Aim

This document is intended as a concise update on the biology of human herpes virus type-8 (HHV-8) in solid organ transplantation (SOT) for transplantation professionals in the UK. The introduction of an HHV-8 screening programme for deceased donors has generated a need within the community to provide a consensus document for clinicians informed by expert opinion while acknowledging that there is insufficient evidence to produce guidelines. It is a statement of consensus and aims to supplement, but not replace, local and regional expert clinical advice.

Human Herpes Virus 8 (HHV-8)

HHV-8 is a large double-stranded DNA virus, which was discovered as the causative agent in Kaposi's sarcoma in 1994 (1). Like other herpes viruses, HHV-8 undergoes lytic and latent phases, establishing a life-long infection, i.e. once infection is established, it is there for life. During the lytic phase there is a massive increase in replication and lysis of the host cell. Activation of the virally encoded "lytic switch" gene, *RTA*, causes HHV-8 to enter the lytic phase, in which viral-encoded genes (at least 85 genes and miRNAs) are expressed and the host cellular machinery is re-directed to the manufacture and assembly of progeny virions. The lytic phase facilitates both the infection of new cells and the onward infection of new hosts.

HHV-8 is thought to infect primarily endothelial cells, monocytes and B lymphocytes. Most non-SOT transmission is thought to occur via saliva but in SOT recipients, allograft-related transmission is thought to occur mainly by passenger mononuclear cells (2). This explains the apparent higher rates of seroconversion in liver, lung and small bowel transplant recipients.

As expected in a herpes virus infection, experimental and clinical data suggest that host immunity by T lymphocytes is important for the control and modulation of HHV-8. Although HHV-8 is necessary to cause certain malignancies, there must also be other co-factors as clinical disease is rare in non-immunosuppressed individuals.

Epidemiology

HHV-8 seroprevalence (antibody positivity) indicates previously acquired infection and carriage of the virus, usually asymptomatically. Detection of virus DNA in plasma or serum of healthy asymptomatic individuals is uncommon, as HHV-8 is strongly cell-associated. Detection of HHV-8 DNA in plasma is associated with a viral replicative state, with a correlation between levels of viral load and disease manifestation. However, disease (such as localised Kaposi's Sarcoma) can occur in the absence of detectable viraemia.

Unlike other herpes viruses, HHV-8 seroprevalence varies significantly across the world. The seroprevalence of HHV-8 approaches 50% in sub-Saharan Africa and up to around 25% in southern Italy. Non-endemic areas such as the United States (US) and Western Europe report seropositivity rates in the general population of 0 to 6%. Higher seroprevalence is observed in certain subgroups such as men who have sex with men (MSM) and intravenous drug users (3); these are important routes of transmission in non-endemic areas.

In the US, an estimated 3-7% of blood donors are seropositive but with minimal rates of HHV-8 DNA detected (none of 684 donors tested) (4). Post-transplant, HHV-8 seroconversion has

been observed in 14-33% of recipients of organs from seropositive donors in France, with viraemia detected in a minority (5), though it should be acknowledged that the assay used and testing time points will influence results. A study from Northern Italy prospectively screened SOT donors and recipients, finding that 4% of donors (10/249) and 18% of recipients (93/517) were HHV-8 seropositive, with 25% of serologically mismatched recipients (D+/R-) seroconverting within 6 months. Re-activated HHV-8 post-transplant was seen in 2.1%, and one individual developed post-transplant Kaposi's sarcoma (6, 7).

HHV-8 Screening in the UK

In June 2023, NHS Blood and Transplant (NHSBT) initiated routine testing of deceased organ donors for HHV-8 antibodies immediately post-donation (8). Knowledge of this virus in the context of transmission through SOT has been incomplete because of the limited availability of suitable antibody tests. However, thorough investigation of more than 15 clusters of serious clinical infections in SOT recipients, which initially involved sending samples abroad for testing, enabled correct assignment of HHV-8 serostatus in all cases investigated by NHSBT. The evaluation work also included anonymised testing of archived organ and blood donor plasma samples; a seropositivity rate between 1.5-3.5% was observed, which was within the expected range. A working group was commissioned by SaBTO to look at HHV-8 in SOT, which culminated in a recommendation to start screening deceased organ donors in the first instance (9).

Given the potentially serious nature of this uncommon condition, NHSBT are undertaking an ongoing assessment of the issue. Since June 2023, NHSBT have screened every deceased organ donor in the United Kingdom for serological evidence of infection with HHV-8. After testing more than 1500 donors the seropositivity rate remains within the range seen during the test evaluation. More recently, a steady increase has been observed due to the reporting of low positives and inconclusive serology results. This increase has been generated by technical issues with the assay and caution needs to be applied during data acquisition.

