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International Survey of Human Herpes Virus 8 Screening and Management in Solid Organ Transplantation

Running Title: **HHV-8 in SOT: an international survey**

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MS, CVD, JMAG, CC, PG: Substantial contributions to the design of the work, revising the work critically for important intellectual content; Final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abbreviations: ELISA: Enzyme-Linked Immunosorbent Assay; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; ESGICH: ESCMID Study Group for Infections in Compromised Hosts; HHV-8: Human Herpes Virus 8; IFA: immunofluorescence assay; KSHV: Kaposi Sarcoma herpesvirus; KICS: KSHV-associate inflammatory cytokine syndrome; KS: Kaposi Sarcoma; MCD: Multicentric Castleman Disease; NAT: nucleic acid testing; PEL: Primary Effusion Lymphoma; mTOR: mammalian target of rapamycin; SOT: solid organ transplant; Tx/Y: median number of yearly transplants

Abstract

Background: HHV-8/Kaposi Sarcoma herpesvirus (KSHV) has been associated with a broad spectrum of diseases in solid organ transplant (SOT) recipients. Primary donor-derived infection can be associated with severe and rapidly fatal non-neoplastic disease, and diagnosis is made with high HHV-8 DNAemia. **Methods:** We carried out an international survey to investigate the current approach to HHV-8 screening and management in SOT since a protocol has not been established by international guidelines. **Results:** A total of 51 transplant centers from 15 countries filled out the survey. HHV-8-associated diseases in SOT have been diagnosed during the previous 5 years in 67% of centers. Pre-transplant serological screening is performed in 17 centers (33%) and post-

transplant HHV-8 nucleic acid testing (NAT) monitoring is performed in 21 centers (41%). Performing HHV-8 NAT monitoring and serological screening were found associated with having diagnosed in the previous 5 years a non-malignant HHV-8-associated disease. **Conclusions**: Serological pre-transplant screening of donors and recipients and post-transplant HHV-8 NAT monitoring recommendations should be standardized. Even though serological assays are not optimal, they could contribute to increasing knowledge on epidemiology and management of HHV-8 associated diseases after SOT.

Introduction

HHV-8/Kaposi Sarcoma herpesvirus (KSHV) is a ɣ-herpesvirus. Seroprevalence ranges from 0-5% in North America, northern Europe, and Asia, between 5-20% in the Mediterranean and Middle East, and more than 50% in some regions of Africa.[1] However, even in low prevalence regions, some populations, such as people living with HIV and men who have sex with men have seroprevalence rates that reach 33- 40%. [2] HHV-8 is the causative agent of Kaposi Sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). It has also been reported to cause bone marrow suppression, clonal gammopathy, and hemophagocytic syndrome.[3, 4, 5, 6] Recently, KSHV-associated inflammatory cytokine syndrome (KICS) has been described in HIV patients and solid organ transplant (SOT) recipients.[7,8] In HHV-8 seropositive SOT patients at the time of transplant, iatrogenic immunosuppression can cause HHV-8 lytic reactivations and uncontrolled expansions of latently infected cells, which may lead to neoplastic disease.[9] Primary donor-derived infection can be associated with severe and rapidly fatal neoplastic or non-neoplastic disease.**Error! Bookmark not defined.**[10, 11,12,13,14] HHV-8 serological screening is not mandatory, and a standardized HHV-8 management protocol has not yet been established.[15] The lack of a gold

standard in serologic assays for anti-HHV-8 antibodies is a major obstacle to routine implementation of screening protocols, and the principal reason why the true prevalence of HHV-8 infection may be underestimated.**Error! Bookmark not defined.** Our survey, endorsed by the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) and SITA (Società Italiana di Terapia Antinfettiva), investigated the current approach of transplant centers to screening and management of HHV-8 in SOT recipients.

