Infezioni virali e trapianti di organo solido

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SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

The Transplantation Society

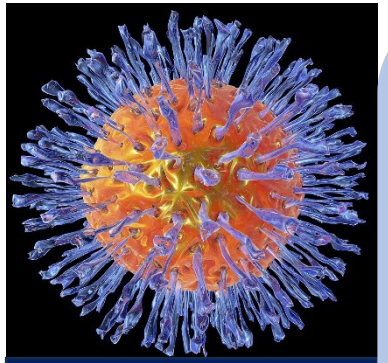
ISMETT Istituto di Ricovero e Cura a Carattere Scientifico

UPMC LIFE CHANGING MEDICINE

TID Transplant Infectious Disease

Transplant Infectious Disease

Infezioni virali più comuni nel trapianto di organo solido



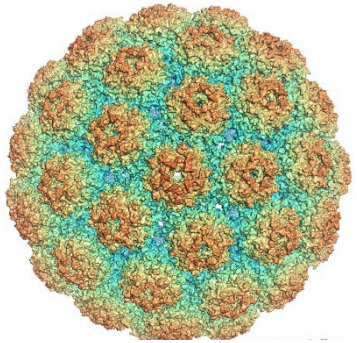
Virus Herpetici

Herpes simplex 1 e 2
Varicella zoster
Epstein-Barr virus
Cytomegalovirus
Human herpesvirus-6 (HHV6)
HHV7
HHV8/Kaposi sarcoma-associated herpesvirus

Virus Respiratori

Adenovirus
Virus Respiratorio sinciziale
Influenza e Parainfluenza
Metapneumovirus
SARS-CoV-2

Epatite B
Epatite C
Papillomavirus
HIV
Parvovirus B19
Torque tenovirus
….



Polyomaviruses

BK,
JC virus

Rare: human T lymphotropic virus, hepatitis E virus, rabies virus, lymphocytic choriomeningitis virus, measles, mumps, dengue, zika, norovirus..

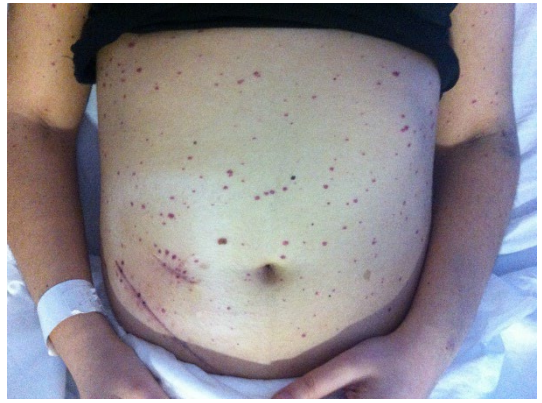
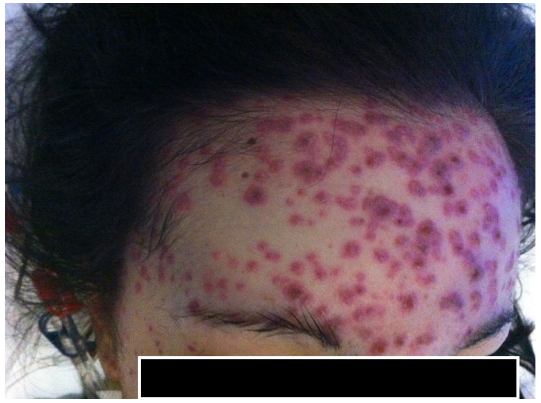
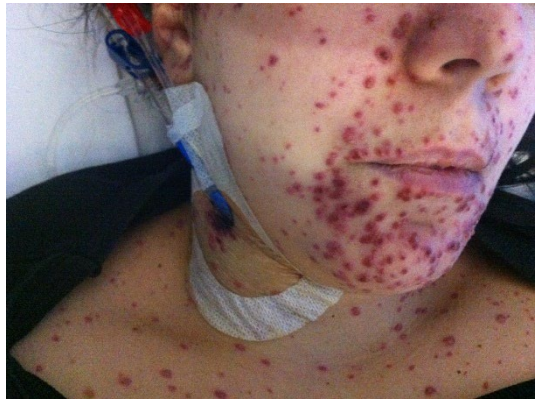
- ✓ Terapia immunosoppressiva
- ✓ Infezioni
- ✓ Deplezione Linfocitaria
- ✓ “Net state of immune suppression”

Ospite Immunocompromesso

Riattivazione di infezioni Latenti (R+)

Infezioni Primarie Severe e/o Atipiche (R-)

22 anni, trapianto di rene 1 mese prima per Nefrite Lupica. Febbre e Lesioni petecchiali

Serology	
Serology	
VZV IgM	NEGATIVO
VZV IgG	POSITIVO

Immune?
A rischio di riattivazione?

11-Apr-2012 10:13	VZV DNA (Tampone Vescicolare)	
VZV DNA	POSITIVO	
Metodica VZV DNA	Real Time PCR. I.L.: 1000 - 1.000.000 copie/mL	

17-Apr-2012 06:49	VZV DNA (Plasma)	
VZV DNA	7250	[copie/mL]
Metodica VZV DNA	Real Time PCR. I.L.: 1000 - 1.000.000 copie/mL	

