A N J H

Past and perspectives in

Kaposi's sarcoma

Celeste Lebbe, MD PhD
Saint-Louis University Hospital — APHP
Université Paris Cité, France

Disclosures

Investigator and / or consultant and / or speaker and / or research funding:

BMS **MSD** **Regeneron** **Pierre Fabre** **Novartis**

No conflict of interest related to the present content.

Outline

01 Epidemiology of Kaposi's sarcoma

02 Post-transplant KS and HHV-8

03 The unsolved enigma of the KS progenitor

04 Immune responses in KS

05 KS management — current standards & emerging therapies

SECTION 01

Epidemiology of KS

Kaposi's sarcoma — four clinical subtypes

01

Classic KS

Elderly men, Mediterranean & Eastern European origin

02

Endemic KS

Sub-Saharan Africa, all ages, HIV-negative

03

HIV-associated KS

AIDS-defining malignancy; aggressive

04

Post-transplant KS

Iatrogenic immunosuppression (SOT)

Factors and cofactors

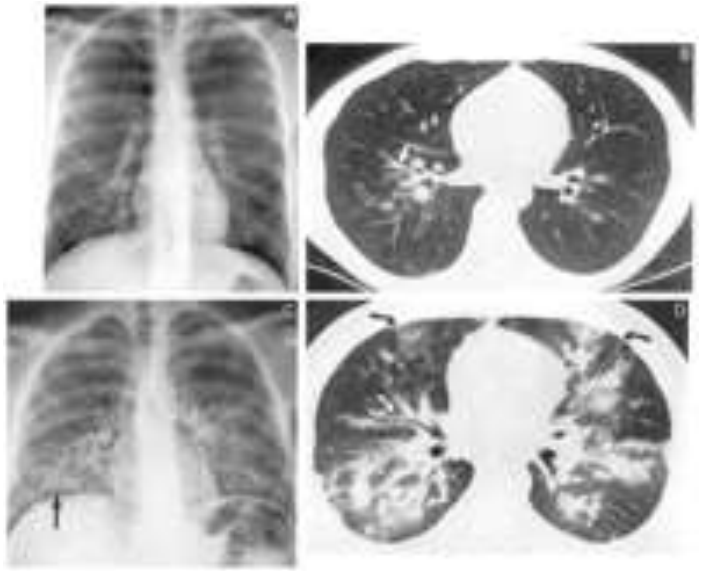
HHV-8 infection : all

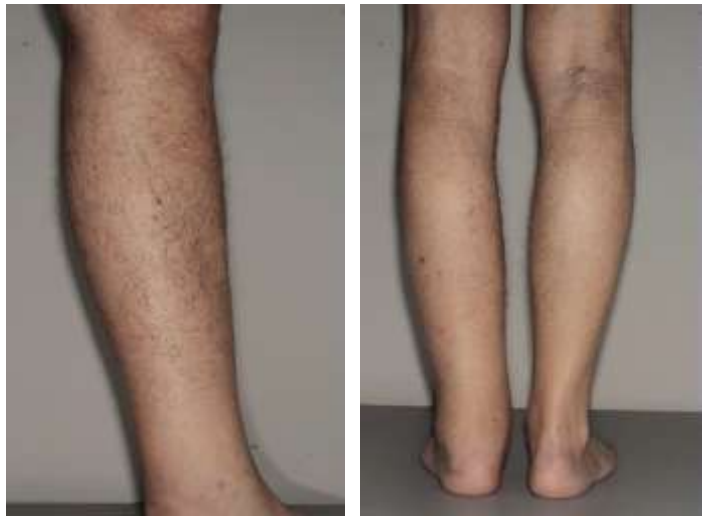
Immunosuppression

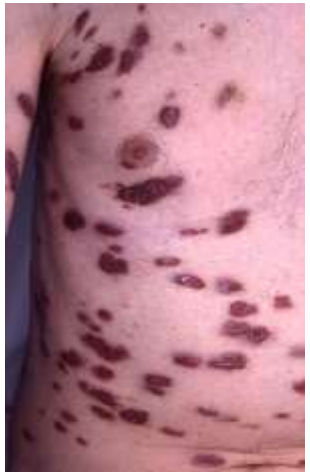
Hormonal factors

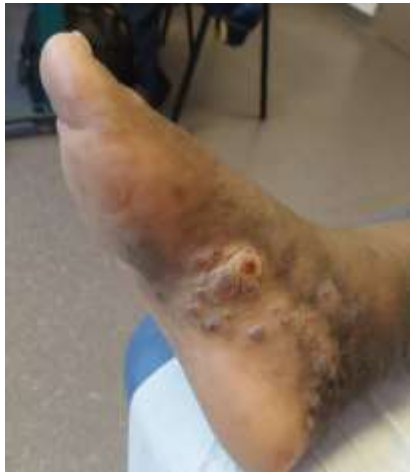
Host genetics

Kaposi's sarcoma — clinical presentation across subtypes



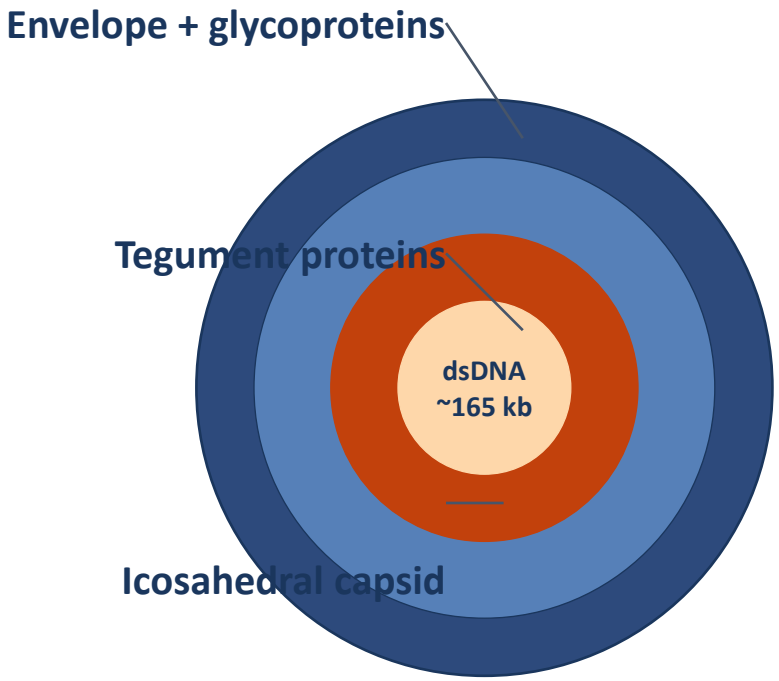






HHV-8 / KSHV — the causal agent

Kaposi sarcoma–associated herpesvirus

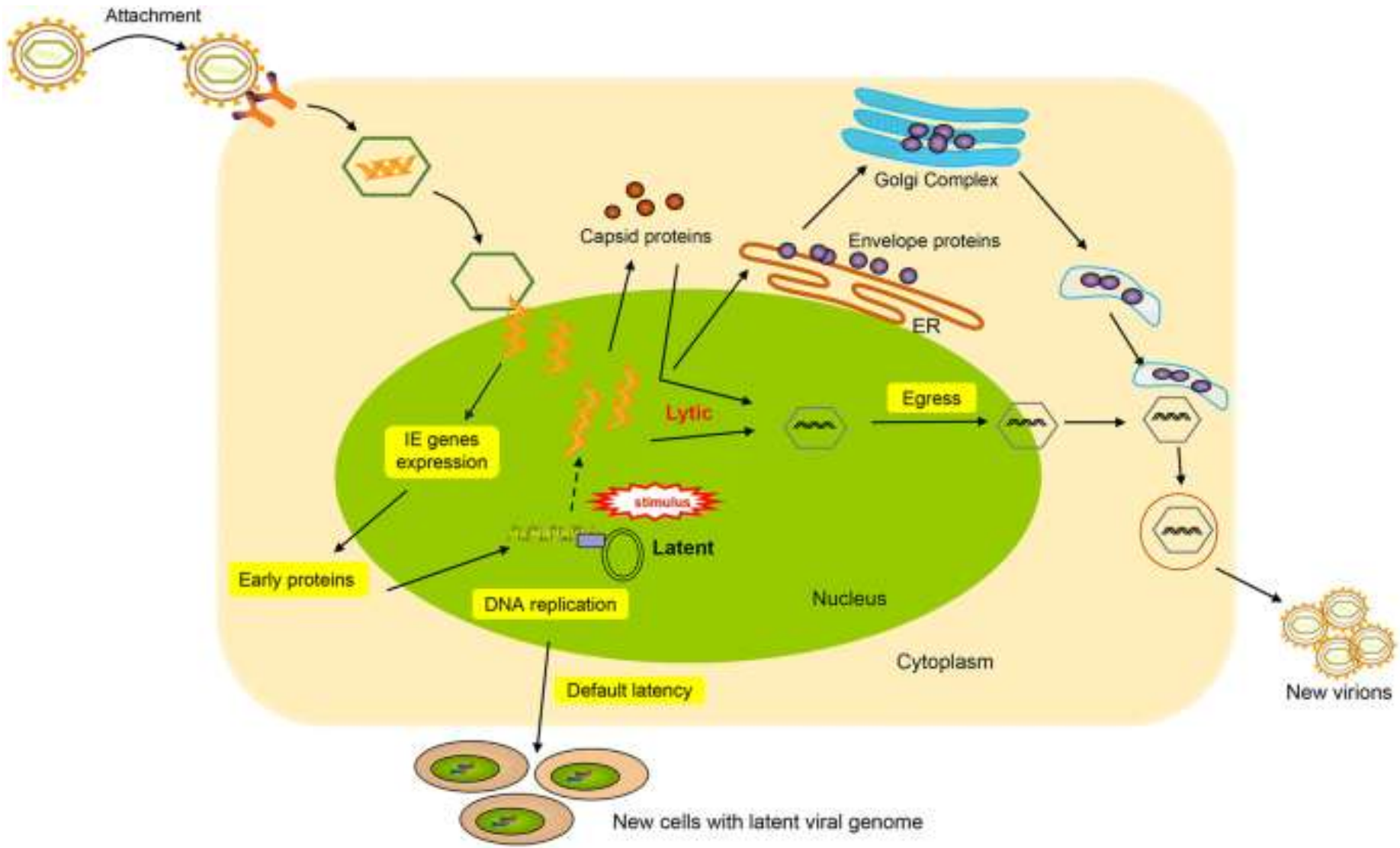


Family	γ-Herpesviridae
Genus	Rhadinovirus
Genome	Double-stranded DNA, ~165 kb
Discovery	Chang & Moore, 1994

OR ≈ 100 Odds ratio for detection of HHV-8 in KS tissues — strongest viral-cancer association ever reported

Adapted from Yan et al., 2019; Chang et al., Science 1994

HHV-8 — latent vs lytic cellular cycle



Adapted from Yan et al., 2019. Default latency in newly infected cells; stimulus-triggered lytic reactivation produces new virions.

