLE HISTORY
Received 21 July 2019
Revised 8 October 2019
Accepted 24 October 2019

KEYWORDS
Coinfection; human gamma herpesvirus 8; human immunodeficiency virus; pregnant women; prevalence

Introduction

Human gammaherpesvirus 8 (HHV-8) is the etiologic agent of Kaposi's sarcoma (KS), one of the most common cancers in individuals infected with human immunodeficiency virus (HIV). The overall KS incidence in HIV-infected people is 481.54 per 100,000 person-years worldwide. The KS incidence of HIV-positive women is reported as 172.18 per 100,000 person-years [1]. An estimated 17.4 million adult women are infected with HIV worldwide [2].

KS may develop during pregnancy [3], as changes in the immune system during this period may contribute to increased herpesvirus viremia and subsequent tumorigenesis. In addition, immune changes in HIV-coinfected pregnant women may further impair immunosurveillance for HHV-8 infection [3,4].

Vertical transmission of HHV-8 may occur during pregnancy [5] and high viral load of this herpesvirus in cervicovaginal secretions influences intrapartum transmission [4]. Rare cases of KS in newborns suggest that HHV-8 vertical infection could lead to early KS, especially in children infected with HIV [6]. HHV-8 infection in pregnancy is additionally proposed to present a risk factor for HIV-1 vertical transmission [7].

Mechanisms promoting cooperation between HIV-1 and HHV-8 may culminate in the spread of these viruses within the host organism, AIDS progression, and KS development [8]. The HHV-8 seroprevalence rates range from 1.7 to 80.7% in HIV-infected pregnant women worldwide [9]. To address the lack of data of HHV-8 infection in this population group in Brazil, we have investigated the prevalence of HHV-8 infection in pregnant women with HIV in this study.

Materials and methods

This study was retrospective in design, and all 131 HIV-infected pregnant women were recruited between April 2005 and August 2008 at the Nova Iguaçu General Hospital, Rio De Janeiro State, Brazil. This is a referral center for the care and treatment of HIV-infected pregnant women located on the outskirts of Rio de Janeiro. Sociodemographic, clinical and

CONTACT Vanessa S. de Paula vdepaula@ioc.fiocruz.br Laboratory of Molecular Virology, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, 4365, Brazil Av, Manguinhos, Rio De Janeiro, Brazil

laboratory information were abstracted from medical records.

Inclusion criteria were as follows: samples collected during the second and third trimesters of pregnancy, HIV infection confirmed using enzyme-linked immunosorbent assay, any ethnicity/color, age, marital status, maternal education level, and family income.

The sociodemographic variables used were: ethnicity/color (white, black, brown/mulatto, indigenous), marital status (living with a partner or not), degree of schooling (illiterate, incomplete elementary school, complete elementary school, high school, and higher education), family income (no income, up to one salary, two or three salaries, four or five salaries, and > five salaries), maternal age at the time of HIV diagnosis (up to 15 years, 16–20 years, 21–30 years, 31–40 years, and ≥41 years); and HIV diagnosis during current gestation (yes or no).

With regard to clinical and laboratory variables, all HIV-infected pregnant women received combined antiretroviral therapy, with 91.6% (120/131) patients displaying cluster of differentiation $CD4^+$ T lymphocyte counts of >200 cells/mm^3 of blood.

Serum samples were collected and stored at −20 °C until testing for HHV-8 infection. Immunofluorescence assays (IFA) were used for detection of antibodies against HHV-8 latency-associated nuclear antigen (LANA) and lytic antigens, as reported previously [10]. Samples were considered seropositive for HHV8-specific antibodies in cases where at least one of the assays (IFA–LANA or IFA–lytic) was positive.

Serum samples with HHV-8 anti-LANA and antilytic antibodies from individuals with KS were used as positive controls and those without HHV-8 anti-LANA and antilytic antibodies from blood donors as negative controls.

Viral DNA was extracted from homogenized samples using the High Pure Viral Nucleic Acid Kit (Roche, NJ, USA) according to the manufacturer's instructions. DNA was stored at −70 °C until sample analysis. Viral DNA was analyzed in triplicate *via* real-time polymerase chain reaction (qPCR) as described previously [11], which amplified HHV-8 minor capsid protein gene/open reading frame (ORF) 26 (66 bp). In addition, a synthetic standard curve (5′-TTCGTGCCCCATAAATGACACATTGGCGTATATATGGCGGAACTTGATCTATGCGTTACATCATCCGGGGCCCCTGATA-3′) with an initial titer of 10^7 copies/mL in a dilution series (10^1–10^7) was designed for qPCR.

