

HHV8/KSHV infection in SOT: Unmet Needs

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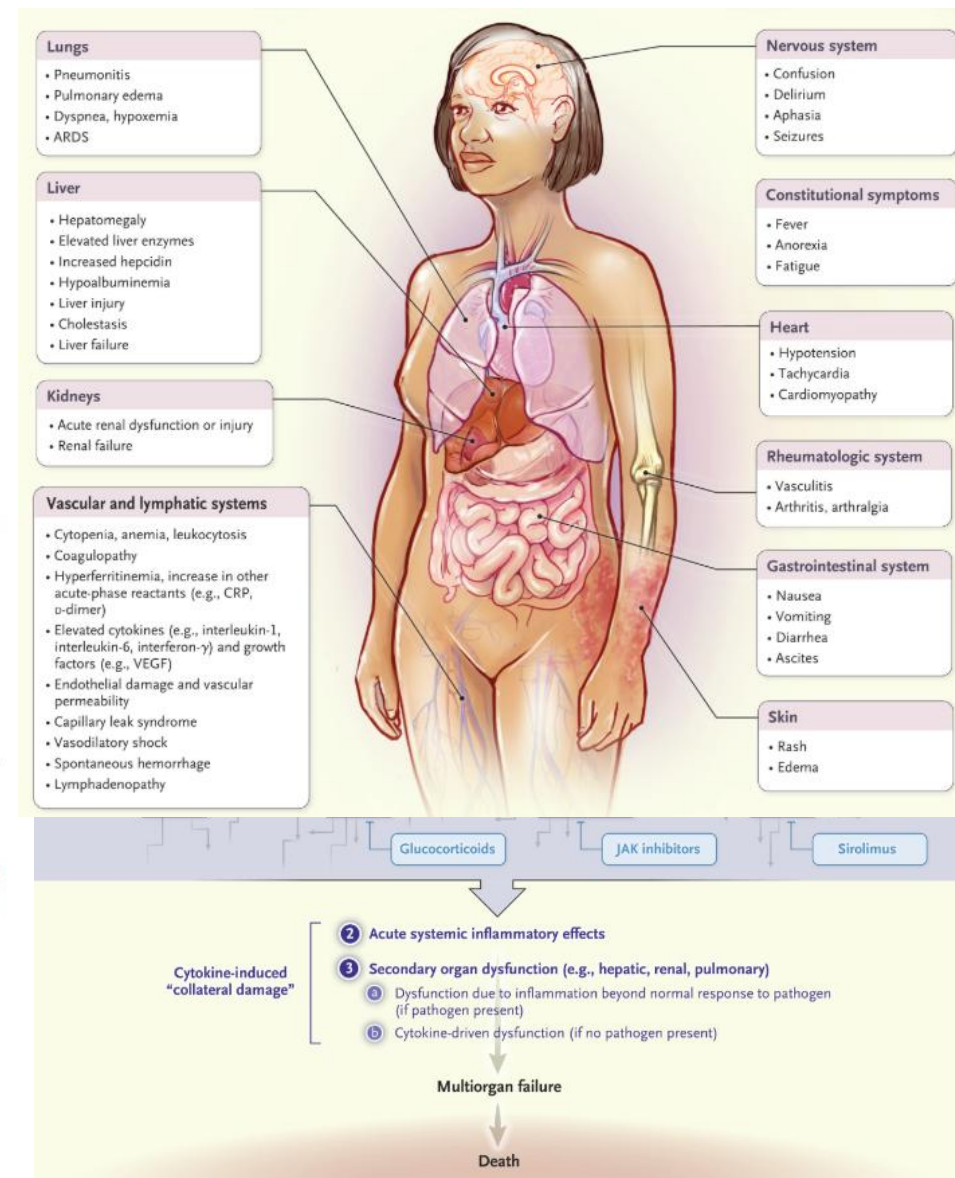
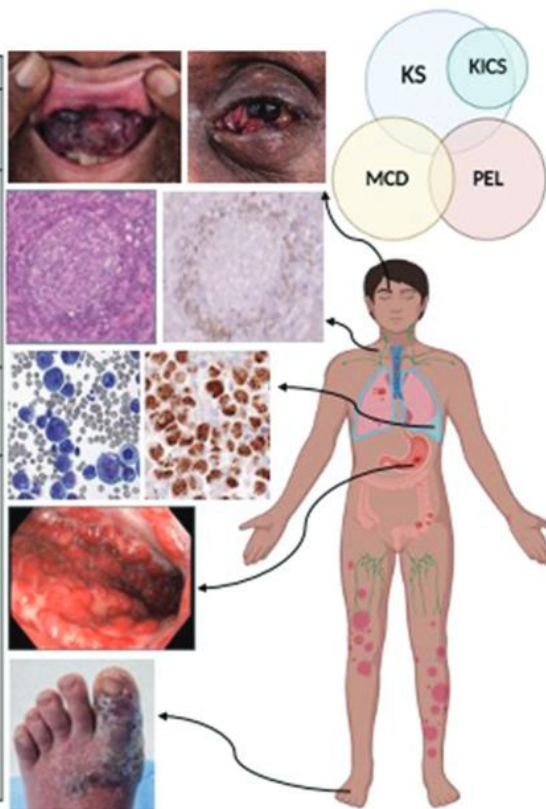
Transplant Infectious Disease

