EMERGING INFECTIONS INVITED ARTICLE

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Human Herpesvirus 8: Current Issues

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Although human herpesvirus 8 (HHV-8) is the etiologic agent of Kaposi sarcoma (KS), there are no formal guidelines for the clinical management of HHV-8 infection. In patients infected with human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART) is the best tool for the prevention of KS. In patients who have undergone transplantation, KS is often managed by curtailing immunosuppressive therapies, despite the potential adverse consequences for graft survival. Interventions related to HHV-8 infection might improve the management of KS in immunocompromised patients. However, knowledge from HHV-8 research cannot yet be translated into clinically useful interventions. Achieving clinical utility will require the commercial development of diagnostic tools currently available only in research settings and the evaluation of potential interventions. Such interventions might include the use of HHV-8 diagnostics to identify patients at high risk and to aid in the early detection of KS, prophylaxis with antiviral drugs to prevent KS, treatment of KS with antiviral drugs, and donor/recipient screening for organ transplantation.

More than a century passed between the initial description of Kaposi sarcoma (KS) and the discovery by Chang and Moore [1] and their colleagues of its etiologic agent, human herpesvirus 8 (HHV-8, also widely known as "KS-associated herpesvirus"). In the few years since its discovery in 1994, the virus has been linked to a handful of other diseases (table 1) that occur most commonly and more severely in immunocompromised patients such as HIV-infected persons and organ transplant recipients.

HHV-8 is a member of the γ-herpesvirus subfamily; of the human herpesviruses, it is most closely related to Epstein-Barr virus [2]. It shares with these viruses some aspects of how it establishes and maintains latency in cells of lymphoid origin, as well as the mechanism by which it can be reactivated to a lytic state. The virus encodes a dozen genes of obvious host origin, including genes that encode proteins that can modulate immune responses, apoptosis, and cell growth. No other herpesvirus has accumulated such a diverse arsenal of host-derived genes. The role of these proteins in HHV-8 pathogenesis is under active study but will not be discussed further in the present article.

Although it is clear that HHV-8 is the etiologic agent of KS, there are no formal guidelines relating to the clinical management of HHV-8 infection [3]. However, we believe that available data are sufficient to begin developing and evaluating strategies for translating HHV-8 research knowledge into clinical utility. This translational effort will entail a careful evaluation of the efficacy of clinical management strategies and the commercial development of diagnostic tools that are currently available only in research settings. Our intent in the present review is to provide a brief background on the biological characteristics of HHV-8 and to outline the research gaps that must be bridged so that the diagnosis, monitoring, and treatment of HHV-8 infection can play a role in the prevention and clinical management of KS.

LABORATORY MARKERS

HHV-8 activity can be monitored via assays that detect either the virus itself (its proteins or nucleic acids) or the host response to infection (antibodies or cellular immune response) (table 2) [4]. Efficient systems for culturing HHV-8 from samples of infected tissues or bodily fluids have not been developed. In situ immunohistochemistry or nucleic acid hybridization can be used to verify and localize HHV-8 infection in tissues and could be useful to confirm the presence of KS lesions early in
Table 1. Diseases associated with human herpesvirus 8 (HHV-8).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Properties</th>
<th>Evidence of causal association</th>
</tr>
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<tbody>
<tr>
<td>KS</td>
<td>Four epidemiological forms: AIDS-associated, African endemic, classical or Mediterranean, and transplant-associated (male predominance)</td>
<td>Very strong: fulfills commonly used criteria for causality</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>A subset of body cavity lymphomas; usually harbor Epstein-Barr virus in addition to HHV-8; rare, most common in patients with HIV; rapid course, poor prognosis</td>
<td>Strong, but too few cases to completely fulfill causality criteria; possibly confounded by association with Epstein-Barr virus</td>
</tr>
<tr>
<td>Febrile rash illness</td>
<td>In children</td>
<td>Moderate: small number of cases</td>
</tr>
<tr>
<td>Acute bone marrow failure</td>
<td>Reported in 3 transplant recipients</td>
<td>Moderate: small number of cases</td>
</tr>
<tr>
<td>Multicentric Castleman disease</td>
<td>Most common in patients with HIV; not always associated with HHV-8, sometimes associated with PEL or KS</td>
<td>Moderate: too few cases to completely fulfill causality criteria; disease can occur in absence of HHV-8, especially in HIV-negative patients</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td>Weak: proposed association is not supported by balance of laboratory and epidemiological evidence</td>
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</tbody>
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NOTE. KS, Kaposi sarcoma; PEL, primary effusion lymphoma.

the progression of the disease; this has already become an important diagnostic tool for histopathologists at some centers. At the moment, the testing of patient specimens is restricted to research settings, because few reagents or assays for HHV-8 are commercially available (and none in US Food and Drug Administration [FDA]–licensed formats).

