HHV-8/KSHV in Solid Organ Transplantation: Screening, Risk stratification and Clinical Management

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UPMC LIFE CHANGING MEDICINE

Disclosures

Nothing to disclose

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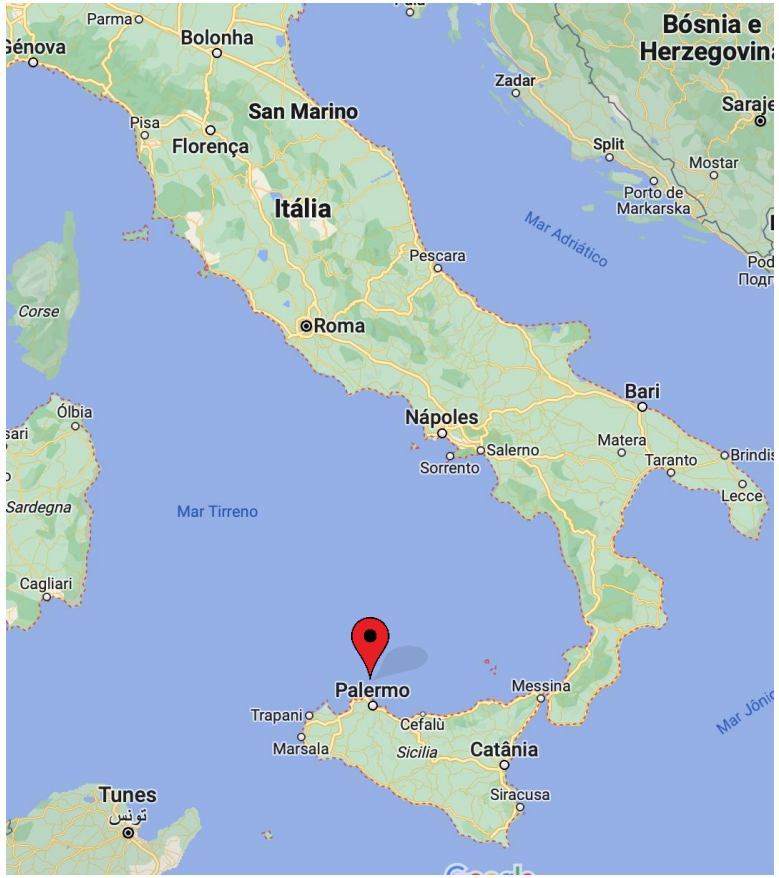
Some Context



ISMETT (*Mediterranean Institute for Transplantation and Advanced Specialized Therapies*) is a Solid Organ Transplant Center, partner of University of Pittsburgh Medical Center

In 2011, in ISMETT a **protocol to promptly detect HHV-8 infections and treat related diseases** has been developed.

Universal HHV-8 serology is performed on **all donors and recipients** to stratify the risk of post-Tx HHV-8-related disease

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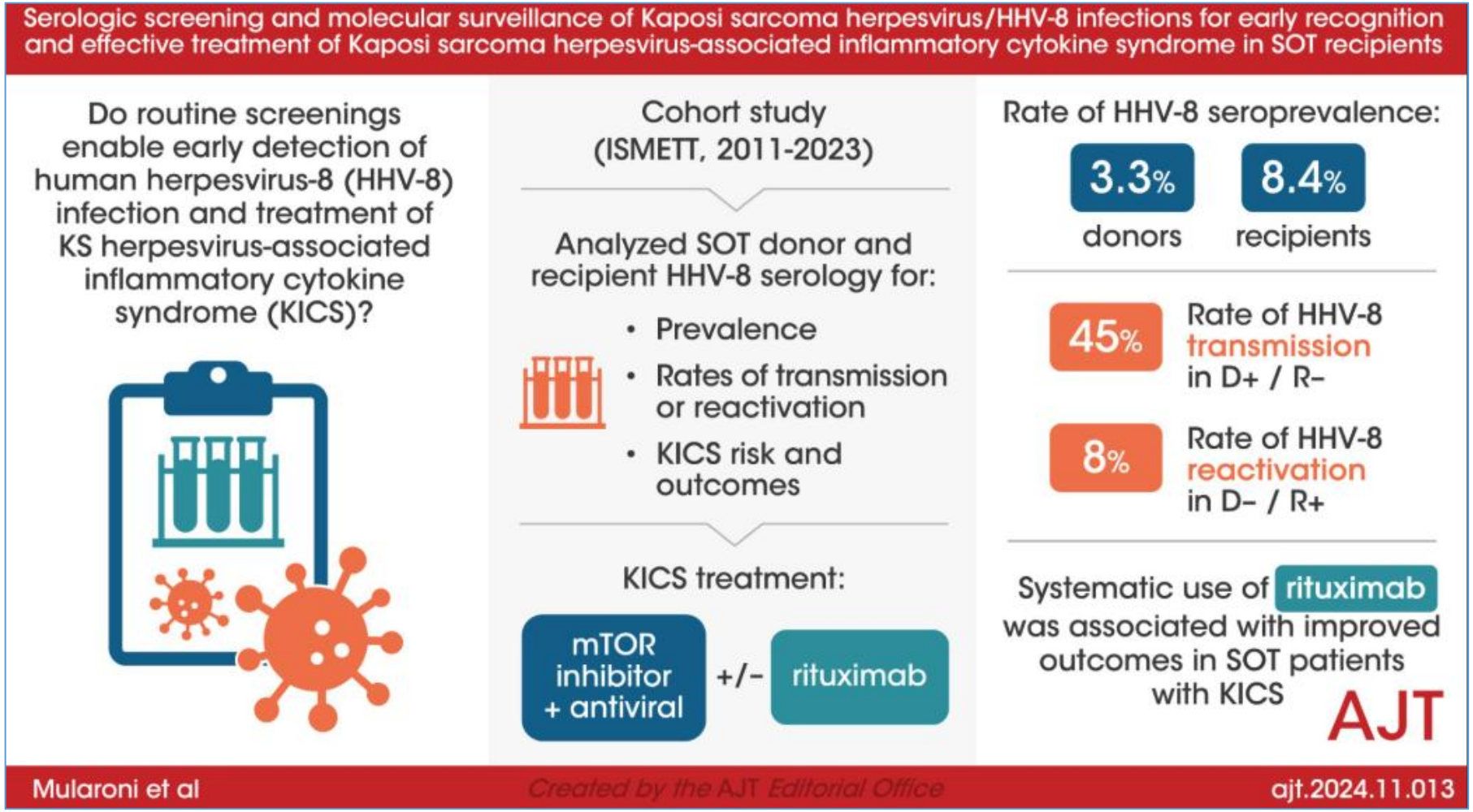
Some Context

ORIGINAL ARTICLE · Articles in Press, November 15, 2024 · *Open Access*

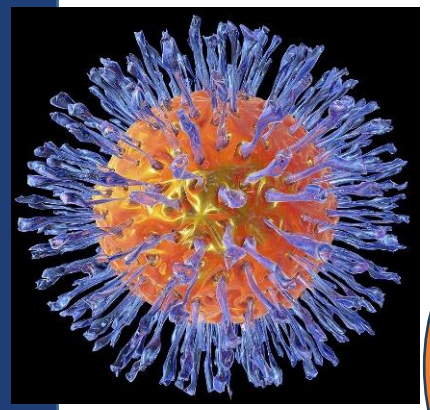
Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients

Alessandra Mularoni [1] · Andrea Cona [1] · Matteo Bulati [2] · ... · Pier Giulio Conaldi [2] · Paolo Antonio Grossi [20] · Mario Luppi [9]



May 2025 AJT Editor's Choice Article

Herpesviruses in SOT



Lifelong nonproductive infection of the host, **reactivation** when immunity wanes (older age, underlying disease, or immunosuppression)

1. Human Cytomegalovirus
2. Epstein–Barr Virus
3. Varicella Zoster Virus
4. Herpes Simplex Virus
5. Human Herpesvirus 6A and 6B and 7
6. **Human Herpesvirus 8/Kaposi sarcoma-associated Herpes Virus**

Prevention:

- Determination the serostatus of donor and recipient
- Antiviral prophylaxis
- Viral load monitoring
- Preemptive therapy
- Vaccination
- Education and hygiene

Therapeutic strategies:

- Antiviral treatment
- Immunosuppression adjustment
- Management of complications

Herpesviruses in SOT

DIRECT EFFECTS

- Fever and neutropenia
- End-organ disease (pneumonia, gastritis, colitis, encephalitis)

INDIRECT or IMMUNOMODULATORY EFFECTS

- **Systemic immunosuppression → Opportunistic infections:**
  Aspergillus after CMV, Pneumocystis after CMV, CMV/EBV coinfection >risk of PTLD
- **Inflammation and Cytokine Syndrome** → HHV-8 and KICS
- **Rejection** and **chronic graft disfunction** → release of proinflammatory cytokines

ONCOGENESIS

- EBV: PTLD
- HHV-8: Kaposi sarcoma (KS), Lymphoma

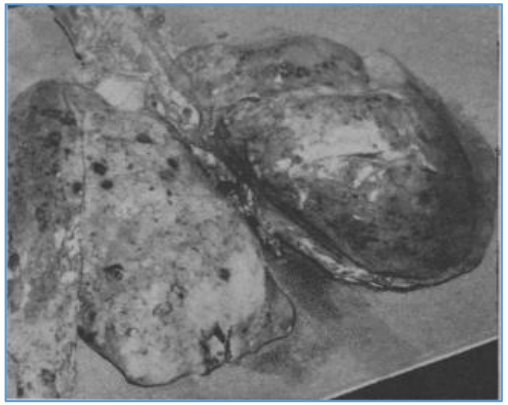
Human Herpesvirus 8/
Kaposi sarcoma-associated Herpes Virus

Characteristics, Life cycle and Seroprevalence

Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is a double-stranded DNA **oncogenic virus**, belonging to the family of the **γ-herpesvirus**

Moritz Kaposi (1872)

Kaposi Sarcoma was described for the first time by **Moritz Kaposi**



Siegel et al (1969)

The **first case of post-transplant KS** in a kidney transplant recipient

Philadelphia (1993)

AIDS epidemic caused a dramatic rise in the incidence of KS

Yuan Chang and Patrick Moore (1994)

Chang and Moore discovered unique DNA sequences in KS lesions from AIDS patients

Kaposi M. 1982. doi:10.3322/canjclin.32.6.342
Siegel JH et al. 1969 .doi:10.1001/jama.1969.03150210077009
Chang Y and Moore P et al. 1994. doi:10.1126/science.7997879

