




ORIGINAL ARTICLE

Donor-derived human herpesvirus 8 and development of Kaposi sarcoma among 6 recipients of organs from donors with high-risk sexual and substance use behavior

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Kaposi sarcoma (KS) can develop following organ transplantation through reactivation of recipient human herpesvirus 8 (HHV-8) infection or through donor-derived HHV-8 transmission. We describe 6 cases of donor-derived HHV-8 infection and KS investigated from July 2018 to January 2020. Organs from 6 donors, retrospectively identified as HHV-8-positive, with a history of drug use disorder, were transplanted into 22 recipients. Four of 6 donors had risk factors for HHV-8 infection reported in donor history questionnaires. Fourteen of 22 organ recipients (64%) had evidence of posttransplant HHV-8 infection. Lung recipients were particularly susceptible to KS. Four of the 6 recipients who developed KS died from KS or associated complications. The US opioid crisis has resulted in an increasing number and proportion of organ donors with substance use disorder, and particularly injection drug use history, which may increase the risk of HHV-8 transmission to recipients. Better awareness of the risk of posttransplant KS for recipients of organs from donors with HHV-8 infection risk could be useful for recipient management. Testing donors and recipients for HHV-8 is currently challenging with no validated commercial serology kits available. Limited HHV-8 antibody testing is available through some US reference laboratories and the Centers for Disease Control and Prevention.

KEYWORDS

clinical research/practice, donors and donation: donor-derived infections, infection and infectious agents, infectious disease

1 | INTRODUCTION

Kaposi sarcoma (KS) is a cutaneous malignancy caused by human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated

herpesvirus. There are four epidemiological forms of KS that are all associated with some form of immunosuppression: AIDS-related KS, classic KS in Mediterranean Europe, endemic KS in sub-Saharan Africa, and iatrogenic KS in transplant recipients.¹

Abbreviations: CDC, Centers for Disease Control and Prevention; CNI, calcineurin inhibitor; DTAC, Disease Transmission Advisory Committee; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HIV, human immunodeficiency virus; IDU, injection drug use; IRD, increased risk donor; KS, Kaposi sarcoma; MMF, mycophenolate mofetil; MSM, men who have sex with men; OPTN, Organ Procurement and Transplantation Network; PHS, Public Health Service.

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In the United States, HHV-8 infection and KS are primarily associated with human immunodeficiency virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS). In the US HIV population, HHV-8 has transmission routes similar to that of HIV, mainly men who have sex with men (MSM) behavior and injection drug use (IDU).¹⁻⁴ HHV-8 seroprevalence is 2%-5% among US blood donors,⁵ 7%-9% among blood transfusion recipients,⁶ 15%-25% among HIV-negative MSM, and 40%-50% among HIV-positive MSM.² HHV-8 seroprevalence has not been assessed in the context of US organ transplantation; however, solid organ transplant (SOT) recipients are at 60- to 200-fold elevated risk for KS compared to the general population because of their medical immunosuppression.^{1,7} Transplant-associated KS more often results from reactivation of HHV-8 in previously infected patients.⁸ Donor-derived KS is less common but associated with higher rates of severe illness and mortality.⁹⁻¹¹

Historically, MSM behavior and IDU have been associated with risk of donor HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. With the goal of minimizing possible transmission of these infections during transplantation, the 2013 Public Health Service (PHS) guidelines recommended ascertainment of 11 donor risk factors for HIV, HBV, and HCV, including substance use disorder, MSM behavior and incarceration in the 12 months prior to death. Donors with one or more risk factors are designated as increased risk donors (IRDs) per these recommendations. Due largely to the current US opioid crisis, a growing number and proportion of organ donors are IRDs, increasing from 8.9% in 2010 to 26.3% in 2017.¹² Because HHV-8 infection shares risk factors with HIV, HBV, and HCV infection, increasing numbers of IRD may elevate the risk of donor-derived HHV-8 and development of KS. The present report describes 6 unrelated cases of donor-derived KS from various transplant centers in the United States that were investigated by the Centers for Disease Control and Prevention (CDC) within an 18-month period, July 2018 to January 2020.