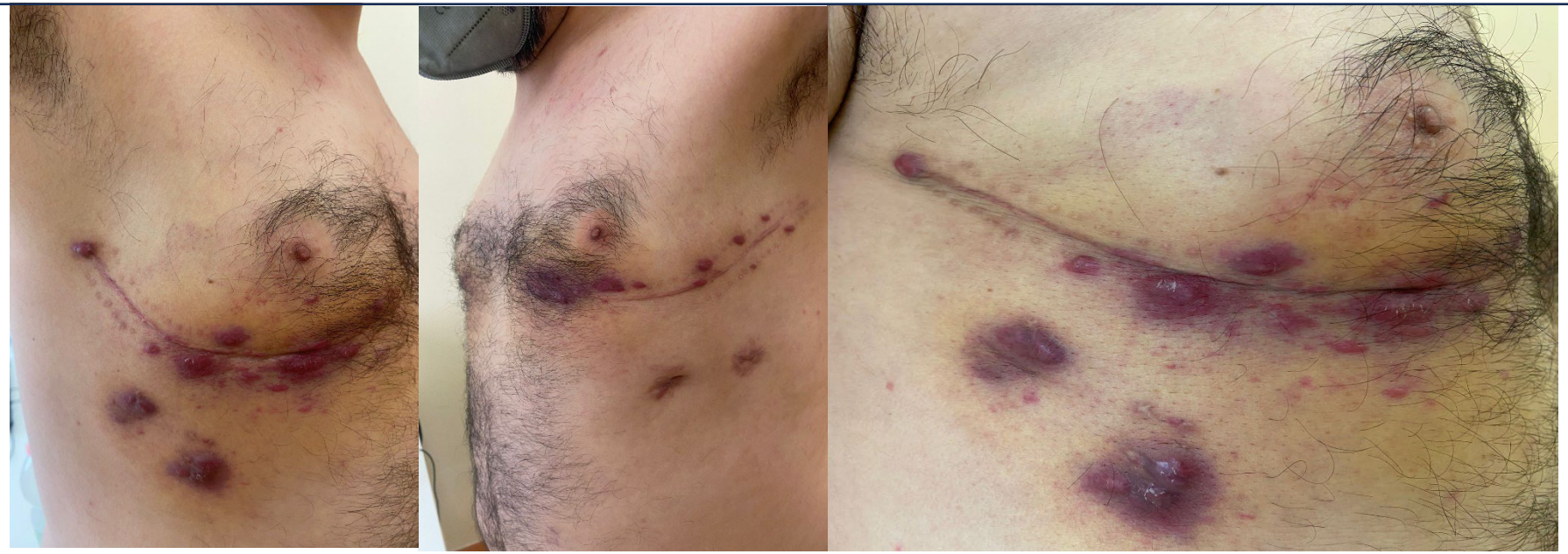
✓ Terapia immunosoppressiva
✓ Infezioni
✓ Deplezione Linfocitaria
✓ “Net state of immune suppression”

Ospite Immunocompromesso

Riattivazione di infezioni Latenti (R+)

Infezioni Primarie Severe e/o Atipiche (R-)

Uomo di circa 40 anni. 4 mesi prima sottoposto a trapianto di Polmone da Donatore HHV8 + / Ricevente HHV8 –



Sarcoma di Kaposi cutaneo e viscerale e Severa Sindrome citochinica (KICS)

Effetti delle Infezioni Virali nel Trapiantato

❖**DIRETTI:** Febbre e neutropenia (CMV); polmonite (virus respiratori); epatite (HCV, HBV)…

❖**EFFETTI INDIRETTI o IMMUNOMODULATORI**

- **Immunosoppressione sistemica** →Infezioni Opportunistiche: *Aspergillus* post CMV/RSV/COVID, *Pneumocystis* post CMV, coinfezione CMV/ EBV maggior rischio di PTLD
- **Infiammazione e Sindrome Citochinica**→ HHV8 e KICS
- **Rigetto** → rilascio di citochine proinfiammatorie

❖**ONCOGENESI:** HBV e HCV: HCC, EBV: PTLD, HPV, HHV8: KS, Lymphoma

Sen P, Sci Adv. 2020; Kalil AC, Ann Intern Med. 2005; Fishman JA, N Engl J Med. 2007; Haidar G, Singh N., Curr Opin Infect Dis 2017

Adenovirus

- In SOTr cistite emorragica e nefrite, (tx di rene) polmonite (tx di polmone), epatite (tx fegato), enterocolite (tx intestino), malattie disseminate. Associato con perdita del graft.
- Infezione primaria/ trasmessa dal donatore oppure riattivazione di infezione latente
- Diagnosi: elevato sospetto clinico e ricerca con PCR ed eventuale biopsia. Bassa sensibilità del test Antigenico
- **Terapia**
- Il cardine della gestione è la riduzione della Immunosoppressione
- Cidofovir, brincidofovir possibili opzioni terapeutiche ma non approvate da FDA/EMA
- Immunoterapia adottiva infusione di Linfociti T citotossici Adenovirus-specifici

