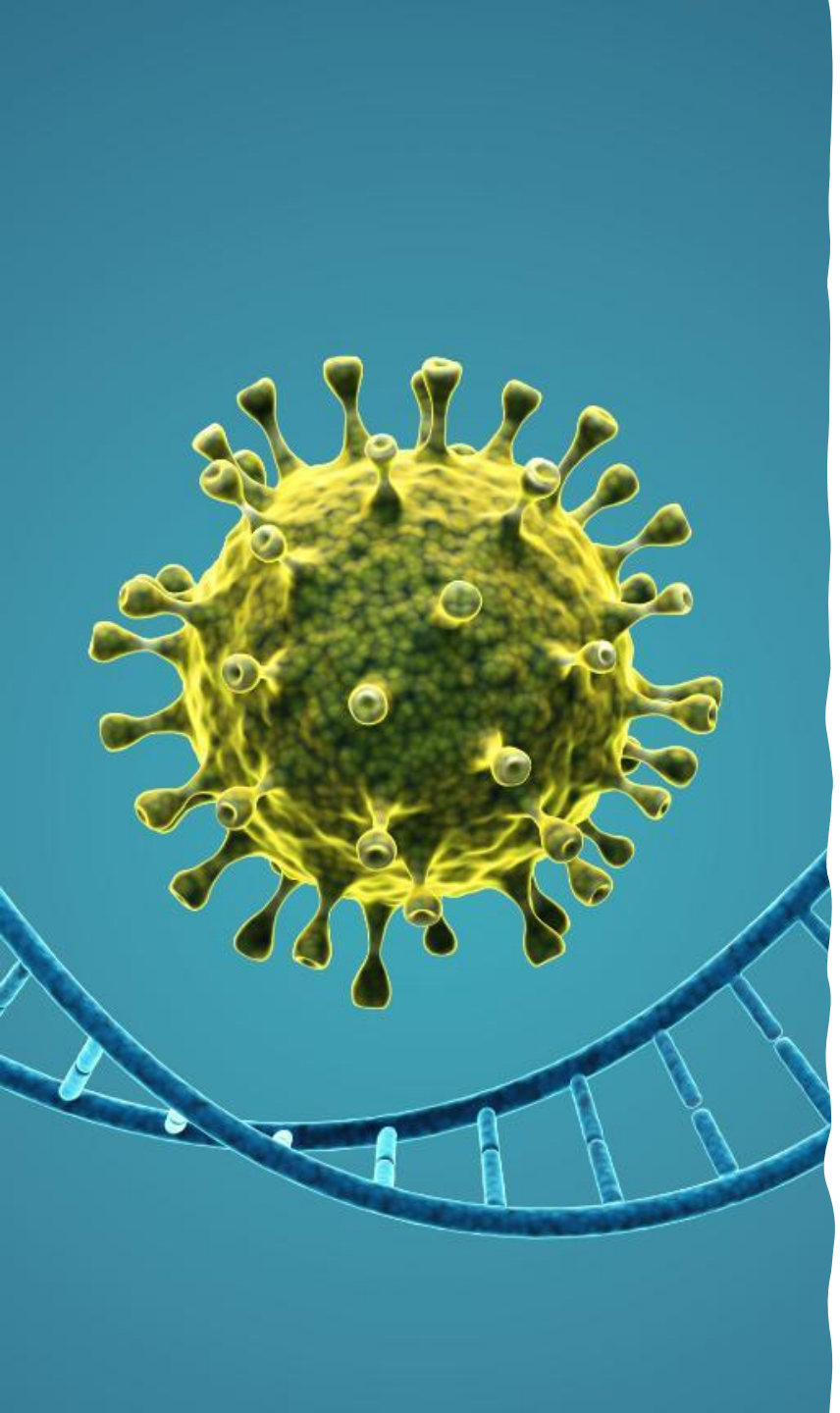
HHV8

Professor D M Manas

Medical Director OTDT (NHSBT)



Overview of HHV-8

HHV-8 Virus Characteristics

HHV-8 is a DNA virus from the herpesvirus family known for causing Kaposi's Sarcoma.

Seroprevalence and Distribution

HHV-8 has low prevalence in non-endemic regions, with 3 - 5% seroprevalence in the UK.