2 | METHODS

2.1 | Clinical and epidemiologic investigation

Transplant centers with KS cases are required to report suspected donor derived infections to the Organ Procurement and Transplantation Network (OPTN)/Disease Transmission Advisory Committee (DTAC), which monitors the transmission of disease through organ transplantation. DTAC examines potential transmission cases reported to the OPTN in an effort to confirm transmissions where possible. A subset of DTAC cases are investigated by the CDC, typically those with high public health significance, severe outcomes, multiple recipients, donors with known risk factors, or infections for which there are no commercial tests. All organ donor and recipient medical records were reviewed. All donors were deceased. Donor medical and social history data were provided by individuals knowledgeable of the donor lifestyle as part of organ procurement evaluation. In the current study these individuals self-identified as family, friend, partner, or roommate.

Donor history responses were reviewed for HHV-8 risk factors; high-risk sexual behavior including MSM, substance use disorder, and history of incarceration within the previous 12 months. All recipients of organs from a common donor were grouped for these analyses. The index case was defined as the first recipient from each group who developed KS resulting in reporting to OPTN/DTAC, and a portion of cases underwent subsequent CDC investigation.

2.2 | Diagnosis of KS and HHV-8 testing

All recipient tumor samples showed variable degrees of spindle cell proliferations that were positive for at least one vascular immunohistochemical marker (CD31, CD34, ERG) and positive for HHV-8, confirming a diagnosis of KS. To investigate whether KS in recipients may have resulted from donor-derived HHV-8 infection, archived blood samples from the 6 donors and from their 22 recipients pretransplant (when available) and at least 3 months posttransplant were retrieved and sent to the CDC for HHV-8 serology and PCR testing. All samples were tested for IgG antibodies to HHV-8 using 2 enzyme immunoassays (EIAs) based on the K8.1 and orf65 viral genes and a whole cell lytic immunofluorescence assay (IFA). These 3 serology tests were developed or modified in-house by CDC and have a combined sensitivity of 96.3% based on testing patients with KS and specificity of 97.5% based on testing US blood donors.^{5,6} Samples were also tested for HHV-8 DNA using TaqMan-based real-time PCR targeting the viral open reading frame 25 region as described previously.¹³

3 | RESULTS

3.1 | HHV-8 infection status of 6 donors and 22 recipients

All 6 organ donors were HHV-8 antibody and/or DNA positive (Table 1); 5 of 6 were antibody positive and one donor (#5) who was an active IDU, was antibody negative and DNA positive, indicating very recent primary infection. The donors were all male, 18- to 54-years-old; 5 of 6 were younger than 40-years-old. All six donors had a history of substance use disorder. Four donors had known risk factors for HHV-8 infection; MSM (Donors 2 and 6) or IDU (Donors 4 and 5). Donors 1 and 3 had probable risk factors for HHV-8 infection as regular users of methamphetamine (also heroin and cocaine for Donor 3), which is associated with high-risk sexual behaviors (trading sex for drugs and money)^{14,15} and IDU.¹⁶ Organs from 6 donors were transplanted into 22 recipients (Table 2). Four of the 6 index cases had pretransplant serum available, which demonstrated absence of HHV-8 infection prior to transplantation. The other 2 index cases had no pretransplant serum and no reported risk factors for HHV-8 infection. Overall, 14 of 22 (64%) organ recipients had evidence of posttransplant HHV-8 infection. Four of 6 index (67%) cases were lung recipients. Four of 6 index cases (67%) died directly from KS or from complications involving KS as described below.