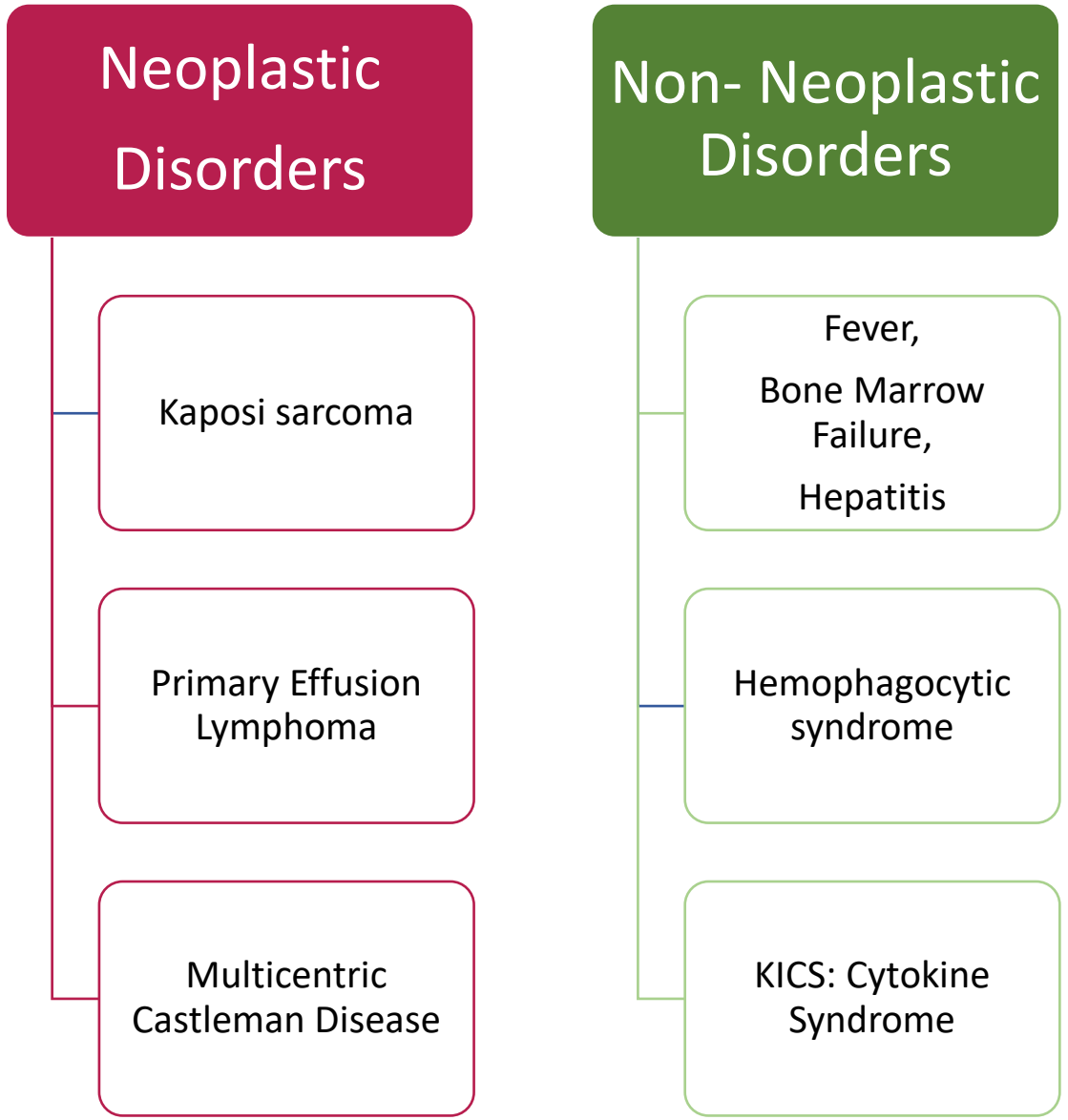
Ison MG. Clin Infect Dis. 2006; Florescu DF, Clin Transplant. 2019; Londeree J, Pediatr Transplant. 2020; Sudhindra P, Cureus. 2019; Omar M, Transplantation 2023

Human Herpes Virus 8 (HHV8) Kaposi Sarcoma Herpes Virus (KSHV)

Infezione da HHV8 associata a un vasto spettro di malattie in SOT.

Donor derived infection (DDI) è stata associata ad una sindrome citochinica rapidamente fatale (KICS: Kaposi Sarcoma Herpes Virus Cytokine Syndrome).

Ad ISMETT è stato sviluppato un protocollo che ha lo scopo di intercettare rapidamente la trasmissione di HHV8 nei D+/R- allo scopo di trattare precocemente le malattia associate.



Riva, Blood, 2012

blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

HOW I TREAT | NOVEMBER 15, 2012

How I treat HHV8/KSHV-related diseases in posttransplant patients

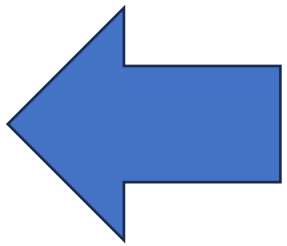
Giovanni Riva, Mario Luppi, Patrizia Barozzi, Fabio Forghieri, Leonardo Potenza

Check for updates

Blood (2012) 120 (20): 4150–4159.

Table 1. HHV8-related neoplastic and non-neoplastic diseases in posttransplantation patients

HHV8-related posttreatment diseases	Clinical presentations and histopathologic features	Monitoring tests	Therapeutic options*
Neoplastic			
KS	Cutaneous or mucosal lesions; visceral involvement; hematologic manifestations. HHV8$^+$ spindle cells; inflammatory infiltrates	HHV8 viral load (Q-PCR): useful; HHV8 T-cell quantitation (ELISPOT): useful	Reduction of IS or switch to SRL (II-3); CHT (liposomal anthracyclines; II-3); antivirals (III)
MCD	Lymphadenopathy; systemic inflammatory symptoms. HHV8$^+$ plasmablasts in mantle zone of follicles; vascular hyperplasia	HHV8 viral load (Q-PCR): useful; HHV8 T-cell quantitation (ELISPOT): investigational	Reduction of IS or switch to SRL (III); rituximab (II-3); CHT (CVP, CHOP, R-CHOP) (II-3); antivirals (III)
PEL	Pleural, peritoneal, pericardial effusions; HHV8$^+$ plasmablasts with immunoblastic and anaplastic features	HHV8 viral load (Q-PCR): useful; HHV8 T-cell quantitation (ELISPOT): investigational	Reduction of IS (III); CHT (CHOP) (II-3); antivirals (III)
Non-neoplastic			
Plasmacytic B-cell proliferation	Polyclonal HHV8$^+$ B-cell proliferations, in lymph nodes and visceral organs; systemic inflammatory symptoms	HHV8 viral load (Q-PCR): useful (also for diagnosis)	Reduction of IS (III); rituximab (III); antivirals (III)
BM failure	Acute bone marrow failure, often with plasmacytosis and signs of HPS; hepatosplenomegaly and severe pancytopenia; systemic inflammatory symptoms; skin maculopapular rash	HHV8 viral load (Q-PCR): useful (also for diagnosis)	Reduction of IS (III); rituximab (III); antivirals (III)
Hepatitis	Elevated liver enzymes; systemic inflammatory symptoms; skin maculopapular rash	HHV8 viral load (Q-PCR): useful (also for diagnosis)	Reduction of IS (III); antivirals (III)



HHV8 Cytokine Syndrome KICS

Clinical Infectious Diseases
MAJOR ARTICLE

Clinical Features and Outcomes of Patients With Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated Inflammation: Prospective Characterization of KSHV Inflammatory Cytokine Syndrome (KICS)

Mark N. Polizzotto,[1,a] Thomas S. Uldrick,[1] Kathleen M. Wyvill,[1] Karen Aleman,[1] Vickie Marshall,[1] Victoria Wang,[1] Denise Whitby,[3] Stefania Pittaluga,[2] Elaine S. Jaffe,[2] Corina Millo,[4] Giovanna Tosato,[2] Richard F. Little,[1] Seth M. Steinberg,[4] Irini Sereti,[1] and Robert Yarchoan[1]