HHV-8 — latent and lytic phases

A reversible viral life-cycle balancing persistence and dissemination

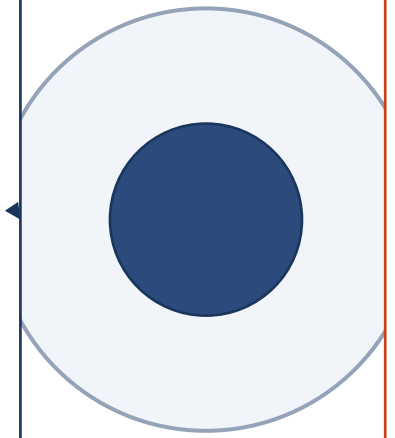
Latent phase

LANA (ORF73)
episome maintenance

v-Cyclin, v-FLIP
proliferation & anti-apoptosis

Kaposin, miRNAs
tumour-promoting non-coding RNAs

Persistent infection
of spindle cells



Host cell

Lytic phase

RTA (ORF50)
master switch — lytic reactivation

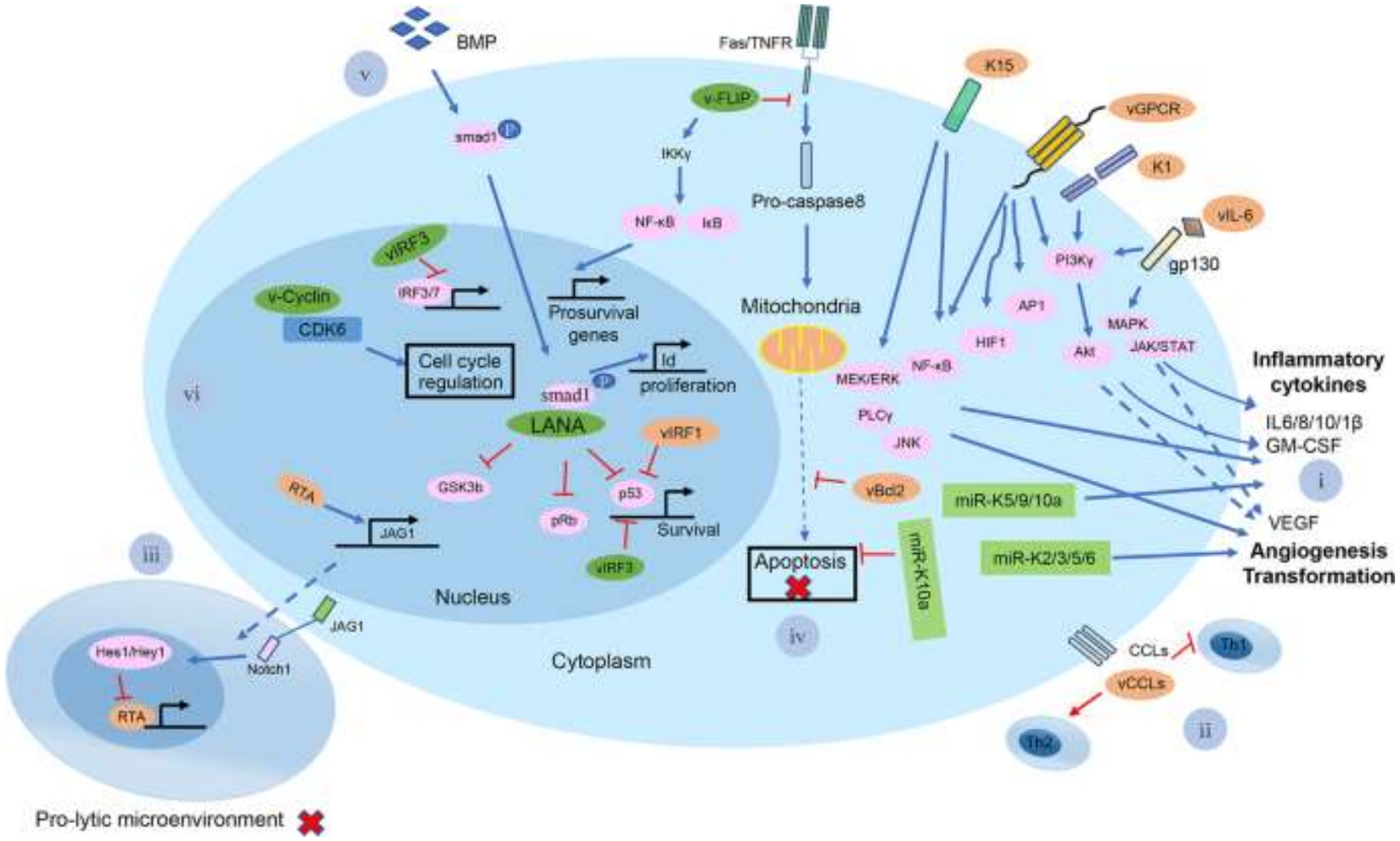
K8.1, ORF65
structural proteins

vGPCR, vIL-6
paracrine signaling & angiogenesis

Viral spread
and inflammation

Adapted from Yan et al., 2019; Cesarman et al., Nat Rev Dis Primers 2019

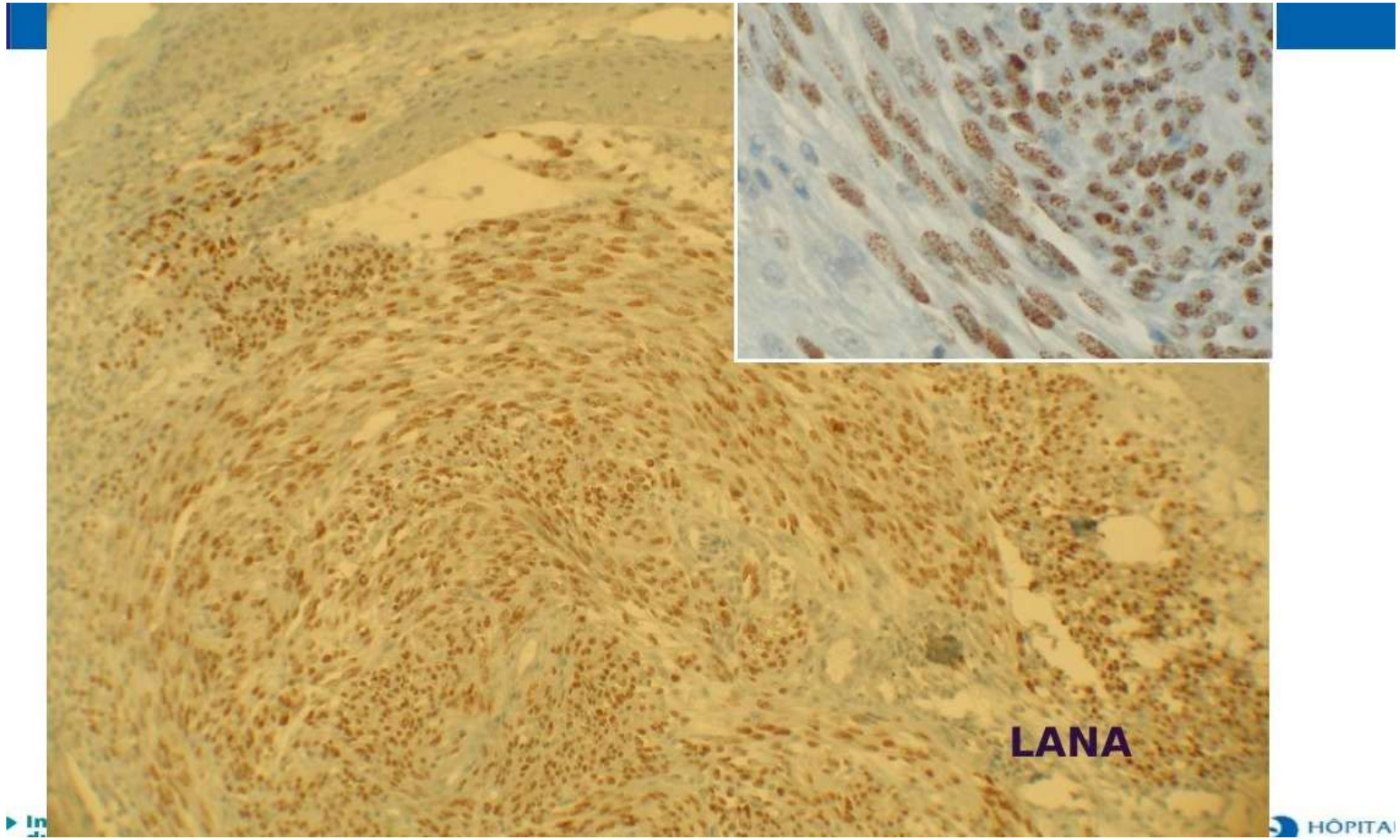
KSHV — molecular pathways driving KS, PEL and MCD



Adapted from Lange P. et al., Trends in Microbiology 2020. Latent viral proteins (LANA, v-Cyclin, vFLIP) and lytic factors (RTA, vGPCR, vIL-6, K1, K15, miRNAs) converge on cell-cycle control, NF-κB activation, angiogenesis (VEGF) and inflammatory cytokine release.

Diagnostic confirmation — LANA immunohistochemistry

Nuclear LANA staining of spindle cells confirms KSHV-driven KS



Anti-LANA (ORF73) IHC — punctate nuclear staining pattern characteristic of HHV-8 latency in tumour spindle cells.

Epidemiology of KS — global picture

GLOBAL

>34 000

Estimated new cases of KS worldwide in 2020

BURDEN

73 %

Of cases occurring in sub-Saharan Africa (>70 %HIV related)

TREND

↓ since cART

Incidence sharply reduced in PLHIV in HIC

KS remains a major HIV-associated malignancy in low- and middle-income countries, while incidence has declined in high-income settings since the cART era.