TABLE 1 Cause of death, sexual behavior, substance use history, and incarceration among selected HHV-8 infected organ donors—United States, July 2018 to January 2020

Donor #	Cause of death	Sexual risk for HHV-8 infection	Substance use history	Incarceration last 12 mo	HHV-8 antibody	HHV-8 DNA copies/mL
1	Stroke	Sexual preference listed as unknown	Inhalation (meth, marijuana)	No	Positive	Not detected
2	Seizure	MSM	Inhalation (marijuana)	No	Positive	1.18E+04
3	Stroke	None reported	Inhalation (meth, cocaine, heroin)	No	Positive	Not detected
4	Heroin overdose	None reported	Inhalation + Injection (cocaine, heroin)	Yes	Positive	Not detected
5	Endocarditis	Partner with history of IDU	Injection (heroin)	Yes	Negative	1.13E+04
6	Suicide by hanging	MSM, Sex for drugs	Inhalation (meth, cocaine, heroin)	No	Positive	Not detected

Note: All donors were male ages 18-54 years. Only Donor 2 had history of prior residence in an HHV-8 endemic region. Abbreviations: HHV-8, human herpesvirus 8; Meth, methamphetamine; MSM, men who have sex with men.

TABLE 2 HHV-8 infection and Kaposi sarcoma outcomes among recipients of organs from HHV-8–positive donors

Donor #	Recipient #	Organ	Pretransplant HHV-8 Ab	Posttransplant HHV-8 Ab/PCR VL	KS/time from transplant to KS
1	1 (Index)	Bilateral lung	Negative	Positive/negative	Yes/7 mo
	2	Liver	Not available	Positive/1.13E+04	No
2	1 (Index)	Bilateral lung	Negative	Positive/negative	Yes/4 mo
	2	Rt kidney	Negative	Negative/negative	No
	3	Lt kidney + pancreas	Negative	Positive/1.21E+04	No
	4	Heart	Negative	Negative/negative	No
	5	Liver	Not available	Positive/negative	No
3	1 (Index)	Liver	Not available	Positive/8.07E+03	Yes/11 mo
	2	Heart + Lt kidney	Not available	Negative/negative	No
	3	Rt kidney	Not available	Negative/negative	No
4	1 (Index)	Bilateral lung	Not available	Positive/9.61E+03	Yes/8 mo
	2	Rt kidney	Negative	Positive/negative	No
	3	Heart	Negative	Negative/negative	No
	4	Liver	Not available	Negative/negative	No
	5	Lt kidney + pancreas	Negative	Positive/negative	No
5	1 (Index)	Lt kidney	Negative	Positive/1.07E+04	Yes/5 mo
	2	Rt kidney	Negative	Positive/negative	No
	3	Liver	Not available	Positive/negative	No
6	1 (Index)	Bilateral lung	Negative	Positive/7.57E+03	Yes/12 mo
	2	Rt kidney	Not available	Negative/negative	No
	3	Lt kidney	Negative	Negative/negative	No
	4	Liver	Negative	Positive/6.06E+03	No

Recipients were ages 33-72 years.

Abbreviations: HHV-8, human herpesvirus 8; KS, Kaposi sarcoma; VL, viral load, copies HHV-8/mL blood.

3.2 | Clinical summaries for six KS cases

3.2.1 | Donor 1, index recipient

A female patient with chronic obstructive pulmonary disease underwent lung transplantation. She received basiliximab as induction and

tacrolimus, mycophenolate mofetil (MMF), and prednisone as maintenance immunosuppression. Six months after transplantation, she presented with abdominal pain and diffuse adenopathy. Positron emission tomography (PET) showed [¹⁸F]-fluorine deoxyglucose (FDG)-avid right axillary, inguinal, and hilar lymph nodes and right-sided lung nodules (Figure 1, panels A and C). A core needle biopsy of the right