Latent Infection and Risks

HHV-8 establishes lifelong latency

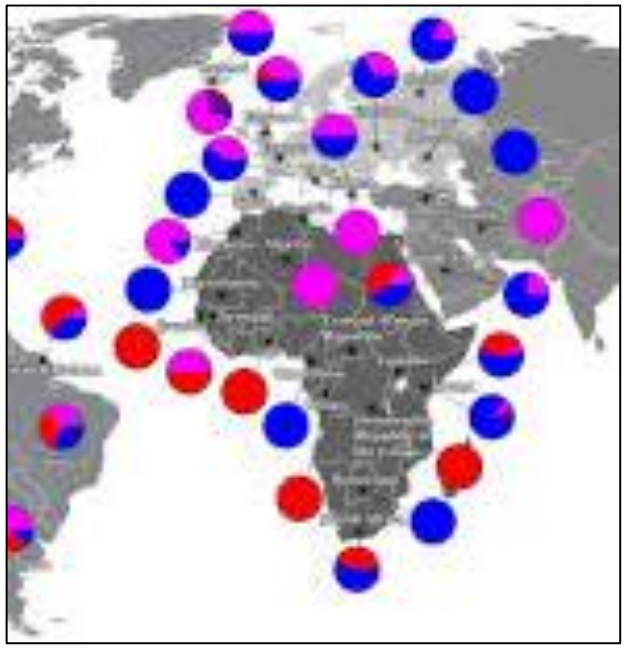
Poses risk of reactivation for transplant patients.

Clinical Importance for Transplants

Critical for transplant clinicians to reduce viral reactivation risks and improve outcomes.

Endemic Areas:

- **Areas of High prevalence**
- **Sub-Saharan Africa:** Rates of HHV-8 infection are very high in many parts of this region.
- **Mediterranean Basin and Middle East:**
- Italy (Sicily), Greece, Israel, and Saudi Arabia have **intermediate to high prevalence rates.**
- **Parts of South America:** Specifically, Amerindian populations have shown higher rates of the virus.
- **Northwestern China:** endemic in this area.



- **Areas of Intermediate Prevalence:**
- **Parts of the Middle East:** Some areas have shown higher seroprevalence than non-endemic regions.

- **Low Prevalence/Non-Endemic Areas:**
- **USA and Western Europe:** The virus is less common in the general population, with low reported infection rates.
- **Northern Europe, North America, and most of Asia:** The virus is generally less prevalent here.

Associated Diseases

Kaposi's Sarcoma

Kaposi's Sarcoma is a vascular tumor affecting skin, mucous membranes, and organs, common in immunosuppressed patients.

Multicentric Castleman's Disease

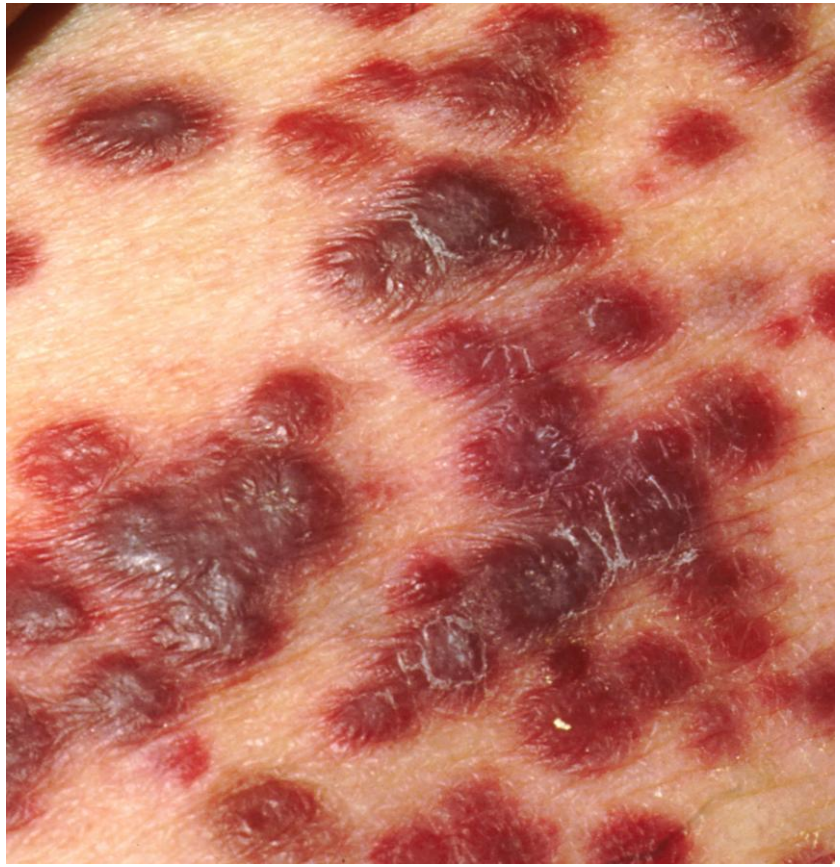
MCD is a lymphoproliferative disorder linked to HHV-8, causing enlarged lymph nodes and systemic symptoms.