**Serological testing.** HHV-8 antigens that are targeted by the serological response come in 2 broad categories: latent and lytic. The major latent antigen is latent nuclear antigen 1, which is encoded by open reading frame (ORF)–73. The major lytic antigens are ORF65 (a capsid protein) and K8.1 (a membrane-associated glycoprotein). Because of the lack of standardization and commercial availability, we cannot recommend specific assays or formats for clinical use. In multicenter comparisons, apparently similar assays have had substantial differences in performance [4].

**HHV-8 DNA in bodily fluids.** In HHV-8–seropositive men who have sex with men (MSM), HHV-8 DNA is detected by PCR most frequently and at the highest concentration in samples of oral fluids. It can also be found in PBMCs, less frequently in plasma, and much less frequently in semen specimens, prostatic secretions, and urethral or anal swab specimens. Men who secrete the virus in oral fluids tend to do so persistently; among secretors, the frequency of detecting HHV-8 DNA in oral swabs obtained daily was only modestly higher for men who tested seropositive for HIV [5].

**TRANSMISSION**

Sexual contact is an important route of HHV-8 transmission. The seroprevalence of HHV-8 among groups reporting high numbers of sexual contacts is much higher than in the general population. HHV-8 seroprevalence is particularly high in MSM, in whom HHV-8 seroprevalence increases with numbers of male sex partners, and is higher in men who report having other sexually transmitted infections [6]. Although HHV-8 infection is less common among heterosexuals, female commercial sex workers have higher rates of infection than do women in the general population [7]. Among women who did not report injection drug use, HHV-8 seropositivity was associated with syphilis seropositivity and participation in commercial sex [7].

Although a number of sexual transmission routes have been hypothesized, no single sexual behavior has been clearly identified as most risky for HHV-8 transmission [8]. Because HHV-8 DNA is found most commonly in the oral cavity [5], sexual practices that lead to the transfer of oral fluids may be important. In addition, oral exposure to feces during sex has been debated as a risk factor for KS, and oral-anal sex has been implicated in some, but not all, studies of HHV-8 transmission.

Table 2. Means of diagnosis of human herpesvirus 8 infection.

<table>
<thead>
<tr>
<th>Type of assay</th>
<th>Potential clinical application</th>
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<tbody>
<tr>
<td>Antibody detection</td>
<td>Identification of individuals with KS risk; transplant donor/recipient matching</td>
</tr>
<tr>
<td>Antigen detection</td>
<td>KS and PEL diagnosis or confirmation</td>
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<tr>
<td>In situ nucleic acid detection</td>
<td>KS and PEL diagnosis or confirmation</td>
</tr>
<tr>
<td>PCR nucleic acid detection</td>
<td>Detection of noncutaneous KS; possible marker of KS progression</td>
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</tbody>
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NOTE. KS, Kaposi sarcoma; PEL, primary effusion lymphoma.
routes [8]. However, HHV-8 DNA is rarely detected in anal swab specimens [5, 9]. Associations between HHV-8 and anal sex in MSM might be explained by the presence of HHV-8 in saliva, which is sometimes used as a lubricant for anal sex (Jim Braun, personal communication).

HHV-8 is also transmitted via close, nonsexual contact. In Africa, HHV-8 seroprevalence is relatively high in children, and seroprevalence can reach adult levels before adolescence [10–12]. Children are more likely to be HHV-8 seropositive if they have mothers or siblings who are seropositive [11]. Although the precise mode of nonsexual transmission has not been clearly established, the relatively frequent occurrence of HHV-8 DNA in oral fluids suggests that transmission may occur via shedding from the oral cavity. In the general population of the United States and other developed countries, nonsexual transmission appears to be infrequent.

HHV-8 appears to be transmissible, although less frequently, via exposure to blood. In the past, bloodborne transmission of HHV-8 has been discounted because HHV-8 transmission via blood transfusions has not been demonstrated and because groups with a risk of blood exposure (e.g., patients with hemophilia and injection drug users) have lower rates of KS than do MSM. However, in a large cohort of women, HHV-8 seropositivity increased with increasing injection drug use, even after controlling for sexual behavior, and it was significantly associated with hepatitis C virus (HCV) infection, a surrogate marker for injection drug use. These results suggest that HHV-8 is transmitted via needle sharing and, thus, via exposure to blood, albeit less commonly than other bloodborne viruses, such as hepatitis B virus, HCV, and HIV [7].