Materials and Methods

The survey was carried out between June and October 2019. We e-mailed a questionnaire reviewed by an ESGICH expert panel to 160 clinicians from 140 centers and 22 countries. Ethics Committee approval was not required. We did an analysis to identify characteristics associated with serological screening and post-transplant HHV-8 NAT monitoring. Centers were classified as low or high prevalence of HHV-8 when the literature indicated HHV-8 IgG seroprevalence in the corresponding country less or equal 6% or more than 6%, respectively. Continuous variables are expressed as median with range, and categorical variables as number and percent values, and compared, respectively, with Mann-Whitney test and chi-square (or Fisher's exact test if required). A p value ≤0.05 was considered statistically significant. All analyses were done with the Statistical Package for Social Sciences (SPSS for Windows version 22.0, SPSS Inc., Chicago, IL, USA).

Results

A total of 51 transplant centers from 15 different countries filled out the survey: Italy (23 centers), Spain (8 centers), U.S.A. (4 centers), Brazil (2 centers) and one center each from Argentina, Belarus, Canada, France, Greece, Israel, the Netherlands, Slovenia, Sweden, Switzerland and the U.K. Three questionnaire responses were anonymous.

Transplant programs included liver transplantation in 42 centers [median number of yearly transplants (Tx/Y): 50, range: 3-160], kidney in 47 centers (Tx/Y: 80, range: 10-300), lung in 22 (Tx/Y: 20, range: 1-105), heart in 26 (Tx/Y: 20, range: 1-96), bowel in 9 (Tx/Y: 1, range: 1-3), and pancreas in 24 (Tx/Y: 6, range: 1-25). Because (val)ganciclovir is known to influence HHV-8 replication, we investigated the approach for CMV prevention in CMV D+/R- recipients: antiviral prophylaxis was used in 34 centers (67%), preemptive strategy in 12 and in 5 centers the approach varied depending on the type of transplant.

Overall, 34 centers (67%) did not perform any screening for HHV-8. The remaining 17 centers (33%) performed serology before or immediately after transplant. Routine screening was performed only in recipients in 9 centers, both donor and recipients in 4 centers, only in donors in 2 centers, and in 2 centers the screening of donors or recipients was based on risk factors and/or country of origin. Variables associated with serological screening for HHV-8 were: being in a high (>6%) HHV-8 seroprevalence country , being an Italian center, presence of protocol for post-transplant HHV-8 NAT monitoring and having diagnosed at least one case of non-malignant disease (e.g., KICS-like syndrome) in the previous 5 years (Table 1).

Enzyme-linked immunosorbent assay (ELISA) was the preferred serological assay for serological diagnosis (14 centers), followed by immunofluorescence assay (IFA) (in 10 centers lytic and latent antigen, in 1 only lytic, in 1 only latent).

Transplant suitability was not influenced by the HHV-8 serology results in any center.

Thirty centers (59%) did not perform HHV-8 NAT monitoring after transplant, 10 (20%) monitored HHV-8 DNAemia only in symptomatic patients, 3 (5.8%) performed universal HHV-8 NAT monitoring and 8 (15.6%) used different risk-based approaches (1 only monitored R+, 1 only monitored D+/R- , 2 D+/R- and R+ , 1 D+/R- with symptoms and 3 only monitored patients with risk factors). The most

used test for HHV-8 DNAemia monitoring was quantitative commercial PCR (52%). The frequency of post-transplant HHV-8 NAT monitoring widely differed between centers.

According to the responses, characteristics associated with HHV-8 NAT monitoring were: Italian transplant program, performing serological screening and having diagnosed a non-neoplastic HHV-8-related disease in the previous 5 years. The use of anti-CMV prophylaxis was associated with lower rates of post-transplant HHV-8 NAT monitoring (Table 1).

The most common approach in cases of detectable HHV-8 DNAemia was reducing immunosuppression (n=29, 57%) and/or switching from calcineurin inhibitor to m-TOR inhibitor (n=23, 45%), with or without antivirals.

Only 2 centers tested HHV-8-specific T-cell responses with interferon gamma-Elispot.

Overall, 67% of centers diagnosed HHV-8-associated diseases in the previous five years, being cutaneous KS (n=16) and visceral KS (n=16) the most frequent ones. A non-malignant disease was reported by 14 centers, MCD was reported by 8 centers, and PEL by 4. Thirty centers (59%) reported a previous diagnosis of severe HHV-8 disease (any disease other than cutaneous KS).