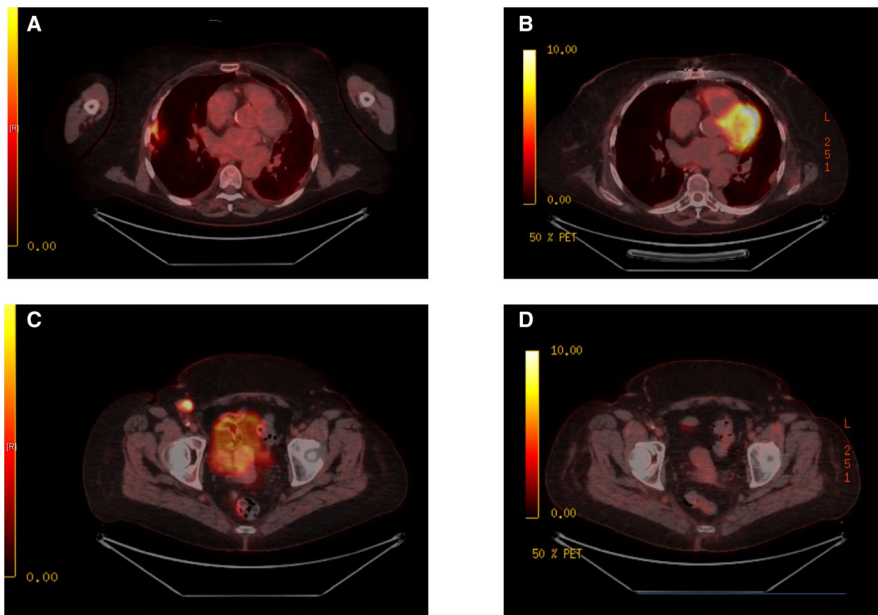


FIGURE 1 PET scan in Case 1 demonstrating FDG-avid right lung nodule (panel A) and right inguinal lymph node (panel C). Follow-up PET scan demonstrating resolution of chest nodule (panel B) and inguinal lymph node (panel D) FDG avidity

inguinal lymph node revealed KS. MMF was discontinued, tacrolimus was reduced, and sirolimus was added. She underwent weekly treatment with paclitaxel and had radiographic resolution of the adenopathy and pulmonary nodules on repeat PET after 5 months and she was doing well 19 months after diagnosis (Figure 1, panel B and D).

3.2.2 | Donor 2, index recipient

A male patient with a history of cystic fibrosis underwent bilateral lung transplantation. He received basiliximab as induction and tacrolimus, azathioprine, and prednisone as maintenance immunosuppression. Azathioprine was held at 3 months for leukopenia and transitioned to MMF once resolved. Five months after transplantation, he presented with cough and shortness of breath. Chest computed tomography (CT) revealed bilateral pulmonary nodules, consolidation, and pleural effusions (Figure 2, panel A). He underwent a left lower lobe wedge biopsy, which revealed KS (Figure 2, panels B,C,E,F). MMF was discontinued and tacrolimus changed to sirolimus. He had progression of pulmonary lesions and monthly doxorubicin was initiated. He completed 6 cycles and has continued sirolimus and prednisone. At 18 months after transplantation, chest CT showed resolution of the lesions (Figure 2, panel D).

3.2.3 | Donor 3, index recipient

A male patient with a history of cryptogenic cirrhosis and hepatocellular cancer underwent liver transplantation. He received no induction immunosuppression and was maintained initially on tacrolimus, MMF, and prednisone. MMF was discontinued after an episode of *Clostridioides difficile* colitis. He was readmitted 11 months after transplantation with generalized weakness, vomiting, and diarrhea. Abdominal CT revealed inguinal lymphadenopathy. Right inguinal

node biopsy was performed and KS was diagnosed. PET showed diffuse lymphadenopathy in the bilateral axillary, mediastinal, supradiaphragmatic, retroperitoneal, and inguinal lymph node chains, with moderate FDG uptake in the thorax and upper abdomen. A liver biopsy performed for worsening ascites and elevated bilirubin showed moderate acute cellular rejection (ACR), which was treated with methylprednisolone. He received one dose of rituximab, but he declined additional chemoradiation and died.