Primary Effusion Lymphoma

PEL is a rare B-cell lymphoma presenting in body cavities, associated with HHV-8 infection.

Inflammatory Syndromes

HHV-8 causes KICS and HLH, severe inflammatory conditions with cytokine dysregulation and hyperinflammation.



HHV-8 Associated Diseases In Transplantation

@TheTxIDJournal @katesolivia

Kates *et al.* ***Transplant Infectious Diseases.*** 2024.

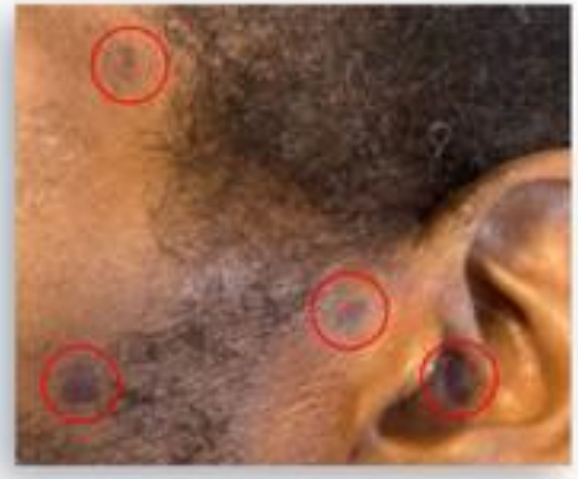
Spindle Cell Neoplasm

Kaposi Sarcoma

Cutaneous
- Extremities, ears, nose, palate
- Koebner phenomenon (incisions)

Lymph Node

Visceral
- GI tract
- Lung
- Allograft



Lymphoproliferative Disorders

with Systemic inflammation
- *Fever*
- *Lymphadenopathy*
- *Hepatosplenomegaly*
- *Edema & effusions*
- *Cytopenias*
- *Elevated CRP/ESR*
- *HHV-8 viremia*
- *Elevated IL-6*

Rituximab to treat severe inflammation (even in CD20- PEL)

Primary Effusion Lymphoma

Body cavity effusions
- Pleural
- Peritoneal
- Pericardial

Extracavitary masses

Multicentric Castleman Disease
- Lymphadenopathy
- Polyclonal hypergammaglobulinemia

KSHV Inflammatory Cytokine Syndrome
- Exclusion of MCD or PEL

Transmission

Reactivation of pre-transplant infection

More likely:
- Kidney recipients
- Kaposi sarcoma
- Late presentation
- Non-severe disease

Donor-derived HHV-8

More likely:
- Liver or lung recipients
- Early presentation
- Severe disease
- Multisystem disease

New post-transplant infection

Donor-derived HHV-8 positive malignant cells

Research Questions:
- Donor/recipient seroprevalence
- Disease incidence & outcomes
- Optimal screening & monitoring

Transmission Routes

Donor-Derived Transmission

Transmission through infected donor organs is a significant concern in organ transplantation.