Fu et al., Lancet Glob Health 2023; doi:10.1016/S2214-109X(23)00349-2

KS risk persists in PLHIV despite immune restoration

Even in PLHIV with restored immunity (CD4 > 500 / mm³), the risk of KS remains markedly elevated compared with the general population.

× 60

Relative risk of KS for patients with a recent CD4 > 500 / mm³

× 35

Relative risk with CD4 > 500 for ≥ 2 years AND HIV viral load < 500 copies / mL

Costagliola et al., 2021 — French Hospital Database on HIV (FHDH-ANRS CO4)

HIV-associated KS — clinical phenotypes

Viremic KS

Detectable HHV-8 viremia; younger patients, lower CD4, often more aggressive disease.

Aviremic KS Classic-like KS in PLHIV

Undetectable HHV-8 viremia; controlled HIV, indolent course, lower visceral involvement.
Older PLHIV, long-term virologic control, presentation similar to classic KS.

Caby et al., Clin Infect Dis 2021; Severin, AIDS 2021; Palich, Cancers 2021

Classic & endemic KS — sparse recent data

No recent large-scale incidence data for classic and endemic KS. Incidence is markedly higher in Mediterranean countries.

United Kingdom

0.014

cases / 100 000 person-years

Sardinia (Italy)

0.77 – 2.43

cases / 100 000 person-years

≈ 100× higher incidence

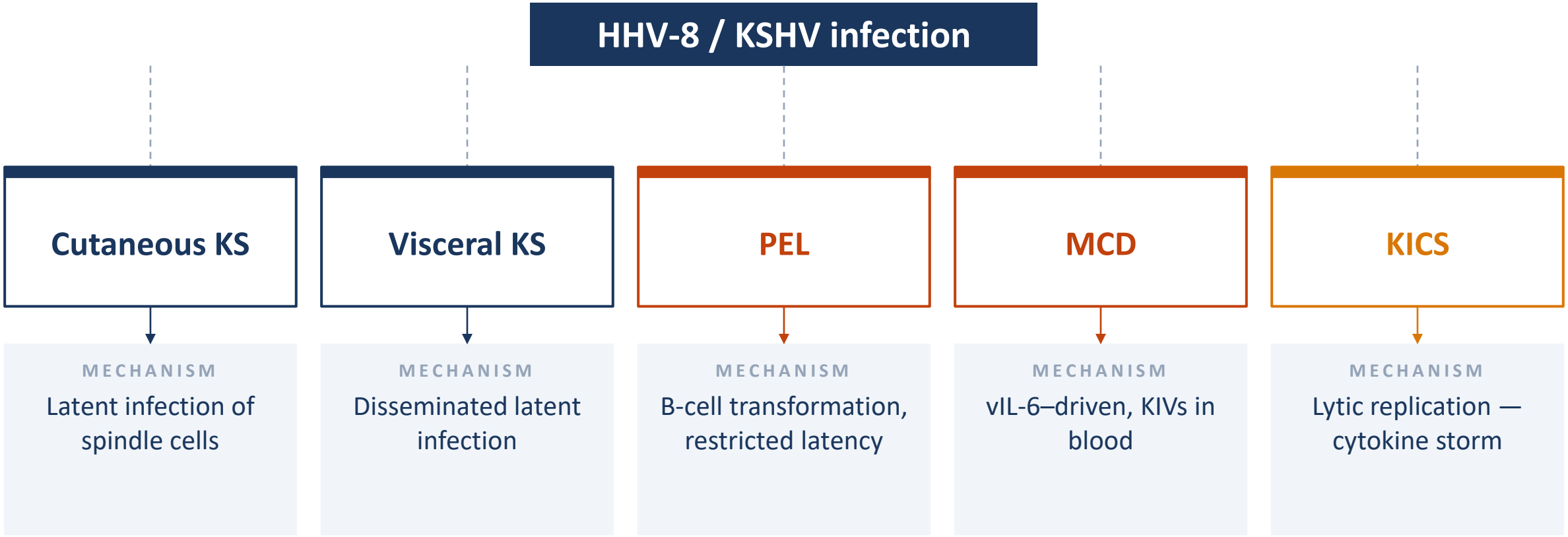
Cottoni 1996 — Grulich 1992 — Hjalgrim 1996

SECTION 02

Post-transplant KS and HHV-8

DISEASE SPECTRUM

Five faces of HHV-8 / KSHV in transplant recipients

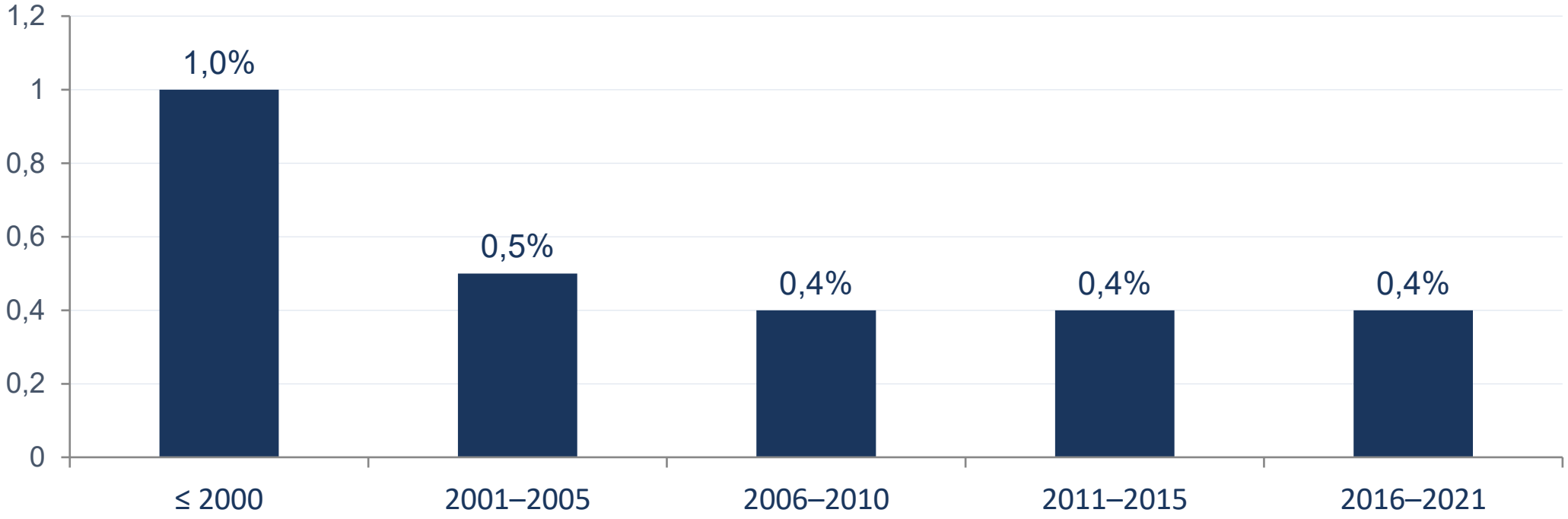


Latency-restricted genes drive vascular and B-cell tumours · Uncontrolled lytic replication drives the cytokine storm of KICS

Mularoni et al., Transpl Infect Dis 28 (2026) e70179

KS incidence in SOTR — France (Agence de la biomédecine)

Cumulative incidence of KS in solid organ transplant recipients



Marked decrease in post-transplant KS incidence over the past two decades, attributed to reduced immunosuppression intensity and earlier conversion to mTOR inhibitors.

Source: Agence de la biomédecine — French national transplant registry

KS incidence in SOTR — international trends

Standardized incidence ratios (SIR) of KS in solid organ transplant recipients have declined since the 2000s, in both US and European cohorts.

Cahoon et al. (US)

Risk of KS after solid organ transplantation — United States, 1987–2014

SIR ↓

Sharp decline after first post-transplant year

Int J Cancer 2018;143:2741–2748

Piselli et al. (Italy)

Incidence of KS after kidney transplantation — Italy, 1997–2016

Within 3 yrs ↓

Reduced risk both within and beyond 3 years post-transplant

Int J Cancer 2019

RISK AND PRESENTATION

Post-transplant KS: frequent visceral involvement

× 400

Higher KS risk in SOT recipients vs general population

20–50 %

Of PT-KS cases involve viscera (GI, lung, graft)

20–40 %

Involve lymph nodes — often without skin lesions

When to suspect KS in a SOT recipient

- Violaceous macules / plaques (limbs, palate, scars)
- Lymphadenopathy or graft dysfunction without cause
- Respiratory symptoms (esp. lung recipients)
- GI bleeding, unexplained anaemia → endoscopy + biopsy
- Confirm with LANA IHC; FDG PET/CT to stage