The characteristics associated with previous diagnosis of non-neoplastic HHV-8-associated disease were: performing pre-transplant serological screening, post-transplant HHV-8 NAT monitoring, and Italian centers. The use of anti-CMV prophylaxis was associated with lower probability of reporting a non-neoplastic disease (Table 1).

Discussion

Our international survey showed that only 33% of the participating centers performed pre-transplant HHV-8 serological screening, with varying rates from 37.5% of centers in HHV-8 high prevalence areas, and 0% in low prevalence areas. In Italy, 57% of centers performed serology,

compared to 8% in the other countries. Although the screening rate varied between high and low risk epidemiological areas, it was far from uniform even in the same regions.

Serology screening for certain viral infections is a well-established component of the risk mitigation strategy and is vital for optimizing post-transplant outcomes.[16] International guidelines mandate pre-transplant CMV and EBV serology screening. While it does not represent a contraindication to transplantation, a seronegative recipient matched with a seropositive donor (D+/R−) will require intensive monitoring and post-SOT prevention strategies. HHV-8 serology screening of SOT donor and candidate is not recommended by international guidelines, but it may be useful to assess the risk of post-transplant HHV-8 disease. **Error! Bookmark not defined.**

Organs should not be excluded based on HHV-8 serology results, but information on the HHV-8 status provides the opportunity to monitor clinically and/or virologically patients at risk for HHV-8-related disease.**Error! Bookmark not defined.** In cases of D+/R− mismatch, close monitoring of the recipient by HHV-8 NAT could promptly identify donor-derived HHV-8 infection. The knowledge of a positive HHV-8 DNA is important as allows the clinician to modulate the immunosuppression and improve the likelihood of early diagnosis of complications since timely recognition and treatment of HHV-8 disease has been associated with better outcomes when compared to late diagnosis of symptomatic disease. [17] Monitoring symptomatic patients should be part of the management of any patient with suspicion of HHV-8 associated disease.

Regarding serological diagnosis, we did not find a clear preference between IFA or ELISA. In a recent multicenter, prospective evaluation of six HHV-8 serological assays, only two lytic antigen-based IFAs demonstrated agreement with the predefined reference standard.**Error! Bookmark not defined.** Despite the lack of optimal assay, this should not be a limitation for donor and recipient screening since the result does not affect transplant suitability, it could be performed in the days following

transplantation in a reference laboratory to obtain maximum reliability, and might contribute to better identification of risk for HHV-8 associated pathology.

PT-KS is the most frequently reported HHV-8-associated disease in SOT, with well characterized diagnosis and treatment. Since the discovery of HHV-8 in 1994,[18] there has been accumulating evidence of HHV-8-induced non-neoplastic diseases, uncommon but life threatening, following primary infection or reactivation in SOT.[Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.,19] These conditions have non-specific clinical manifestations and are not associated with the classical KS cutaneous lesions, which lead to diagnostic challenges. The diagnosis of a non-malignant HHV-8 disease requires a high index of suspicion and is mainly based on the detection of high levels of HHV-8 DNAemia**Error! Bookmark not defined.**, so diagnosis might be difficult in centers that do not perform HHV-8 NAT. In our study, among 17 centers that did not report HHV-8-associated complications, 14 did not monitor HHV-8 NAT, and 13 did not perform serology. On the contrary, performing HHV-8 NAT monitoring and serological screening were characteristics associated with having diagnosed an HHV-8-related non-malignant disease. Therefore, it is possible that HHV-8-associated non-neoplastic diseases may be underreported/underdiagnosed in centers without HHV-8 NAT availability. Another possible explanation is that centers in which patients had previous received diagnosis of KICS-like syndrome or other non-malignant severe HHV-8-associated disease, have implemented HHV-8 NAT monitoring because of this previous experience. In the absence of HHV-8 NAT testing, clinical manifestations of HHV-8-related disorders could have been attributed to other etiologies or classified and treated as non-specific hemophagocytic or inflammatory syndromes.