Risk Factors

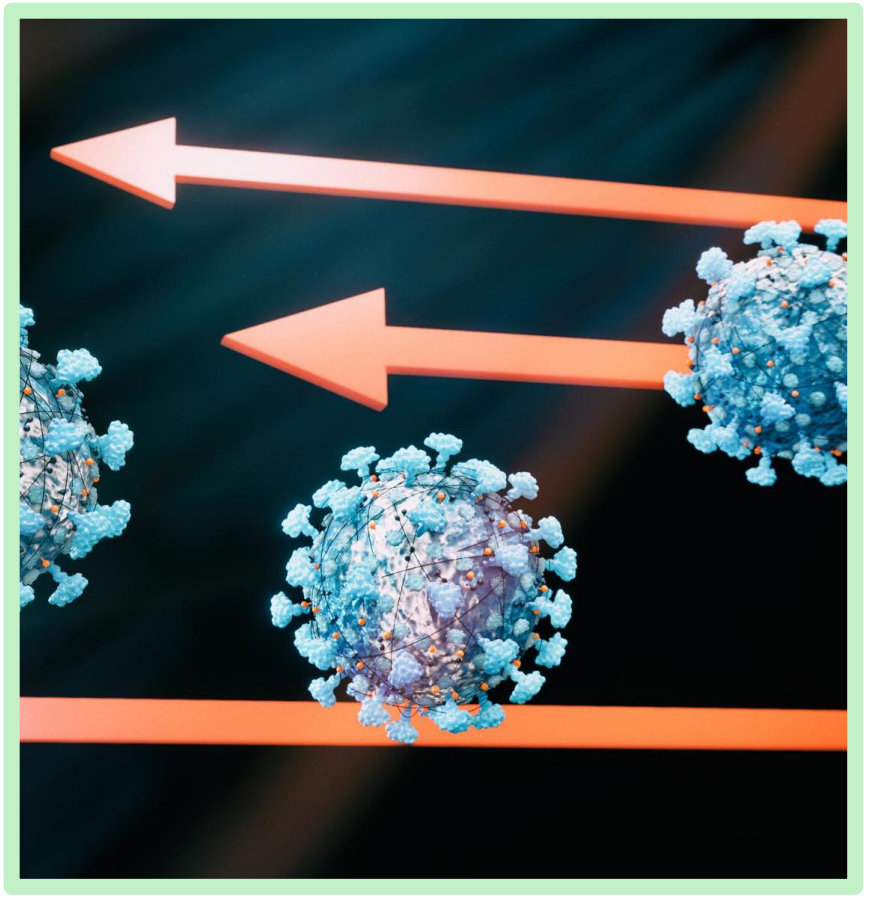
Risk factors include donors from **endemic regions, MSM, and injecting drug users.**

Rare Blood Transfusion Transmission

Though **rare,** HHV-8 transmission via blood transfusion has been documented.

Importance of Screening

Thorough donor screening and risk assessment are crucial to prevent post-transplant complications.



Clinical Impact in Transplant Recipients

HHV-8 Risk in Transplants

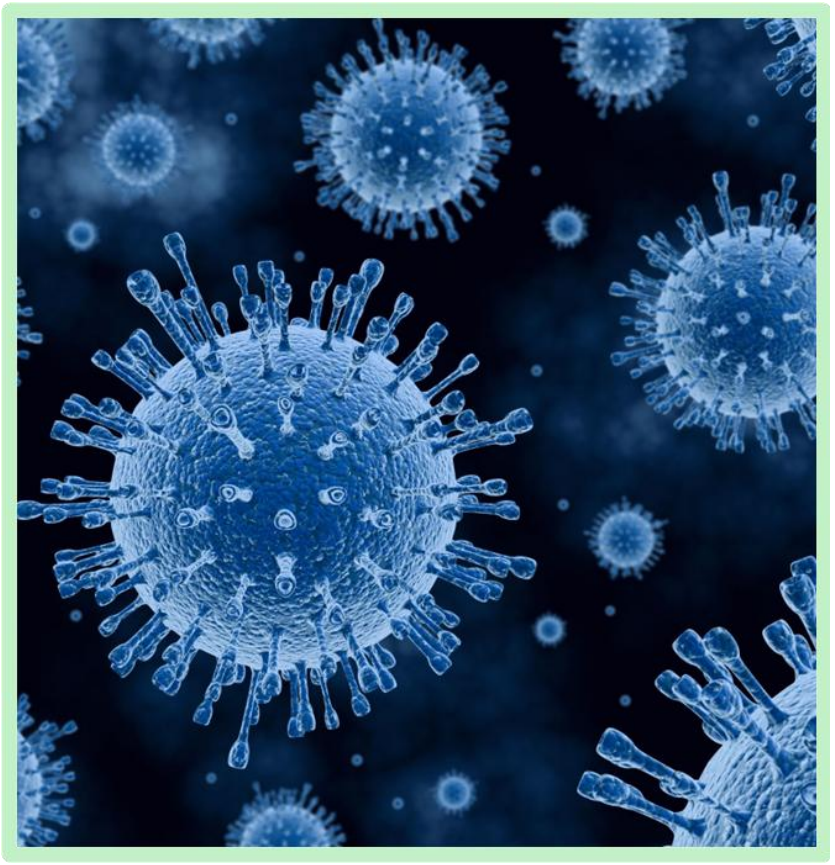
HHV-8 **reactivation** poses serious risks in immunosuppressed transplant recipients, causing severe diseases like KS, MCD, and PEL.

Diagnostic Challenges

Nonspecific symptoms and overlap with other complications delay HHV-8 related disease diagnosis post-transplant.