Highest-risk profile

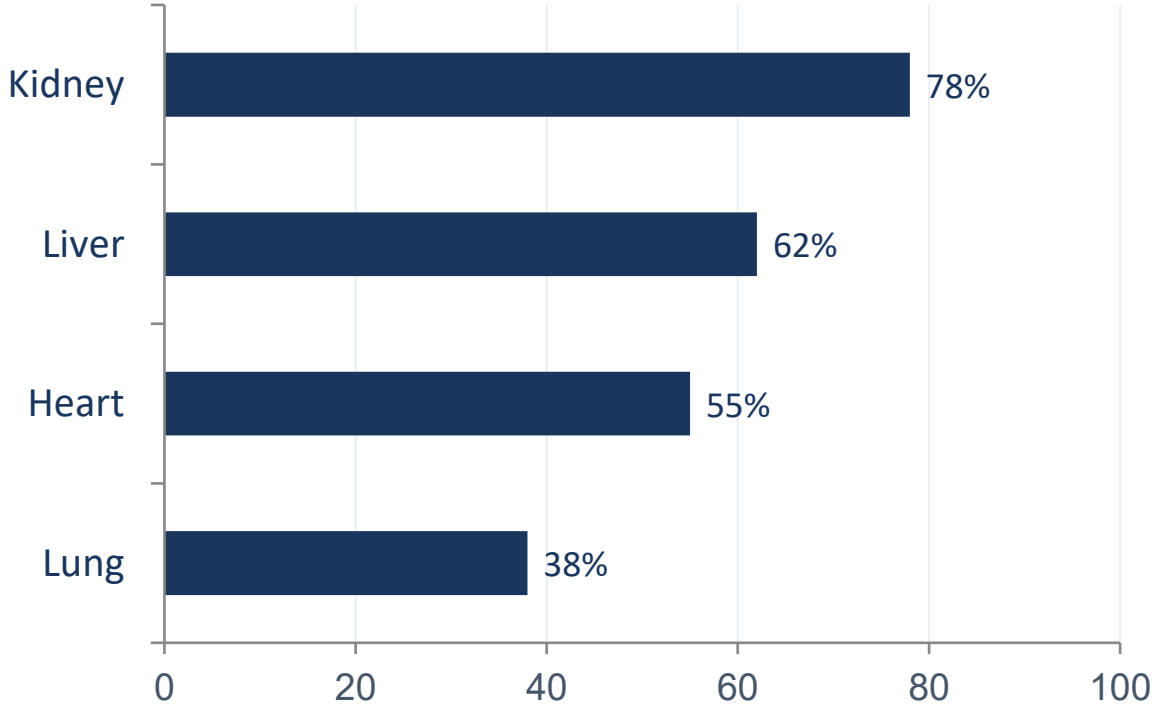
Donor status	D+/R− primary infection — earlier, more severe
Organ type	Lung recipients carry highest reported incidence
Timing	Most cases within first 18 months post-transplant
Host factors	Male, older age, Mediterranean / sub-Saharan origin
Co-syndromes	Concurrent KICS, MCD or HLH may complicate

Mularoni et al., Front Immunol 2026 · doi:10.3389/fimmu.2026.1698179

OUTCOMES AND MANAGEMENT

Survival by organ and stepwise management

Overall survival (%) by transplanted organ



Pooled from 100 studies, 663 PT-KS cases (Mularoni 2026)

Stepwise management

1. **Modulate immunosuppression**
   Reduce CNIs; convert to mTOR inhibitor (sirolimus / everolimus).
2. **Local therapy for skin-limited**
   Cryotherapy, excision, IL chemo, radiotherapy, imiquimod.
3. **Systemic therapy**
   First line PLD; second line paclitaxel.
4. **Treat concurrent KAD**
   KICS / MCD: rituximab ± anti-IL-6; ICIs investigational.

Mularoni et al., Front Immunol 2026

FOCUS · PRIMARY EFFUSION LYMPHOMA

PEL: rare, aggressive, almost uniformly fatal in SOT

PEL is a rare non-Hodgkin lymphoma classically presenting usually as lymphomatous effusions in pleural, peritoneal or pericardial cavities, without solid tumour masses.

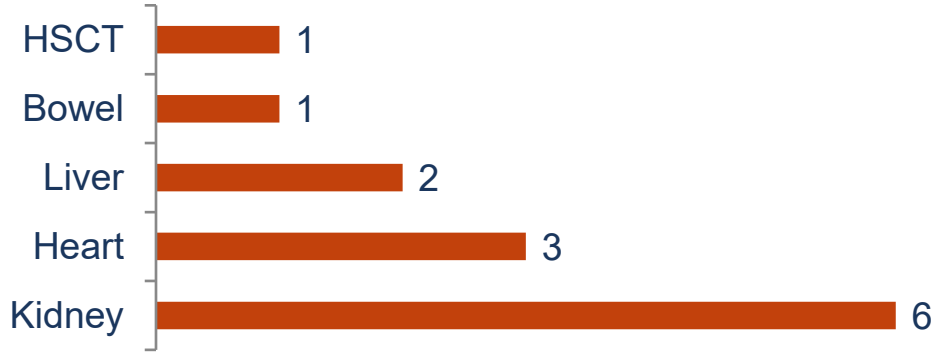
Pathogenesis

HHV-8/KSHV–driven B-cell transformation with restricted latency. Plasmablastic cells express LANA, vIL-6, IRF4 and cytoplasmic IgMλ. EBV co-infection common.

Clinical course

Aggressive; poor response to conventional regimens. 13 PT-PEL cases in recent review — all fatal within months. KS co-occurred in 4/13.

13 PT-PEL cases by organ



100 % mortality within months despite chemotherapy

Mularoni et al., Transpl Infect Dis 28 (2026) e70179

KSHV-MCD — Lurain et al. 2018

Multicentric Castleman Disease

Clinical

Intermittent fevers, night sweats, fatigue, weight loss, edema, diffuse lymphadenopathy and splenomegaly. CRP and KSHV viral load track active disease.

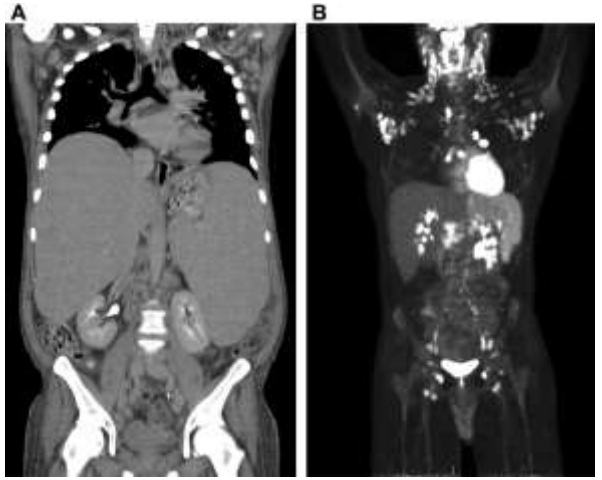


Fig. 2 — CT & ^{18}FDG-PET

Histology

KSHV-infected plasmablasts in the mantle zone form polyclonal microscopic collections ("microlymphomas"); cytoplasmic IgM, λ-restricted, LANA-1+, vIL-6+, EBV−.

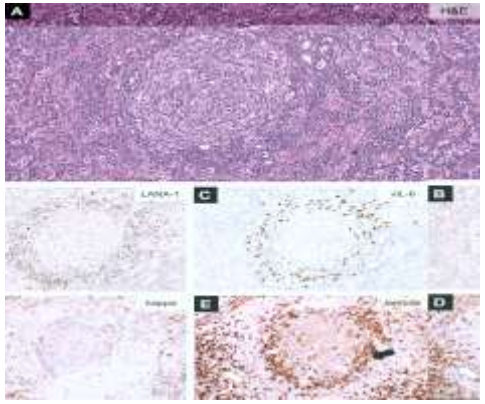


Fig. 3 — H&E, LANA-1, vIL-6, λ/κ

RESEARCH · BLOOD ADVANCES 2023

Circulating KSHV-infected viroblasts (KIVs) in active KSHV-MCD

Martin de Frémont, Vanjak et al. — Hôpital Saint-Louis, Université Paris Cité

78 %

Of patients with active KSHV-MCD show circulating KIVs (14 / 18)

0 / 40

Controls (KSHV+ and KSHV−) show this population

IgM^{+} λ^{+} CD38^{high}

Surface signature defining a circulating KIV (also CD24^{-})

KSHV Inflammatory Cytokine Syndrome (KICS)

A severe, often donor-derived complication mimicking culture-negative sepsis

Defining criteria

- High HHV-8 viral load
- Elevated CRP
- No Castleman disease
- ≥ 2 clinical or laboratory findings
- Fever, oedema, cytopenias, effusions

Why it matters

- Dominant donor-derived KSHV event in SOT
- Rapidly fatal if missed — mimics septic shock
- Non-specific hyperinflammation, high IL-6 / IL-10
- Often without skin involvement

Combine antivirals with mTOR switch etoposide and rituximab when KICS occurs.

Goldman JD, La Hoz RM, Am J Transplant 2025;25:898–899

HHV-8 seroprevalence — French national study

Multicenter study (Jan 2004 – Jan 2005). All donors and recipients screened by latent-IFA and lytic-IFA at transplantation.

French donors

Seroprevalence

1.05 %

Positive: 40 / 3 819

Exhaustiveness: 97.5 %

Regional range: 0 % (North) → 2.1 % (Paris)

Kidney recipients

Seroprevalence

2.11 %

Positive: 149 / 5 130

Exhaustiveness: 74.2 %

Regional range: 0.9 % (West) → 6.2 % (Paris)

Frances et al., Am J Transplant 2009

REVIEW · TRANSPLANT INFECTIOUS DISEASE · 2026

HHV-8 / KSHV in solid organ transplantation

An updated review of HHV-8 / KSHV–associated diseases (KADs) in SOT recipients, focused on the emerging entity KICS — KS Herpesvirus Inflammatory Cytokine Syndrome — and on screening / risk-mitigation strategies for donors and recipients.

3–4 %

Donor seroprevalence (EU)

Italy, France, Netherlands

8–18 %

Recipient seroprevalence (EU)

Highest in liver recipients

41 %

HIV+ kidney recipients (US, HOPE)

Nambiar et al., 2025

× 400

PT-KS relative risk vs. general pop.

Penn, 2000

CDC update (Sept 2025) — increasing reports of suspected donor-derived HHV-8/KSHV in SOT recipients, presenting as KS, KICS, or other KADs. The signal underscores the need for systematic screening.

Mularoni et al., Transpl Infect Dis 28 (2026) e70179 · doi:10.1111/tid.70179

HHV-8 seroconversion in OTR — French prospective studies

≈ 30 %

Seroconversion rate in HHV-8 seronegative OTR transplanted from an HHV-8 positive donor

Key observations

- No difference according to organ type
- Morbidity: 0.3 – 4 % HHV-8–associated events
- Mostly Kaposi's sarcoma
- Sometimes fatal haemophagocytic syndrome
- Low incidence of positive HHV-8 viremia among seroconverters

Frances, Am J Transplant 2009 — Lebbe, Am J Transplant 2013

HHV-8 seroprevalence — Dutch pilot (UMCG, 2025)

Retrospective pilot at UMCG, 2022–2023 — IFA Lytic IgG, n = 144 donors + 145 recipients

2.8 %

Donors positive

(4 / 144)

10.3 %

Recipients positive

(15 / 145)

2.5 %

Estimated D+/R−

Mismatch risk

Universal HHV-8 screening not warranted at UMCG given low D+/R− probability and < 1 clinical HHV-8 case per year out of 235 SOTs.

Seroprevalence is not static — globalisation and changing demographics require periodic reassessment.