Regarding HHV-8 disease management, our survey shows that most clinicians followed consensus recommendations advising careful reduction of immunosuppression and switching regimens

containing calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors. **Error! Bookmark not defined.,Error! Bookmark not defined.**

Multicentric prospective trials are needed to investigate the rate of donor-derived HHV-8 transmission in mismatched recipients and evaluate the spectrum of HHV-8-associated diseases due to primary infection or reactivation. In patients at-risk, the optimal approach to HHV-8 NAT monitoring is still to be defined. Studies should also evaluate the utility of antivirals and mTOR inhibitors for the prevention and treatment of HHV-8-associated diseases, the dynamic of development of HHV-8-specific T-cell mediated immunity, and to validate immunomonitoring protocols aimed at optimizing immunosuppressive therapy to prevent HHV-8-associated disease.

Our study has some limitation, since it is a survey and it is not based in precise patient real data, so it is not possible to establish any causative link and it serves more as a foundation for further studies to confirm if HHV-8 monitoring could lead to earlier and better diagnosis of HHV-8 associated disorders. Moreover, almost half of the included centers were Italian, thus providing unbalanced representation of worldwide activity. However, the fact that the management varied also within the same countries proves the point that better understanding of optimal management is required. Moreover, testing in the same center may vary depending on the organ transplant type but none of the centers reported that attitudes varied depending on the organ transplanted. In conclusion, 67% of the centers participating in our survey have experience in diagnosing HHV-8-associated disease after SOT, suggesting that HHV-8 infection is an important complication, potentially underestimated in this setting. Despite that, only 33% of centers performed pre-transplant serological screening and 41% post-transplant HHV-8 NAT monitoring. The epidemiology of HHV-8 infection and related diseases remains poorly defined in SOT recipients, and multicenter studies are needed to define the need for screening not only in endemic regions. This may represent an emerging threat due to more intensive migratory activity and expanded acceptance of grafts (such organs from HIV-infected

donors). This survey is the starting point to plan future collaborative studies to improve our current knowledge on the epidemiology of HHV-8 and develop prevention and management strategies for HHV-8-related disease after SOT.

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• **Data Availability Statement**: The data that support the findings of this study are available from the corresponding author upon reasonable request

Supporting Information Statement: Additional supporting information can be found online in the Supporting Information section at the end of the article.

• **Legends**: **Table 1**: Variables associated with HHV-8 serological screening and HHV-8-DNA monitoring.

Table 1: **Variables associated with HHV-8 serological screening and HHV-8-DNA monitoring.**

Characteristics	**All centers, n=51**	**Centers that screen for HHV-8 IgG, n=17 (33%)**	**Centers that do not screen for HHV-8 serology, n=34 (67%)**	**p**	**Centers that monitor HHV-8-DNA, n= 29 (57%)**	**Centers that do not monitor HHV-8-DNA, n= 22 (43%)**	**p**
Prevalence of HHV-8 IgG positivity (n=48)°				**0.044**			0.35
High	40	15 (37.5)	25 (62.5)		17 (42)	23 (58)	
Low	8	0 (0)	8 (100)		2 (25)	6 (75)	
Country (n=48) °				**<0.0001**			**0.021**
Italy	23	13 (56.5)	10 (43.5)		10 (43)	13 (57)	
Other *	25	2 (8)	23 (92)		19 (76)	6 (24)	
Organ transplanted							
Liver tx	42	14 (33.3)	28 (66.7)	1	15 (38)	27 (64)	0.087
No liver tx	9	3 (33.3)	6 (66.7)		6 (67)	3 (33)	
Kidney tx	47	15 (31.9)	32 (68.1)	0.461	20 (43)	27 (57)	0.493
No kidney tx	4	2 (50)	2 (50)		1 (25)	3 (75)	
Lung	22	4 (18.2)	18 (81.8)	**0.046**	7 (32)	15 (68)	0.237
No lung tx	29	13 (44.8)	16 (55.2)		14 (48)	15 (52)	
Heart	26	5 (19.2)	21 (80.8)	**0.029**	10 (38.5)	16 (61.5)	0.688
No heart	25	12 (48)	13 (52)		11 (44)	14 (56)	
Pancreas tx	25	6 (24)	19 (76)	0.166	9 (36)	16 (64)	0.451
No pancreas	26	11 (42.3)	15 (57.7)		12 (46)	14 (54)	
Bowel tx	9	1 (11.1)	8 (89.9)	0.119	3 (33)	6 (67)	0.598