ISMETT *Istituto di Ricovero
e Cura a Carattere
Scientifico*

UPMC **LIFE
CHANGING
MEDICINE**

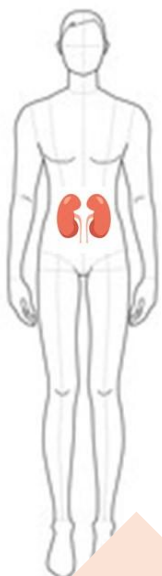
Kaposi sarcoma herpesvirus (KSHV)/HHV-8 infection can cause severe diseases in SOT

KAD subtype	Diagnostic criteria
Kaposi Sarcoma (KS)	Biopsy of a KS lesion with appropriate histopathology (spindle-shaped cells) and presence of KSHV confirmed by immunohistochemistry of latency-associated nuclear antigen (LANA) expression
Multicentric Castleman Disease (MCD)	- Lymph node with characteristic pathological change with evidence of inflammatory signs or symptoms Laboratory abnormalities: Elevated CRP, anemia, thrombocytopenia, hypoalbuminemia Clinical criteria: Constitutional symptoms (fevers, night sweats, weight loss) hepatosplenomegaly, edema
Primary Effusion Lymphoma (PEL)	Cytology of effusions or affected tissue (large cells with round to irregular nuclei and prominent nucleoli with varying amounts of basophilic cytoplasm) along with LANA positive neoplastic cells
Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS)	- At least 2 clinical manifestations from at least 2 categories: Symptoms: Fever, fatigue, edema, cachexia, respiratory symptoms, GI disturbance, arthralgia/myalgia, altered mental state, neuropathy Laboratory abnormalities: Anemia, thrombocytopenia, hypoalbuminemia, hyponatremia Radiographic abnormalities: Lymphadenopathy, splenomegaly, hepatomegaly, body cavity effusions - Evidence of systemic inflammation (CRP ≥ 3 g/dL) - Elevated KSHV viral load in plasma (≥ 1000 copies/mL) or peripheral mononuclear cells ≥ 100 copies/10^6 cells) Diagnosis of exclusion - no pathologic evidence of MCD or PEL Requires biopsy of any lymphadenopathy if present