Roo-Brand G. et al., J Med Virol 2025;97:e70477

Donor-derived KSHV in SOT — US CDC alert (MMWR 2026)

CDC investigation, United States — January 2021 to September 2025

46

Deceased donors suspected of transmitting KSHV

153

Transplant recipients received 185 organs

× 5

Increase vs. the prior 5-year period

Donor-derived transmission still occurs in < 0.5 % of all recipients — benefits of transplantation continue to outweigh the risk.

Kracalik I. et al., MMWR Morb Mortal Wkly Rep 2026;75(8):99–105

CDC investigation — donor profile & recipient outcomes

Donor profile (n = 46)

- Median age 38.5 yrs · 67 % male
- 96 % HIV-negative
- 67 % history of inhaled / injected drug use
- 17 % history of incarceration
- 86 % KSHV-positive when tested post-procurement

Recipient outcomes (n = 153)

- Median age 58.5 yrs · 50 % male · 98 % HIV-negative
- 74 (48 %) developed post-transplant KSHV infection
- 45 developed Kaposi sarcoma
- **25 (16 %) recipients have died**
- Median time to first symptoms: 208 days

Kracalik I. et al., MMWR 2026;75(8):99–105

HHV-8 serological assays — clinical limits

Available formats

- Immunofluorescence (IFA — latent / lytic)
- Western blot
- ELISA

Clinical limitations

- No standardised methodology
- No international controls available
- Sensitivity ranges 80 – 90 %+
- Optimal serological technique not established

⚠ Clinical utility for daily practice remains limited.

Donor screening — current recommendations still relevant?

Universal screening of donors for KSHV is generally not necessary.

Targeted screening

Donor-derived primary KSHV infection may be severe — anti-lytic and anti-latent antibodies are recommended for donors/recipients from high-prevalence areas.

D+/R− monitoring

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

Post-transplant KS in patients with HIV

French CRISTAL and DIVAT cohorts — prevalence of Kaposi sarcoma

All transplanted

CRISTAL cohort

0.18 %

All transplanted

DIVAT cohort

0.46 %

Transplanted with HIV

CRISTAL cohort

0.66 %

Transplanted with HIV

DIVAT cohort

0.50 %

Charpentier et al., Transplantation 2019;103:e22–e28

Post-transplant KS in PLHIV — key findings

Timing	KS occurred during the first year post-transplant in most cases
HIV control	Undetectable HIV viral load at KS diagnosis
Visceral involvement	Only 2 / 7 patients
Management	5 / 7 — switch from CNI to mTOR inhibitor; 5 — reduction of immunosuppression
Outcomes at 1 yr	4 complete responses, 3 partial responses

KS in transplanted patients with HIV does not show aggressive features and is managed with the usual post-transplant KS protocol.

CLINICAL INFECTIOUS DISEASES · MAJOR ARTICLE

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

Nambiar, Liang, Labo, et al.
on behalf of the HOPE in Action Investigators

Clin Infect Dis 2026; 82(4):709–719 · Published 5 May 2025

SLIDE 2 · CONTEXT

Background and objectives

Background

KSHV (HHV-8) causes a spectrum of post-transplant disease (KAD): skin and visceral KS, multicentric Castleman disease, lymphoma, and KICS.

Seroprevalence is high in PLHIV (38–70 %) and MSM, vs. 3–7 % in US blood donors — raising concern that HIV D+/R+ kidney transplantation under the HOPE Act could increase KAD risk.

Objectives

- Measure KSHV seroprevalence in recipients with HIV and in donors with/without HIV.
- Identify risk factors for KSHV seropositivity.
- Characterize post-transplant changes in KSHV seroresponses.
- Quantify the incidence and severity of KAD after HIV D+/R+ kidney transplantation.

Nambiar et al., Clin Infect Dis 2026;82(4):709–719

SLIDE 3 · METHODS

Design, cohort, and assay

418

Kidney recipients with HIV

215 D+/R+, 203 D−/R+

29

US transplant centers

Across 3 HOPE studies

30

KSHV antigens

In the multiplex serology panel

Population & follow-up

- Transplants Mar 2016 – Mar 2024 across 3 HOPE in Action studies
- Recipients on ART, HIV RNA suppressed, CD4 ≥ 200 cells/µL
- Serology at weeks 13, 26, 52 and 104 post-transplant

Definitions & analysis

- Seropositivity: 2-plex (ORF73 and/or K8.1); 5-plex and 30-plex also reported
- Modified Poisson regression, separate models for males and females
- KAD captured as a serious adverse event regardless of severity

Nambiar et al., Clin Infect Dis 2026;82(4):709–719

KSHV in HIV D+/R+ kidney transplantation (HOPE Act)

418 kidney recipients with HIV across 29 US centres — 3 HOPE in Action studies, 2016–2024

KSHV seroprevalence — 2-plex panel

40.6 %	up to 60 %	25.2 %	7.5 %
Recipients with HIV	MSM recipients with HIV	Donors with HIV	Donors without HIV

Key findings

- MSM status — only independent predictor of KSHV (RR 1.51 males; RR 2.39 male donors)
- KAD incidence 0.63 / 100 PY (5 cases / 791 PY); median onset 18 months
- Only 1 of 5 KAD cases was donor-attributable — most skin-limited and resolved

Nambiar P. et al., Clin Infect Dis 2026;82(4):709–719

SLIDE 5 · CONCLUSIONS

Implications for HOPE Act practice

01 High seroprevalence, concentrated by behavior

KSHV seropositivity reached 40.6 % in recipients and 25.2 % in donors with HIV — up to 60 % in MSM recipients — vs. 7.5 % in donors without HIV.

02 Post-transplant KAD is uncommon and usually mild

Incidence 0.63 / 100 PY. Most cases were skin-limited KS that responded to topical therapy or modest IS changes; no fatalities.

03 Donor-derived KSHV transmission was rare

Only 1 of 5 KAD cases was donor-attributable. Conventional 2-plex serology may miss latent donor infection.

Findings support the safety and continued expansion of HIV D+/R+ kidney transplantation.

HHV-8 in SOT — clinical implications

01 Targeted screening

Universal screening is debated. Tailor donor/recipient serology to local seroprevalence and risk factors (HIV, MSM, drug-use).

02 Highest-risk window

Median time from transplant to disease is 9–11 months. Closer monitoring of D+/R− and R+ during year 1.

03 Recognise KICS early

Rapidly fatal if missed. Non-specific hyperinflammation, high IL-6/IL-10 and HHV-8 viraemia should prompt work-up.

04 Standardise treatment

IS reduction and mTOR conversion are common. Antivirals and rituximab remain uncertain — prospective studies needed.

Adapted from Bonazzetti 2025, Kracalik 2026, Goldman 2025, Mularoni 2017

SECTION 03

The unsolved enigma of the KS progenitor

KS — proliferation of spindle cells

Hybrid phenotype expressing endothelial, lymphendothelial, and other lineage markers

Endothelial markers

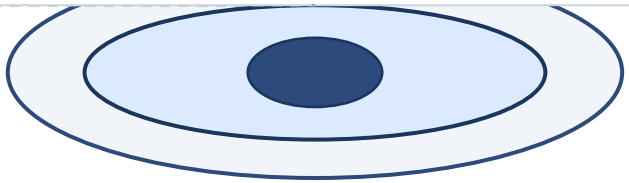
- CD31
- CD34
- Factor VIII

Lymphendothelial markers

- LYVE-1
- Podoplanin
- VEGFR3

Other lineage markers

- Smooth muscle
- Dendritic cell
- Macrophage



Spindle cell

> *Lymphendothelial transcriptional signature confirmed by microarray analysis — Wang et al., Nat Genet 2004.*

Historical milestone — in vitro KS cell characterisation

1995

The Lancet

Vol. 345 · 8958 · p.1180

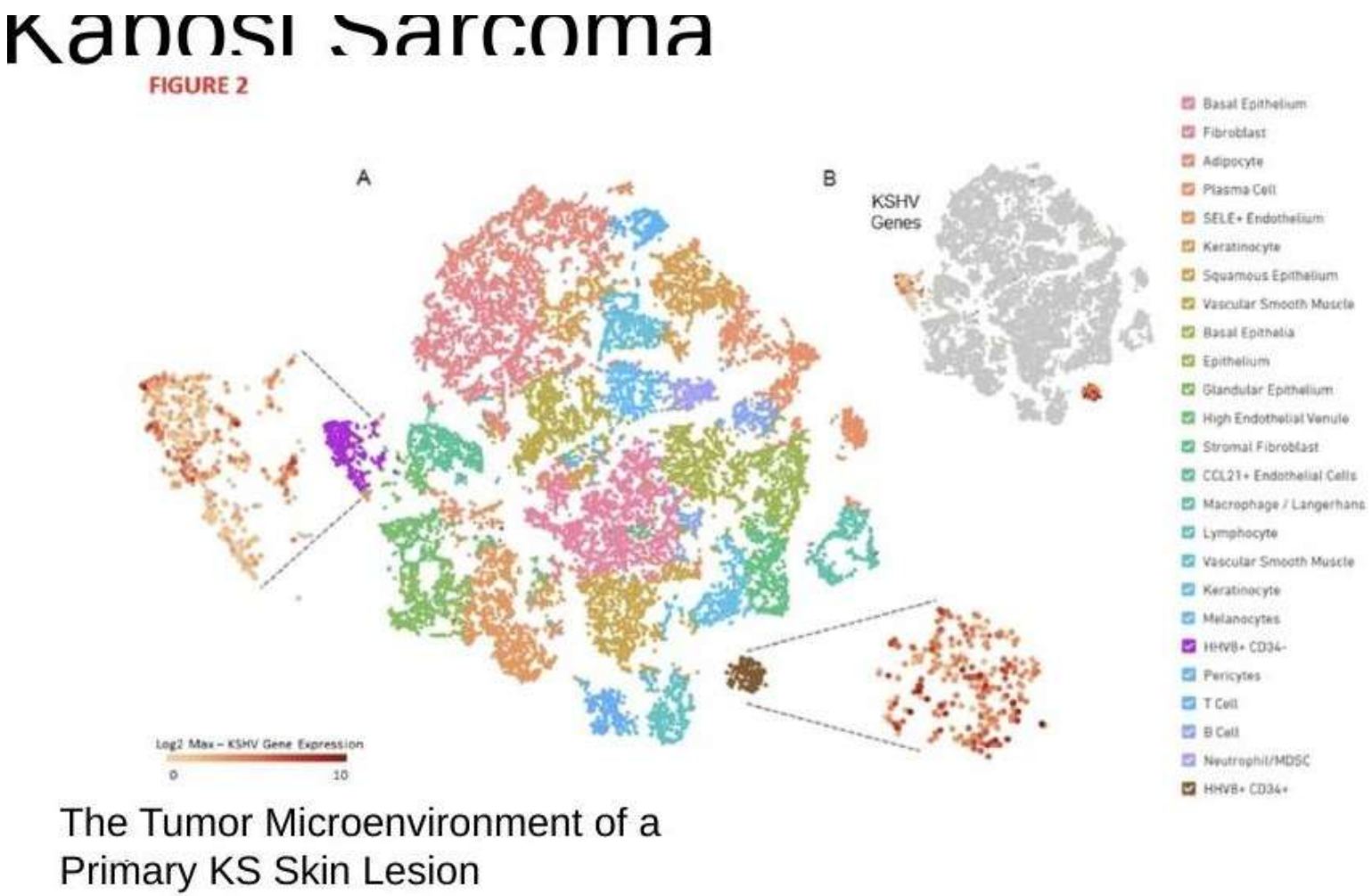
Lebbé C. et al.