3.2.4 | Donor 4, index recipient

A male patient with a history of respiratory bronchiolitis interstitial lung disease underwent bilateral lung transplantation. He did not receive induction immunosuppression and initial maintenance immunosuppression consisted of tacrolimus, MMF, and prednisone. Early in the postoperative period he was given stress dose steroids for de novo class I donor specific antibodies. Eight months after transplantation, he received a prednisone taper for ACR. The following month, he developed autoantibodies to collagen type V and α 1 tubulin. He was treated for presumptive antibody-mediated rejection with plasma exchange, intravenous Ig, rituximab, anti-thymocyte globulin, and a prednisone taper. He continued to experience shortness of breath, and a bronchoscopy showed chronically inflamed mucosa. Endobronchial biopsy from the right lung identified KS (Figure 3). MMF was discontinued and tacrolimus dose was lowered, and he continued low-dose prednisone. He began initial treatment with monthly liposomal doxorubicin. After the fourth dose, he developed febrile neutropenia with worsening shortness of breath. A follow-up computed tomography (CT) scan showed bilateral confluent lung nodules with his Epstein-Barr virus PCR elevated at 242486, consistent with Post-Transplant Lymphoproliferative Disorder. Continuous renal replacement therapy, vasopressors, and ventilatory support were initiated. He continued to decline and died 1 month later.

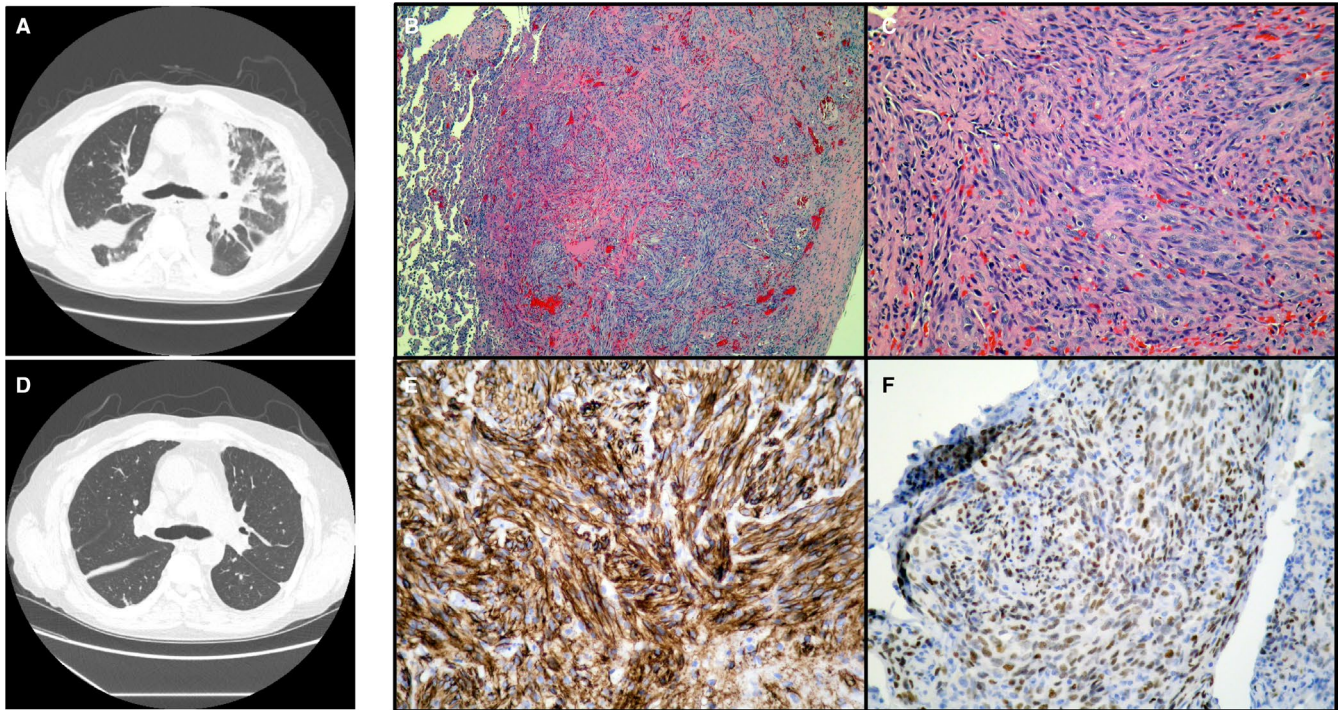
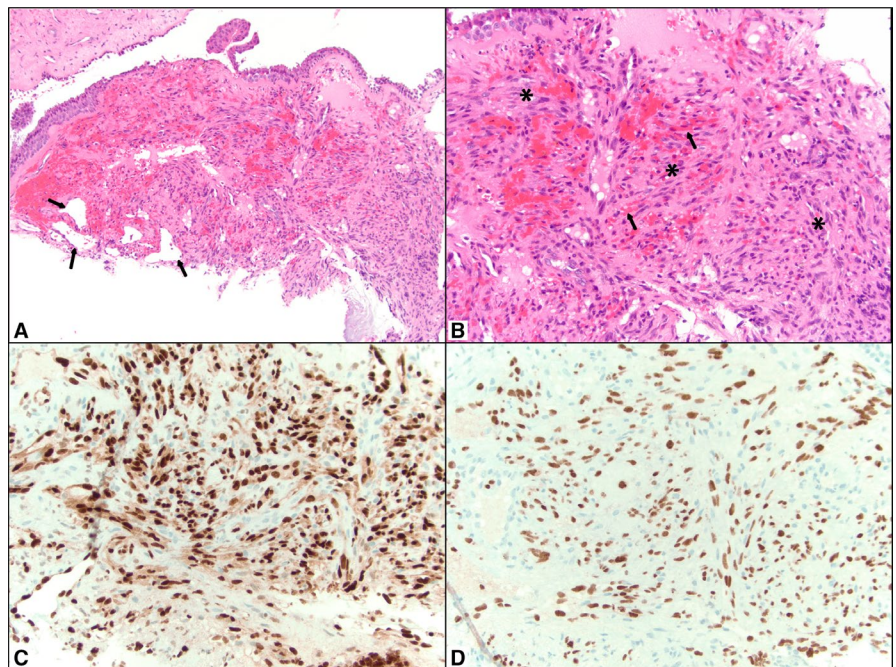