Importance of Early Detection

Early recognition and intervention improve outcomes and reduce morbidity in transplant recipients with HHV-8 diseases.



Diagnosis and Monitoring

Serological Assays Limitations

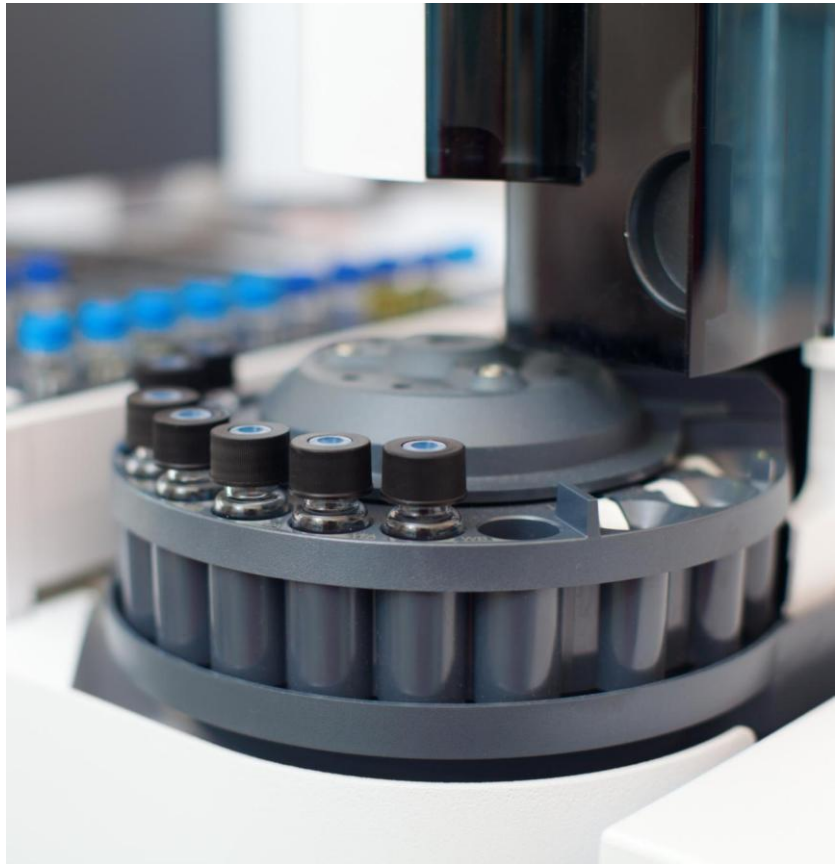
Serological tests (IF) detect HHV-8 antibodies but have variable sensitivity and specificity, limiting clinical utility.

PCR Testing for Diagnosis

PCR testing detects viral DNA in blood or tissue, providing a definitive diagnosis especially during reactivation.

Monitoring High-Risk Patients

Regular monitoring is recommended for high-risk transplant patients to enable early detection and treatment of HHV-8 reactivation.



UK Guidelines and Recommendations

Donor Screening Guidelines

UK guidelines recommend screening deceased organ donors for HHV-8 antibodies to reduce transmission risk.

Risk Assessment Protocols

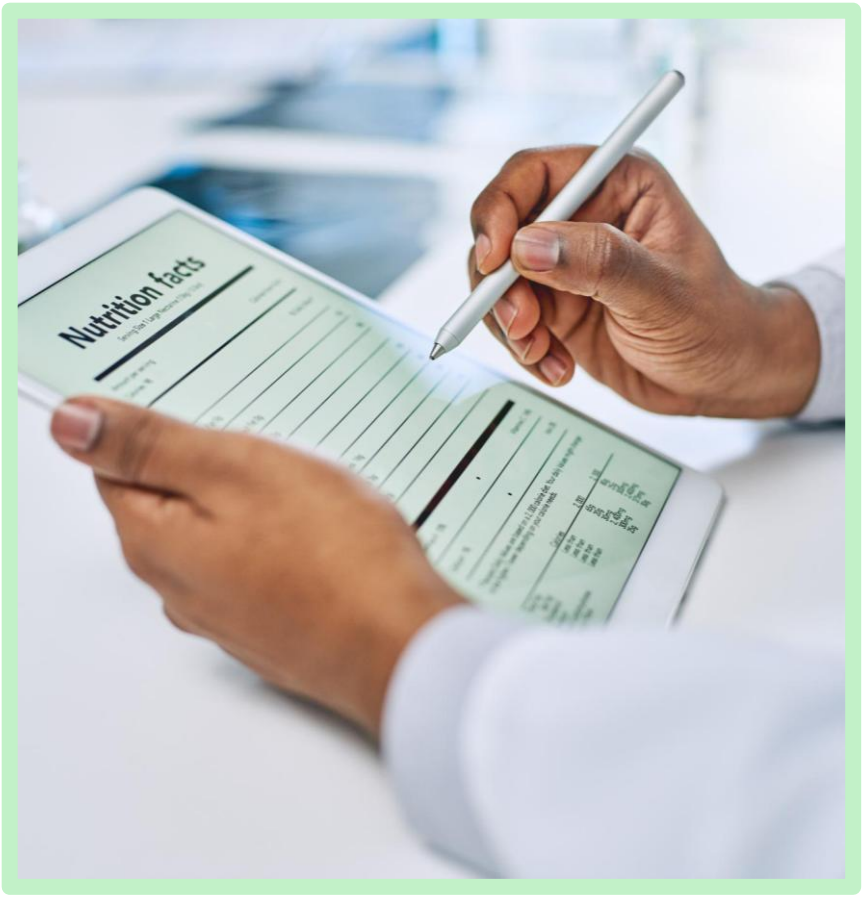
Organs from seropositive donors undergo thorough risk assessments before transplantation decisions.

