Epstein-Barr virus in oral mucosa from human immunodeficiency virus positive patients

LARISSA SANTOS1, KÁTIA AZEVEDO2, LICINIO SILVA3, LEDY OLIVEIRA2

1 Department of Microbiology and Parasitology, Fluminense Federal University, Niterói, RJ, Brazil.
2 College of Medicine, Fluminense Federal University, Niterói, RJ, Brazil.
3 Department of Statistics, Fluminense Federal University, Niterói, RJ, Brazil.

Study conducted at the Department of Microbiology and Parasitology, Fluminense Federal University, Niterói, RJ, Brazil.

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*Correspondence: Departamento de Microbiologia e Parasitologia Universidade Federal Fluminense Address: Rua Prof. Emilio Meio, 101, Niterói, RJ - Brazil ZIP Code: 24210-130 Phone: +55 21 2629-2430 Fax: +55 21 2629-2433 mipledy@centroin.com.br

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INTRODUCTION

Epstein-Barr virus (EBV), a member of the Herpesviridae family, is a common virus worldwide. Human EBV infections are often asymptomatic and persistent. Primary infection occurs in B lymphocytes of the oropharyngeal mucosa where lytic and latent infections take place. Although EBV replication in oral epithelial cells is an infrequent event, the virus is usually shed in and transmitted by saliva.1 EBV interacts with the host by infecting B lymphocytes and inducing the proliferation of infected cells. Following a proliferative phase, EBV enters a latent phase and can be reactivated, giving rise to the production of infectious progeny that can be transmitted to other individuals.2

EBV strains are classified as type 1 or 2 according to variations in the regions encoding EBV nuclear antigen 2 (EBNA-2), 3A (EBNA-3A), 3B (EBNA-3B) and 3C (EBNA-3C).3 EBV type 1 is prevalent in most of populations studied.4,5 However, other studies have revealed that in specific geographic areas, the prevalence of EBV type 1 is similar to the prevalence of EBV type 2.6

Risk factors for EBV infection and its genotypes have not been fully investigated. EBV seropositivity studies suggest an association with socioeconomic factors, specifically among children of low socioeconomic status.7 In adults, oral transmission can be masked by other modes of transmission, such as sexual contact.8 Epidemiologically, EBV type 2 strains are more frequently associated with HIV-positive individuals and homosexual HIV-positive males as well as with sexual contact.9,10

Studies have shown a higher prevalence of EBV among HIV-seropositive individuals than the general population (Table 1).
EBV carriers in the HIV-seropositive group merit concern due to the pathogenic and even malignant potential of the virus. Although in most cases, EBV infection is linked to benign diseases, the virus can produce malignancies. In most individuals, a lifelong chronic infection with EBV is free from complications due to suppression from normal immune systems. However, patients with acquired immunosuppression are at a high risk for developing both benign and malignant conditions.

All latent viral genes express proteins to activate and maintain the proliferation of B cells (latency III program). EBNA-2 is one of the first viral genes expressed after infection and is essential for the immortalization of B cells and the establishment of latent infection. The expression of EBNA-2 is associated with the pathogenesis of oral hairy leukoplakia, a benign AIDS-related disease. The hairy leukoplakia (HLP) lesion is a unique example of a permissive infection with EBV in the tongue epithelium. Among other gene products, the EBNA-2 protein has been shown to activate the expression of the EBV receptor CD21. The broad spectrum of EBNA-2 functions involves virus-host interactions, including cell signaling molecules, adapters, genes involved in cell cycle regulation, and leukocyte chemotaxins.

In light of the potential damage Epstein-Barr virus can cause in those living with HIV, we describe the results of screening for EBV and its subtypes, variables associated with EBV-HIV coinfection and EBNA-2 expression in an HIV-infected population.

### METHODS

Between 2009 and 2010, oral cavity scrapes were taken from 150 HIV-infected adults who were representative of the HIV-positive population of the state of Rio de Janeiro. The size of the sample was determined considering lower EBV expected frequencies in this population, according to specialized reference.