FIGURE 2 CT scan in Case 2 showing lung nodules and consolidation at diagnosis (panel A) and subsequent resolution (panel D). Lung biopsy showing proliferating spindle cells with extravasated red blood cells (panels A, B, A: hematoxylin & eosin 10 \times ; B: hematoxylin & eosin 20 \times). Immunohistochemical stain for CD31 20 \times (panel E) and human herpesvirus 8 (HHV-8) 20 \times (panel F)

FIGURE 3 Histopathology in Case 4. Proliferation of monomorphic spindle cells with associated dilated vessels (arrows in panel A). The cells form ill-defined fascicles (asterisks in B) and are separated by spaces containing erythrocytes (arrows in B). A: Hematoxylin & eosin 10 \times . B: Hematoxylin & eosin 20 \times . Immunohistochemical stain for ETS-related gene (ERG) 20 \times (panel C) and human herpesvirus 8 (HHV-8) 20 \times (panel D)



3.2.5 | Donor 5, index recipient

A male patient with a prior unilateral nephrectomy and end-stage renal disease underwent kidney transplantation. At transplantation, he was given anti-thymocyte globulin and was maintained initially on tacrolimus, MMF, and prednisone. Because the donor had HCV infection, the recipient was treated with glicaprevir and pibrentasvir

for 12 weeks. Five months after transplantation, a transplant renal biopsy was performed for worsening renal function and suggested ACR. He received 3 doses of methylprednisolone and 1 dose of anti-thymocyte globulin. He developed CMV infection (CMV PCR: 14000 IU/mL) and was treated with ganciclovir. A repeat renal biopsy showed diffuse infiltrative KS. A PET-CT scan showed enlarged FDG-avid retroperitoneal, inguinal, and mesenteric nodes.