Identifying High-Risk Donors

Guidelines stress identifying donors from endemic areas or with behavioral risk factors to ensure safety.

Preventive Strategies Importance

With no HHV-8 vaccine available, preventive measures and screening are vital for transplant safety.



Management Strategies

Early Recognition and Diagnosis

Timely identification of HHV-8-related diseases in transplant recipients is critical to improve patient outcomes.

Treatment Strategies

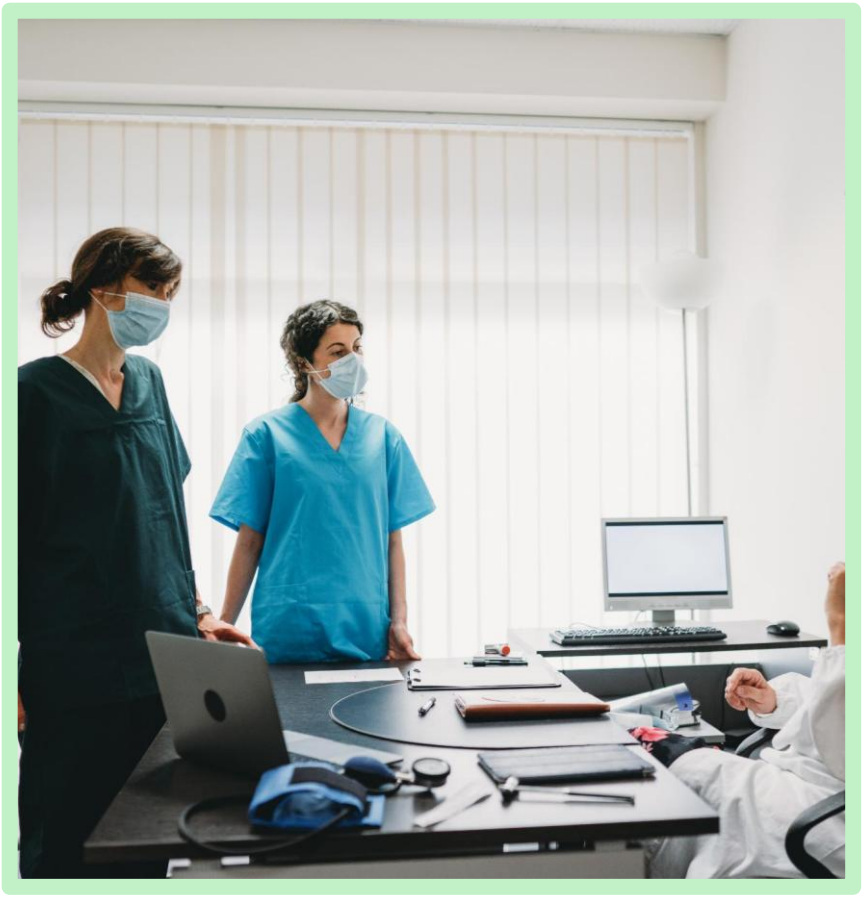
Management includes immunosuppression reduction, antiviral therapy, and chemotherapy for malignancies like KS and PEL.

Supportive Care and Monitoring

Ongoing care and monitoring for complications are essential to ensure patient safety and treatment effectiveness.