When the donor result is provided to transplant centres, and where the donor has serological evidence of HHV-8 infection, a suggested protocol for recipient follow up is provided at https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/. This algorithm is informed by the investigation of past cases and was reviewed by the SaBTO HHV-8 working group. The algorithm relies on establishing donor and recipient serostatus followed by ongoing testing for HHV-8 antibodies and DNA in the recipient. Time to seroconversion and first positive PCR result in the recipient's plasma vary from days to several weeks, depending on currently unidentified factors, hence there is a need for extended follow-up. During the initial phase of primary infection, viral DNA will be detectable in plasma but that alone does not indicate that disease will ensue. Unlike other herpes viruses such as CMV and EBV, the plasma viral load detectable at this initial stage is not very high and could be missed depending on assay sensitivity and time of blood sampling. In a typical, uncomplicated primary infection, the lytic antibody becomes detectable, titres go up quickly, and the viral load declines and becomes undetectable as the virus is controlled and enters latency. In some SOT recipients, the course is different, and the viral load continues to rise beyond 3 logs and can rapidly increase by several logs over a period of weeks. The monitoring of viral dynamics, together with the clinical context for each patient are required to avoid delayed diagnosis, should disease develop.

What to consider if informed that an organ donor is positive for HHV-8

- Inform the recipient
- Provide information regarding the low likelihood of clinical infection
- Discuss the potentially serious forms of infection and what to look out for
- Explain the screening process and handling of samples (see https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/)
- Discuss possible treatments and the need for multi-disciplinary team consultation in the unlikely event of clinical infection occurring

NOTE: Laboratory reports contain information on the donor result profile. Please note that "inconclusive" or "weak" reactive serology" in the absence of detectable viral DNA constitute about 2% of positive results. There is currently no confirmatory serological test for HHV-8 and these results are reported as "inconclusive". As a precautionary measure, the advice in this instance is to consider recipient follow up, using a less intense algorithm (see https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/). This is relevant for overall risk assessment, patient, and clinician information. The likelihood of a true positive and of subsequent transmission is very low, if any. This is very different from the scenario where the donor tests strongly positive for HHV-8 antibodies, particularly when viral DNA is also detected.

NOTE: In clinical practice, recipients' pre-transplant HHV-8 status may be determined from the first post-transplant sample sent, given HHV-8 is not routinely tested for pre-transplantation. A negative antibody result precludes the need to identify an archived pre-transplant sample. If the initial antibody result is positive, an archived pre-transplant sample should be sent for confirmation.

Post-exposure prophylaxis or pre-emptive treatment

There are currently no data to guide the role of any intervention following the notification of a positive HHV-8 donor result.

Clinical Disease

In immunocompetent hosts, most primary infections are asymptomatic although occasionally lymphadenopathy, rash and a mild systemic illness may occur, particularly in children.

Although best known by its association with Kaposi's sarcoma, HHV-8 is also linked to other rare but important syndromes in SOT, particularly when infection is acquired through the allograft, namely:

- Visceral or disseminated Kaposi's sarcoma
- Multicentric Castleman's disease (MCD)
- HHV-8 associated lymphomas (e.g. Primary effusion lymphoma (PEL), extracavitary PEL)
- Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS) +/- haemophagocytic syndrome
- Combination of disease types

Seropositivity in the recipient or evidence of viral replication should generate increased clinical vigilance for symptoms and/or signs consistent with HHV-8-related clinical diseases, facilitating the possibility of earlier intervention e.g. immunomodulatory therapies such as rituximab can be used in inflammatory syndromes, cytotoxic drugs in proven Kaposi's sarcoma, and a combined approach in patients with multiple HHV-8-related diagnoses. Cases should be jointly managed with appropriate experts.

While evidence for *in vitro* action of some antivirals such as foscarnet, ganciclovir and cidofovir supports a possible role in situations where there is ongoing viral replication, there is no evidence to support their use in isolation, which could lead to delays in diagnosis and treatment of specific disease types.

A low threshold for investigation of HHV-8 related diseases is important as there are management options for the different conditions (10). Cytological and histological diagnosis are essential. Modulation of immunosuppression and use of mTOR inhibitors has become a first line approach and should be considered. Growing awareness of the spectrum of disease that HHV-8 can cause is an important step, with due consideration regardless of donor and recipient serostatus.

Moving forward more information will be collected and the findings will be shared with the community again over the coming months.

Specific conditions associated with HHV-8

1. **Kaposi's sarcoma (KS)**
    a. Usually presents with red, purple or brown lesions on the skin or mucous membranes with predilection for extremities. Visceral disease may occur and portends a worse prognosis.
    b. Important to demonstrate HHV-8 in tissue by immunocytochemistry.
    c. Manage in association with clinical colleagues in Oncology, HIV and Virology (11-13). Chemotherapy is required for aggressive disease.
    d. Reduce immunosuppression and consider switching calcineurin inhibitors (CNI) to sirolimus (14, 15). Reducing immunosuppression alone can lead to remission in 30% of SOT recipients (16).
    e. Antivirals are not used as HHV-8 is not in lytic phase.