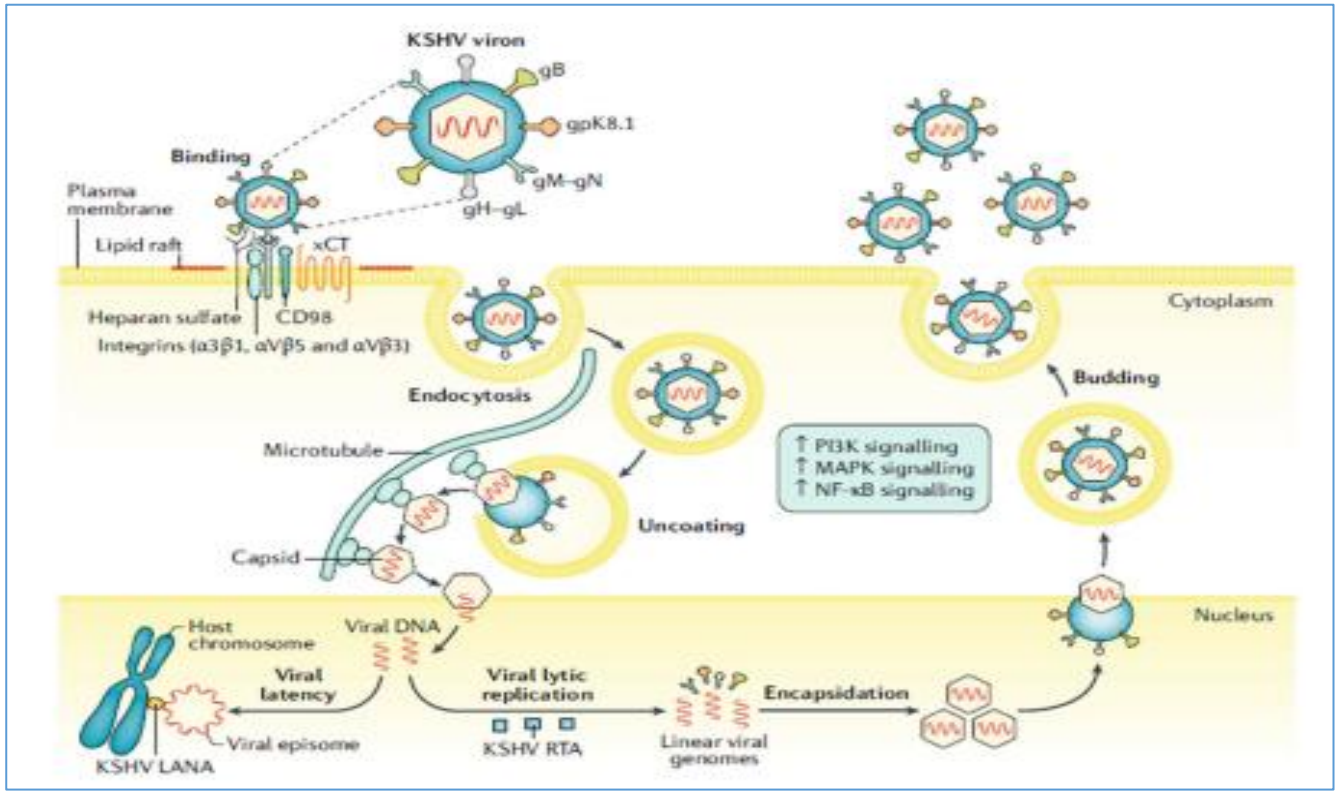
HHV-8 characteristics and life cycle

HHV-8 infects **B cells**, **endothelial cells**, **macrophages** and **monocytes**

The life cycle alternates between latent and lytic phases

ROUTE OF TRANSMISSION:

- **Saliva**
- **Sexual contact**
- **Intravenous or inhalation drug use**
- **Blood transfusions**
- **Solid organ transplantation**



Cesarman E. et al Nat Rev Dis Primers. 2019 PMID: 30705286

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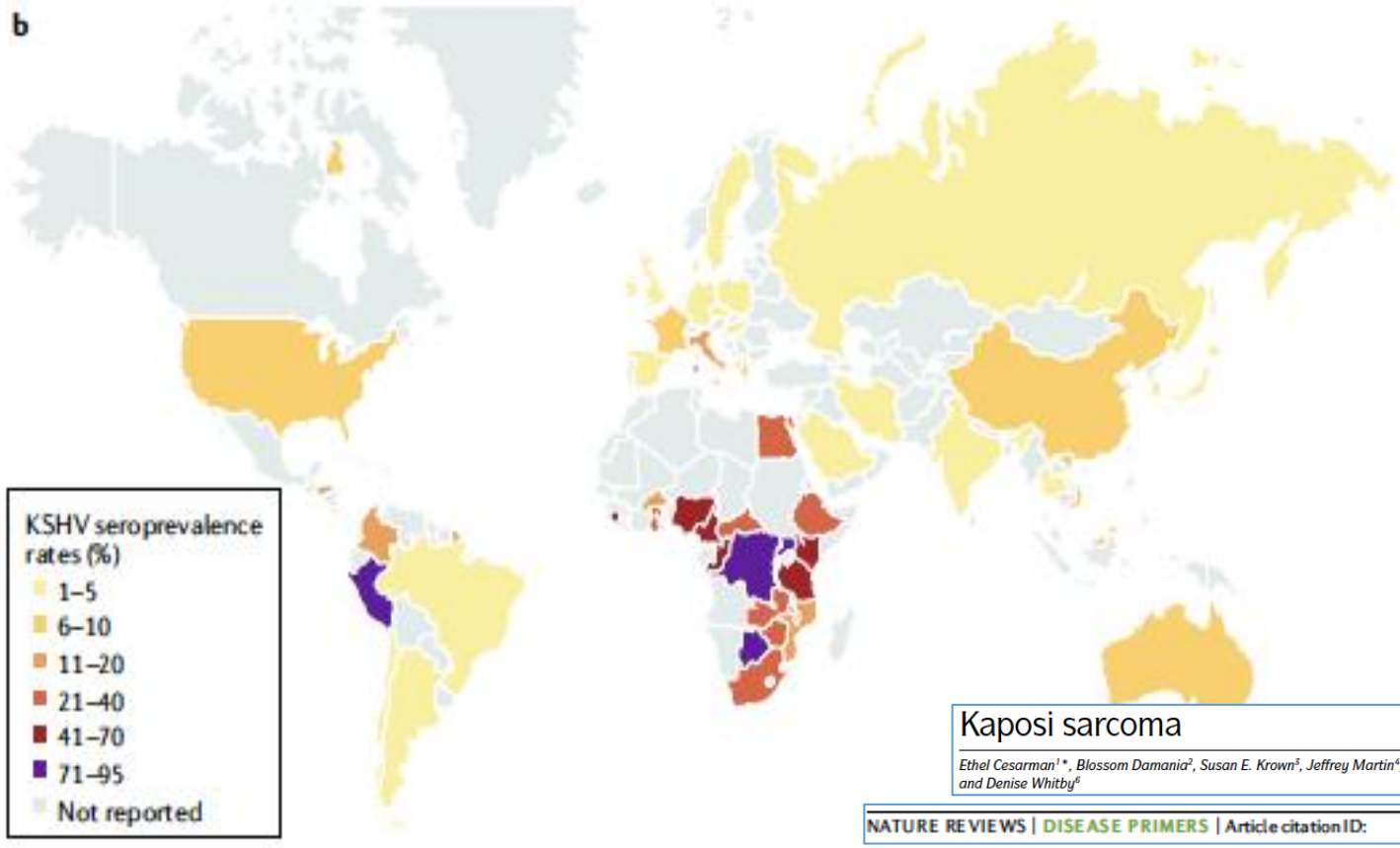
HHV-8 seroprevalence

Geographic and Population-Based Differences in HHV-8 Prevalence

- Sub-Saharan Africa: 50%
- Mediterranean Basin and Eastern Europe: 5-30%
- Northern Europe and U.S.: 1-10%
- Some populations (HIV and MSM) 40-60%



Kaposi sarcoma

Ethel Cesarman[1], Blossom Damania[2], Susan E. Krown[3], Jeffrey Martin[4], Mark Bower[5] and Denise Whitby[6]*

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2019) 5:9

Cesarman E et al Nat Rev Dis Primers. 2019 PMID: 30705286
Liu Z et al. Journal of Medical Virology. 2018 doi:10.1002/jmv.24960

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HHV-8 seroprevalence in Solid Organ Transplantation

Multicenter Prospective Study for Laboratory Diagnosis of HHV8 Infection in Solid Organ Donors and Transplant Recipients and Evaluation of the Clinical Impact After Transplantation

Angela Chiereghin, BScD, PhD,[1] Patrizia Barozzi, BScD, PhD,[2] Evangelia Petrisli, MD,[1,3] Giulia Piccirilli, BScD,[1] Liliana Gabrielli, MD,[1] Giovanni Riva, MD, PhD,[2] Leonardo Potenza, MD, PhD,[2] Gianni Cappelli, MD,[4] Nicola De Ruvo, MD, PhD,[5] Irene Libri, BScD,[6] Umberto Maggiore, MD,[6] Maria Cristina Morelli, MD,[7] Luciano Potena, MD, PhD,[8] Paola Todeschini, MD, PhD,[9] Dino Gibertoni, PhD,[10] Manuel Labanti,[11] Gabriela Sangiorgi, MD,[11] Gaetano La Manna, MD, PhD,[9] Antonio Daniele Pinna, MD, PhD,[7] Mario Luppi, MD, PhD,[3] and Tiziana Lazzarotto, BScD, PhD[12]

(*Transplantation* 2017;101: 1935–1944)

Donors 4%
Recipients 18%

ORIGINAL ARTICLE

HOPE in action: A prospective multicenter pilot study of liver transplantation from donors with HIV to recipients with HIV

Christine M. Durand [1], Sander Florman [2], Jennifer D. Motter [3], Diane Brown [1], Darin Ostrander [1], Sile Yu [3], Tao Liang [1], William A. Werbel [1], Andrew Cameron [3], Shane Ottmann [3], James P. Hamilton [1], Andrew D. Redd [1 4], Mary G. Bowring [3], Yolanda Eby [5], Reinaldo E. Fernandez [1], Brianna Doby [6], Nazzarena Labo [7], Denise Whitby [7], Wendell Miley [7], Rachel Friedman-Moraco [8] ...Dorry L. Segev [3]

Liver Tx recipients with HIV 21%

ORIGINAL ARTICLE · Articles in Press, November 15, 2024 · *Open Access*

Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients

Alessandra Mularoni [1] · Andrea Cona [1] · Matteo Bulati [2] · ... · Pier Giulio Conaldi [2] · Paolo Antonio Grossi [20] · Mario Luppi [9]

Donors 3.3%
Recipients 8.4%

Journal of Medical Virology WILEY JOURNAL OF MEDICAL VIROLOGY

LETTER TO THE EDITOR OPEN ACCESS

Human Herpesvirus 8 in Solid Organ Transplant Donors and Recipients: Need for Screening? A Dutch Seroprevalence Pilot Study