Participants were invited to enroll in the study during routine standard-of-care visits to 450 patients registered in the outpatient HIV clinic of the Infectious Diseases Service of the Antonio Pedro Teaching Hospital, in Niterói, Rio de Janeiro, Brazil. Of these individuals, 145 were asymptomatic, and the remaining five patients, who exhibited oral lesions, were excluded from the study. Samples were collected by scraping the oral mucosa after clinical examination. Demographic, behavioral and HIV infection-related data were obtained via a structured questionnaire. The Ethics Committee of the College of Medicine at UFF approved the protocols for sample collection and informed consent.

CD4 counts were determined by Flow Cytometric Immunophenotyping using standard protocols. Plasma HIV-1 RNA levels were measured in virology quality assurance–certified laboratories according to the same program with the Chiron Versant HIV-1 RNA 3.0 Assay (Bayer Corporation, Emeryville, California, USA) in accordance with the manufacturer’s instructions; the lower threshold of detection was 50 copies/mL. All assays were performed in a laboratory participating in the National STD and AIDS Program.

DNA was extracted from samples using either the phenol-chloroform method or a commercial assay kit (Invisorb, Uniscience). EBV detection and typing were performed using generic and nested PCR, respectively. For EBV DNA detection, the primer pair E2P1: 5’-AGGGATGCCTGGACACAAGA-3’, B95.8 coordinates 1813-1833, and E2P2: 5’-TGGTGCTGCTGGTGGTGGCAAT-3’, B95 coordinates 2409-2366, which amplify a 596 bp DNA sequence specific to the EBNA-2 gene, were used. Amplification was performed in a 50 µL reaction mixture (1X PCR buffer, 200 mM dNTPs, 1.5 mM MgCl2, 50 pmol

### TABLE 1

EBV infection survey in normal oral mucosa in HIV-positive and HIV-negative patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Number of patients</th>
<th>EBV %</th>
<th>HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amornthatree et al., 2011</td>
<td>Thailand</td>
<td>49</td>
<td>80</td>
<td>+</td>
</tr>
<tr>
<td>Robaina et al., 2008</td>
<td>Brazil</td>
<td>27</td>
<td>51</td>
<td>+</td>
</tr>
<tr>
<td>Ammatuna et al., 2001</td>
<td>Italy</td>
<td>57</td>
<td>42.1</td>
<td>+</td>
</tr>
<tr>
<td>Mao &amp; Smith, 1993</td>
<td>UK</td>
<td>60</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Kunimoto et al., 1992</td>
<td>Japan</td>
<td>91</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Scully et al., 1998</td>
<td>UK</td>
<td>—</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Cruz et al., 1997</td>
<td>Netherlands</td>
<td>12</td>
<td>8.3</td>
<td>-</td>
</tr>
<tr>
<td>Sand et al., 2002</td>
<td>Sweden</td>
<td>67</td>
<td>7.3</td>
<td>-</td>
</tr>
</tbody>
</table>
of each primer, 0.25 U of Taq polymerase and 5 µL of sample) with 40 cycles of amplification. Each cycle included a denaturing step at 94°C for 30 seconds, an annealing step at 58°C for 30 seconds, and a chain elongation step at 72°C for 60 seconds using a thermal cycler (Veriti, Applied Biosystems). The b-actin gene was amplified as an internal positive control using 0.1 pmol of each primer. PCR products were analyzed on 1.5% agarose gel with ethidium bromide staining for the visualization of DNA under ultraviolet light.

To type EBV-positive samples, nested PCR was performed by internal amplification of 2 µL of the primary PCR products. The Ap1/Ap2 and Bp1/Bp2 primer pairs (Life Technologies, S. Paulo, Brazil) amplified 497 bp and 150 bp products from EBV-1 and EBV-2, respectively. The inner primers used were as follows: Ap1: 5’-TCTTGA TAG GATCCGCCTAGG ATA-3’, B95.8 coordinates 1843-1856; Ap2: 5’-ACCGTGGTTCTGGACTATCTG GAT C-3’, B95.8 coordinates 2338-2314, to detect the 497 bp fragment; BPI: 5’-CAT GGT AGCCTTAGA TA-3’, B95.8 coordinates 2085-2104; and BP2: 5’-AGA CTTAGTTGATGCCCT AG-3’, coordinates 2234-2215 to detect the 150 bp fragment.26,27 Nested PCR was performed with 25 cycles consisting of the following steps: 94°C for 30 seconds, 58°C for 30 seconds, and 72°C for 45 seconds, with a final elongation step at 72°C.26 Positive and negative controls were also included. To prevent false-positive results, in addition to the standard controls, a sample containing extracted non-EBV DNA was amplified with the EBV-specific primers. Nested PCR products were analyzed by the same methods as the primary generic PCR products.