Multidisciplinary Collaboration

Coordination among transplant specialists, infectious disease experts, and oncologists optimizes patient care quality.



Treatment:

Reduction of immunosuppression	•First-line approach for less severe disease. •Effectiveness depends on disease stage and individual response. •Risk of allograft rejection must be carefully weighed.
mTOR inhibitors (Sirolimus/Everolimus):	•Conversion from calcineurin inhibitors (CNIs) can lead to KS regression, often with less rejection risk than RIS alone. •Mechanism involves anti-angiogenic and anti-proliferative effects.
Chemotherapy:	•Used for advanced or visceral KS and for lymphomas. •Liposomal anthracyclines (e.g., doxorubicin) are common.
Rituximab:	•Anti-CD20 monoclonal antibody used for B-cell driven diseases like MCD and PEL. •May be life-saving in severe non-malignant syndromes like KICS, particularly following primary infection.
Antivirals:	•Ganciclovir, foscarnet, and cidofovir can inhibit HHV-8 replication. •Most useful for primary infection with high viral load, but less effective for established latent infection in KS. •Can be used preemptively in high-risk D+R- patients, but evidence is limited.

UK Deceased organ donor screening

- ALL donor samples tested post-donation for HHV-8 lytic and latent antibodies
- HHV-8 DNA tested for if serology positive, for additional information and not as a screening tool
- Follow up of recipients from the above donors
  - HHV-8 antibodies and DNA 1,2,3,6,9 and 12 months post-transplant
  - HHV-8 antibody applied to first post-transplant sample; if reactivity seen, pre-transplant baseline sample tested
  - Virological and clinical monitoring if new infection detected
- New infection= Lytic antibody seroconversion + viraemia

Donor HHV-8 antibody screening results
June 2023 to July 2025

- **Lytic and latent immunofluorescence antibody applied to ALL proceeding deceased organ donors, post-implantation**

Screening result	Number (% of total screened) n=3269
Total number sero-reactive	249 (7.56%)
Proceeding donors	208

PCR applied to samples that gave indeterminate or positive antibody results

10 (4.8% of sero-reactive proceeding donors)	=	viral DNA detected (PCR)

Outcome of recipient follow up

Donor		Recipient					
Antibody screening result	Proceeding donors	Numbers requiring follow-up					
		Kidney	SPK	Liver	Heart	Lung	Other
Sero-reactive	208	340	14	119	24	16	9

21 recipients seroconverted and became viraemic
ALL new documented infections were in recipients from PCR positive donors

Donor		Recipient					
Viral DNA	Proceeding donors	Number of recipients with new infection					
		kidney	PK	Liver	Heart	Lung	Other
PCR positive	10 (4.8%)	9 of 16	2 of 2	9 of 9	0 of 2	1 of 1	0

Observed transmission rate and recipient outcome by organ type

	Liver recipients	Kidney recipients
Transmission rate	100% (9 of 9)	56% (9 of 16)
HHV-8 related death	56% (5 of 9)	0% (0 of 9)

- **9 newly infected kidney recipients have not had demonstrable HHV-8 related disease**
- **They have future lifetime risk of reactivation**

- **Cases observed before introduction of HHV-8 screening:**
  - **HHV-8 disease in kidney recipients who had acquired infection from the donor**
  - **Transmission has also been observed where donor was HHV-8 PCR negative**

NHSBT Working group

Recommendations for deceased organ donors

- Universal screening should continue for all donors, until a better alternative strategy is demonstrated to be applicable in practice
- HHV-8 DNA testing by a suitably sensitive nucleic acid technique (NAT) for all deceased organ donors to be added to the current antibody testing
- Testing for antibody and viral DNA to continue post-donation until suitable, fully validated assays and pathways are identified for use pre-donation
- The organisation responsible for organ donor characterisation should proceed immediately to identify suitable assays and pathways to enable implementation of the proposed recommendations, including pre-donation NAT testing, at the earliest possible timepoint

Recommendations for potential living donors

- Potential living donors should be screened for HHV-8 by a suitable, fully validated serology assay.
  - Seropositive donors should be tested by NAT during the transplant work-up, and have it repeated immediately before donation.
  - Seropositive potential kidney donors should be tested by NAT before registration in the UK living kidney donor scheme, and again immediately before donation
- In the event of a suitable, fully validated assay not being available to establish a person's HHV-8 antibody status, a suitable, fully validated NAT assay could be used to identify donors at the highest risk of HHV-8 transmission
- Results and outcomes must be recorded; proven or suspected donor-derived transmissions or diagnosis of HHV-8 related disease in solid organ transplant recipients must be reported centrally to NHSBT.