Geesje Roo-Brand | Xuewei Zhou | Coretta Van Leer-Buter | Marjolein Knoester

Donors 2.8%
Recipients 10.3%

Clinical Infectious Diseases MAJOR ARTICLE IDSA OXFORD

Kaposi Sarcoma–Associated Herpesvirus Risk and Disease in Kidney Donors and Transplant Recipients With Human Immunodeficiency Virus in the United States

Puja H. Nambiar,[1,a] Tao Liang,[2,a,@] Nazzarena Labo,[3,@] Jonathan Hand,[4,@] Emily A. Blumberg,[5,@] Meenakshi M. Rana,[6] Sander Florman,[7] Brandy Haydel,[7,@] Michele I. Morris,[8,@] Joanna Schaenman,[9] Moreno M. S. Rodrigues,[2] William A. Werbel,[2,@] Mary G. Bowring,[2] Rachel J. Friedman-Moraco,[10] Peter Stock,[11] Valentina Stosor,[12,@] Shikha Mehta,[13] Alexander J. Gilbert,[14,@] Nahel Elias,[15,@] Sapna A. Mehta,[16] Catherine B. Small,[17] Ghady Haidar,[18] Maricar Malinis,[19,@] Marcus R. Pereira,[20] Saima Aslam,[21] David Wojciechowski,[22,@] Ricardo La Hoz,[22,@] Carlos A. Q. Santos,[23,@] Senu Apewokin,[24] Jose A. Castillo-Lugo,[25] Karthik Ranganna,[26] Megan Morsheimer,[27] Allan Massie,[16,@] Dorry L. Segev,[16,@] Wendell Miley,[3] Vickie Marshall,[3,@] Denise Whitby,[3,@] Aaron A. A. Tobian,[2,a] and Christine M. Durand[2,a,@]; on behalf of the HOPE in Action Investigators

Kidney Tx recipients with HIV 41%
Donors with HIV 25%
Donors without HIV 8%

Chiereghin A, Barozzi P, Luppi M Transplantation. 2017 Aug;101(8):1935-1944. doi: 10.1097/TP.0000000000001740
Mularoni A, Cona A, Am J Transplant. 2025;25(5):1070-1085. doi:10.1016/j.ajt.2024.11.013
Roo-Brand G, Knoester M. et al. J Med Virol. 2025 doi: 10.1002/jmv.70477
Nambiar PH. Et al. Clin Infect Dis. May 2025. doi:10.1093/cid/ciaf229
Durand CM et al. Am J Transplant. 2022;22(3):853-864. doi:10.1111/ajt.16886

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Lack of Recommendation on screening and management

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION

Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Rebecca Pellett Madan[1] | Jonathan Hand[2] | on behalf of the AST Infectious Diseases Community of Practice

4 | HHV-8 RECOMMENDATIONS AND LEVEL OF EVIDENCE

4.1 | Diagnosis

Serology is of limited utility in the diagnosis of acute HHV-8 related disease post-transplant (strong, low).

In endemic regions, pretransplant donor and recipient HHV-8 serologic screening may be helpful to stratify disease risk after transplant (weak, low).

Targeted pretransplant HHV-8 serologic screening of at-risk donors and recipients or those from endemic regions may be considered in low seroprevalence regions (weak, very low).

Guide to the quality and safety of

ORGANS FOR TRANSPLANTATION

European Committee on Organ Transplantation (Partial Agreement) (CD-P-TO)

EDQM 9th Edition 2025

8.6.2.17. *Kaposi sarcoma-associated herpes virus or human herpes virus 8*

Take note!

Universal screening of donors for KSHV is generally not necessary. However, since donor-derived primary KSHV infection may be associated with severe disease, screening of donors for KSHV anti-lytic and anti-latent antibodies is recommended for donors and recipients coming from areas with high prevalence.

- In cases of D+/R– mismatch, close monitoring of the recipient for KSHV-DNA in blood is recommended in order to identify infection early.

ISTITUTO SUPERIORE DI SANITÀ

CENTRO NAZIONALE TRAPIANTI

October 2024

Screening not recommended

In case of positive HHV-8 Ab in the donor, follow up of the recipient:

- Monthly HHV-8 DNA for 6 months post-tx
- HHV-8 Ab at 3 and 6 months pos-tx
- If no seroconversion follow up with HHV-8 DNA every 3 months

GOV.UK

Independent report

SaBTO virology subcommittee recommendations on KSHV: executive summary

Updated 13 March 2025

Main recommendation

We recommend the introduction of universal serological screening of deceased donors for KSHV infection. To begin with, such testing should be centralised. The programme should be monitored and reviewed to inform necessary changes.

Pellett Madan R, Hand J; Clin Transplant. 2019 doi: 10.1111/ctr.13518
EDQM. Guide to the quality and safety of organs for transplantation. 9th Edition, 2025
CENTRO NAZIONALE TRAPIANTI 2024
https://www.gov.uk/government/publications

The spectrum of HHV-8 associated diseases

The spectrum of HHV-8 associated diseases

REVIEW ARTICLE OPEN ACCESS

HHV-8/KSHV in Solid Organ Transplantation: Current Gaps of Knowledge and Future Directions

Alessandra Mularoni[1,2] | Andrea Cona[1,2] | Malgorzata Mikulska[3,4] | Francesca Pecoraro[5] | Carlotta Piazza[5] | Elda De Vita[1,2] | Giada Pietrosi[1,2] | Matteo Bulati[1] | Tiziana Lazzarotto[3,4] | Mario Luppi[5]

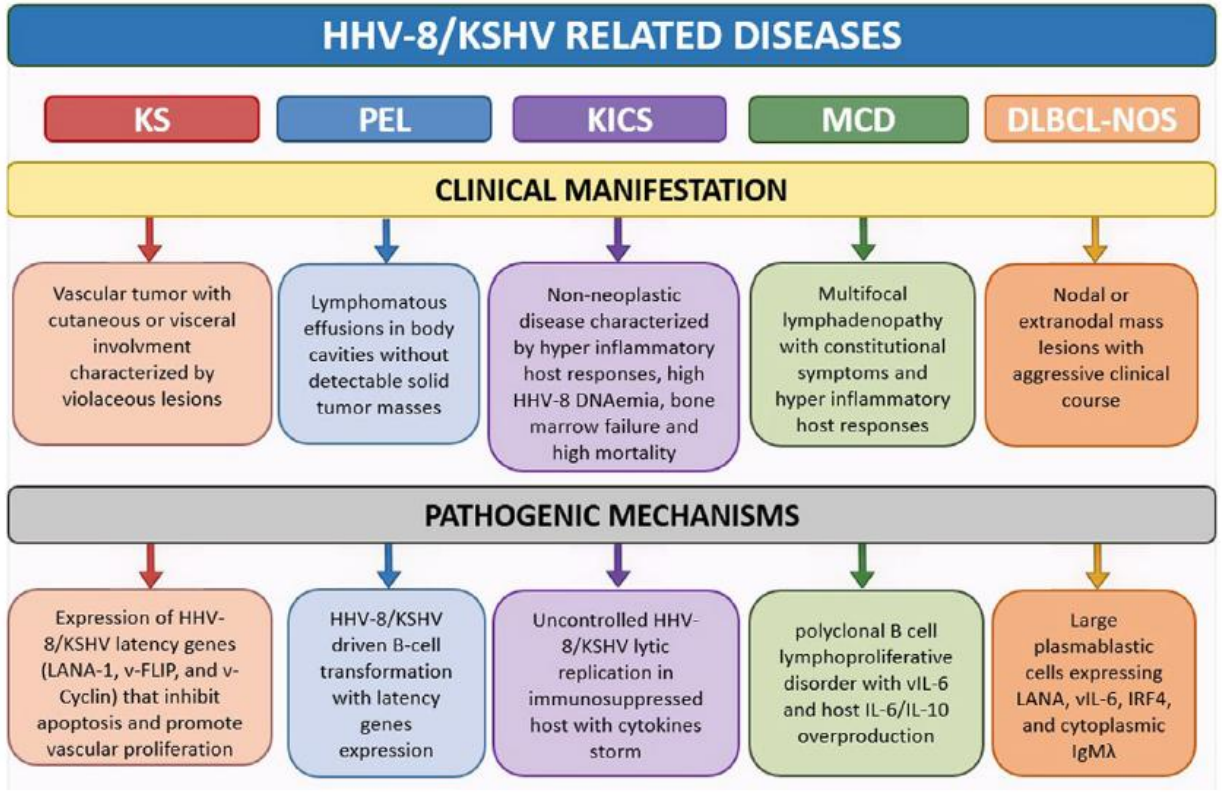

FIGURE 1 | Clinical spectrum of HHV-8/KSHV-related diseases in the SOT setting.

KICS:

*"a non-neoplastic HHV8-related disease characterized by **fever**, **hyper-inflammatory host responses**, rarely, **bone marrow failure and organ damage** but without the characteristic histopathology of MCD"*

Mularoni A, Cona A, Mikulska M. Transpl Infect Dis. 2026 Jan 30:e70179. doi: 10.1111/tid.70179

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HHV-8 infection in Solid Organ Transplant recipients

HHV-8 related clinical manifestations in SOT

The severity, timing, and type of HHV-8-related disease may differ by transplanted organ, donor and recipient serostatus and the degree of immunosuppression

- KS is the most common manifestation
- Other neoplastic manifestations (**PEL, LCL, MCD**) very rare in SOT
- **KICS** more common in SOTs following primary infection rather than reactivation

Lung Transplantation

TO THE EDITOR: We would like to expand on the review by Christie et al. (Nov. 14 issue)[1] by discussing the emerging pathogenic role of Kaposi's sarcoma–associated herpesvirus (KSHV) infection, also known as human herpesvirus 8 (HHV-8) infection. Dollard et al. reported that lung-transplant recipients in the United States appeared to be particularly susceptible to the transmission of HHV-8 from deceased organ donors; HHV-8 infection was followed by fatal Kaposi's sarcoma in most cases.[2] Most of the donors had a history of high-risk sexual behavior, injection-drug use, or both.[2] In southern Italy, the risk of Kaposi's sarcoma among lung-transplant recipients early in the post-transplantation period is greater than the risk of this cancer in the general population.[3] In addition, in a series of solid-organ transplant recipients from Sicily (Italy), a geographic area where HHV-8 is endemic,[4] seroprevalence was 6.9% among 145 lung-transplant recipients, and 1 of 2 HHV-8–mismatch patients (seropositive donor and seronegative recipient) had a primary HHV-8 infection, followed by fatal, disseminated Kaposi's sarcoma and KSHV-associated inflammatory cytokine syndrome (KICS).[5] Recognition of post-transplantation Kaposi's sarcoma and KICS in lung-transplant recipients from donors at risk for HHV-8 infection may allow better management of recipient care and lifesaving interventions.[2,5]

Mario Luppi, M.D., Ph.D.,[1] Andrea Cona, M.D., Ph.D.,[2] and Alessandra Mularoni, M.D.[2]

[1]University of Modena and Reggio Emilia, Modena, Italy; [2]IRCCS Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy.