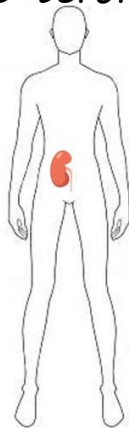


Donor
67 yo italian man

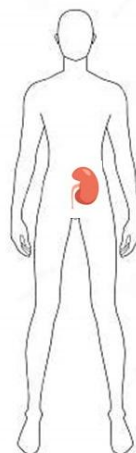


On stored samples:
HHV-8 serology positive
HHV-8 DNA positive

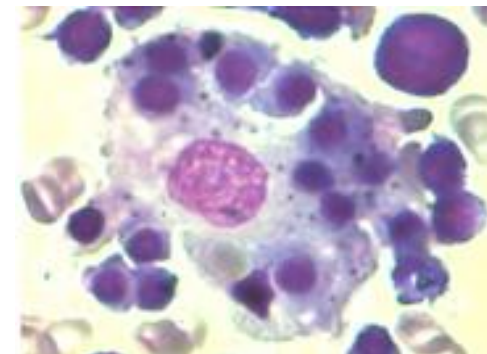
Recipient A
61 yo
HHV-8 seronegative



Recipient B
44 yo
HHV-8 seronegative



**Disseminated Kaposi
Sarcoma**
Cytopenia
Haemophagocytosis



pegylated liposomal
doxorubicin and foscarnet



Recovered

4 months after transplant

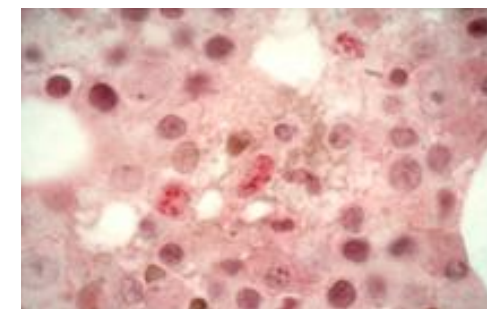
HHV-8 serology positive
HHV-8 DNA positive

antivirals and i.v.
immunoglobulins



died of MOF
in 1 month

Fever
Splenomegaly
Pancytopenia
Bone Marrow Failure



The incidence of HHV-8-associated disease in SOT is increasing

← growing population of SOTr with prolonged life expectancy, increased awareness

Update from the U.S. Centers for Disease Control and Prevention

Sept. 30, 2025

Update from CDC: Increased Reports of Kaposi Sarcoma-associated herpesvirus (KSHV)

- During 2021– 2025 CDC has received **increasing reports of suspected organ donor-derived HHV8 infection resulting in Kaposi sarcoma, KICS, or other related complications in SOT recipients**
- Presence of HHV8 risk factors should not result in **deferral** of donors

Clinicians should **maintain a high level of suspicion for HHV8** in recipients with culture-negative sepsis (may be KICS) and other signs or symptoms of KAD→ To enable **prompt diagnosis and reporting**

- **Recipient testing** should include both molecular and serologic assays, when available:
- **Access to commercially-available serologic testing is currently limited in the United States.**

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 antivirals

4

Patients with KICS receive **Anti-CD20 Mab** (Rituximab) with antivirals

Rate of seroprevalence **Donors 3.2% Recipients 8.4%**

49
D+/R-

155
R+

Rate of transmission 45%
HHV-8 related disease 26.5%
Mortality 18%

Rate of reactivation 8%
HHV-8 related disease 2%
Mortality 1.3%

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

PRE- Intervention

2011-2016:

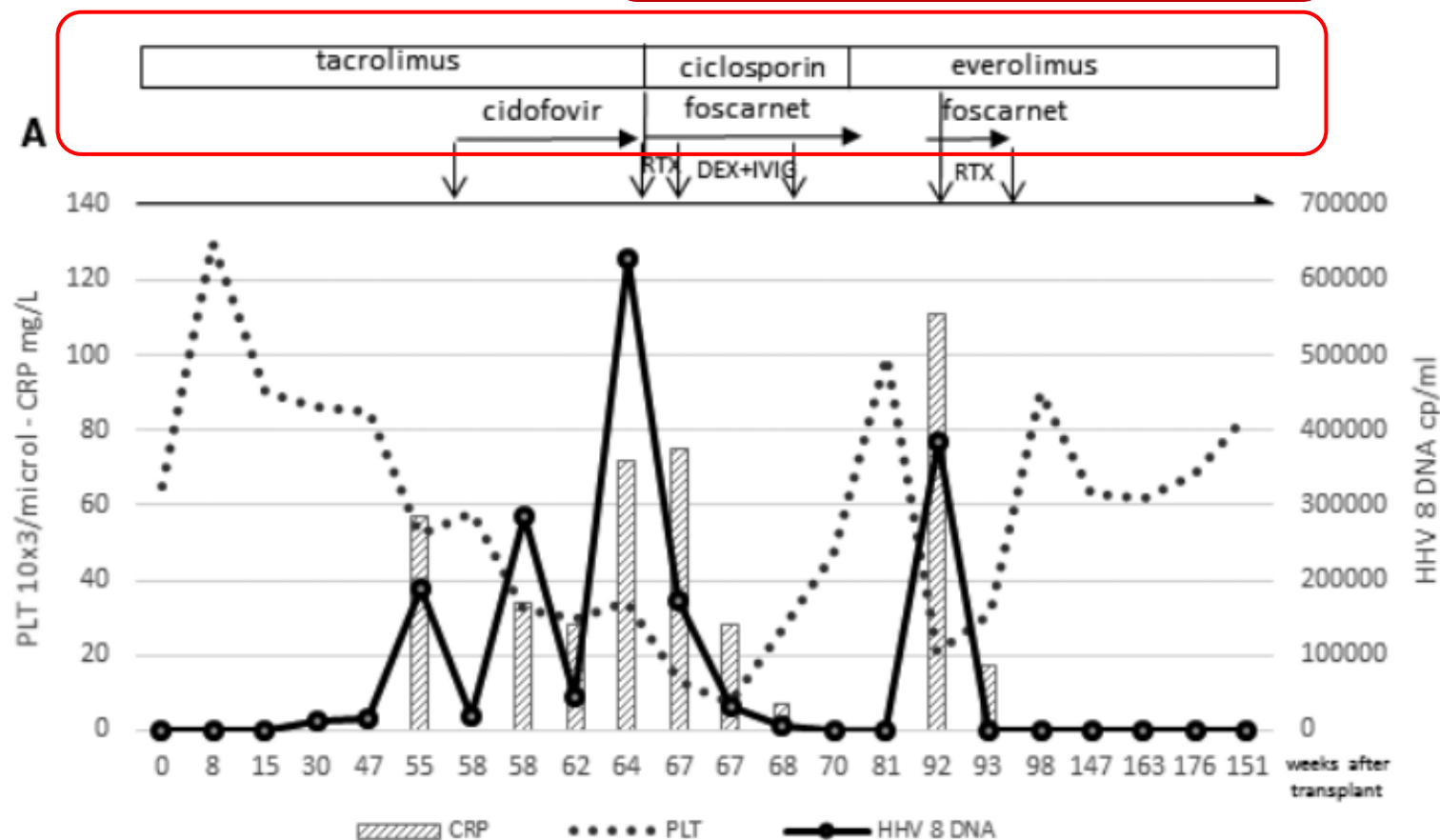
Treatment of advanced symptomatic disease with **Antivirals only**
(Foscarnet/Cidofovir)

Mortality 75%

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, A. Gallo, G. Riva, P. Barozzi, M. Miele, G. Cardinale, G. Vizzini, R. Volpes, P. Grossi, D. Di Carlo, A. Luca, T. Trenti, M. Luppi, P. G. Conaldi