Viral DNA was analyzed via nested PCR that amplified a 233-bp fragment from HHV-8 ORF 26, as described previously [12]. Each PCR reaction contained 500-nM primer (forward/reverse). Amplification products were visualized on 1.5% agarose with ethidium bromide staining.

In both PCR assays, serum samples positive for HHV-8 DNA from individuals with KS were used as positive controls and serum samples without HHV-8 DNA from blood donors as negative controls.

The study was approved by the Oswaldo Cruz Foundation Ethics Committee (number 895.159/CAEE:28183314.7.0000.5248) and all participants signed an informed consent form.

Descriptive statistical analyses were performed for variables related to sociodemographic information on HIV-positive pregnant women, with absolute and relative frequency calculations. As the prevalence of HHV-8/HIV coinfection was extremely low, inferential statistics, initially planned for analysis of risk factors, could not be performed.

Results

HIV-positive pregnant women were 16 years or older with an average age of 26.3 ± 6.3 years. All sociodemographic data are presented in Table 1.

Antibodies against HHV-8 LANA and lytic antigens (Figure 1) were detected in one pregnant woman (0.8%; 1/131) aged 29 years who had a $CD4^+$

Table 1. Sociodemographic characteristics of HIV-infected pregnant women in this study.

Variables	*N* participants (%)
Ethnicity/color	
White	38 (29)
Black	39 (29.8)
Brown/mulatto	53 (40.5)
Indigenous	01 (0.8)
Marital status	
Living together with a partner	100 (76.3)
Not living with a partner	31 (23.7)
Degree of schooling	
Illiterate	03 (2.3)
Incomplete elementary school	76 (58)
Complete elementary school	36 (27.5)
High school	15 (11.5)
Higher education	01 (0.8)
Family income[a]	
No income	17 (13.3)
Up to one salary	54 (42.2)
Two or three salaries	47 (36.7)
Four or five salaries	05 (3.9)
>5 salaries	05 (3.9)
Maternal age at the time of HIV diagnosis (years)[a]	
Up to 15	01 (0.8)
16–20	33 (25.4)
21–30	69 (53.1)
31–40	23 (17.7)
≥41	04 (3.1)
HIV diagnosis in current gestation	
Yes	90 (68.7)
No	41 (31.3)

N: number of participants.
[a]Missing variables.

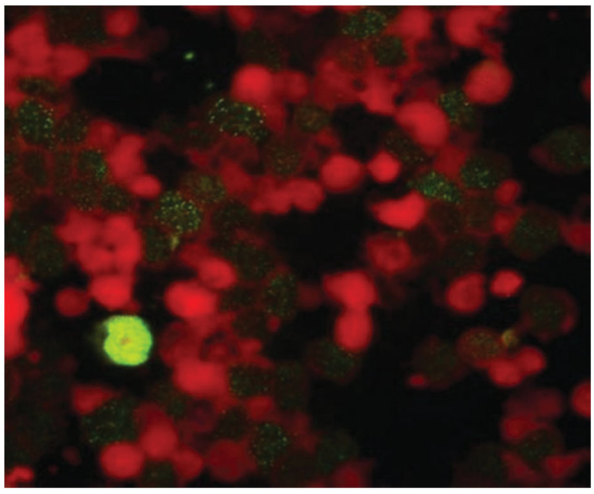

Figure 1. HHV-8-specific antibody-positive serum in IFA-LANA and IFA-Lytic assays (100×). IFA–LANA-positive pattern with typical speckled fluorescence in the nucleus, indicating reactivity of antibodies to latent antigens. IFA–lytic-positive pattern with cytoplasmic fluorescence observed during the lytic phase of virus replication.

T lymphocyte count of 540 cells/mm^3 blood and 50 copies/mL HIV viral load. HHV-8 DNA was undetectable in all HIV-positive pregnant women.

Discussion

The low HHV-8 seroprevalence (0.8%; 1/131) detected in HIV-infected pregnant women from our Brazilian area corroborates with earlier data obtained by other groups from nonendemic regions. In the USA, a country with low HHV-8 seroprevalence [13], Goedert et al. [14] reported the presence of HHV-8 antibodies in only 2/118 (1.7%) pregnant women with HIV infection. In contrast, in endemic regions, such as Africa (Ethiopia, Gambia, Uganda, Zambia, Cameroon, and Burkina Faso), HHV-8 seroprevalence rates in HIV-positive pregnant women were significantly higher, ranging from 12 to 80.7% [9].

Although epidemiological data of HHV-8 infection are still scarce in Brazil, our country is considered nonendemic for this infection [15]. To our knowledge, this is the first study to investigate the prevalence of HHV-8 in pregnant women with HIV from Brazil.