Dr. Luppi can be contacted at mario.luppi@unimore.it.

No potential conflict of interest relevant to this letter was reported.

1. Christie JD, Van Raemdonck D, Fisher AJ. Lung transplantation. N Engl J Med 2024;391:1822-36.
2. Dollard SC, Annambhotla P, Wong P, et al. 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. Am J Transplant 2021;21:681-8.
3. Piselli P, Busnach G, Citterio F, et al. Risk of Kaposi sarcoma after solid-organ transplantation: multicenter study in 4,767 recipients in Italy, 1970-2006. Transplant Proc 2009;41:1227-30.
4. Whitby D, Luppi M, Barozzi P, Boshoff C, Weiss RA, Torelli G. Human herpesvirus 8 seroprevalence in blood donors and lymphoma patients from different regions of Italy. J Natl Cancer Inst 1998;90:395-7.
5. Mularoni A, Cona A, Bulati M, et al. Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients. Am J Transplant 2024 November 16 (Epub ahead of print).

DOI: 10.1056/NEJMc2416119

THE AUTHORS REPLY: Luppi et al. call attention to the emerging issue of donor-derived HHV-8 infections. We agree with their statements and the importance of the articles referenced in their letter. To this, we would add that the United Kingdom recently instituted a national surveillance program to address this issue.[1]

Jason D. Christie, M.D.,[1] Dirk Van Raemdonck, M.D., Ph.D.,[2] and Andrew J. Fisher, Ph.D., B.M., B.S.[3]

Luppi M, Cona A, Mularoni A. Lung Transplantation. N Engl J Med. 2025. doi: 10.1056/NEJMc2416119

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HHV-8 related diseases

Kaposi Sarcoma

Kaposi Sarcoma

Kaposi sarcoma in solid organ transplant recipients: updates in epidemiology, diagnosis, treatment and prevention

Alessandra Mularoni[1,2], Andrea Cona[1,2*], Carlotta Piazza[3], Francesca Pecoraro[3], Patrizia Barozzi[4] and Mario Luppi[4]

CLINICAL PRESENTATION

- most … **…lish lesions** (mac…
- it ma… **…er phenomenon”)**
- PT-KS… …lesions, and a more aggre… …f donor and recip…
- KS is …
- In the …
- absol… **…000 person-years in SOT recipients**, and 1.5 per 100,000 person-years in the general population
- some authors reported higher incidence of KS among **lung transplant recipients**

Mularoni A, Cona A, Piazza C, Pecoraro F, Barozzi P and Luppi M (2026). Front. Immunol. 17:1698179. doi: 10.3389/fimmu.2026.1698179

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Kaposi Sarcoma

Kaposi sarcoma in solid organ transplant recipients: updates in epidemiology, diagnosis, treatment and prevention

Alessandra Mularoni[1,2], Andrea Cona[1,2*], Carlotta Piazza[3], Francesca Pecoraro[3], Patrizia Barozzi[4] and Mario Luppi[4]

KAPOSI SARCOMA CHARACTERISTICS BY ORGAN TYPE

- SR including a total of 100 studies for a total of **663 KS cases** in SOT:
  - 452 (68%) cases in Kidney Tx recipients
  - 103 (15%) in Liver Tx recipients
  - 63 (9.5%) in heart Tx recipients
  - 45 (6.8%) in lung Tx recipients

- Among studies that reported clinical outcome, **overall survival was 66.5% (241/362)**
- Highest survival among kidney and Liver recipients [70% (196/279) and 63% (27/43)]
- Lower survival among heart and lung [46% (6/13) and 44% (12/27)]

Mularoni A, Cona A, Piazza C, Pecoraro F, Barozzi P and Luppi M (2026). Front. Immunol. 17:1698179. doi: 10.3389/fimmu.2026.1698179

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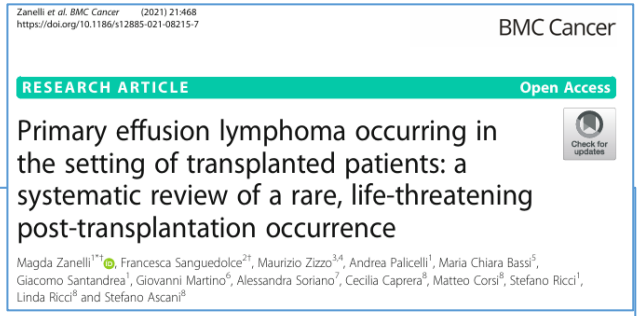
HHV-8 related diseases

Primary Effusion Lymphoma
AND
Multicentric Castleman Disease

Primary Effusion Lymphoma



CLINICAL PRESENTATION

- PEL is an uncommon, aggressive subtype of non–Hodgkin lymphoma
- malignant effusions in body cavities without solid masses
- the diagnosis is typically based on the identification of HHV-8/KSHV positive malignant lymphoid cells expressing CD45 within body-cavity effusions

EPIDEMIOLOGY

- Only a limited number of PEL cases have been documented in the SOT setting
- Recent SR conducted by Zanelli et al. describing **13 PT-PEL cases** (six in KTx, three in HTx, two in OLTx, one in bowel transplant recipient, and one in a HSCT recipient)
- All patients were male, with a mean age at disease onset of 54.9 years, while the average onset was 8 years PT; KS was concurrently present in 4 out of the 13 cases; all the reported cases died

Zanelli M, Sanguedolce F, Zizzo M, et al (2021) BMC Cancer. https://doi.org/10.1186/S12885-021-08215-7

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Multicentric Castleman Disease

CLINICAL PRESENTATION

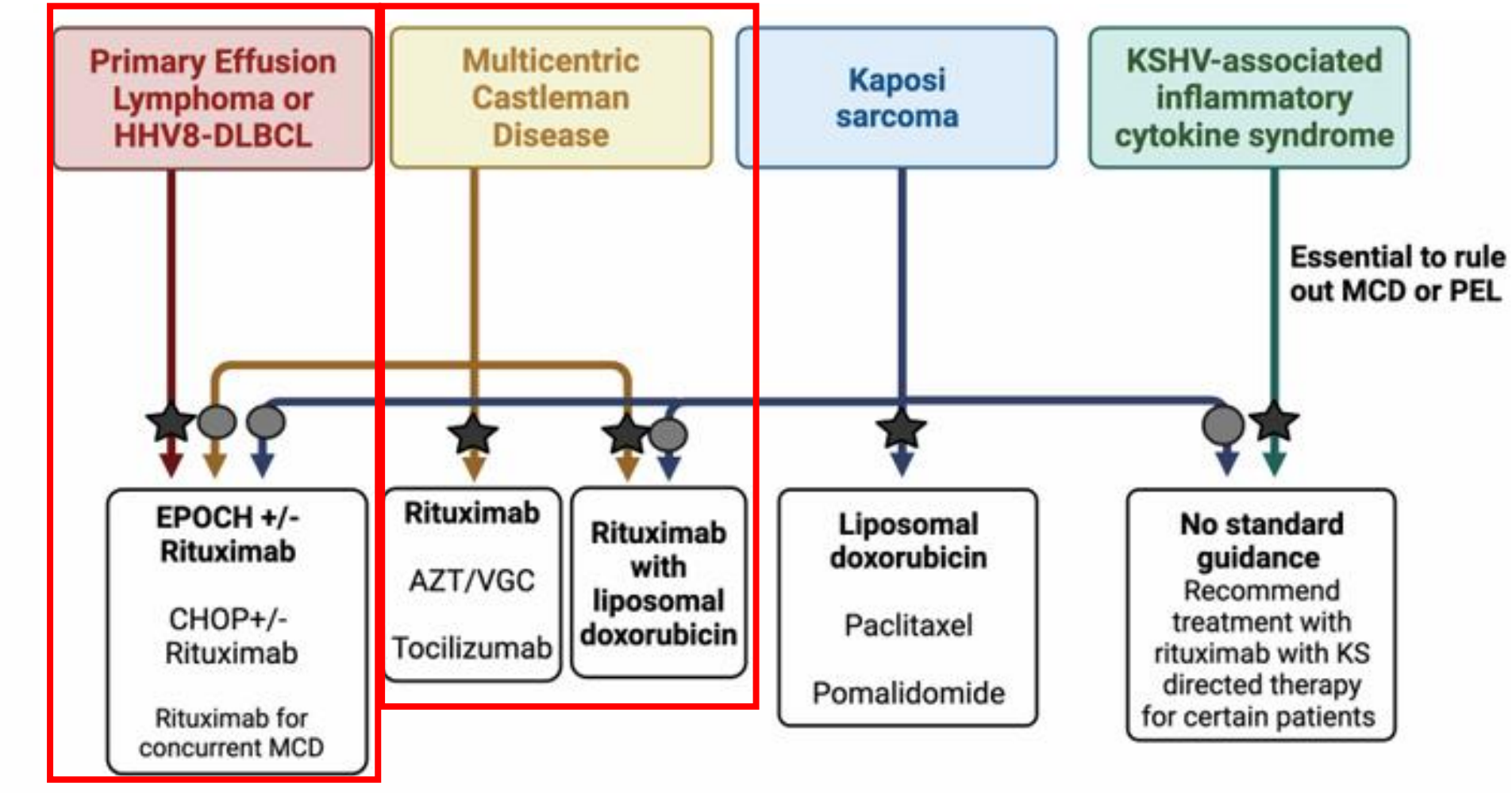
- **polyclonal B cell lymphoproliferative disorder** characterized by widespread lymphadenopathy and inflammatory features, with episodic flares of systemic symptoms and aberrant host immune responses with elevated inflammatory markers and high HHV-8/KSHV DNAemia that can lead to organ damage and, eventually, death
- Clinical manifestations: fever, fatigue, night sweats, weight loss, peripheral edema, cytopenia, skin rashes, and involvement of respiratory and gastrointestinal systems, organomegaly, and lymphadenopathy

DIAGNOSIS

- Definitive diagnosis of MCD requires histopathological confirmation, via excisional lymph node biopsy
- HHV-8/KSHV infected **IgMλ restricted polyclonal plasmablasts** within the mantle zone of B-cell follicles, with immunohistochemical staining positive for LANA

Mularoni A, Cona A, Piazza C, Pecoraro F, Barozzi P and Luppi M (2026). Front. Immunol. 17:1698179. doi: 10.3389/fimmu.2026.1698179