Characterisation of in vitro KS-derived cells

- Spindle-cell cultures from HIV-negative classic KS lesions
- Demonstrated a mixed endothelial / mesenchymal phenotype
- Documented in vitro response to interferon-α
- Foundational work for the KS progenitor hypothesis

Lebbé C. et al., Lancet 1995;345(8958):1180

Single-cell transcriptomic landscape of primary KS



Rauch A. et al., 2025. Cellular heterogeneity within a primary KS skin lesion: HHV-8⁺ CD34⁺ spindle cells, lymphatic-endothelial subsets, infiltrating myeloid and lymphoid populations.

Single-cell transcriptomic analysis of KS

The tumour microenvironment of primary KS skin lesions (Rauch et al., 2025)

Cellular diversity

Tumour cells coexist with myeloid populations, T and B lymphocytes, and stromal cells.

Latent vs lytic

Lytic and latent KSHV-infected cells coexist within the same primary lesion.

CD8 T-cell expansion

Expansion of $CD8^+$ T-cell clones in primary KS — local antigen-driven response.

KSHV +: Endothelial phenotype

Tumour spindle cells display a hybrid lymphatic-endothelial / mesenchymal program.

The KS progenitor enigma — KSHV-induced MEndT / EndMT

Naipauer J. et al., Trends Mol Med 2023. doi:10.1016/j.molmed.2022.12.003

MEndT

Mesenchymal → Endothelial

Mesenchymal stem cell → ↓ KSHV, *infection* → **KSHV-infected endothelial-like spindle cell**

FROM — TO

EndMT

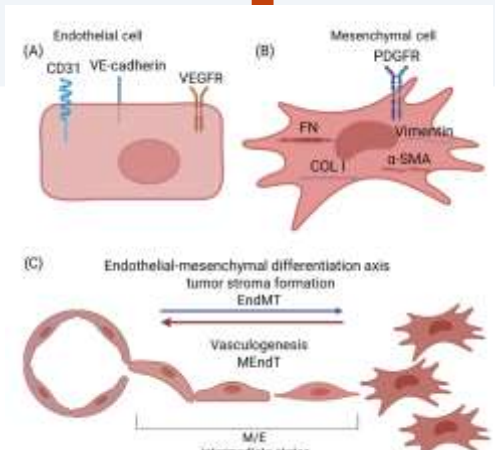
Endothelial → Mesenchymal

Endothelial cell → ↓ KSHV, *infection* → **KSHV-infected mesenchymal-like spindle cell**

FROM — TO

Bidirectional plasticity

The KS progenitor remains debated: a plastic mesenchymal-endothelial cell may give rise to spindle cells via KSHV-driven phenotypic transitions.



KSHV genome sequencing — multiple infections, low intra-host variance

Findings

- Multiple KSHV infections detected within individual hosts.
- Novel polymorphisms identified across the viral genome.
- Important consequences for vaccine developemnt.

Key insight

KSHV-associated diseases do not cluster by viral genotype.

Disease phenotype is driven by host factors and tumour-microenvironment biology rather than by viral strain alone.

Marshall V. et al., 2024

The debate on KS clonality — is KS a true cancer?

X-chromosome inactivation studies

Delabesse 1997	Gill 1998	Rabkin 1995 (AIDS)	Yuan 2015
Polyclonal	**Clonal & polyclonal**	**Clonal**	**Clonal**

HHV-8 terminal repeat (TR) analysis

Duprez 2007

Oligoclonal KS — including multiple distinct clones within the same patient.

Heterogeneous evidence — KS is likely an oligoclonal disease arising from independent infectious / proliferative events, not a single clonal expansion.

Ruiz E. et al., Cancers 2022

Chromosomal aberrations in KS — clonal evolution

Tumour mutational burden

9.9 / Mb

Low overall — higher in aggressive KS

Recurrent chromosomal events

- Early (patch) KS: clonal loss of chromosome Y in 9/9 male patients
- Late (nodular) KS: additional CNV in chromosomes 16, 17, 21, X, Y
- Loss of Y in 20/23 male KS overall
- More common in endemic vs AIDS-associated KS

CGH array on micro-dissected KS lesions supports a clonal origin.

EARLY

Clonal loss of Y

→

LATE

Additional chromosomal aberrations

Ruiz E., Cancers 2022 — Delyon J., Lancet Oncol 2022 — Malouf G., JEADV 2022

SECTION 04

Exploring immune responses in KS

Cancer risk in PLHIV and SOTR — meta-analysis

Systematic review and meta-analysis

Cancer risk in people living with HIV and solid organ transplant recipients.

KEY TAKEAWAY

KS displays one of the highest standardised incidence ratios among virally-driven malignancies in both immunosuppressed populations — confirming the central role of immune control in HHV-8 oncogenesis.

Jin F. et al., Lancet Oncology 2024;25:933–944

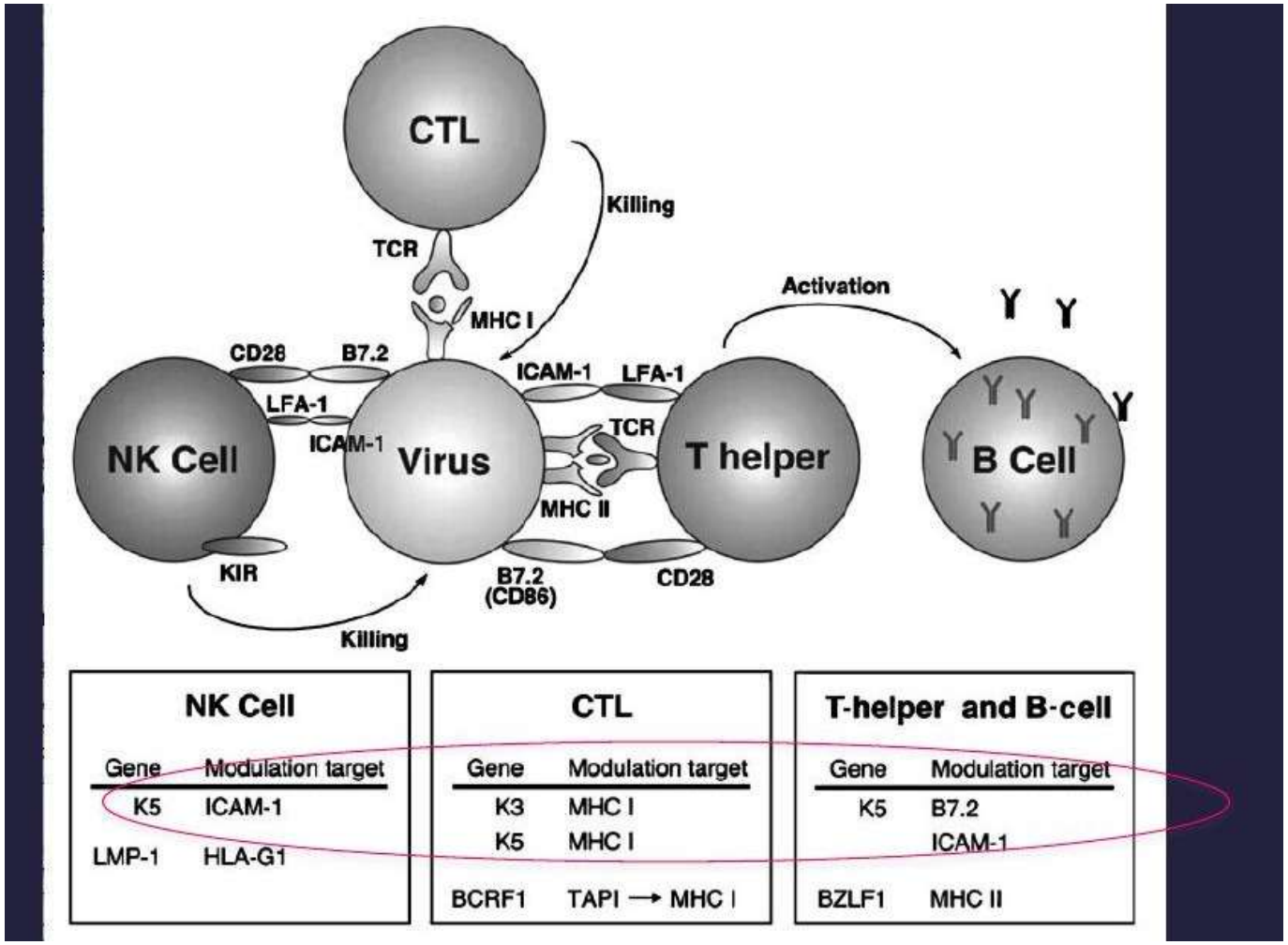
Inborn errors of immunity associated with KS

Genetic immune deficiencies predisposing to KS — even in otherwise immunocompetent individuals

IFNGR1	STIM1	OX40 (TNFRSF4)	WAS	XMEN
IEI	IEI	IEI	IEI	IEI
Interferon γ receptor 1	Stromal interaction molecule 1	T-cell co-stimulation deficiency	Wiskott–Aldrich syndrome	X-linked MAGT1 deficiency

Béziat V. et al., 2021 — Inborn errors of immunity & KSHV oncogenesis

HHV-8 — multiple strategies for immune evasion



Viral genes K3, K5, BCRF1 and BZLF1 modulate MHC-I, ICAM-1, B7.2 and HLA-G1 to escape NK-cell, CTL and T-helper/B-cell responses.