Table 1. Working Case Definition of KSHV-inflammatory Cytokine Syndrome (KICS)

1. Clinical manifestations	
a. Symptoms	b. Laboratory abnormalities
Fever	Anemia
Fatigue	Thrombocytopenia
Edema	Hypoalbuminemia
Cachexia	Hyponatremia
Respiratory symptoms	c. Radiographic abnormalities
Gastrointestinal disturbance	Lymphadenopathy
Athralgia and myalgia	Splenomegaly
Altered mental state	Hepatomegaly
Neuropathy with or without pain	Body cavity effusions
2. Evidence of systemic inflammation	
Elevated C-reactive protein (≥3 g/dL)	
3. Evidence of KSHV viral activity	
Elevated KSHV viral load in plasma (≥1000 copies/mL) or peripheral blood mononuclear cells (≥100 copies/10^6 cells)	
4. No evidence of KSHV-associated multicentric Castleman disease	
Exclusion of MCD requires histopathologic assessment of lymphadenopathy if present.	

The working case definition of KICS requires the presence of *at least 2* clinical manifestations drawn from *at least 2 categories* (1a, b, and c), together with each of the criteria in 2, 3, and 4.

Abbreviations: KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease.

KICS descritta per la prima volta in HIV (2016)

We described the first case of KICS (nonneoplastic complication)after liver and kidney transplant in an HIV-negative patient.

She was successfully treated by a combination of modification of the immunosuppressive regimen, immunomodulation and anti-CD20 monoclonal therapy.

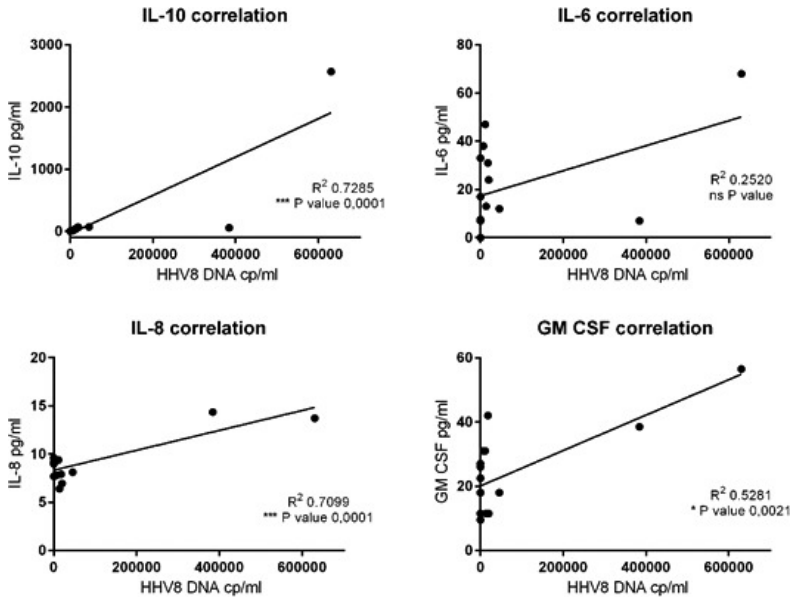
American Journal of Transplantation
AST American Society of Transplantation ASTS

Case Report | Full Access

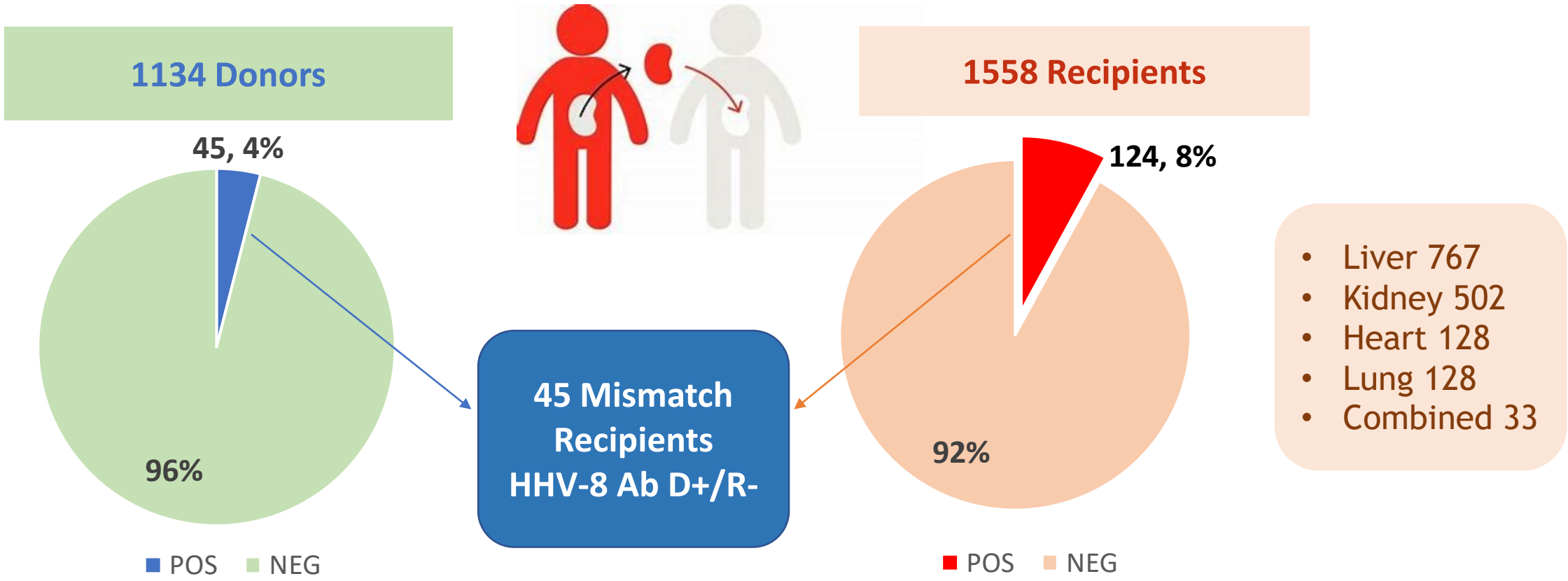
Successful Treatment of Kaposi Sarcoma–Associated Herpesvirus Inflammatory Cytokine Syndrome After Kidney–Liver Transplant: Correlations With the Human Herpesvirus 8 miRNome and Specific T Cell Response