PEL and MCD treatment



Patel R, Lurain K, Yarchoan R, Ramaswami R (2023). Expert Rev Anti Infect Ther. https://doi.org/10.1080/14787210.2023.2247161

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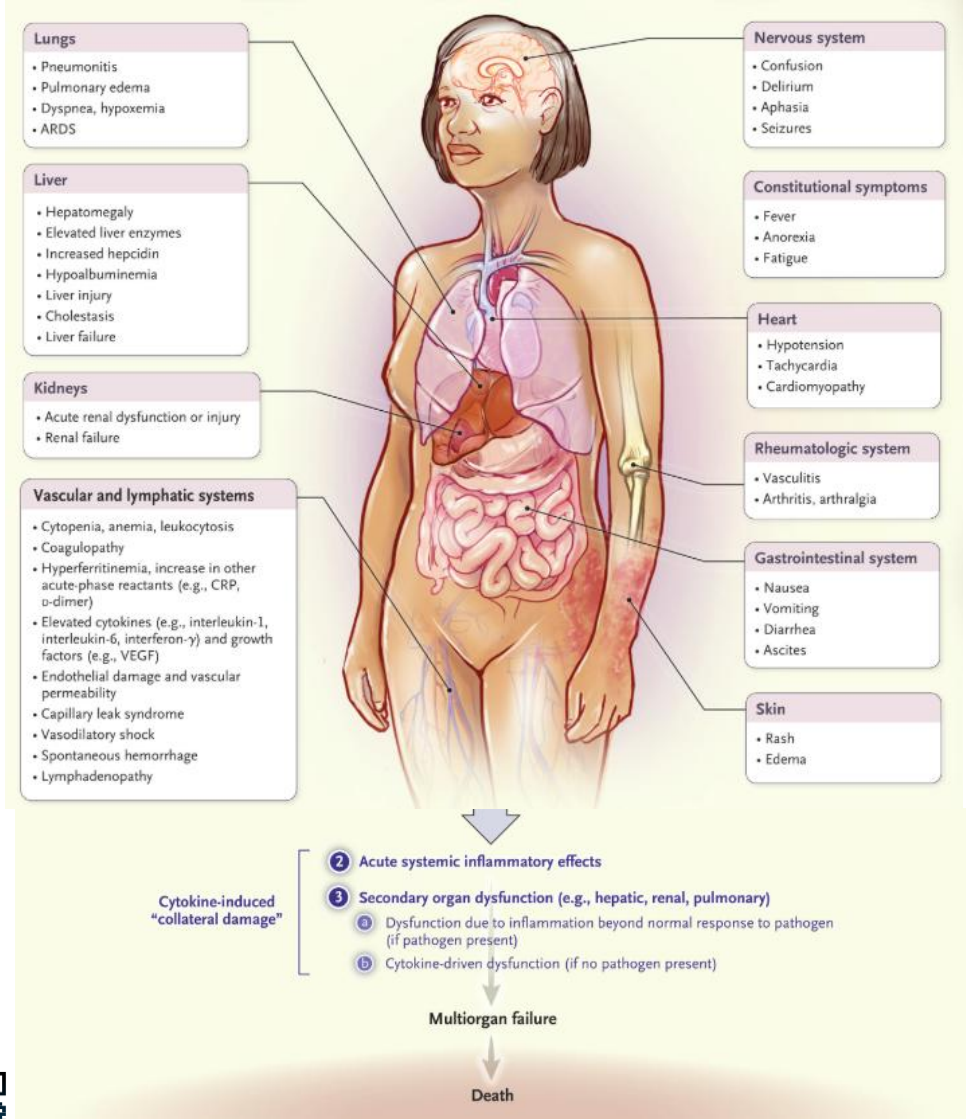
HHV-8 related diseases

Kaposi Sarcoma associated Inflammatory Cytokine Syndrome (KICS)

KICS in Solid Organ Transplant recipients



KICS:

"a non-neoplastic HHV8-related clinical manifestation characterized by fever, hyper inflammatory host responses, bone marrow failure and organ damage but without the characteristic histopathology of MCD"

Viral Sepsis

life-threatening organ dysfunction due to a dysregulated host response to viral infection

Cytokine Storm

several disorders of immune dysregulation, characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction

Polizzotto MN et al. 2016. PMID: 26658701; Fajgenbaum DC., N Engl J Med. 2020

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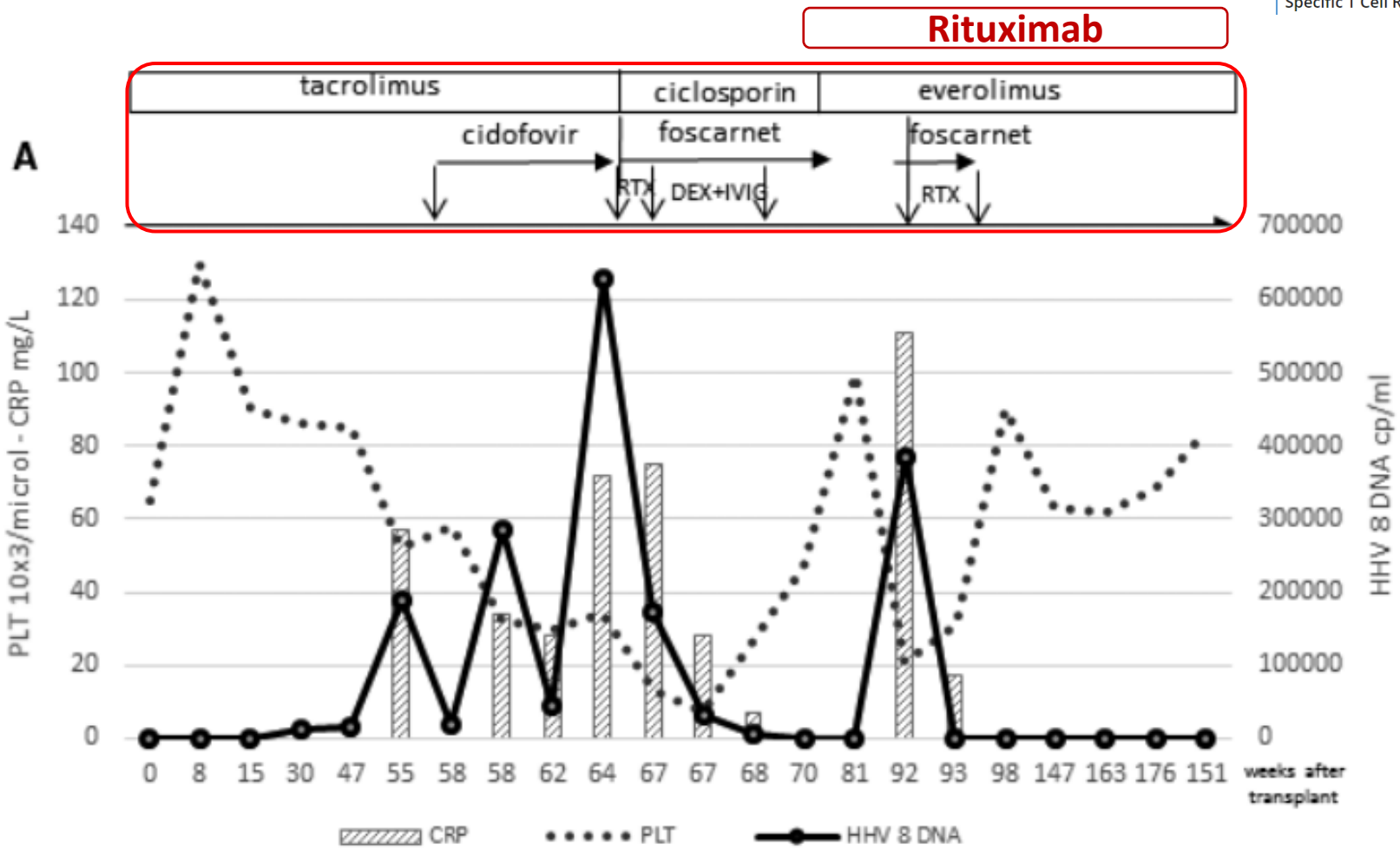
KICS in Solid Organ Transplant recipients

American Journal of Transplantation | AST | ASTS

Case Report | Full Access

Successful Treatment of Kaposi Sarcoma–Associated Herpesvirus Inflammatory Cytokine Syndrome After Kidney–Liver Transplant: Correlations With the Human Herpesvirus 8 miRNome and Specific T Cell Response

..., P. Barozzi, M. Miele, G. Cardinale, G. Vizzini, R. Volpes, P. Grossi, M. Luppi, P. G. Conaldi



Mularoni A et al. Am J Transplant. 2017

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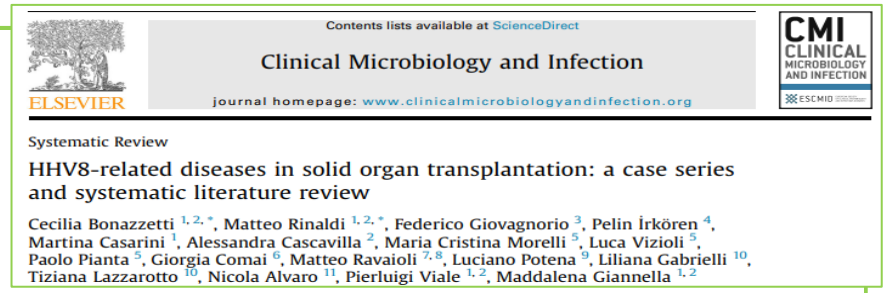
KICS in Solid Organ Transplant recipients

91 studies, 337 cases of HHV-8 diseases among 19,283 SOT



- rates of HHV-8 related disease: **18% in D+/R-**, 8% in R+, 0.1% in D-/R-

- Reported diseases:
  - **cutaneous and visceral KS** (246/296, **83%**)
  - **KSHV-associated DLBCL** (16/296, **5.4%**), **MCD** (10/296, **3.4%**) and **PEL** (5/296, **1.7%**)
  - **KICS (14/296, 4.7%) → 10/14 (64%) treated with Rituximab/Tociluzumab**

- **Overall mortality in KICS 6/14 (43%):**
  - **mortality in treated with Rituximab/tocilizumab: 1/9 (11%)**
  - **mortality in untreated: 4/5 (80%)**

Bonazzetti C, Giannella M et al. Clin Microbiol Infect. 2025 doi: 10.1016/j.cmi.2025.07.019

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KICS - treatment

How I treat HHV8/KSHV-related diseases in posttransplant patients

*Giovanni Riva,[1] *Mario Luppi,[1] *Patrizia Barozzi,[1] *Fabio Forghieri,[1] and *Leonardo Potenza[1]

[1]Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto, Università di Modena e Reggio Emilia, UO-C Ematologia, AOU Policlinico, Modena, Italy