RNA for reverse transcriptase polymerase chain reaction (RT-PCR) was extracted with Trizol® Reagent (Invitrogen, S. Paulo, Brazil). The resulting RNA was quantified on Qubit® 2.0 Fluorometer (Invitrogen). For cDNA synthesis, 2 pmol of each of the specific primers described above (EP1/EP2, expected size 596 bp, exon-flanking primers) was added to 10 µL of RNA followed by heating for 5 min at 65°C. Reverse transcription was performed using SuperScript™ III Reverse Transcriptase (Invitrogen, S. Paulo, Brazil) for 1 hour at 55°C followed by a 15 minutes incubation at 70°C. The resulting cDNA was used as a template for generic and nested PCR using the EBV-specific primers described above. Controls were performed using RNA-free water.

A databank was generated and analyzed using the SPSS version 17 statistical package. To identify associations between possible risk factors and the presence of EBV and EBV-1 and EBV-2 separately, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Relationships between the surveyed variables and active EBV infection were identified by univariate analysis. Multivariate analyses were conducted using logistic binary regression models between all variables and EBV infection.

### Results

A total of 145 HIV-seropositive patients without clinical oral lesions, of whom 77 (53.1%) were female and 68 (46.9%) were male and ranging from 19 to 75 years of age (mean = 41.38, median = 41, SD = 10.35 years), were recruited for the study. Among the self-referred ethnic groups, white (66.2%) was the most prevalent category, and most of the subjects reported education at or above high school level (57.2%). Nearly half of the study population claimed to have a stable sexual partner (54.5%), 73.8% were currently non-smokers, and 56.6% were ex-smokers. With respect to HIV infection status, 61.4% of patients had an undetectable HIV viral load, 75.9% of participants reported being diagnosed more than 4 years prior, and 85.5% were undergoing antiviral therapy. At the time of our study, 12.4% of patients had a CD4+ cell count below 200 CD4+ cells/mL; 35.2% had 201-500 CD4+ cells/mL; and 52.4% had more than 500 CD4+ cells/mL.

In our study, EBV DNA was detected in 48.3% of the samples, 23 (32.85%) of which only contained EBV type 1, 32 (45.71%) only contained EBV type 2, and 10 (14.28%) contained both types. Among the EBV-positive samples, five (7.14%) could not be identified and were referred to as unclassified types because the first PCR run was positive and the second was negative. Of the total, 35 (24.1%) samples were positive by the first PCR assay with general EBV DNA primers. The determination of positivity for the remaining samples was only possible through nested PCR with type-specific primers (Table 2).

| TABLE 2 Overall distribution of active EBV and subtypes in oral smears from HIV-infected patients from the Antonio Pedro Teaching Hospital, in Niterói, Rio de Janeiro, Brazil (2010) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient         | EBV (%)         | EBV-1 (%)       | EBV-2 (%)       | EBV-1/EBV-2 (%) | Unclassified (%) |
| Positive        | 70 (48.3)       | 23 (32.8)       | 32 (45.7)       | 10 (14.28)      | 5 (7.14)        |
| Negative        | 75 (51.7)       | 47 (67.2)       | 38 (54.3)       | 60 (85.72)      | 65 (92.86)      |

1 N=145; 2 N=70; 3 Detection only by generic PC.
EBNA-2 mRNA was detected in 32 (45.7%) positive samples, of which, 14 (20%) were typed only as EBV-1 and the other 14 (20%) were typed only as EBV-2. Of the remaining smears, 1.4% was positive for EBNA-2 mRNA in samples with both types of EBV, and 4.3% were unclassified.