Rituximab



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POST-Intervention

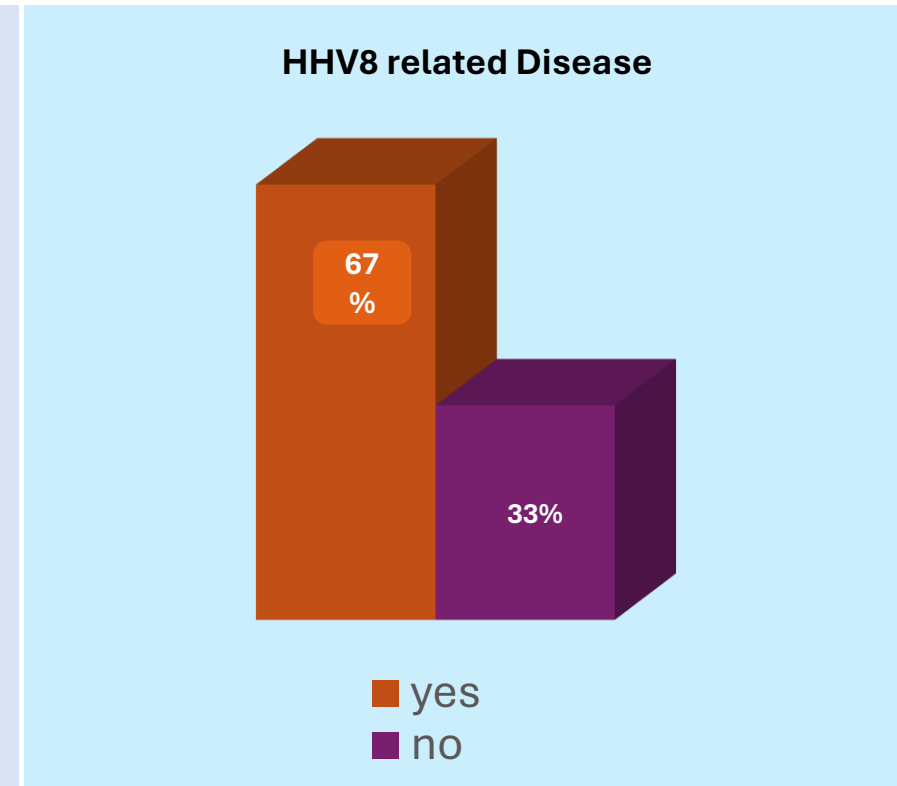
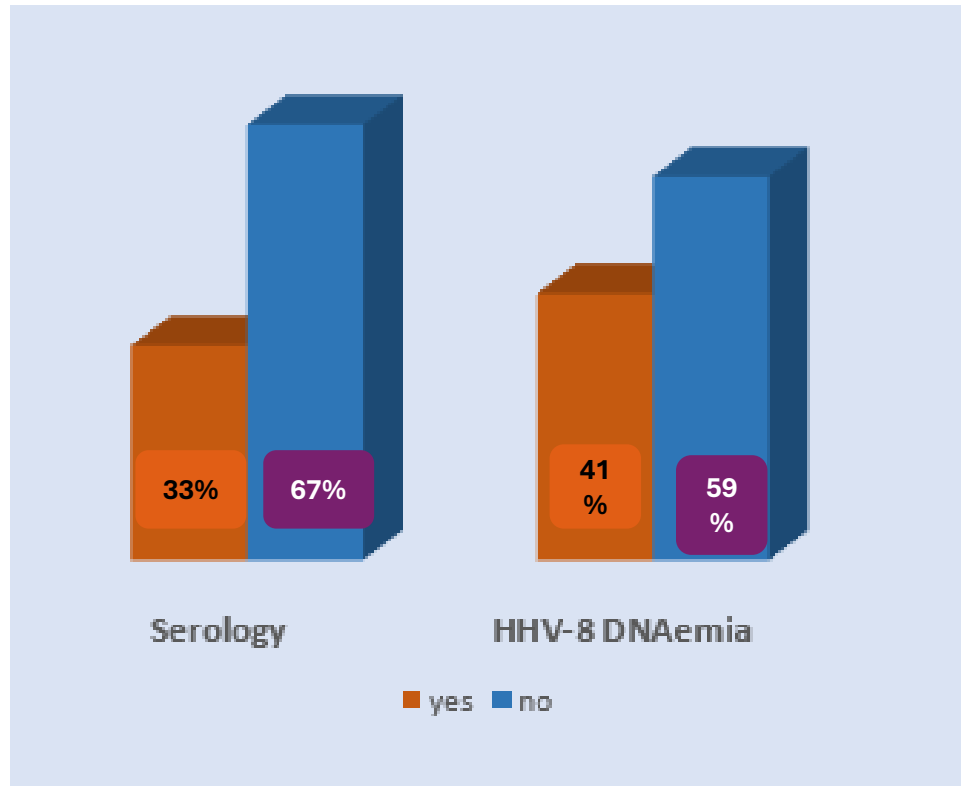
2017-2023:

Detectable HHV8DNA -> **early switch to m-TOR inhibitor** and strict **clinical surveillance**
KICS -> rituximab + antivirals

Mortality
14%

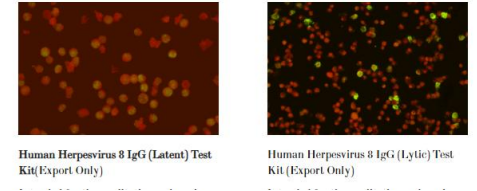
International Survey: HHV-8 screening in SOT

51 centers from 15 countries



Risk assessment based on serological match of donor and recipient is the key to **identify the highest-risk group** for close surveillance and **risk mitigation** strategies

Screening: We need a standardized test



- **IFA-ScimedX:** the gold standard, it uses human lymphocytes expressing **lytic and latent HHV8 antigens**.