- IS reduction
- mTOR inhibitors
- Antivirals
- Rituximab

- mTORs have an **anti-proliferative effect**
- Switch from CNI to mTORs has also been associated with simultaneous **HHV-8-specific cytotoxic T cell recovery**

blood

CORRESPONDENCE | APRIL 1, 2006

Severe human herpesvirus-8 primary infection in a renal transplant patient successfully treated with anti-CD20 monoclonal antibody

Olivier Thaunat, Marie-France Mamzer-Bruneel, Felix Agbalika, Françoise Valensi, Marcia Venditto, Céleste Lebbe, Camille Frances, Romain Kania, Lucienne Chatenoud, Corinne Antoine, Srinivas Kaveri, Henri Kreis, Emmanuel Morelon

American Journal of Transplantation

Volume 17, Issue 11, November 2017, Pages 2963-2969

Case Report

Successful Treatment of Kaposi Sarcoma–Associated Herpesvirus Inflammatory Cytokine Syndrome After Kidney–Liver Transplant: Correlations With the Human Herpesvirus 8 miRNome and Specific T Cell Response

A. Mularoni[1†], A. Gallo[2†], G. Riva[3,4†], P. Barozzi[3†], M. Miele[9], G. Cardinale[5], G. Vizzini[6], R. Volpes[6], P. Grossi[1,7], D. Di Carlo[2], A. Luca[8], T. Trenti[4], M. Luppi[3†], P.G. Conaldi[2,9†]

Thaunat O. et al. Blood 2006

Riva G, Luppi M, Barozzi et al. Blood. 2012 Nov 15;120(20):4150-9. doi: 10.1182/blood-2012-04-421412

Mularoni A. et al. AJT 2017

UPMC | IRCCS ISMETT Palermo

KICS - treatment

REVIEW ARTICLE OPEN ACCESS

HHV-8/KSHV in Solid Organ Transplantation: Current Gaps of Knowledge and Future Directions

Alessandra Mularoni[1,2] | Andrea Cona[1,2] | Malgorzata Mikulska[3,4] | Francesca Pecoraro[1] | Carlotta Piazza[1] | Elda De Vita[1,2] | Giada Pietrosi[1,2] | Matteo Bulati[1] | Tiziana Lazzarotto[5,6] | Mario Luppi[7]

Treatment		Number	Alive	Dead	Survival
KICS alone (n=18) + KICS/HLH (n=2)					
Rituximab plus (n=9)	steroids	1	1		**100%**
	mTORi + cytokine adsorbing hemofilter	1	1		
	mTORi + antivirals	3	3		
	mTORi + antivirals + steroids	4	4		
Tocilizumab plus (n=2)	mTORi	2	2		**100%**
No rituximab (n=9)	no treatment	2		2	**0%**
	antivirals	5		5	
	mTORi + antivirals	2		2	
KICS + other KADs (n=7)					
mTORi plus (n=3)	tocilizumab + antivirals + doxorubicin (KS)	1	1		**67%**
	Lyposomal doxorubicin (KS)	1	1		
	tocilizumab + lyposomal doxorubicin + rituximab (MCD)	1		1	
No mTORi (n=4)	Lyposomal doxorubicin + tocilizumab (KS)	2	1	1	**25%**
	antivirals + lyposomal doxorubicin + rituximab (KS)	1		1	
	antivirals + rituximab (KS+lymphoproliferative disorder)	1		1	

Abbreviation: HLH, hemophagocytic lymphohistiocytosis; KADs, HHV-8/KSHV-associated diseases; KICS, Kaposi's Sarcoma-associated Herpesvirus Inflammatory Cytokine Syndrome; KS, Kaposi Sarcoma; MCD, Multicentric Castleman disease; mTORi, mammalian target of rapamycin inhibitors.

FIGURE 2 | Treatment of all reported cases of KICS and survival rate.

Mularoni A, Cona A, Mikulska M et al. Transpl Infect Dis. 2026 Jan 30:e70179. doi: 10.1111/tid.70179

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The ISMETT experience

KICS in SOT – ISMETT Protocol

1. • Since 2011, **HHV8 serology** (IFA lytic and latent) on all Donors and Recipients
2. • In R+ and D+/R- SOTr, plasmatic **HHV8 DNA** periodical monitoring and strict clinical follow-up
3. • Since 2017, protocol for early treatment of patient with detectable viremia with early **switch to mTOR inhibitors** (with or without antivirals)
4. • Patients with KICS receive **Anti-CD20 Mab** (Rituximab)

Mularoni A, Cona A, Luppi M et al. Am J Transplant. 2025 PMID: 39551265

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KICS in SOT – ISMETT Protocol

ORIGINAL ARTICLE · Articles in Press, November 15, 2024 · *Open Access*

Serologic screening and molecular surveillance of Kaposi sarcoma herpesvirus/human herpesvirus-8 infections for early recognition and effective treatment of Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome in solid organ transplant recipients

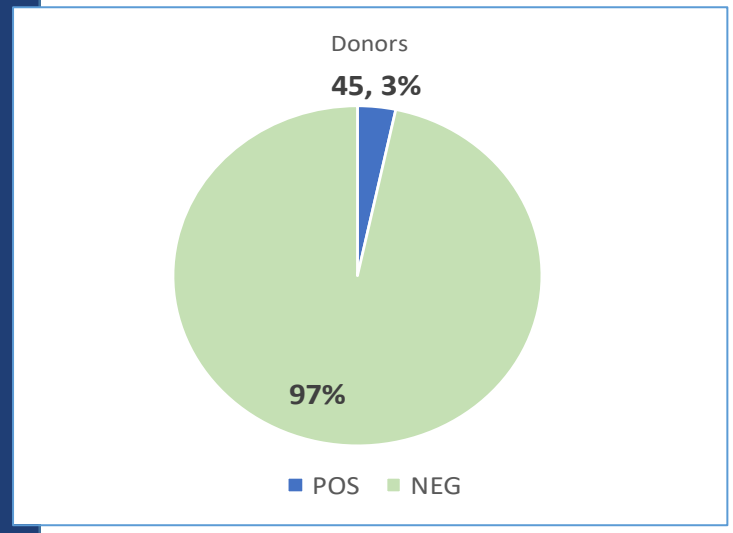
Alessandra Mularoni [1] · Andrea Cona [1] · Matteo Bulati [2] · ... · Pier Giulio Conaldi [2] · Paolo Antonio Grossi [20] · Mario Luppi [9]

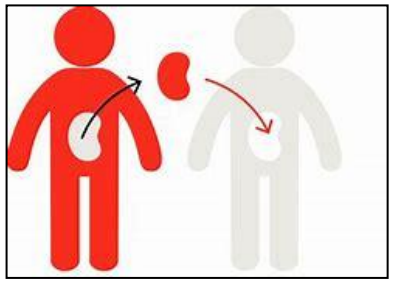
Rate of HHV-8 seroprevalence:

3.3% donors

8.4% recipients

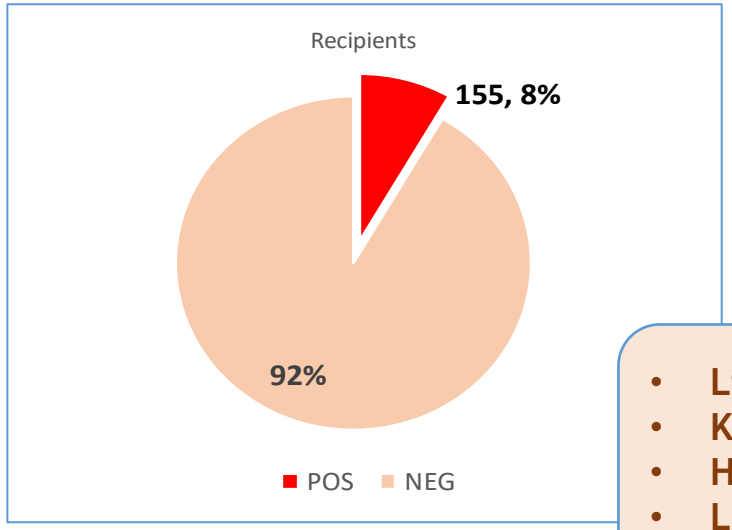
1349 Donors





49 Mismatch Recipients D+/R-

1856 Recipients



- Liver 10% (96/944)
- Kidney 6% (39/616)
- Heart 6% (10/151)
- Lung 7% (10/145)

Mularoni A, Cona A, Luppi M et al. Am J Transplant. 2025 PMID: 39551265

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Rate of HHV-8 transmission and disease