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

First published: 10 May 2017 | https://doi.org/10.1111/ajt.14346 |

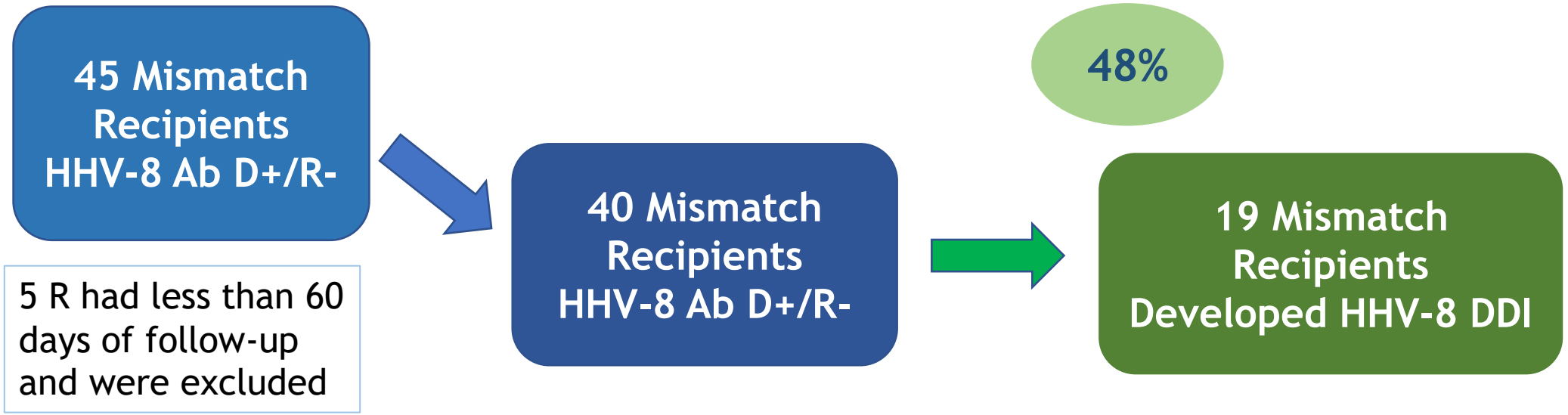


1. Screening for HHV8 serology (IFA lytic and latent) on consecutive Donors and Recipients between January 2011 and July 2022 to determine risk of HHV8 DDI



Mularoni et al, Oral communication, American Transplant congress 2023

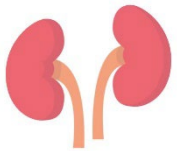
2. Determine the rate of HHV8 DDI transmission



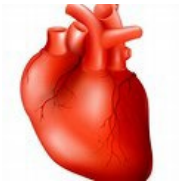
HHV8 DDI strict monitoring by
- HHV8 DNA [Real-time polymerase chain reaction (PCR) assay]
- HHV-8 serology

Donor Derived Infection
- Detectable HHV-8 DNA
- HHV-8 Ab Seroconversion

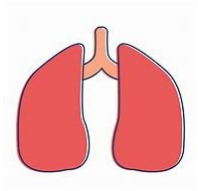
2 a. Rate of HHV8 transmission per organ



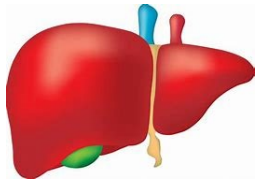
9 Mismatch → Zero DDI



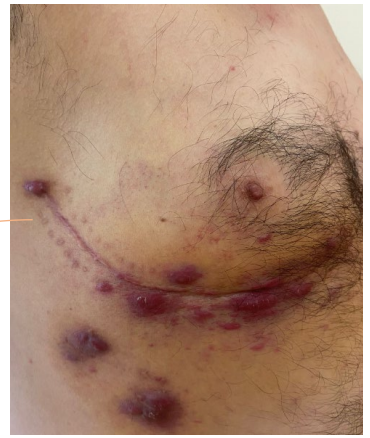
2 Mismatch → Zero DDI

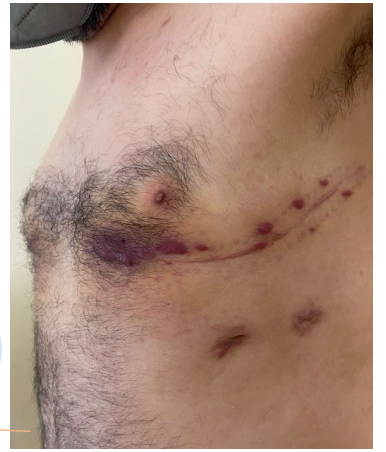


2 Mismatch → One DDI



27 Mismatch → 18 DDI (66%)





18 DDI → 12 developed HHV8-related non neoplastic disease → **6 KICS**
Kaposi Sarcoma Herpes Virus Cytokine Syndrome

Since 2017 we established a protocol of early treatment of patient with detectable HHV8DNA with early switch to m-TOR inhibitor (with or without antiviral); patients with KICS received anti-CD20 Mab

PRE- Intervention 2011-2016:
Treatement of advanced symptomatic disease with Antivirals (Foscarnet or Cidofovir)

7 liver Recipients with HHV8-DDI:
6 developed Non-Neoplastic Disease

4 KICS

Survival 50%
(3 of 6 patients died)

POST-Intervention (2017-2022):
- **Detectable HHV8DNA** -> early switch to m-TOR inhibitor and strict clinical surveillance
- **KICS** -> anti-CD20 +or- antivirals and m-TOR inhibitor

11 liver Recipients with HHV8-DDI:
6 developed Non-Neoplastic Disease

2 KICS

Survival 100%
(0 of 6 patients died)

HHV8

- Donor screening for HHV8 Ab to identify recipients at risk is strongly advised; however lack of standardized serology is the major limiting factor to support this recommendation.
- In the High-Risk group (D+/R-) strict HHV8DNA monitoring, clinical surveillance, early introduction of m-TOR inhibitor can prevent development of KICS and use of anti-CD20 Ab in case of KICS may have a major impact on mortality.