Differences in the frequency and function of HHV8-specific CD8 T cells between asymptomatic HHV8 infection and Kaposi sarcoma

Marion Lambert, Monique Gannagé, Alexandre Karras, Michal Abel, Christophe Legendre, Delphine Kerob, Felix Agbalika, Pierre-Marie Girard, Celeste Lebbe, and Sophie Caillat-Zucman

It is unclear how the immune response controls human herpesvirus 8 (HHV8; also known as Kaposi sarcoma–associated herpesvirus [KSHV]) replication and thereby prevents Kaposi sarcoma (KS). We compared CD8 T-cell responses to HHV8 latent (K12) and lytic (glycoprotein B, ORF6, ORF61, and ORF65) antigens in patients who spontaneously controlled the infection and in patients with posttransplantation, AIDS-related, or classical KS. We found that anti-HHV8 responses were frequent, diverse, and strongly differentiated toward an effector phenotype in patients who controlled the infection. Conversely, HHV8-specific CD8 cells were very rare in patients who progressed to KS, and were not recruited to the tumoral tissue, as visualized by in situ tetramer staining of KS biopsies. Last, HHV8-specific CD8 T cells were observed in a seronegative recipient of an HHV8-infected graft who remained persistently aviremic and antibody negative, suggesting that specific cytotoxic T lymphocytes (CTLs) may provide protection from persistent HHV8 infection. These results support the crucial role of cellular immune responses in controlling HHV8 replication, in preventing malignancies in latently infected subjects, and in conferring genuine resistance to persistent infection. They may also have important implications for the design of prophylactic and therapeutic HHV8 vaccines, and for adoptive immunotherapy of KS. (Blood. 2006; 108:3871-3880)

Introduction

OPEN ACCESS Freely available online PLOS PATHOGENS

Human Herpesvirus 8 (HHV8) Sequentially Shapes the NK Cell Repertoire during the Course of Asymptomatic Infection and Kaposi Sarcoma

Stéphanie Dupuy[1], Marion Lambert[1], David Zucman[2], Siméon-Pierre Choukem[3¤], Sara Tognarelli[1], Cécile Pages[4], Céleste Lebbé[4], Sophie Caillat-Zucman[1]*

1 Institut National de la Santé et de la Recherche Médicale (INSERM), U986, Hôpital St-Vincent de Paul; Université Paris Descartes, Faculté de Médecine, Paris, France, **2** Hôpital Foch, Service de Médecine Interne, Suresnes, France, **3** AP-HP, Hôpital Saint-Louis, Service d'Endocrinologie; Université Paris Diderot, Faculté de Médecine, Paris, France, **4** AP-HP, Hôpital Saint-Louis, Service de Dermatologie; Université Paris Diderot, INSERM U976 Skin Research Center, Paris, France

Abstract

The contribution of innate immunity to immunosurveillance of the oncogenic Human Herpes Virus 8 (HHV8) has not been studied in depth. We investigated NK cell phenotype and function in 70 HHV8-infected subjects, either asymptomatic carriers or having developed Kaposi's sarcoma (KS). Our results revealed substantial alterations of the NK cell receptor repertoire in healthy HHV8 carriers, with reduced expression of NKp30, NKp46 and CD161 receptors. In addition, down-modulation of the activating NKG2D receptor, associated with impaired NK-cell lytic capacity, was observed in patients with active KS. Resolution of KS after treatment was accompanied with restoration of NKG2D levels and NK cell activity. HHV8-latently infected endothelial cells overexpressed ligands of several NK cell receptors, including NKG2D ligands. The strong expression of NKG2D ligands by tumor cells was confirmed in situ by immunohistochemical staining of KS biopsies. However, no tumor-infiltrating NK cells were detected, suggesting a defect in NK cell homing or survival in the KS microenvironment. Among the known KS-derived immunoregulatory factors, we identified prostaglandin E2 (PGE2) as a critical element responsible for the down-modulation of NKG2D expression on resting NK cells. Moreover, PGE2 prevented up-regulation of the NKG2D and NKp30 receptors on IL-15-activated NK cells, and inhibited the IL-15-induced proliferation and survival of NK cells. Altogether, our observations are consistent with distinct immunoevasion mechanisms that allow HHV8 to escape NK cell responses stepwise, first at early stages of infection to facilitate the maintenance of viral latency, and later to promote tumor cell growth through suppression of NKG2D-mediated functions. Importantly, our results provide additional support to the use of PGE2 inhibitors as an attractive approach to treat aggressive KS, as they could restore activation and survival of tumoricidal NK cells.

Citation: Dupuy S, Lambert M, Zucman D, Choukem S-P, Tognarelli S, et al. (2012) Human Herpesvirus 8 (HHV8) Sequentially Shapes the NK Cell Repertoire ... Kaposi Sarcoma. PLoS Pathog 8(1): e1002486. doi:10.1371/journal.ppat.1002486

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 45

Research Paper

PD-1 mediates functional exhaustion of activated NK cells in patients with Kaposi sarcoma

Asma Beldi-Ferchiou[1,2,11], Marion Lambert[1,2], Stéphanie Dogniaux[3], Frédéric Vély[4,5], Eric Vivier[4,5], Daniel Olive[6], Stéphanie Dupuy[1], Frank Levasseur[1], David Zucman[7], Céleste Lebbé[8], Damien Sène[1,2,9], Claire Hivroz[4], Sophie Caillat-Zucman[1,2,10]

Progressive loss of T cell control tracks with disease severity

ELISpot — IFNγ responses to LANA, K8, K12, gB (peak DNAemia)

Asymptomatic

Strongest HHV-8–specific T cell responses; effective immune control despite persistent viral replication.

KICS

Weaker responses; partial immune dysfunction combined with excessive cytokine production.

Kaposi's sarcoma

Most impaired responses; profound exhaustion supports cellular immunity failure in tumour development.

CLINICAL IMPLICATIONS

Monitoring

Combine HHV-8 DNAemia, inflammatory cytokines and T cell functionality for early detection and risk stratification — especially in D+/R– recipients.

Therapeutic targets

KICS: IL-6 blockade, PD-1 / LAG-3 inhibition, rituximab (?).

KS: HGF / c-Met axis, $CD163^{+}$ TAMs.

Both: Switch CNI → mTOR inhibitor (sirolimus / everolimus).

T-cell response in KS — TIL repertoire

TIL diversity

- Largely idiosyncratic and polyclonal
- Low frequency of T cells with known antigenic specificity
- Intra-subject sharing of antigen specificity across lesions

Persistent response

- T-cell signature against KSHV persists across body sites
- Persists over time in both epidemic and endemic KS
- Evidence of long-lived antigen-driven memory

Ravishankar B. et al., 2024

KS microenvironment — exhausted immunity

Characterisation of the KS tumour microenvironment

Myeloid skew

Predominance of M2-polarised macrophages — pro-tumour, anti-inflammatory phenotype.

CD8 exhaustion

Effector-memory $CD8^+$ T cells expressing LAG-3, TIGIT and TOX — signature of chronic antigenic stimulation.

Therapeutic implication

Multiple checkpoint receptors are co-expressed — combination immunotherapy may be needed beyond single-agent PD-1 blockade.

Neumeyer S. et al., Virology 2025;601:110286

SECTION 05

KS management — current standards and emerging therapies

KS — proposed staging workup

1 Clinical examination

All subtypes — essential

2 HIV serology

Mandatory at diagnosis

3 Standard blood tests

CBC, EPP, CRP, electrolytes, creatinine, liver, glucose

4 HHV-8 viraemia

Recommended in HIV-KS and post-transplant KS

5 CD4 count

In people living with HIV

6 Histology

Diagnostic confirmation — biopsy

7 Total-body CT scan

AIDS-associated and iatrogenic KS

8 Endoscopy

If symptomatic or extensive cutaneous disease

Pagès C. et al., EDF/EADO/EORTC Guidelines — Eur J Cancer 2019;114:117–127

Endemic KS is more severe than classic KS

Classic KS (CKS)	Endemic KS (EKS)
Older patients	Younger patients at diagnosis
Predominance on extremities	More extensive cutaneous disease
Indolent course	More frequent extracutaneous involvement
Limited extracutaneous involvement	Lower response to systemic therapy

Grolleau C. et al., 2024

KS management — guiding principles by subtype

HIV-associated KS	cART optimisation ± systemic chemotherapy
Post-transplant KS	Immunosuppression reduction (++ switch to mTOR inhibitor) ± systemic therapy
Classic / endemic KS	No treatment or local therapy; systemic therapy infrequent — reserved for extensive or symptomatic disease

Lebbé C. et al., Eur J Cancer 2020 — Benajiba L. et al., 2021

Liposomal daunorubicin (LD) — pivotal phase III trials

Trial	Regimen	Patients (n)	Outcome
Northfeld **J Clin Oncol 1998**	LD 20 mg/m² vs ABV q2w × 6 cycles	258 no prior anthracycline	ORR 46 % vs 25 % Similar OS Less alopecia, neuropathy
Osoba **Cancer Invest 2001**	LD 20 mg/m² vs BV q3w × 6 cycles	232 no prior chemo	ORR 59 % vs 23 % Similar OS
Gill **J Clin Oncol 1996**	LD 40 mg/m² vs ABV q2w	232 no prior chemo	ORR 25 % vs 28 % Similar OS — less toxicity