First DNAemia: median 71 days
Time to KICS: 85 days after SOT

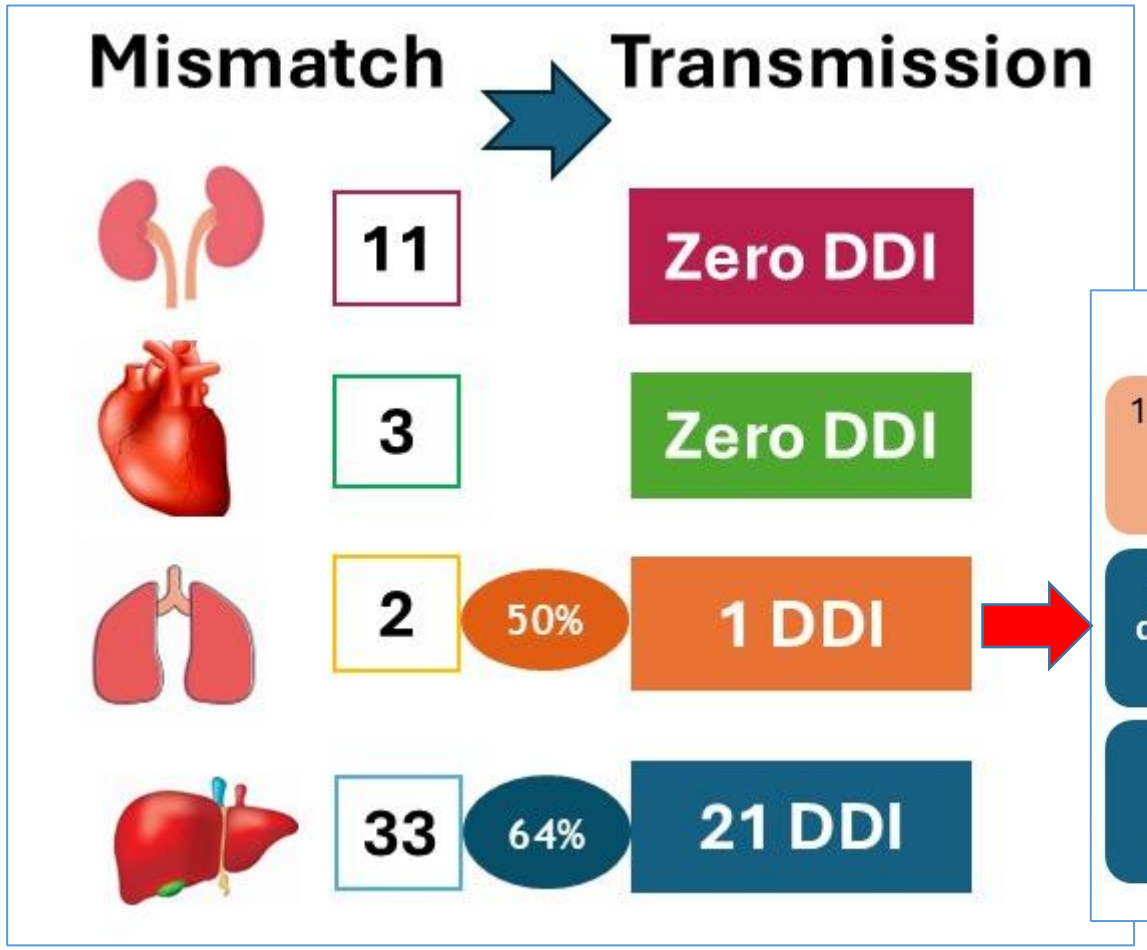
49 Mismatch Recipients HHV-8 Ab D+/R-

HHV8 DDI monitoring by
- HHV8 DNA
- HHV-8 serology

45%

22 D+/R- Developed HHV-8 DDI

Donor Derived Infection
- Detectable HHV-8 DNA
- HHV-8 Ab Seroconversion



Mularoni A, Cona A, Luppi M et al. Am J Transplant. 2025 PMID: 39551265

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Clinical outcomes and management of KICS

PRE- Intervention
2011-2016:
Treatment of advanced symptomatic disease with **Antivirals** (Foscarnet/Cidofovir)

POST-Intervention
2017-2023:
- **Detectable HHV8-DNA** → early **switch to m-TOR inhibitor** and strict clinical surveillance
- **KICS** -> **rituximab** + antivirals

7 OLTx with HHV8-DDI	11 OLTx with HHV8-DDI	3 OLTx with primary HHV-8 (D-/R-)	1 Lung Tx with DDI
4 KICS	**3 KICS**	**2 KICS** **1 KICS+KS**	**1 KS+KICS**
Mortality 75% (3 of 4 patients died)	**Mortality 14%** (1 of 7 patients died)		

Mularoni A, Cona A, Luppi M et al. Am J Transplant. 2025 PMID: 39551265

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cytokine expression patterns during KICS

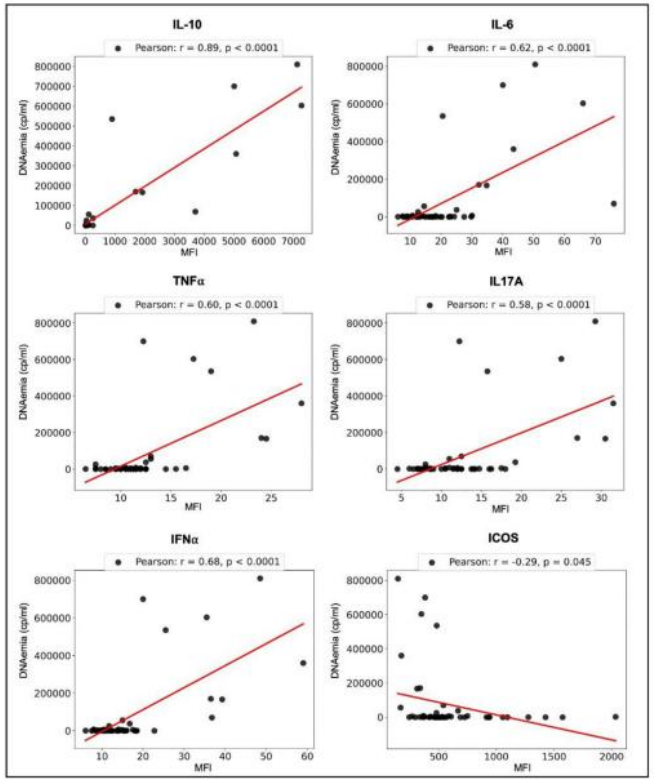

Figure 4. Correlation analysis of DNAemia vs cytokine levels in 16 cases (14 patients), including 6 asymptomatic/mildly symptomatic with HHV-8 DNAemia patients, 6 with KICS, and 4 with KS. Pearson's rank correlation (two-tailed) was obtained using cumulative parameters obtained for all time points analyzed (T0, T1, and T2). The significance (*P* and *r* values) is indicated in each panel. HHV-8, human herpesvirus-8; KICS, Kaposi sarcoma herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; ICOS, inducible T cell costimulator; IL, interleukin; IFNα, interferon alfa; MFI, mean fluorescence intensity; TNFα, tumor necrosis factor alpha.

significant positive correlation of viremia with IL-10, IL-6, TNF-α, IL-17A, and IFN-α

A. Mularoni et al. American Journal of Transplantation xxx (xxxx) xxx

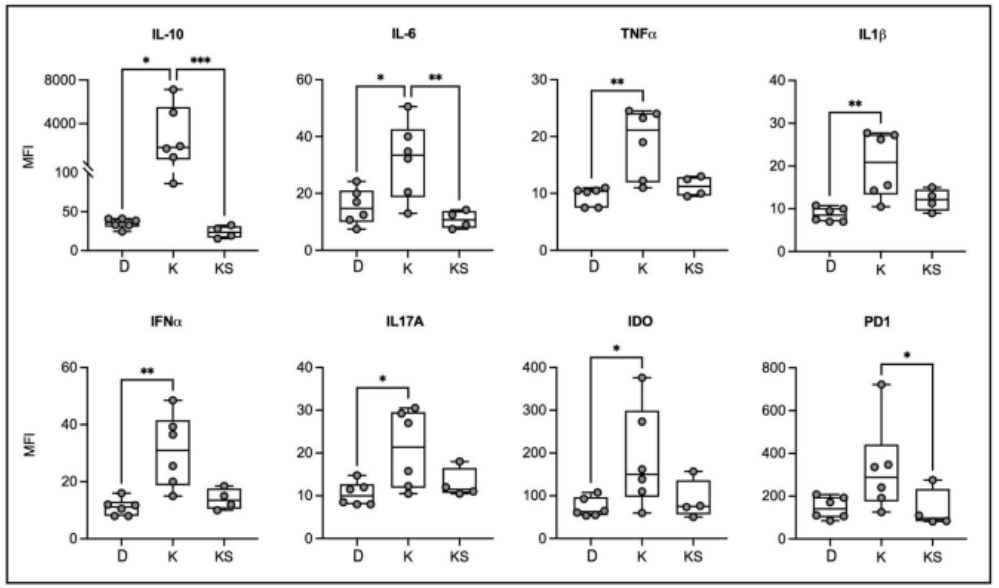

Figure 5. Plasma levels of IL-10, IL-6, TNFα, IL1β, IFNα, IL17A, IDO, and PD-1 during higher DNAemia (T1) in patients with DNAemia (D), Kaposi sarcoma herpesvirus inflammatory cytokine syndrome(K), and Kaposi sarcoma (KS). *$P \leq .05$, ** $\leq .01$, ***$P \leq .001$. IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IFNα, interferon alfa; MFI, mean fluorescence intensity; PD-1, programmed death-1; TNFα, tumor necrosis factor alpha.

- **increase of IL-10 and IL-6 in patients with KICS compared to both patients with DNAemia and KS**
- **higher levels of TNFα, IL-1β, IFNα, IL-17A, and IDO in KICS than in DNAemia patients**

Mularoni A, Cona A, Luppi M et al. Am J Transplant. 2025 PMID: 39551265

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Global data and Risk Mitigation Strategies

Global data and Risk Mitigation

Several cases of fatal primary HHV-8 infection in SOT recipients in the UK

- 2015-2021: clusters involving 27 recipients
- **transmission rate 52%** (14 of 27)
- **mortality 57%** (8 of 14)

GOV.UK

Independent report

SaBTO virology subcommittee recommendations on KSHV: executive summary

Updated 13 March 2025

Expert committee review and economic analysis for donor screening implementation

Main recommendation

We recommend the introduction of universal serological screening of deceased donors for KSHV infection. To begin with, such testing should be centralised. The programme should be monitored and reviewed to inform necessary changes.

https://www.gov.uk/government/publications/sabto-virology-subcommittee-recommendations-on-kshv-infection/sabto-virology-subcommittee-recommendtaions-on-kshv-executive-summary

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Global data and Risk Mitigation

Abstract# OA31.6
Lessons from a Newly Implemented Organ Donor Screening for Human Herpes Virus Type 8 in the UK
I. Ushiro-Lumb[1], A. Dalla Pria[2], C. Geoghegan[1], M. Bower[2], R. Baker[1], J. Neuberger[3], D. Manas[1], *[1]NHS Blood and Transplant, [2]Chelsea and Westminster Hospital, [3]University Hospitals Birmingham*

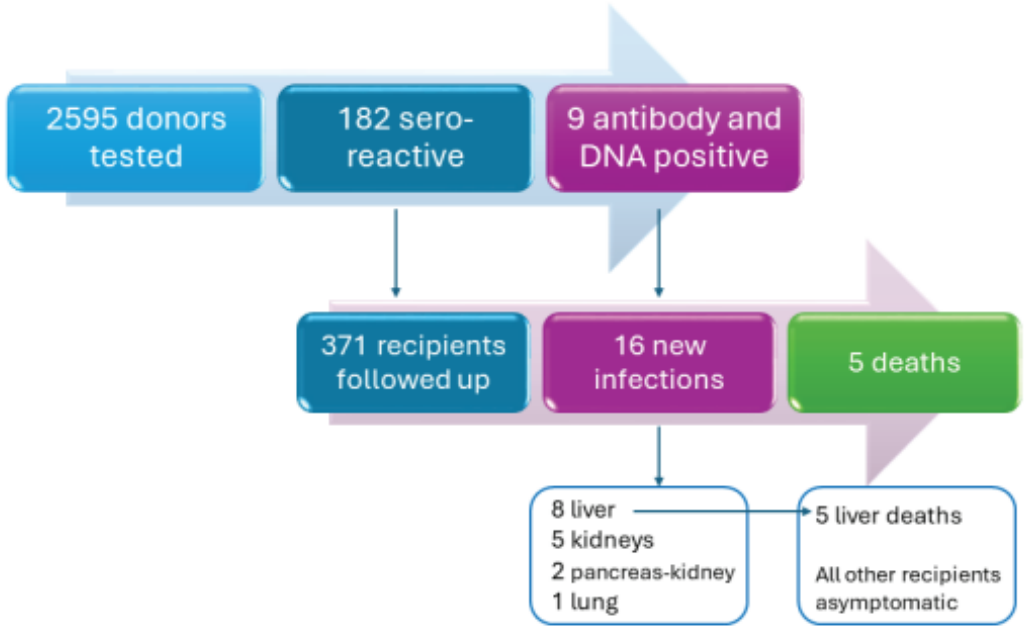
WTC 2025
World Transplant Congress
San Francisco, USA | August 2-6