Limitations: It is a manual test that relies on the operator performing the technique, **time-consuming and operator-dependent**.

- **ELISA test:** could be **partially automatized** and has the advantage of being **independent of microscopic slide reading**. Data on his performance are conflicting
- **A reliable HHV-8 serology test should be made available for clinical research and for identifying high-risk patients.**

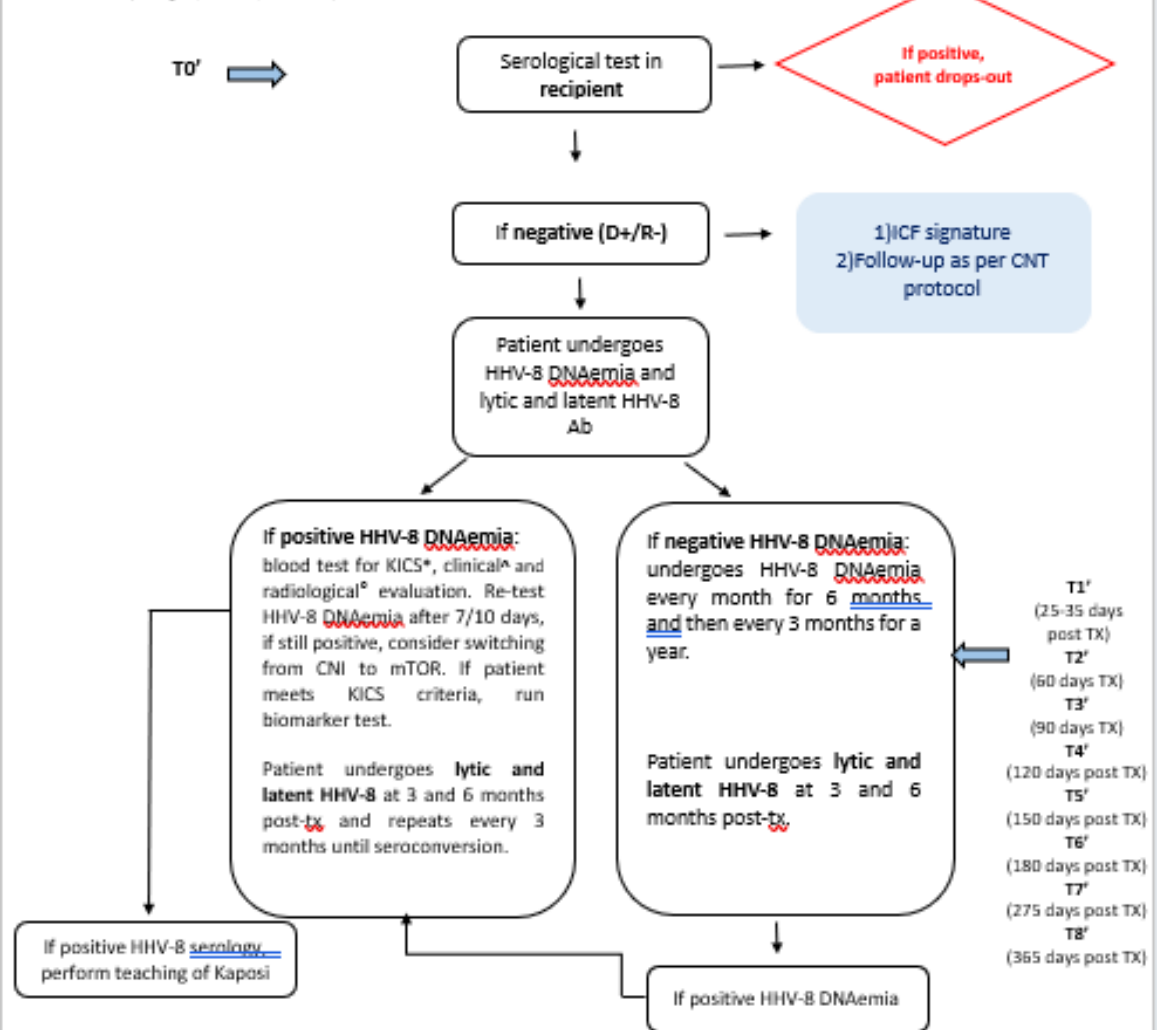
Monitoring and Therapeutic Protocols

- What is the **cut off of DNAemia** that **predict disease**? Role of **Digital PCR**?
- What are the mechanisms driving HHV-8 infection toward **neoplastic or inflammatory** disease? **Comparative immunological profiling** could help identify key pathways and guide interventions.
- Potential role of **new antivirals** (Maribavir inhibits EBV transcription)? **Artesunate?**
- **HHV8 Quantiferon/IGRA** could predict the evolution to **Disease**? an inverse relationship between detection of virus-specific T-cell responses and virus control has been reported for almost all Herpes viruses.
- **Multivirus-specific T-cell therapies incorporating HHV-8 antigens** to restore antiviral immunity in transplant recipients