Mularoni et al, Oral communication, American Transplant congress 2023

Citomegalovirus

- L'insorgenza della malattia da CMV in assenza di profilassi varia in base a:
  - ❖Tipo di trapianto (Polmone e Intestino)
  - ❖Match Sierologico
    - Alto Rischio: D+/R- (non hanno pool di CMV-specific CD8+ memory T cells)
    - Rischio Intermedio: R+ (CD4+ and CD8+ T-cell exhaustion)
  - ❖Tipo di immunosoppressione: minore incidenza con mTOR inhibitors maggiore con thymoglobuline, alemtuzumab e belatacept
  - ❖Coinfezione con altri herpesvirus (ad es.HHV-6)

Haidar G, Singh N., Curr Opin Infect Dis 2017
L. Azevedo, Clinics, 2015

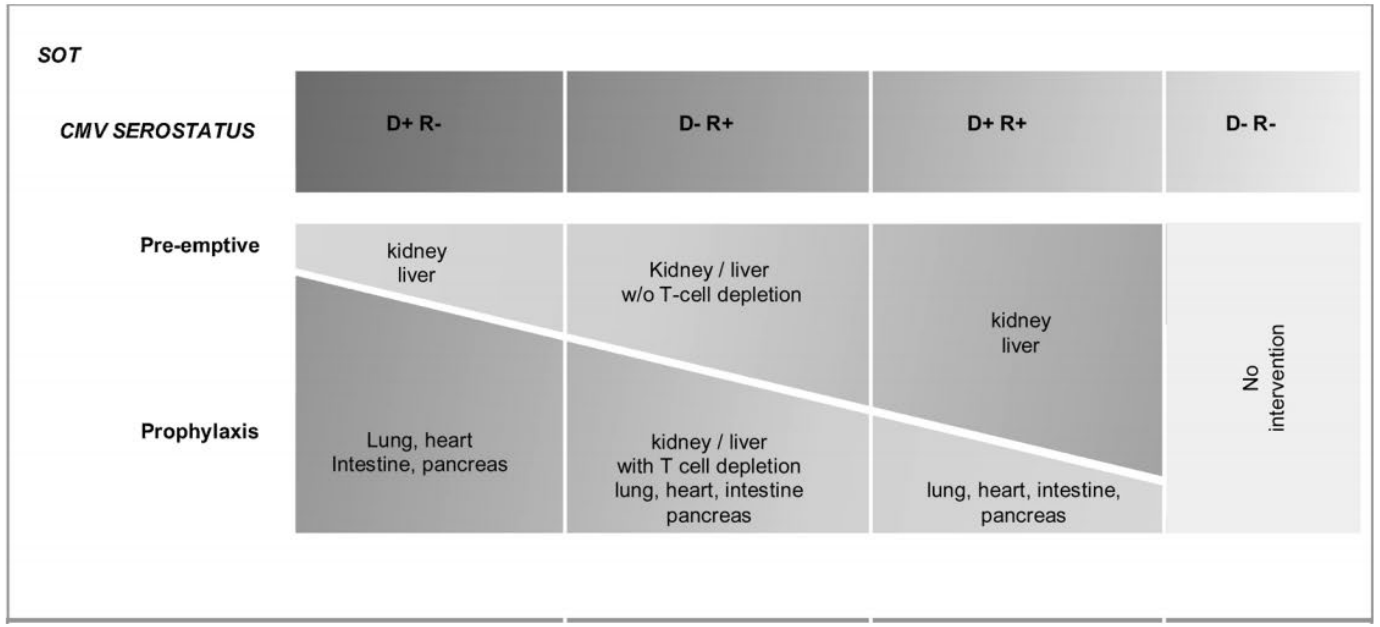
Strategie di gestione del CMV

Journal of Clinical Virology
Volume 123, February 2020, 104211

Review

CMV infection management in transplant patients in Italy

Paolo Antonio Grossi [a, b], Fausto Baldanti [c], Massimo Andreoni [d, e, f], Carlo Federico Perno [d, e, f]



Gli approcci variano a seconda del tipo di organo trapiantato e del profilo di rischio:

- **Profilassi**: farmaci antivirali a tutti I pazienti “a rischio” per un periodo di tempo definito (3-12 mesi dopo SOT).
- **Pre-emptive**: CMV DNAemia misurata secondo uno schema definite e l’antivirale viene somministrato quando I livelli di CMV raggiungono il livello di allerta MA la infezione è ancora asintomatica.

	Antiviral prophylaxis	Preemptive therapy
Clinical efficacy	Yes (based on large randomized controlled clinical trials)	Yes (based on fewer and smaller trials), including D+/R− kidney and liver recipients
Ease of application	Easier to coordinate	More difficult to coordinate
		Viral load thresholds not defined; each program should develop viral load thresholds for various clinical indications
Delayed-onset CMV disease	Common in CMV D+/R− transplant recipients (postprophylaxis delayed-onset CMV disease)	Less common
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Lesser drug toxicity with shorter courses of antiviral therapy
Indirect effects (graft loss, mortality, and opportunistic infections)	Positive impact (meta-analyses and limited comparative trials)	Very limited data
Drug resistance	Yes	Yes