No bowel	42	16 (38.1)	26 (61.9)		18 (43)	24 (57)	
Use of anti-CMV prophylaxis				**0.001**			**0.041**
Yes	34	7 (20.6)	27 (79.4)		11 (32.4)	23 (67.6)	
No	14	10 (71.4)	4 (28.6)		9 (64.3)	5 (35.7)	
Performing HHV-8 DNA monitoring				**0.000**			
Yes	21	13 (61.9)	8 (38.1)		/	/	
No	30	4 (13.3)	26 (86.7)		/	/	
Diagnosis of at least one case of invasive HHV-8-associated disease in the previous 5 years§				0.07			0.126
Yes	30	13 (43.3)	17 (56.7)		15 (50)	15 (50)	
No	21	4 (19)	17 (81)		6 (28.6)	15 (71.4)	
Diagnosis of at least one case of non-neoplastic HHV-8-associated disease (e.g., KICS-like) in the previous 5 years				**0.027**			**0.007**
Yes	14	8 (57.1)	6 (42.9)		10 (71.4)	4 (28.6)	
No	37	9 (24.3)	28 (75.7)		11 (29.7)	26 (70.3)	

°3 responders were anonymous *Argentina, Belarus, Brazil, Canada, France, Greece, Israel, Netherlands, Slovenia, Spain, Sweden, Switzerland, U.K., U.S.A. § Excluding cutaneous KS

References

[1] Moore PS. The emergence of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8). N Engl J Med. 2000 Nov 9;343(19):1411-3. doi: 10.1056/NEJM200011093431912. PMID: 11070109.

[2] Liu Z, Fang Q, Zuo J, Minhas V, Wood C, Zhang T. The world-wide incidence of Kaposi's sarcoma in the HIV/AIDS era. HIV Med. 2018; 19(5): 355- 364.

[3] Haidar G, Singh N.Viral infections in solid organ transplant recipients: novel updates and a review of the classics.. Curr Opin Infect Dis. 2017 Dec;30(6):579-588.

[4] Riva G, Luppi M, Barozzi P, et al. L. How I treat HHV-8/KSHV-related diseases in posttransplant patients. Blood. 2012; 120(20): 4150- 4159.

[5] Thaunat O, Mamzer-Bruneel MF, Agbalika F, et al. Severe human herpesvirus-8 primary infection in a renal transplant patient successfully treated with anti-CD20 monoclonal antibody. Blood. 2006 Apr 1;107(7):3009-10. doi: 10.1182/blood-2005-08-3213. PMID: 16554487.

[6] Luppi M, Barozzi P, Schulz TF,et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med. 2000 Nov 9;343(19):1378-85. doi: 10.1056/NEJM200011093431905. PMID: 11070102.

[7] Polizzotto MN, Uldrick TS, Wyvill KM, 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 Mar 15;62(6):730-738. doi: 10.1093/cid/civ996.

[8] Mularoni A, Gallo A, Riva G, et al. 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. Am J Transplant. 2017; 17(11): 2963- 2969.

[9] Razonable RR. Human herpesviruses 6, 7 and 8 in solid organ transplant recipients. Am J Transplant. 2013 Feb;13 Suppl 3:67-77; quiz 77-8. doi: 10.1111/ajt.12008. PMID: 23347215.

[10] Dollard SC, Douglas D, Basavaraju SV, et al. Donor-derived Kaposi's sarcoma in a liver-kidney transplant recipient. Am J Transplant. 2018; 18(2): 510- 513

[11] Riva G, Barozzi P, Quadrelli C, et al. Human herpesvirus 8 (HHV-8) infection and related diseases in Italian transplant cohorts. Am J Transplant. 2013; 13(6): 1619- 1620.

[12] Luppi M, Barozzi P, Santagostino G, Trovato R, Schulz TF, Marasca R, Bottalico D, Bignardi L, Torelli G. Molecular evidence of organ-related transmission of Kaposi sarcoma-associated herpesvirus or human herpesvirus-8 in transplant patients. Blood. 2000 Nov 1;96(9):3279-81. PMID: 11050015.