He underwent a transplant nephrectomy, but the resection margins were positive for KS. MMF and tacrolimus were discontinued. Because of persistent inguinal lymphadenopathy, a lymph node biopsy was performed a month later, which confirmed metastatic KS and the recipient died while awaiting chemotherapy.

3.2.6 | Donor 6, index recipient

A female patient with idiopathic pulmonary fibrosis underwent bilateral lung transplantation. She received basiliximab as induction and tacrolimus, MMF, and prednisone as maintenance immunosuppression. One year later, she presented with abdominal pain, nausea, and jaundice. CT scan showed diffuse lymphadenopathy, pulmonary nodules, and biliary dilatation. A right-sided chest tube was placed for worsening hypoxia and a left supraclavicular lymph node biopsy was performed. The lymph node biopsy confirmed KS. She developed worsening multiorgan system failure and died 3 weeks later.

3.2.7 | Status of other recipients

As of March 2020, none of the other 16 organ recipients from these 6 donors were showing signs or symptoms of KS, with times from transplantation of 13-27 months. The time from transplantation to diagnosis of KS for the 6 index cases was 4-12 months, with a mean of 7.8 months (Table 2), consistent with posttransplant KS risk being highest within 1 year of surgery.¹¹ For the 16 recipients exposed to HHV-8 but without KS, limited clinical information was provided to the CDC, but several center contacts indicated that follow-up care would not be altered except for extra vigilance for any signs or symptoms of KS.

4 | DISCUSSION

This report describes the transmission of HHV-8 from 6 deceased organ donors to 14 of 22 (64%) recipients, 6 of whom subsequently developed KS. The recipients with KS were shown ($n = 4$) or presumed ($n = 2$) to be previously HHV-8 seronegative. Two of the donors had HHV-8 DNA in their blood, which is only rarely detected in individuals who do not have KS disease^{5,17} and indicates recent primary infection or reinfection. Most of the donors had a history of high-risk sexual behavior and/or IDU. Relatively low rates of posttransplant KS (163 cases/264 624 transplants) were reported for 1987-2014 in a comprehensive analysis of KS among US transplant recipients.¹¹ KS incidence was highest within 1 year of transplantation, significantly lower 1-3 years after transplantation, and decreased sharply thereafter.¹¹ The risk of HHV-8 transmission in the current transplant setting is unknown, with no prevalence data among organ donors. The identification of HHV-8 in several donors, all with substance use disorder and some with high-risk sexual behavior, suggests that organ donation in the setting of the US opioid crisis may pose a growing risk of HHV-8 transmission and KS.

There are several notable features of the 6 KS cases described here. The mortality rate was very high; 4 of 6 recipients died due to KS or associated complications. Known risk factors for KS-related mortality include recipient HHV-8 seronegativity and older age.^{11,18} Additional risk factors may have included profound immunosuppression after transplantation, specifically receiving agents such as anti-thymocyte globulin (2 of 4 cases), which cause prolonged T cell immune depletion, and late presentation or delayed recognition of KS (2 of 4 cases). Next, although lung transplants comprise only 8% of all SOTs¹⁹ and 14 of 22 recipients had evidence of posttransplant HHV-8 infection (5 liver, 4 lung, 3 kidney, and 2 kidney and pancreas), 4 of the 6 recipients who developed KS received lung transplants. The reason for the apparent higher KS risk with lung transplantation in this group remains unclear and further study may show whether it was related to drug use. HHV-8 is shed in the saliva of infected persons²⁰ and aspiration of saliva during inhalational drug use could elevate viral levels in the lung relative to other organs. Another potential mechanism may be local inflammation in lungs from chronic inhalation drug use.^{21,22} The inflammatory process recruits leukocytes to injured tissue and HHV-8 is leukocyte associated. Despite the possibility of increasing donor-derived HHV-8 infection, awareness and management can greatly improve outcome such that the benefits of organ acceptance are thought to outweigh the risk of declining an organ.