HHV-8 transmission from mother to child before or during birth is uncommon. Of 89 infants born to HHV-8–seropositive mothers, HHV-8 DNA was found in the PBMCs of only 2 infants [15]. Nearly all HHV-8–seropositive infants born to seropositive mothers later become seronegative, which suggests that positive results are due to the transfer of maternal antibodies [12]. Children in the United States have a very low prevalence of infection, and, in countries where HHV-8 seroprevalence is higher, most infections occur after age 24 months [11, 12, 14].

**PRIMARY INFECTION**

Some features of primary HHV-8 infection are beginning to emerge. In Egypt, where the seroprevalence of HHV-8 is relatively high, primary HHV-8 infections were detected in 6 (7%) of 86 immunocompetent children with a febrile syndrome of undetermined origin. In most cases, primary infection was documented by nested PCR oral fluid specimens and seroconversion within 6 months and was associated with fever (temperature, ≥38°C) and maculopapular rash that resolved uneventfully; there was no lymphadenopathy or oral ulceration [14]. In HIV-negative MSM, primary HHV-8 infection was identified as seroconversion coincident with the detection of viral DNA in peripheral blood and the development of HHV-8–specific CD8+ T cell responses [15]. Primary infections were associated with nonspecific symptoms that included diarrhea, fatigue, localized rash, and lymphadenopathy. As might be expected, in the small number of cases identified thus far, primary infection in immunocompromised patients was associated with a broader spectrum of more-severe disease, including fever, arthralgia, lymphadenopathy, splenomegaly, cytopenia, and KS [16, 17].

**KS PROGNOSIS IN HIV-INFECTED INDIVIDUALS**

The risk of KS for HHV-8–seropositive, healthy individuals is very low. However, the risk among immunocompromised individuals is much higher. Before the widespread use of HAART, the probability that an HIV-seropositive, HHV-8–seropositive individual would develop KS within 10 years of dual seropositivity was 30%–50% [18–20]. Since the introduction of HAART, the incidence of KS has decreased substantially, although it remains the most common cancer among HIV-infected individuals.

In cohort studies of men who were seropositive for both HIV and HHV-8, KS was most likely to develop in those with low CD4 cell counts [18, 20] or high HIV loads [20] and in MSM [18, 19]. In a cross-sectional study of MSM who were seropositive for both HIV and HHV-8, KS was also associated with the detection of HHV-8 DNA in PBMCs (figure 1) [9].

**HHV-8 AND ORGAN TRANSPLANTATION**

Because posttransplant immunosuppressive therapy is a predisposing factor for KS, HHV-8 infection has considerable clinical significance for transplant recipients. Precise estimates of HHV-8 seroprevalence in the organ donor and recipient populations in the United States are lacking. However, studies conducted in France have reported seroprevalences among donors (8%) [21] and recipients (8%) [22] that are similar to those among the general population. It is likely that the seroprevalence of HHV-8 in organ donors and recipients in the United States is similar to that in its general population as well and is probably somewhat higher than the 3.3% prevalence found among blood donors [23].

Transplant recipients may be infected with HHV-8 before transplantation but may also acquire HHV-8 from infected donor organs. The probability of seronegative transplant recipients becoming infected with HHV-8 because of infected renal al-
lografts has been estimated to be 2%–12% [24, 25]. Transmission from other organs has been suggested but has not been demonstrated to date. A review of the literature found that of 28 cases of posttransplantation KS, 23 (82%) were due to HHV-8 reactivation, and 5 (18%) were due to new infection from the transplanted organ [26].

KS occurs in 0.2%–5% of renal transplant recipients [25]. Because most transplant recipients are not infected with HHV-8, recipients who are infected or who become infected have a relatively high probability of developing KS. Although the data are limited, the range for this probability was estimated to be 8%–37.5% [22, 25]; to a first approximation, this is comparable to the probability of KS developing in MSM who are seropositive for both HIV and HHV-8.

Substantial morbidity and mortality are associated with a diagnosis of KS among transplant recipients. In a large transplant tumor registry, 143 (40.2%) of 356 patients with KS had visceral involvement, and 61 (17.1%) of 356 had KS listed as their cause of death [27]. Although the reduction or cessation of immunosuppressive treatment can lead to the complete remission of KS, among patients undergoing remission, 65% had graft loss or impaired graft function [27], compared with 21% of the overall population of transplant recipients (http://www.patients.unos.org/tpd).