- A **prospective, interventional multicenter study** will be crucial to establish **standardized diagnostics** through collection of serum samples from seropositive patients, unravel the **immunopathogenesis of HHV-8-related diseases**, and develop **tailored therapeutic strategies** to reduce morbidity and mortality in SOT recipients.

Multicenter Prospective Study

- In Italy we are Launching a multicenter study involving **25 SOT centers**
- **Donor Serology** (available post-transplant) will be **performed in 3 hubs**
- Aim: Risk Stratification in order to put in place Risk mitigation strategies
- **International Study?**

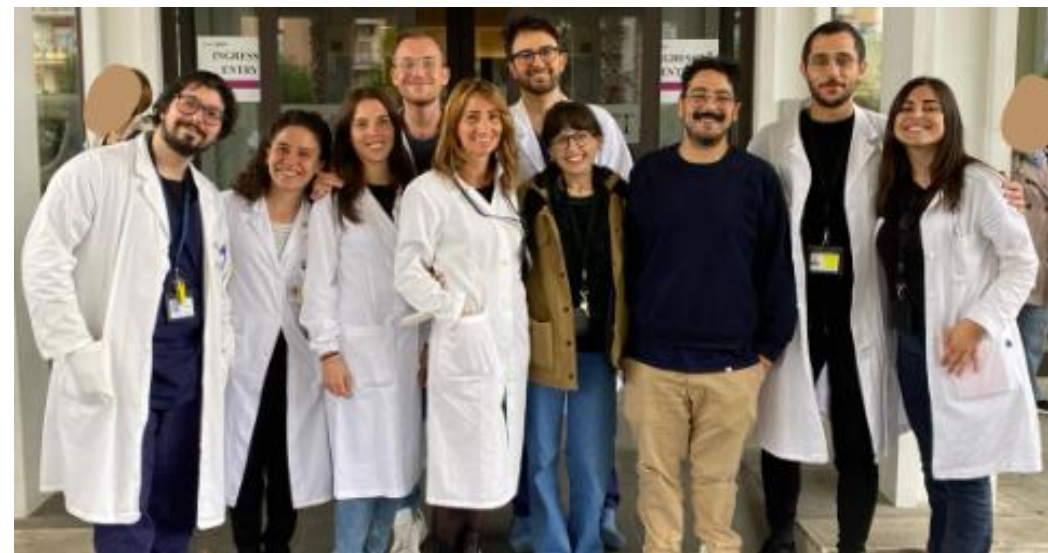
Lytic and latent HHV-8 Ab test on donor serum:
- On site
- Donor's serum storage in biobank and shipment every 20 days at reference hubs (Bologna, Milano, Palermo)



*Hemoglobin, white blood, sodium, urea, creatinine, c-reactive protein, albumin, bilirubin, fibrinogen.

^Fever, fatigue, edema, respiratory symptoms, gastrointestinal disturbance, athralgia, myalgia, cachexia, altered mental state, neuropathy with or without pain, anemia, thrombocytopenia, hypoalbuminemia, hyponatremia.

° Hepatosplenomegaly, lymphadenopathy, body cavity effusions, ascites.



Thank you!

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CHANGING
MEDICINE**