Treatment options for posttransplant KS include reduction of immunosuppression to the lowest possible level that maintains function of the allograft. Regression of KS with less risk to the graft has been obtained by reducing or discontinuing calcineurin inhibitors and adding mammalian target of rapamycin inhibitor (mTORi), such as sirolimus, which is now considered the first-line treatment of KS for transplant recipients.²³ Early diagnosis and better awareness of posttransplant KS, particularly among recipients of organs from donors with HHV-8 risk factors, with overall immunosuppression reduction and conversion to mTOR and use of chemotherapy appears to be associated with improved survival. It is important to note that T cell-depleting antibody therapy may result in prolonged T cell lymphopenia and that reducing or switching immunosuppressive drugs does not always result in an immediate improvement in immune function.²⁴ Although there is no consensus on chemotherapy, some patients will likely benefit from chemotherapy, especially if the disease appears to be progressing or if KS is detected late with advanced disease. The 2 survivors in our group did not receive anti-thymocyte globulin, the disease was detected earlier (~6 months), and both patients were given reduced immunosuppression, had an mTORi added, and received chemotherapy.

These findings on donor behaviors and HHV-8 transmission are subject to limitations. Donors 1 and 3 did not have HHV-8 risk factors (MSM, IDU) listed on the donor questionnaire. However, donor history questionnaires can have incomplete information.²⁵ Donor 1 was noted to be sexually active with unknown gender preference, which may imply MSM behavior, and was a frequent user of methamphetamine, which is associated with high-risk sexual behavior^{14,15} and IDU.¹⁶ Donor 3 was reported to inhale methamphetamine, cocaine, and heroin, which are associated with high-risk

sexual behavior^{14,15} and IDU.¹⁶ Therefore, it is the hypothesis of the authors that inhalation drug use disorder is not a newly identified risk factor for HHV-8 infection but rather is associated with behaviors that are HHV-8 risk factors. Second, pretransplant serum was not available for HHV-8 testing for 4 of 14 (28%) recipients who had posttransplant infection (Table 2). However, given evidence of donor infection, infection of other recipients from the same donors, low HHV-8 population seroprevalence, and lack of HHV-8 risk factors reported for recipients, donor-derived infection is more likely than prior infection in the recipient. Finally, our study lacked detailed data on clinical management of the 16 recipients who did not develop KS.

Future studies may include HHV-8 seroprevalence studies on organ donors that would better elucidate infection rates, especially in view of the growing number and proportion of donors with substance use disorders. Determination of HHV-8 infection requires antibody testing for adequate sensitivity because HHV-8 viremia is rare in seropositive individuals without KS in the United States⁵ and was detectable in only 7% of HHV-8 seropositive organ donors in Italy.²⁶ The HHV-8 serologic tests used for this study are made in-house by the CDC,^{13,27} are labor-intensive, and not practical for routine screening. At present, there are no validated, commercial HHV-8 serologic tests available in the United States. All suspected donor-derived HHV-8 infection and KS should be referred to the OPTN/DTAC for investigation. The CDC can perform HHV-8 testing for posttransplant KS as part of HHV-8 transplant-transmission investigations (sdollard@cdc.gov). In addition, limited US reference laboratories offer HHV-8 serology testing.²⁸

In summary, clinicians caring for recipients of organs from at-risk donors should have awareness of HHV-8 infection and related complications. Proposed revision to the CDC PHS guideline reduces the ascertainment time for donor risk factors from 12 months to 1 month prior to organ donation. For the current study, most donors were MSM or had a history of IDU use, which is often daily, thus donor risk factors presented here would likely still be identified by Organ Procurement Organizations. Donor-derived KS in this series appears to involve the allograft, and it is important to note that allograft dysfunction (acute lung injury, acute kidney injury) may be secondary to allograft KS. Monitoring recipients of these organs for KS development may allow early recognition. In turn, careful reduction of immunosuppression, introduction of an mTORi and consideration of chemotherapy may result in improved survival among these recipients.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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