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES | Full Access

Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable, Atul Humar

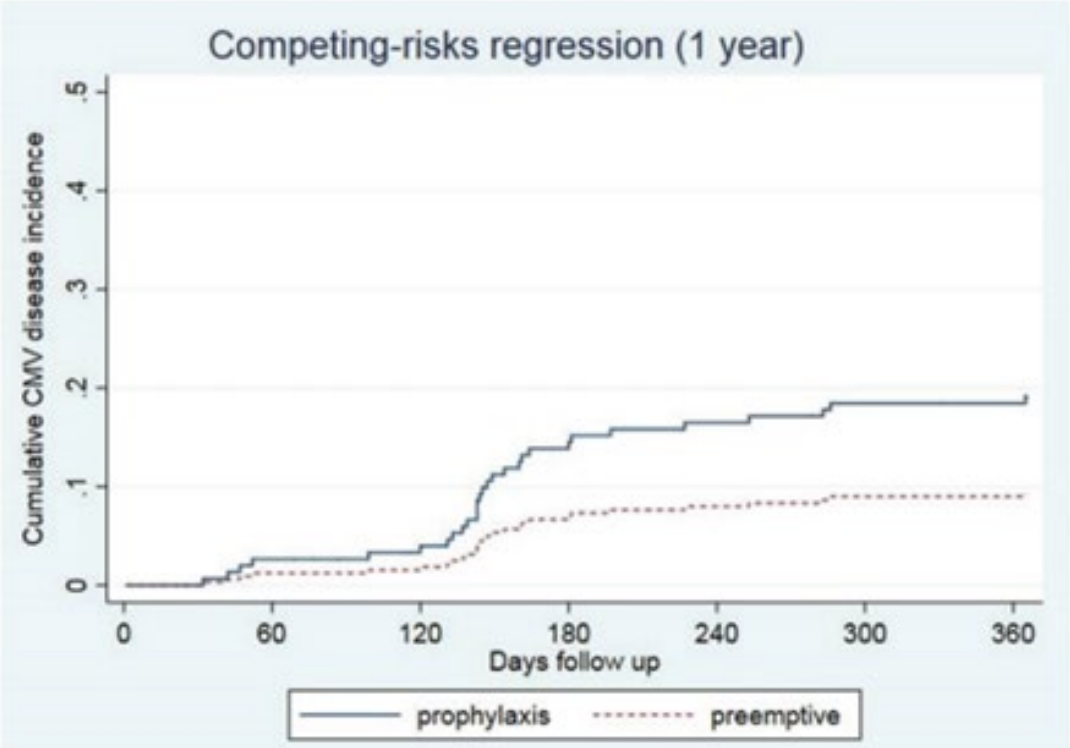
First published: 28 February 2019 | https://doi.org/10.1111/ctr.13512 | Citations: 64

Randomized Controlled Trial > JAMA. 2020 Apr 14;323(14):1378-1387.
doi: 10.1001/jama.2020.3138.

Effect of Preemptive Therapy vs Antiviral Prophylaxis on Cytomegalovirus Disease in Seronegative Liver Transplant Recipients With Seropositive Donors: A Randomized Clinical Trial

Nina Singh [1 2], Drew J Winston [3], Raymund R Razonable [4], G Marshall Lyon [5],

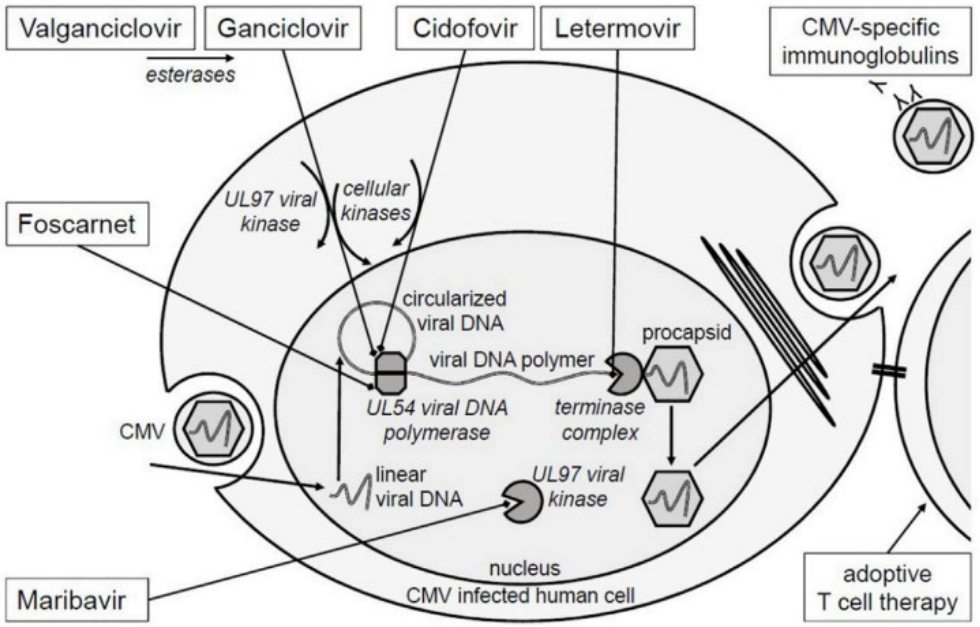
- 100 pazienti in Pre-Emptive therapy (PET), 105 profilassi
- Incidenza di malattia da CMV: 9% in PET e 19% in profilassi (p=0.039)
- La maggiori parte delle malattie insorte post profilassi: 6% PET vs 17% profilassi (p=0.027)
- Outcomes secondari (OI, neutropenia, rigetto acuto, Perdita del graft, mortalità) non differenti nei 2 gruppi



Conclusions. PET significantly reduced the incidence of CMV disease compared with prophy in D+R- LTR, and was associated with similar other clinical outcomes. Current guidelines should be revised to recommend PET over prophylaxis in this setting, and similar trials conducted in other D+R– transplant populations. (Funded by NIAID; ClinicalTrials.gov# NCT01552369.)