2. **Multicentric Castleman's disease (MCD) (17)**
    a. MCD is a polyclonal B cell disorder characterized clinically by intermittent flares of inflammatory symptoms and signs. It can occur coincidentally with KS.
    b. Symptoms may include night sweats, fatigue, fevers and cachexia, together with lymphadenopathy and hepatosplenomegaly.
    c. Findings may include anaemia, thrombocytopenia, hypoalbuminemia, hyponatremia, and elevated inflammatory markers, most notably C-reactive protein (CRP).
    d. Important to demonstrate HHV-8 in excised lymph node by immunocytochemistry.
    e. Manage in association with clinical colleagues in Haematology, Oncology, HIV and Virology
    f. Reduce immunosuppression and consider switching CNI to sirolimus.

g. Successful remission has been achieved with rituximab based regimes (18).
h. Antiviral regimes are not routinely used in isolation (19).
i. Therapy with agents that interfere with IL-6 pathways may be considered as an adjunctive measure only, as no effect on viral homologue of human IL-6 (20).

3. **Primary effusion lymphoma (PEL) and other lymphomas (21)**
   a. Variant of B-cell non-Hodgkin Lymphoma with aggressive clinical course.
   b. Presents with ascites (45%), pleural effusions (75%), pericardial effusions (20%) and rarely in joints or meninges.
   c. Symptoms relate to physical effects of effusions.
   d. Important to demonstrate HHV-8 in nucleus of malignant B cells from effusion by immunocytochemistry. Diagnosis confirmed by flow cytometry of effusate.
   e. Manage in association with clinical colleagues in Haematology, Oncology, HIV and Virology.
   f. Reduce immunosuppression and consider switching CNI to sirolimus. Chemotherapy may also be required.

4. **Other syndromes**
   a. Inflammatory cytokine syndrome (22, 23)
   b. Haemophagocytic syndrome (24)
   c. Encephalitis (25)

Further information is available in several clinical reviews (16, 21, 26-31).

Suggested Code of Practice

1. In pre-transplant discussions, patients should be informed of the potential for transmission from donors of serious viral infections (e.g. hepatitis B and C, HIV and HHV-8). Patients should also be informed that where donor information regarding infection becomes available post-transplantation, this information is used to assist in their management. Not all infections can be tested for, and accuracy of results can vary, so clinical context remains important.
2. Donor samples will be screened by NHSBT post-transplantation and most results will be communicated with implanting centres within 2 weeks of transplant.
3. SOT recipients who receive an organ from an HHV-8 seropositive donor should be counselled regarding the potential risks and informed of the screening programme. We strongly recommend that centres comply with the suggested follow up protocol (see https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/)
4. Such recipients should be reviewed regularly in clinic for the first 12 months after transplantation with regular inspection of skin and mucous membranes. Increased vigilance should be maintained for potential clinical syndromes associated with HHV-8 infection and a low threshold for cross-sectional imaging should be adopted (looking for lymphadenopathy, tumours, effusions, etc).
5. SOT recipients who seroconvert or develop a positive HHV-8 PCR should be discussed with colleagues in virology and consideration should be given to reducing immunosuppression.
6. All cases of recipient HHV-8 infection (defined by a confirmed positive HHV-8 PCR result in the recipient) and development of HHV-8 associated disease should be

reported to NHSBT through the incident reporting system (https://safe.nhsbt.nhs.uk/IncidentSubmission/Pages/IncidentSubmissionForm.aspx)

7. Relevant information on recipients developing HHV-8 infection will be sought from the transplant centres, as data collection is a requirement to inform future guidance.

References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266(5192):1865-9.

2. Barozzi P, Luppi M, Facchetti F, Mecucci C, Alù M, Sarid R, et al. Post-transplant Kaposi sarcoma originates from the seeding of donor-derived progenitors. Nat Med. 2003;9(5):554-61.

3. Dollard SC, Annambhotla P, Wong P, Meneses K, Amin MM, La Hoz RM, 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(2):681-8.

4. Qu L, Jenkins F, Triulzi DJ. Human herpesvirus 8 genomes and seroprevalence in United States blood donors. Transfusion. 2010;50(5):1050-6.

5. Lebbe C, Porcher R, Marcelin AG, Agbalika F, Dussaix E, Samuel D, et al. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. Am J Transplant. 2013;13(1):207-13.

6. Chiereghin A, Barozzi P, Petrisli E, Piccirilli G, Gabrielli L, Riva G, et al. Multicenter Prospective Study for Laboratory Diagnosis of HHV8 Infection in Solid Organ Donors and Transplant Recipients and Evaluation of the Clinical Impact After Transplantation. Transplantation. 2017;101(8):1935-44.