A univariate analysis of individuals with detectable EBV DNA and several variables revealed that a CD4+ cell count lower than 500 cells/mL was the only factor that affected the overall infection. However, when we crossed the same variables with the EBV types separately, we verified that EBV type 1 was affected by CD4 counts below 200 cells/mm³ (OR = 4.41 [95% CI: 1.49-13.03], p = 0.012) and that patients who did not have a stable sexual partner were significantly more likely to be positive for EBV type 2 than those with a stable partner (OR = 2.88 [95% CI: 1.26-6.55], p = 0.017). Moreover, detectable HIV viral load was associated with coinfection with EBV types 1 and 2 (OR = 6.62 [95% CI: 1.32-33.16], p = 0.025). The activity of the EBNA-2 gene was also strongly associated with detectable viral load (OR = 5.67 [95% CI: 1.99-16.13], p = 0.002). No demographic associations were found.

Adjusted ORs were estimated for all risk factors with less than a 10% significance level in the univariate analysis. CD4+ counts lower than 500 cells/mm³ remained a significant variable relative to EBV positivity in HIV-positive individuals. Irrespective of the patient’s immune status, active EBV-2 infection was associated with sexual lifestyle (Table 3).

### Discussion

Here, we investigated several aspects of EBV in the oral epithelial tissues of a random sampling of patients without mouth lesions who were attending an outpatient HIV care service. Oral brushing proved to be an efficient method for collecting epithelial cells. A PCR assay following nested PCR (with type-specific primers) increased the detection of EBV from 35 to 70 EBV-infected persons, thereby demonstrating a 100% improvement by this method.

As shown in Table 1, our results are consistent with previous research performed with similar study populations, which collectively demonstrate that EBV infection of the oral cavity is detected at a higher rate among HIV-infected individuals than among HIV-seronegative individuals. However, these data do not hold true for all herpes virus family members. Carvalho et al., demonstrated a strong correlation between the presence of EBV and CMV in HIV-seropositive individuals but not between the presence of herpes simplex virus (HSV-1) or human herpes virus type 8 (HHV-8).

The detection of replicating EBV DNA in the oral mucosa of HIV-positive individuals may indicate virus reactivation. After primary infection, EBV can induce replicative and latent infection in lymphocytes. The main site of viral persistence is within latently infected lymphocytes, although infectious virus is also released into the saliva from productively infected cells in the oropharynx. The virus persists for the lifetime of the host in balance.

### Table 3: Univariate analysis and adjusted ORs for identifying independent variables in active EBV infection among HIV-positive patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Adjusted OR</th>
</tr>
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<tbody>
<tr>
<td>EBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count ≤ 500</td>
<td>3 (1.52-5.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Detectable HIV viral load</td>
<td>1.98 (0.99-3.94)</td>
<td>0.075</td>
</tr>
<tr>
<td>EBV-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count ≤ 200</td>
<td>4.41 (1.49-13.03)</td>
<td>0.012</td>
</tr>
<tr>
<td>Detectable HIV viral load</td>
<td>2.17 (0.97-4.87)</td>
<td>0.087</td>
</tr>
<tr>
<td>Non-stable sexual partner</td>
<td>2.88 (1.26-6.55)</td>
<td>0.017</td>
</tr>
<tr>
<td>EBV1/EBV2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable HIV viral load</td>
<td>6.62 (1.32-33.16)</td>
<td>0.025</td>
</tr>
<tr>
<td>EBV-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable HIV viral load</td>
<td>5.70 (1.99-16.13)</td>
<td>0.002</td>
</tr>
<tr>
<td>mRNA</td>
<td></td>
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</tbody>
</table>
with the immune system by latently infecting B lymphocytes and replicating in and shedding from the oral mucosa. In the oral mucosa, B cells are stimulated to differentiate after exposure to foreign antigens. Latency, cell proliferation and virus production occur simultaneously at different sites that are linked in dynamic equilibrium. In healthy individuals, systemic reactivation is kept in check by the immune system. However, asymptomatic EBV reactivation periodically occurs in oral mucosa-associated lymphoid tissues. According to Yao et al., these individuals could have been infected with EBV anyway and HIV at an older age, given that they acquired HIV by sexual transmission. Therefore, HIV infection may affect the control of EBV and allow the emergence of detectable EBV determined that the tongue epithelial tissues of HIV-positive individuals supported not only EBV replication but also persistent, non-productive EBV infection. In immunocompromised hosts, decreased EBV-specific cytotoxic T cell activity allows increased virus replication and production in the oropharynx and latently infected circulating B cells.