Patients who are waiting for or have received an organ transplant

- Recommendations for the management of recipients or candidate recipients of organ transplantation are best addressed by the appropriate professional groups collaborative work is expected to enable generation of practice guidance

- Guidance should ideally include not only aspects of testing and monitoring strategies, but also management of recipients who have received organs from HHV-8 infected donors, or who may have suspected or proven HHV-8 related disease

Executive Summary

- Molecular assays: The UK screening program shows that detection of virus DNA in plasma at the time of donation is linked to a high risk of transmission to organ recipients
  - transmission via solid organs is known to occur in the absence of detectable virus DNA in plasma, as the virus is found inside host cells

- The aim is to work towards achieving a status of pre-donation testing of organ donors for HHV-8, whereby donors that confer the highest risk of transmission can be identified through a practically implementable, robust process

Current testing situation

Deceased donors:

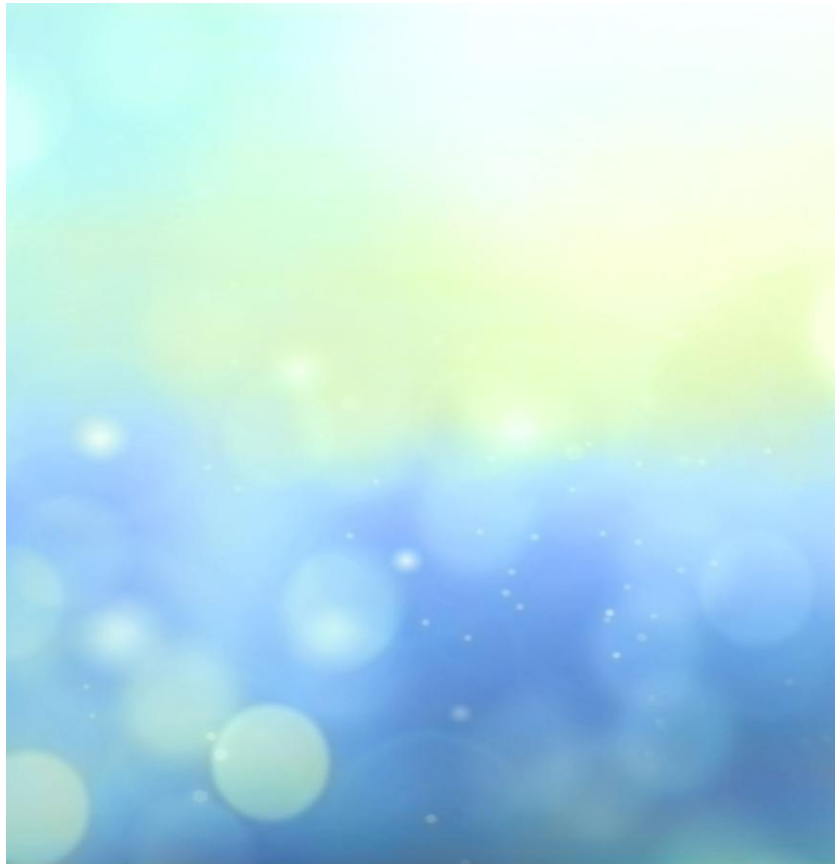
HHV-8 lytic antibody kits out of stock due to production delays

Deceased donors are being tested by PCR only, to identify donors with the highest risk of transmission to organ recipients

When supply is restored, HHV-8 antibody test will be retrospectively applied

Recipients:

Recipients requiring virological monitoring due to donor result are being tested by PCR only; the rationale is to detect initial viraemia during primary infection



SaBTO recommendations awaiting ministerial review

For all those listed for an organ transplant

- All patients listed to receive a transplant should be tested for evidence of HHV8 infection by serology
- Those who are already listed should also be tested

For living organ donors

- Potential living donors should be screened for HHV-8 by a suitable, fully validated serology assay or by NAT testing
- Seropositive donors should be tested by NAT during the transplant work-up, and have the test repeated immediately before donation

For deceased organ donors

- NHSBT should work with laboratories currently performing transplant donor screening to introduce HHV-8 DNA testing with a suitably sensitive nucleic acid technology for all deceased organ donors with
- results to be available to the implanting team prior to implantation; this should be implemented as soon as practicable
- Universal post-implantation antibody screening for HHV-8 should continue for all organ donors but this recommendation should be reviewed once routine pre-implantation NAT testing is in place