7. Pietrosi G, Vizzini G, Pipitone L, Di Martino G, Minervini MI, Lo Iacono G, et al. Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. Am J Transplant. 2011;11(12):2715-23.

8. Ushiro-Lumb I, McGowan O, Foley J, Baker R, Manas D, Clarkson A. 311.3: Introduction of deceased organ donor screening for Human Herpes Virus type 8 in the UK. Transplantation. 2023;107(10S1):72.

9. SaBTO. SaBTO virology subcommittee recommendations on KSHV. DHSC; 2023 31st May 2023.

10. Dalla Pria A, Bower M, Ushiro-Lumb I. Clinical Management of Human Herpesvirus-8 related illnesses in solid organ transplant recipients. Journal of Infection (in press). 2024.

11. Brambilla L, Genovese G, Berti E, Peris K, Rongioletti F, Micali G, et al. Diagnosis and treatment of classic and iatrogenic Kaposi's sarcoma: Italian recommendations. Ital J Dermatol Venerol. 2021;156(3):356-65.

12. Khanmammadov NA, Paksoy N, Doğan İ, Ferhatoğlu F, Saip P, Aydiner A. Efficacy and outcomes of systemic chemotherapy in posttransplant and immunosuppression associated Kaposi sarcoma: Twenty years experience of a tertiary cancer center. Medicine (Baltimore). 2023;102(39):e35383.

13. Naimo E, Zischke J, Schulz TF. Recent Advances in Developing Treatments of Kaposi's Sarcoma Herpesvirus-Related Diseases. Viruses. 2021;13(9).

14. Cordeiro C, Ferreira S, Nobre S, Cunha C, Julião MJ, Brito M, et al. Kaposi sarcoma in three pediatric liver transplantation recipients. Pediatr Transplant. 2023;27(3):e14469.

15. Saowapa S, Polpichai N, Siladech P, Wannaphut C, Tanariyakul M, Wattanachayakul P, et al. Evaluating Kaposi Sarcoma in Kidney Transplant Patients: A Systematic Review and Meta-Analysis. Cureus. 2024;16(1):e52527.

16. Pellett Madan R, Hand J. Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13518.

17. Bower M. How I treat HIV-associated multicentric Castleman disease. Blood. 2010;116(22):4415-21.

18. Ide M, Kawachi Y, Izumi Y, Kasagi K, Ogino T. Long-term remission in HIV-negative patients with multicentric Castleman's disease using rituximab. Eur J Haematol. 2006;76(2):119-23.

19. Staskus KA, Sun R, Miller G, Racz P, Jaslowski A, Metroka C, et al. Cellular tropism and viral interleukin-6 expression distinguish human herpesvirus 8 involvement in Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. J Virol. 1999;73(5):4181-7.

20. Ramaswami R, Lurain K, Peer CJ, Serquiña A, Wang V, Widell A, et al. Tocilizumab in patients with symptomatic Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood. 2020;135(25):2316-9.

21. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood. 2012;120(20):4150-9.

22. Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, et al. Clinical Features and Outcomes of Patients With Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated Inflammation: Prospective Characterization of KSHV Inflammatory Cytokine Syndrome (KICS). Clin Infect Dis. 2016;62(6):730-8.

23. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. Clin Infect Dis. 2010;51(3):350-8.

24. Chesner J, Schiano TD, Fiel MI, Crismale JF. Hemophagocytic lymphohistiocytosis occurring after liver transplantation: A case series and review of the literature. Clin Transplant. 2021;35(8):e14392.

25. Mann I, Morado-Aramburo O, Hasbun R. Emerging shadows: HHV-8-associated encephalitis unveiled in a solid organ transplant recipient. Transpl Infect Dis. 2024;26(4):e14343.

26. Atamna A, Yahav D, Hirzel C. Prevention of Oncogenic Gammaherpesvirinae (EBV and HHV8) Associated Disease in Solid Organ Transplant Recipients. Transpl Int. 2023;36:11856.

27. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis. 2002;2(6):344-52.

28. Hengge UR, Ruzicka T, Tyring SK, Stuschke M, Roggendorf M, Schwartz RA, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. Lancet Infect Dis. 2002;2(5):281-92.

29. Mikulska M, Balletto E, Mularoni A. Human herpesvirus 8 and Kaposi sarcoma: how should we screen and manage the transplant recipient? Curr Opin Infect Dis. 2021;34(6):646-53.

30. Carbone A, Borok M, Damania B, Gloghini A, Polizzotto MN, Jayanthan RK, et al. Castleman disease. Nat Rev Dis Primers. 2021;7(1):84.

31. Cesarman E, Damania B, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma. Nat Rev Dis Primers. 2019;5(1):9.