We employed IFA evaluation of anti-LANA antibodies, generally considered a reference assay for detecting HHV-8 infection, along with IFA-lytic, which are the most commonly used serological tests [16]. In view of a previous report that 5.2% serum samples from HIV-infected individuals negative for HHV-8 antibodies were HHV-8 DNA-positive, we additionally examined for the presence of HHV-8 DNA [17]. Real-time and nested PCR disclosed no detectable HHV-8 DNA in HIV-positive pregnant women, consistent with IFA-based negative serological tests.

In conclusion, HHV-8 prevalence and risk of infection are low in HIV-positive pregnant women from Rio de Janeiro, Brazil. Nevertheless, attention should be given to the emergence of HHV-8 infection in pregnant women infected with HIV and their impact on health in non-endemic countries, since HHV-8 can reactivate during pregnancy and contribute to KS development, increased viral load and vertical transmission of both viruses.

Acknowledgments

The authors thank CAPES and FAPERJ for funding.

Disclosure statement

No potential conflict of interest was reported by the authors regarding the publication of this paper.

Funding

This work was supported by CAPES (Coordination of Superior Level Staff Improvement) [grant No. 1632788]; and FAPERJ (State of Rio de Janeiro Research Support Foundation) [grant No. E-26/203.0928/2016].

Data availability

The datasets used to support the findings of this study are available from the corresponding author upon request.

References

[1] Liu Z, Fang Q, Zuo J, et al. The world-wide incidence of Kaposi's sarcoma in the HIV/AIDS era. HIV Med. 2018;19(5):355–364.
[2] WHO. Number of women living with HIV. World Health Organization; 2019. Available from: https://www.who.int/gho/hiv/epidemic_status/cases_adults_women_children_text/en/.
[3] Brunet-Possenti F, Pages C, Rouzier R, et al. Kaposi's sarcoma and pregnancy: case report and literature review. Dermatology. 2013;226(4):311–314.
[4] Lisco A, Barbierato M, Fiore JR, et al. Pregnancy and human herpesvirus 8 reactivation in human immunodeficiency virus type 1-infected women. J Clin Microbiol. 2006;44(11):3863–3871.
[5] Mantina H, Kankasa C, Klaskala W, et al. Vertical transmission of Kaposi's sarcoma-associated herpes virus. Int J Cancer. 2001;94(5):749–752.
[6] McCarty KA, Bungu Z. Kaposi's sarcoma in a two week old infant born to a mother with Kaposi's sarcoma/AIDS. Cent Afr J Med. 1995;41(10):330–331.
[7] Calabrò ML, Gasperini P, Barbierato M, et al. A search for human herpesvirus 8 (HHV-8) in HIV-1 infected

mothers and their infants does not suggest vertical transmission of HHV-8. Int J Cancer. 2000;85(2): 296–297.

[8] da Silva SR, de Oliveira DE. HIV, EBV and KSHV: viral cooperation in the pathogenesis of human malignancies. Cancer Lett. 2011;305(2):175–185.

[9] Rohner E, Wyss N, Heg Z, et al. HIV and human herpesvirus 8 co-infection across the globe: systematic review and meta-analysis. Int J Cancer. 2016;138(1): 45–54.

[10] Borges JD, Souza VA, Giambartolomei C, et al. Transmission of human herpesvirus type 8 infection within families in American indigenous populations from the Brazilian Amazon. J Infect Dis. 2012;205(12): 1869–1876.

[11] Levi JE, Nascimento MC, Sumita LM, et al. Non-detection of human herpesvirus 8 (HHV-8) DNA in HHV-8-seropositive blood donors from three Brazilian regions. PLoS One. 2011;6(8):e23546.

[12] de Souza VA, Sumita LM, Nascimento MC, et al. Human herpesvirus-8 infection and oral shedding in Amerindian and non-Amerindian populations in the Brazilian Amazon region. J Infect Dis. 2007;196(6): 844–852.

[13] Rohner E, Wyss N, Trelle S, et al. HHV-8 seroprevalence: a global view. Syst Rev. 2014;3:11.

[14] Goedert JJ, Kedes DH, Ganem D. Antibodies to human herpesvirus 8 in women and infants born in Haiti and the USA. Lancet. 1997;349(9062):1368.

[15] Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer. 2010; 10(10):707–719.

[16] Nascimento MC, de Souza VA, Sumita LM, et al. Comparative study of Kaposi's sarcoma-associated herpesvirus serological assays using clinically and serologically defined reference standards and latent class analysis. J Clin Microbiol. 2007;45(3):715–720.

[17] Szalai E, Gerlei Z, Szlãvik J, et al. Prevalence of human herpesvirus-8 infection in HIV-positive patients with and without Kaposi's sarcoma in Hungary. FEMS Immunol Med Microbiol. 2005;43(2):265–268.