We found an appreciable difference between the presence of EBV-1 and EBV-2 subtypes, which were responsible for 47.1% and 60% of the cases, respectively, including co-infections. Although EBV-1 is ubiquitous throughout the world, Yao et al. showed that the incidence of EBV type 2 is higher in HIV-positive homosexual males than in HIV-negative individuals. This study also demonstrated that most HIV patients with detectable EBV type 2 also carried the type 1 strain. In the present study, among 42 patients carrying EBV-2 DNA, only 23.8% were infected with both types. However, we could not genotype five smears because the nested PCR results were negative. The EBNA-2 gene region can harbor polymorphisms. To determine whether polymorphisms account for our failure to type these five samples, another technique, such as sequencing, should be utilized.

We did not identify any demographic differences among HIV-EBV carriers. He et al. also did not find any associations with demographic factors, EBV antibodies and HIV infection despite the fact that some malignant EBV-associated diseases are linked to racial characteristics. However, other studies have not found such associations.

Furthermore, neither HIV viral load nor antiretroviral therapy affected the detection of EBV. Notably, immune status was significantly correlated with EBV and the EBV-1 genotype. Moderate or severe immune-depression modulates EBV infection. EBV and other herpes viruses are frequently found in HIV-positive individuals who have CD4 counts lower than 200 cells/mm³. In our study, the EBV-1 subtype alone was significantly associated with poor immune status. Maybe the breakdown between CD4+ cell counts and EBV-1 favors the active replication of EBV-1 more efficiently than EBV-2. In a study of HIV patients with hairy leukoplakia, Palefsky et al. found that 63% of patients were infected with the type 1 strain and 37% were infected with both EBV subtypes. Interestingly, the EBV-2 strain was detected in patients irrespective of their immune status, although there was a slight trend for CD4 counts lower than 500 cells/mm³. Notably, subtype 2 enters the lytic cycle more readily than subtype 1 does.

Sexual lifestyle was a significant risk factor for the presence of the EBV-2 subtype. We still have no explanation for this finding because the sexual transmission of EBV is a controversial topic. Some studies describe a connection between sexual behavior and EBV infection, whereas others demonstrate that sexual transmission of EBV has not been sufficiently established. Some studies report a link between increased sexual activity and the risk of type 2 detection. In homosexual men, the prevalence of EBV-2 is associated with a large number of sexual partners. And since the virus can also be transmitted by kissing, it is difficult to determine the means of infection among sexual partners. Therefore, these data could be misinterpreted. Ammatuna et al. found that men had an increased rate of EBV infection, but our results did not confirm any linkage between gender and EBV status despite the fact that our participants acquired HIV infection by the sexual route and that the majority of the men in our study reported homosexual behavior (data not shown). Although EBV-2 was prevalent in our study, this subtype was found equally in men and women (p > 0.999). According to these data, we do not agree with the statement that homosexual males have a higher probability of harboring the EBV-2 virus.

Among the EBV-positive HIV patients without productive lesions, 45.7% expressed the EBNA-2 messenger RNA in the oral cavity. Both subtypes expressed mRNA at the same frequencies. Differences in the transforming
capacities of EBV subtypes 1 and 2 strains have been ascribed to differences in the EBNA-2 gene. Oral hairy leukoplakia (a marker for decreased immune cell counts in HIV carriers) is the only epithelial disease in which EBNA-2 is expressed, yet the role of EBNA-2 in this disease is not clear. EBNA-2 detection in oral epithelial tissues is not affected by immune status but is strongly associated with HIV viral load. Miller et al. concluded that increased EBV viral loads are dependent upon increasing HIV loads. Moreover, EBV is an important coinfection in AIDS patients and may contribute significantly to morbidity and mortality in this population.