**Figure 1.** ORs representing the strength of association between Kaposi sarcoma (KS) and different variables. OR are shown on a log scale, and error bars represent 95% confidence intervals [9]. HHV-8, human herpesvirus 8.

The understanding of HHV-8 and its pathogenic properties has increased remarkably since the discovery of the virus, but obstacles remain for translating this knowledge into clinical utility. Diagnostic tools have been developed that are useful in research settings, but they are not yet commercially available in FDA-licensed formats. In addition, little is known about the effectiveness of therapies that target HHV-8. Currently, the best tool for the prevention of KS in HIV-infected patients is HAART [3]. Nevertheless, because HHV-8 is the etiologic agent of KS, interventions related to HHV-8 infection might improve the treatment of HIV-infected patients. Similarly, because HAART is not relevant in transplantation situations, and, because curtailing immunosuppressive therapies to manage KS can have adverse consequences for graft survival, HHV-8–related interventions may also be beneficial for organ transplant recipients.

We list here several potential interventions suggested by our current understanding of the relationship of the virus to disease. The utility and efficacy of such interventions will need careful clinical evaluation and refinement as part of the process of developing a new standard of care for immunocompromised patients who are infected with HHV-8.

**Use of HHV-8 diagnostics to identify patients at high risk and to aid the early detection of KS.** HHV-8 antibody tests are the most sensitive methods for identifying patients who are at risk for KS. Among patients who are seropositive for HHV-8, the periodic monitoring of the HHV-8 load in PBMCs could help identify the subset of patients who are at the highest risk for KS [9, 28]. Such monitoring is likely to be most useful among HIV-infected patients who are not responding to HAART and who have high HIV loads and/or low CD4 cell counts. For these patients, antiviral prophylaxis may help prevent KS (see next paragraph). In addition, for patients whose HHV-8 test results suggest a high risk of KS, in-depth clinical examinations (e.g., chest radiography to detect pulmonary KS) and patient education (e.g., to encourage oral cavity self-examination) could help in the early detection of KS. Early detection may be important, because KS appears to be more likely to improve if it is treated at an early stage. This has been suggested by studies that found a lower KS tumor burden to be a predictor of a complete KS response to HAART in HIV-infected patients [29] and a predictor of complete KS remission in organ transplant recipients who stop taking their immunosuppressive therapy [30]. Similarly, antiviral therapy may prove to be more effective when the KS tumor burden is low.

**Prophylaxis with antiviral drugs to prevent KS.** There is evidence to suggest that prophylaxis with antiviral drugs, such as foscarin, ganciclovir, and cidofovir, protects against the development of KS. Although no drugs are currently li-
censed for HHV-8 therapy, in a large clinical trial, Martin et al. [31] showed that, among patients treated for cytomegalovirus retinitis, both oral and intravenous ganciclovir led to significant decreases in the incidence of KS. Patients at the highest risk for KS (i.e., those with a high HHV-8 load and a high HIV load/low CD4 cell count) might be considered for this intervention, although the potential benefit must be weighed against the cost of drug toxicity.

**Treatment of KS with antitherpes drugs.** Antitherpes agents might be used in conjunction with other therapies, such as HAART or chemotherapy, or in instances in which other therapies have failed. HHV-8 DNA in PBMCs appears to be associated with new lesion development among patients with KS [9, 28]; thus, monitoring PBMCs for HHV-8 DNA may prove useful for guiding the administration of potentially antitherpes drug therapies that would inhibit viral lytic replication and potentially inhibit KS progression. Antitherpes therapy for patients with KS has been described in a handful of case reports, but larger studies will be needed to obtain unequivocal results.

**Donor/recipient screening for organ transplantation.** Although most cases of KS in transplant recipients are the result of HHV-8 reactivation [26], avoiding matches between HHV-8–positive donors and HHV-8–negative recipients would prevent some occurrence of KS. Although the current evidence is insufficient to recommend against performing a transplant on the basis of HHV-8 mismatches, cost/benefit analyses for such strategies are needed that account for transplant type (renal, bone marrow, etc.) and regional prevalence of HHV-8 infection. Regardless of whether donor/recipient seromatching proves to be beneficial, the use of posttransplantation HHV-8 diagnostics to identify recipients at high risk is likely to provide a benefit because of heightened surveillance and the possible prophylaxis or treatment for KS.

**Acknowledgments**

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**References**