GOV.UK
Independent report
SaBTO virology subcommittee recommendations on KSHV: executive summary
Updated 13 March 2025

- Universal, post-Tx testing with lytic and latent IFA
- if positive, donor plasma is tested for viral DNA
- recipient follow-up for early identification of infection and disease manifestation, and any necessary intervention

- **Donors seroprevalence 7%**
- **Transmission rate 4.3%** (16/371)
- Mortality **37.5%** (6/16)
- Among 8 liver recipients, 5 died within six months from Tx of HHV-8-related causes

Deceased organ donor screening for herpes virus type 8 and recipient outcome – May 2023 to December 2024, UK



Ushiro-Lumb I. et al. AJT 2025 Volume 25, Issue 8 Supplement 1

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Global data and Risk Mitigation

2021-2025

U.S. Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Weekly / Vol. 75 / No. 8 March 5, 2026

Kaposi Sarcoma–Associated Herpesvirus Infection and Complications Among Solid Organ Transplant Recipients — United States, January 2021–September 2025

Ian Kracalik, PhD[1]; Pallavi Annambhotla, DrPH[1]; David W. McCormick, MD[1]; Andrew I. Geller, MD[1]; Kelsey McDavid, MPH[1]; Isabel Griffin, PhD[1]; Raymond Lynch, MD[2]; Brianna Doby, MPH[2]; Yoichiro Natori, MD[3]; Sofya Tokman, MD[4]; Christine M. Durand, MD[5]; Camille N. Kotton, MD[6]; Emily Blumberg, MD[7]; Ricardo M. La Hoz, MD[8]; Lauri A. Hicks, DO[1]; Stephanie M. Pouch, MD[9]; Sridhar V. Basavaraju, MD[1]; Donor-Derived KSHV Investigation Group

- transplanted organs from **46 deceased donors** were suspected of having transmitted HHV-8 to **153 recipients**
- Post-transplantation HHV-8 infection has been identified in **74 (48%) of cases** → lung (86%), liver (57%), heart (30%), kidney (22%)

74 transplant recipients with posttransplant KSHV infection:
- 24 lung
- 20 liver
- 16 kidney
- 7 heart
- 3 single kidney + pancreas
- 2 heart + single kidney
- 1 heart + double lung
- 1 kidney + liver

50 recipients with a KSHV related-complication:
- 45 KS
  - 8 multicentric Castleman disease and KS
  - 6 KICS and KS
  - 1 primary effusion lymphoma and KS
  - 1 posttransplant lymphoproliferative disorder and KS
- 3 posttransplant lymphoproliferative disorder
- 1 primary effusion lymphoma
- 1 KICS

HHV-8 related diseases observed in 50 recipients:

- KS in 45 cases
- MCD in 8 cases
- KICS in 7 cases

Mortality:

- 25 (16%) recipients have died

Kracalik I, Annambhotla P, McCormick DW et al. MMWR Morb Mortal Wkly Rep. 2026 Mar 5;75(8):99-105. PMID: 41785153

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Global data and Risk Mitigation

U.S. Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
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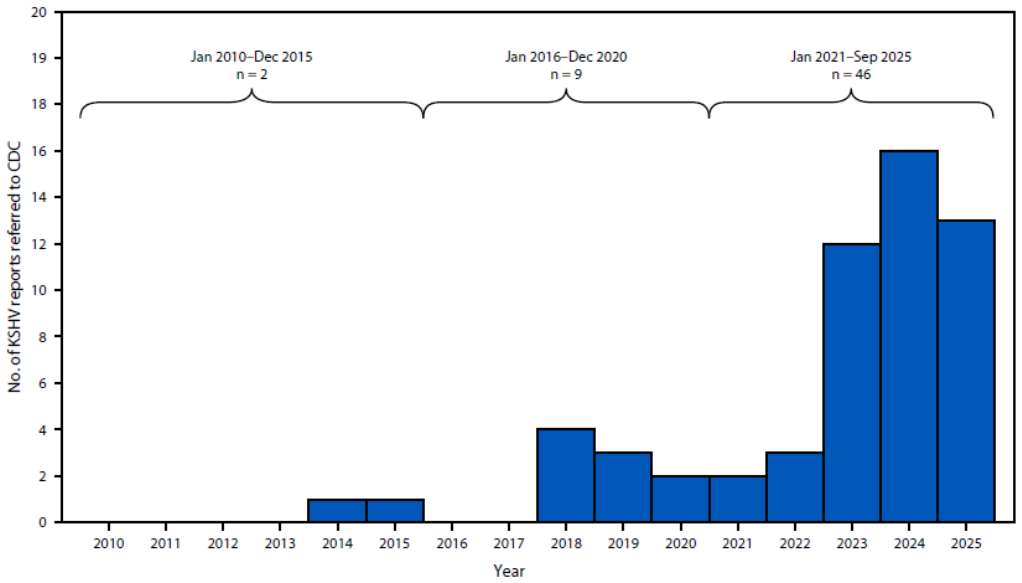
2021-2025

TABLE. Characteristics of organ transplant recipients and deceased solid organ donors whose organs are suspected of having transmitted Kaposi sarcoma–associated herpesvirus — United States, January 2021–September 2025

Characteristic	No. (column %) Donor n = 46	Recipient n = 153
Median age, yrs (IQR)	38.5 (31–51)	58.5 (49–65)
Male sex	31 (67)	76 (50)
Men who have sex with men	15 (33)	2 (1)
HIV-negative	44 (96)	150 (98)
History of nonmedical inhalation or injection drug use	31 (67)	NA
History of incarceration	8 (17)	NA
Testing completed after organ procurement	**29 (64)**	**87 (57)***
Negative molecular or serologic KSHV test result	4 (14)†	13 (15)†
Positive molecular or serologic KSHV test result	25 (86)†	74 (85)†,§
Positive recipient KSHV test result by organ received, n/N (%)		
Lung	NA	24/28 (86)
Liver	NA	20/35 (57)
Heart	NA	7/23 (30)
Kidney	NA	16/72 (22)
Recipient death	**NA**	**25/153 (16)**
Postinfection KSHV-related complication, n/N (%)		
Kaposi sarcoma	NA	45/153 (29)
Multicentric Castleman disease and Kaposi sarcoma¶	NA	8/45 (18)
KICS and Kaposi sarcoma¶	NA	6/45 (13)
Posttransplant lymphoproliferative disorder and Kaposi sarcoma¶	NA	2/45 (4)
Posttransplant lymphoproliferative disorder	NA	4/153 (3)
KICS	NA	1/153 (1)

FIGURE 2. Number of reports* of suspected organ donor–derived Kaposi sarcoma–associated herpesvirus infections in transplant recipients (N = 57) — United States, January 2010–September 2025†



Reasons:

1. Opioid crises?
2. Increased awareness, diagnosis and reporting?

Kracalik I, Annambhotla P, McCormick DW et al. MMWR Morb Mortal Wkly Rep. 2026 Mar 5;75(8):99-105. PMID: 41785153

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To screen or not to screen

Future directions, To screen or not to screen

Received: 5 March 2019 | Accepted: 15 March 2019
DOI: 10.1111/ctr.13548

Clinical TRANSPLANTATION WILEY

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

Screening of donor and candidate prior to solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Maricar Malinis[1] | Helen W. Boucher[2] | on behalf of the AST Infectious Diseases Community of Practice

Test	Candidate	Deceased donor	Living donor
Viral			
HIV			
Human immunodeficiency virus (HIV) antibody/antigen (fourth Generation HIV screening test)	x	x	x
HIV nucleic acid amplification testing (NAT)		x[b]	x[b]
Cytomegalovirus (CMV) IgG antibody	x	x	x
Hepatitis B virus (HBV)			
HBV surface antigen (HBsAg)	x	x	x
HBV core antibody (HBcAb-IgM and IgG, or total core antibody)	x	x	x
HBV surface antibody (HBsAb)	x		
HBV NAT		x[b]	x[b]
Hepatitis C virus (HCV)			
HCV antibody	x	x	x
HCV NAT	x[c]	x	x
Epstein-Barr virus (EBV) antibody (EBV VCA IgG, IgM)	x	x	x
West Nile virus serology or NAT (seasonal)			x

Goals of screening before transplant:

1. Identify conditions which may disqualify either donor or recipient
2. Identify and treat active infection, pre-transplant
3. **Recognize and define the risk of infection**
4. **Develop and implement risk mitigation strategies**

Malinis, M., & Boucher, H. W. et al *Clinical Transplantation, 33*(9), e13548. https://doi.org/10.1111/ctr.13548

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Future directions, To screen or not to screen

Utility of screening:

1.Identify recipients at risk (D+/R- and R+)

2.Early intervention in patients with detectable HHV-8 viremia

3.Early intervention in patients with disease

Interventions:

Risk mitigation strategies:

1.In D+/R- monitoring of clinical condition and viremia

2.In R+, teaching for KS lesions detection

3. IS tapering, switch to mTOR inhibitors

4.Liposomal Doxorubicin for KS, Rituximab therapy for KICS

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Future directions, To screen or not to screen

Limits of HHV-8 screening:

1. **Seroprevalence** is low in most countries

2. **cost-effectiveness** of serological testing, given the relatively low incidence of disease

3. **HHV-8 antibody testing is complex**

4. **Screening of Donors is not feasible before transplantation**

Solutions:

1. **Characteristics of organ donors evolve**

2. **Timely recognition** and treatment → better outcomes

3. assay performance is sufficiently good to identify SOT recipients at increased risk

4. **donor testing can be performed post-transplant** (First DNAemia 71 days; KICS 85 days after SOT)

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Conclusions

- A high level of suspicion for KICS in SOT should be maintained
- While current guidelines do not recommend universal pre-transplant screening of donors and recipients, growing data demonstrate that **awareness, risk stratification, prompt recognition and intervention are beneficial in ensuring better outcomes of recipients with HHV-8 infection and disease**
- **Lack of standardized serology** is the major limiting factor to support this recommendation

Further collaborative studies are needed to better characterize the spectrum of HHV8-related non-neoplastic diseases and to define the optimal therapeutic approach to these syndromes

Alessandra Mularoni

Mario Luppi

Thank you!

acona@ismett.edu

ISMETT *Istituto di Ricovero e Cura a Carattere Scientifico*

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