Some authors have suggested that there is an interaction between EBV and HIV in the regulation of replication. However, the mechanism of this regulation was not fully investigated. Our findings demonstrate an association between EBV activity and increased HIV loads. It is common sense that HIV loads can be linked to decreased CD4 counts. Therefore, the role of moderate/severe immunodeficiency in affecting EBV infection is likely to be dependent upon the presence of HIV. This analysis truly strengthens the evidence for an HIV-EBV interaction.

The strong association between a detectable HIV viral load and EBNA-2 messenger RNA reflects the interaction between both viruses. Being the threshold of detection of HIV RNA 50 copies/mL, we suppose that few viruses are needed to initiate EBV activity, leading to oral lesions that include benign diseases as well as lymphomas. Routine monitoring of HIV viral loads and CD4 counts and adequate therapy may allow the containment of EBV as a self-limiting infection. This study provides guidance for monitoring HIV-infected patients with EBV reactivation in order to prevent future diseases and reduce healthcare costs. We also provide data that increases the understanding of active asymptomatic EBV infection and supports forthcoming studies of opportunistic infections in general.

CONCLUSION

In conclusion, our study detected a high prevalence of active EBV infection in the oral mucosa of asymptomatic HIV-infected patients, nearly half of whom exhibited EBNA-2 gene expression. The expression of EBNA-2 in the oral cavity has been identified as an important co-factor in hairy leukoplakia and is an indication of productive replication in the oral epithelium. Thus, it is a prognostic marker for disease development.

This work has some limitations. In the five patients for whom the subtype could not be identified, we did not perform sequencing because it was beyond the scope of our study. In spite of the fact that HIV positive persons are commonly positive to EBV, the EBV seropositivity was not tested, in order to distinguish between persons carrying latent EBV with detectable EBV DNA (with or without EBNA-2 expression) and those with latent EBV without detectable viral DNA in the mucosa. However, the seropositive status data was not meaningful for the aim of this study. Mixed infections could be underestimated by nested PCR due to differences in the viral loads for each subtype. In a larger study, with an increased number of participants, the impact of some co-factors would likely be stronger.

ACKNOWLEDGEMENTS

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RESUMO

Vírus Epstein–Barr na mucosa oral de pacientes positivos para o vírus da imunodeficiência humana

Objetivo: a taxa de detecção do vírus Epstein-Barr (EBV) é alta em pacientes vivendo com o vírus da imunodeficiência humana. Com o objetivo de contribuir para o entendimento epidemiológico e investigar a atividade do EBV na mucosa oral, foi realizado um estudo de coorte com pacientes HIV positivos.

Métodos: esfregaços orais de 145 pacientes HIV positivos foram coletados entre março de 2010 e março de 2011. A reação de cadeia de polimerase (PCR) internalizada e a PCR reversa (RT-PCR) foram usadas para genotipar o EBV e detectar a expressão do EBNA-2, respectivamente.

Resultados: o DNA do EBV foi detectado em 48,3% dos participantes, dos quais 32,85% eram portadores do EBV-1 e 45,71% de EBV-2. Adicionalmente, 14,28% eram co-infectados por ambos os tipos. O mRNA do gene EBNA-2 foi expresso em 45,7% das amostras positivas para EBV, incluindo 20% por EBV-1 somente, 20% por EBV-2 somente e 1,4% por ambos os genótipos. O estado imune afetou a infeção por EBV, e a positividade para EBV-2 foi significativamente correlacionada com o comportamento sexual dos participantes. A co-infeção por ambos os genótipos de EBV foi dependente da carga viral de HIV e da atividade do gene EBNA-2.
Conclusão: registrou-se uma alta prevalência de EBV em atividade na mucosa oral de indivíduos assintomáticos soropositivos para HIV. O estudo focaliza a necessidade de monitoramento e tratamento de pacientes infectados por HIV com reativação pelo EBV.

**Unitermos:** vírus Epstein-Barr; HIV; genótipos; mucosa oral.

**References**


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