Northfeld 1998; Osoba 2001; Gill 1996

Paclitaxel in HIV-associated KS — phase II evidence

Phase II — dose escalation

REGIMEN

Paclitaxel 135–175 mg/m² q3w

PATIENTS

n = 29
With or without prior chemotherapy

BEST RESPONSE

ORR 71 %

Welles L. et al., J Clin Oncol 1998

Phase II

REGIMEN

Paclitaxel 100 mg/m² q2w

PATIENTS

n = 107
After prior chemotherapy failure

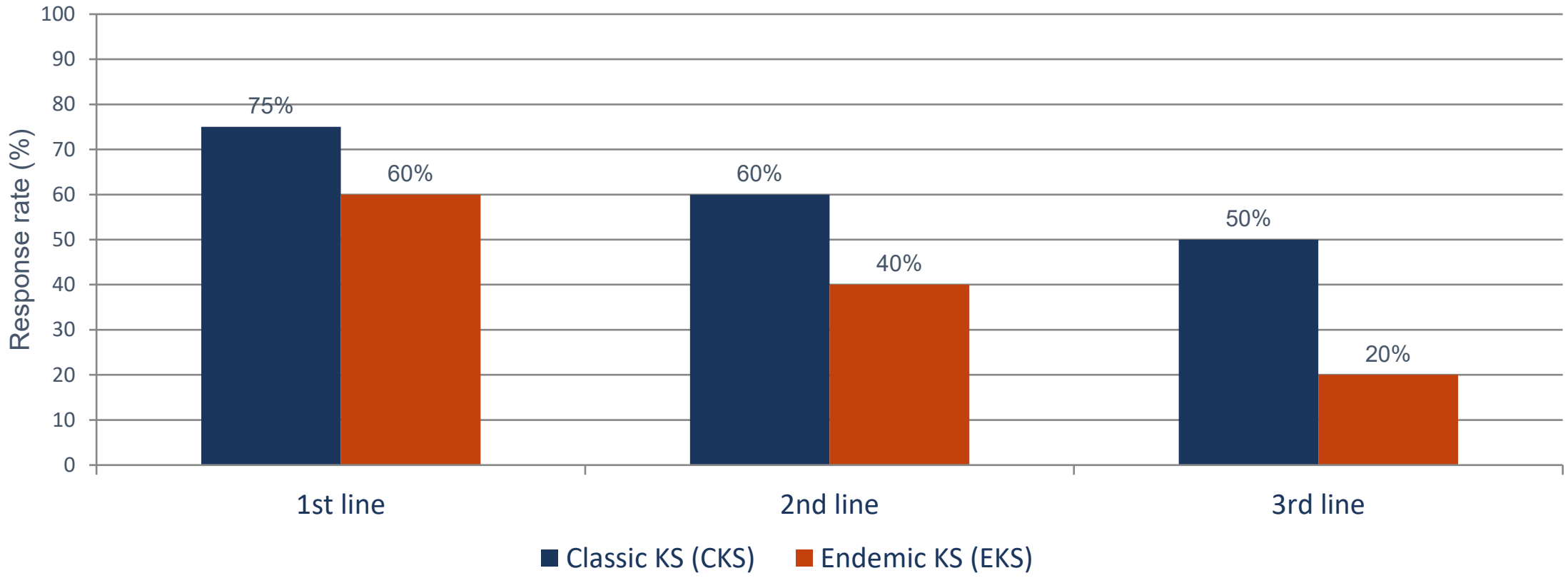
BEST RESPONSE

ORR 56 %

Tulpule A. et al., Cancer 2002

EKS vs CKS — response by line of therapy

Lower response to systemic therapy in endemic KS — illustrative data, Grolleau et al., 2024



mTOR inhibitors in post-transplant KS

Multicentre retrospective cohort — 145 SOTR with KS diagnosed 1985–2011

145

patients across multiple centres

83 %

overall response at 6 months

40 %

complete response at 6 months

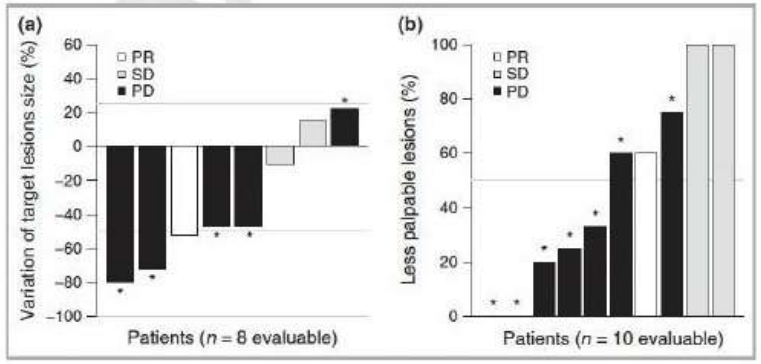
Switch from CNI to mTOR inhibitor (sirolimus / everolimus) is a cornerstone of post-transplant KS management.

Delyon J. et al., J Am Acad Dermatol 2019;81:448–455 — Mourah S. et al., Br J Dermatol 2015

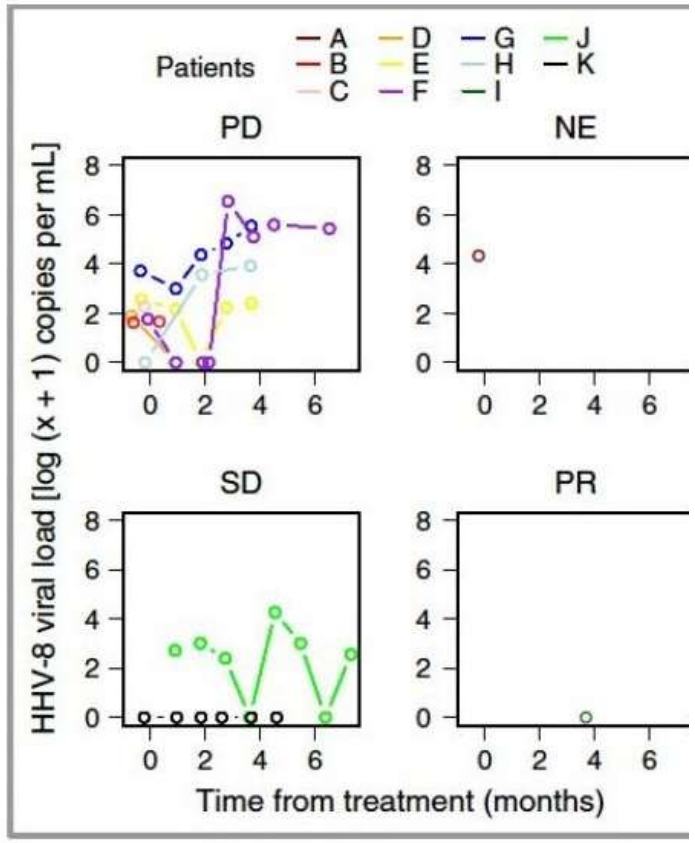
Everolimus in classic KS — paradoxical responses

adoxical simultaneous regression and
gression of lesions in a phase II study of
rolimus in classic Kaposi sarcoma

10.1111/bjd.13897



sion was mainly due to the paradoxical appearance of new Kaposi sarcoma lesions. Waterfall charts showing, at study ercentage change in target lesion size and (b) the percentage of less palpable lesions. The asterisks indicate the patients with verall reductions in target lesion sizes and reduction in palpability, disease progressed in the majority of patients according nical Trial Group definition of progression. PR, partial response; SD, stable disease; PD, progressive disease.



Mourah S. et al., Br J Dermatol 2015. Despite overall reduction in target-lesion size, new lesions appeared in most patients; HHV-8 viral load tracked progression vs response.

Pomalidomide — FDA-approved immunomodulator for KS

ORR

71 %

Phase I–II trial — 28 patients (HIV+ and HIV−)

95 % CI: 51 – 87 %

FDA approval — 2020

Accelerated approval granted for:

- Adults with AIDS-related KS after HAART failure
- HIV-negative adults with KS

Recommended dosing

5 mg once daily on days 1 – 21 of each 28-day cycle, continued until progression or unacceptable toxicity.

Polizzotto MN et al., J Clin Oncol 2016;34:4125–4131

PD-1 blockade in classic / endemic KS — phase II

Pembrolizumab in classic or endemic KS — multicentre, single-arm phase 2 study

N = 17

3 centres, France · Jul 2018 – Dec 2019

71 % previously treated with systemic therapy

Patient characteristics

88 %	53 %	29 %	47 %	53 %	24 %	12 %
Male sex	Sub-Saharan / Caribbean	Mediterranean origin	Classic KS	Endemic KS	LN involvement	LN + bone involvement

Delyon J. et al., Lancet Oncol 2022

Pembrolizumab in classic / endemic KS — efficacy

BORR

70.6 %

95 % CI: 44.0 – 89.7 %

ACTG response criteria

Complete response	**2 (12 %)**
Partial response	**10 (59 %)**
Stable disease	**5 (29 %)**
Progression	**0**

Median follow-up: 25.7 weeks · Discontinuation for toxicity: 2 patients

Delyon J. et al., Lancet Oncol 2022

CITN-12 — Pembrolizumab in HIV-associated KS

Cancer Immunotherapy Trials Network 12 — phase II

62.1 %
Overall response rate

2.9 mo
Median time to response (IQR 1.5 – 8.3)

92.3 %
DOR ≥ 12 months

28.2 mo
Median progression-free survival

Median duration of response: not reached. Durable and clinically meaningful responses in HIV-KS.

Lurain K. et al., J Clin Oncol 2025

MECHANISM

How CDK4/6 inhibition turns a “cold” virally driven tumor visible

01

CDK4/6 blockade

Stops cyclin D / K-cyclin → CDK4/6 activity. Cell cycle arrest at G1/S.

02

DNMT1 degradation

Loss of E2F-driven DNMT1 expression. DNA methylation drops.

03

ERV & viral mimicry

Endogenous retroviruses (ERV3-1) and some viral genes re-expressed; dsRNA sensors triggered.

04

Interferon response

Type I and III IFNs activate STAT1 and NLRC5 → upregulate MHC-I, ICAM-1, B7-2 (and PD-L1).

Concurrent PD-L1 upregulation provides the biological rationale for combining CDK4/6 inhibition with anti–PD-1 therapy.

Take-home messages

01 Heterogeneous disease

KS encompasses four clinically distinct entities sharing HHV-8 as the causal agent and immune dysregulation as a common driver.

02 Persisting risk in PLHIV

Even with restored immunity, the risk of KS remains markedly elevated — favouring continued vigilance and dedicated management.

03 Progenitor still debated

The KS spindle cell likely arises from KSHV-driven MEndT / EndMT transitions; clonality data support an oligoclonal disease.

04 Immunotherapy reshapes management

Pembrolizumab demonstrates durable responses in HIV-associated and classic / endemic KS; rational use in post-transplant settings remains to be defined.

THANK YOU

Questions & discussion welcome.

Céleste Lebbé — Saint-Louis University Hospital, Paris