[13] Chiereghin A, Barozzi P, Petrisli E, et al. Multicenter prospective study for laboratory diagnosis of HHV-8 infection in solid organ donors and transplant recipients and evaluation of the clinical impact after transplantation. Transplantation. 2017; 101(8): 1935- 1944.

[14] Pietrosi G, Vizzini G, Pipitone L, et al. Primary and reactivated HHV-8 infection and disease after liver transplantation: a prospective study. Am J Transplant. 2011; 11(12): 2715- 2723.

[15] Pellett Madan R, Hand J; AST Infectious Diseases Community of Practice. 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 Sep;33(9):e13518. doi: 10.1111/ctr.13518. Epub 2019 Apr 4. PMID: 30844089.

[16] Malinis M, Boucher HW; AST Infectious Diseases Community of Practice. Screening of donor and candidate prior to solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep;33(9):e13548. doi: 10.1111/ctr.13548. Epub 2019 Apr 29. PMID: 30900327

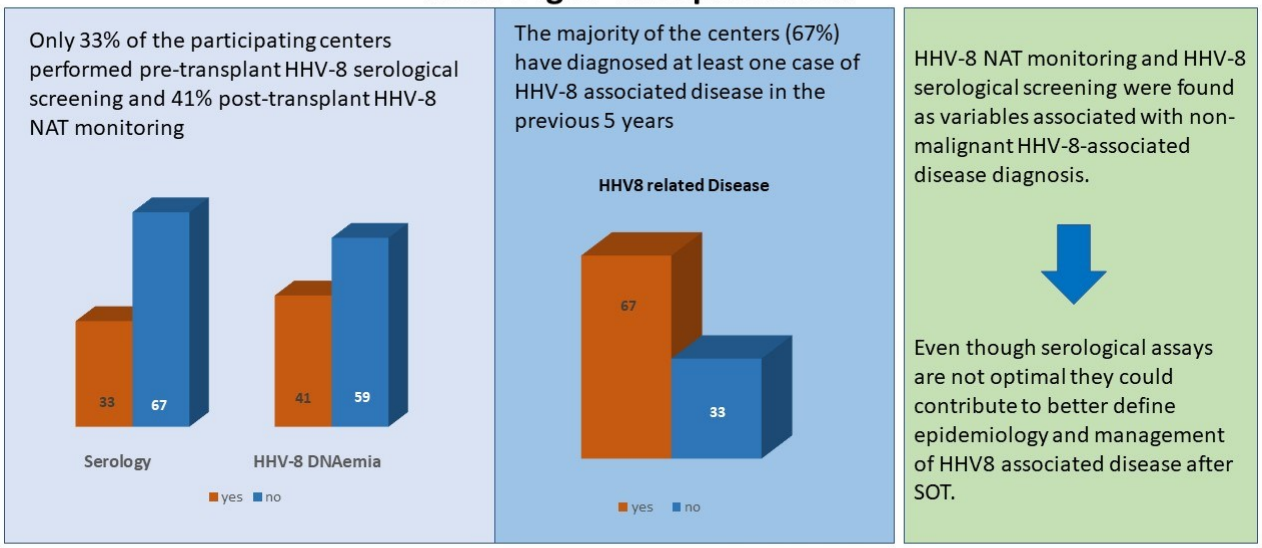
[17] Guide to the quality and safety of ORGANS FOR TRANSPLANTATION 7th edition (EDQM).

[18] Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS. Identification of herpesvirus-like DNA sequences in AIDS associated Kaposi’s sarcoma. Science 266: 1865–9, 1994.

[19] Lebbe C, Porcher R, Marcelin AG, et al. Human herpesvirus 8 (HHV8) transmission and related morbidity in organ recipients. Am J Transplant. 2013 Jan;13(1):207-13. doi: 10.1111/j.1600-6143.2012.04290.x. Epub 2012 Oct 11. PMID: 23057808.

Visual Abstract-

International Survey of Human Herpes Virus 8 Screening and Management in Solid Organ Transplantation



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TRANSPLANT INFECTIOUS DISEASE