Profilassi e Terapia CMV

Terapia	Profilassi
• **Ganciclovir/Valganciclovir**	• **Ganciclovir/Valganciclovir** • Sviluppo di resistenza (0.4-11.9%) • Leucopenia/Neutropenia (incidenza 30.5%) • **Letermovir** • Inibitore della terminasi virale non-inferiore a valganciclovir per profilassi



Fisher CE, *Clin Infect Dis*. 2017; Yadav DK, *Front Immunol*. 2022; Kotton, TID, 2023; Walti C, Transpl Int 2023
Hayes M, Am J Transplant. 2022; Kotton CN, Infect Dis Ther. 2023; A.P Limaye, JAMA, 2023; Yadav DK, Front Immunol. 2022

Letermovir

JAMA

QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION

422 Men
167 Women

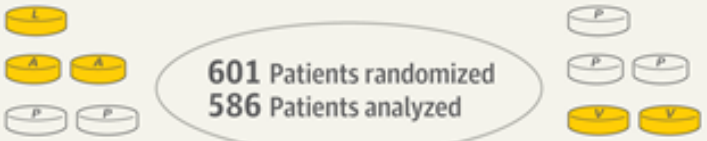
Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: 50 years

LOCATIONS

94 Hospitals worldwide

INTERVENTION



301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir
10.4% (30 of 289 patients)

Valganciclovir
11.8% (35 of 297 patients)

Letermovir was noninferior to valganciclovir:
Stratum-adjusted difference, **−1.4%**
(95% CI, −6.5% to 3.8%)

© AMA

Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. Published online June 6, 2023. doi:10.1001/jama.2023.9106

B Probability of no events of neutropenia or leukopenia

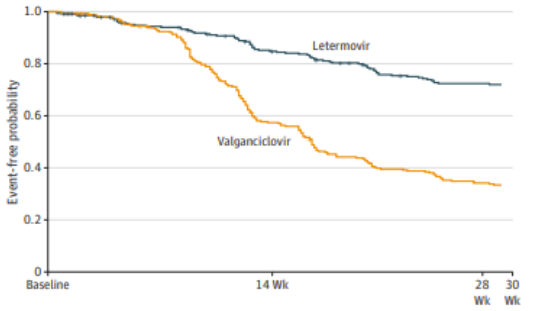
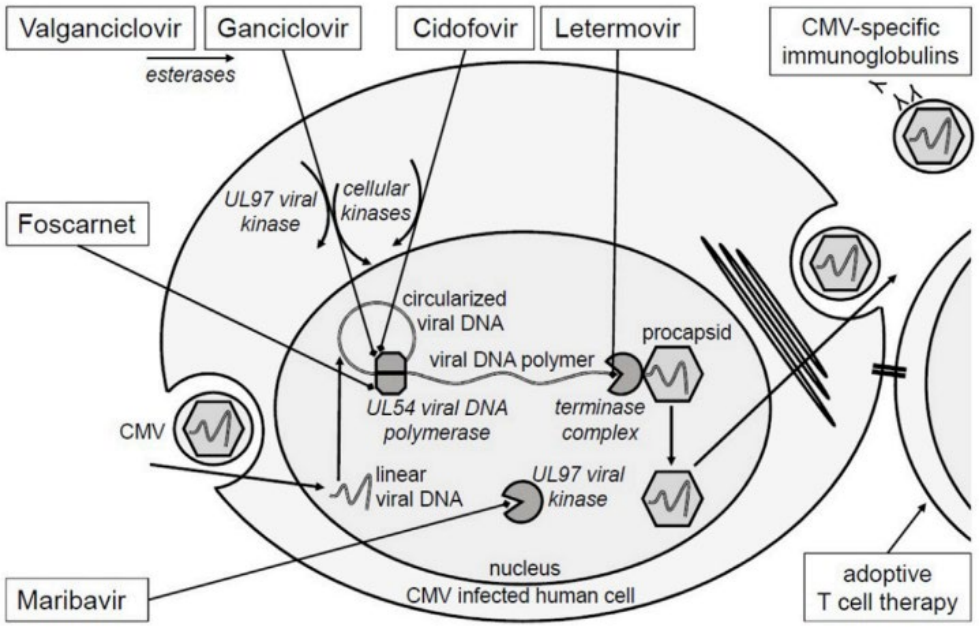


Table 2. Adverse Events Through Week 28 in the Safety Population[a]

Adverse event	No. (%) Letermovir (n = 292)	Valganciclovir (n = 297)	Difference (95% CI), %[b]
Adverse event summary			
≥1 adverse event	271 (92.8)	276 (92.9)	−0.1 (−4.4 to 4.2)
Serious adverse events[c]	106 (36.3)	113 (38.0)	−1.7 (−9.5 to 6.1)
Drug-related adverse events[d]	58 (19.9)	104 (35.0)	−15.2 (−22.2 to −8.0)
Serious drug-related adverse events[c,d]	4 (1.4)	15 (5.1)	−3.7 (−7.0 to −0.9)
Death	2 (0.7)	1 (0.3)	0.3 (−1.3 to 2.2)
Discontinued due to adverse events	12 (4.1)	40 (13.5)	−9.4 (−14.1 to −4.9)
Discontinued due to serious adverse events[c]	6 (2.1)	14 (4.7)	−2.7 (−5.9 to 0.3)
Discontinued due to drug-related adverse events[d]	8 (2.7)	26 (8.8)	−6.0 (−10.1 to −2.4)
Discontinued due to serious drug-related adverse events[c,d]	2 (0.7)	7 (2.4)	−1.7 (−4.2 to 0.4)
Adverse events in ≥10% of participants			
Diarrhea	92 (31.5)	85 (28.6)	2.9 (−4.5 to 10.3)
Tremor	53 (18.2)	52 (17.5)	0.6 (−5.6 to 6.9)
Urinary tract infection	41 (14.0)	42 (14.1)	0.1 (−5.8 to 5.6)
Peripheral edema	39 (13.4)	38 (12.8)	0.6 (−4.9 to 6.1)
Hypomagnesemia	37 (12.7)	39 (13.1)	−0.5 (−5.9 to 5.0)
Leukopenia	33 (11.3)	110 (37.0)	−25.7 (−32.3 to −19.1)
Hypertension	33 (11.3)	36 (12.1)	−0.8 (−6.1 to 4.5)
Increased creatinine	30 (10.3)	41 (13.8)	−3.5 (−8.9 to 1.8)
Hypophosphatemia	30 (10.3)	35 (11.8)	−1.5 (−6.7 to 3.6)
Hyperkalemia	27 (9.2)	32 (10.8)	−1.5 (−6.5 to 3.4)
Nausea	25 (8.6)	33 (11.1)	−2.5 (−7.5 to 2.3)
Fatigue	18 (6.2)	32 (10.8)	−4.6 (−9.3 to −0.1)
Neutropenia	8 (2.7)	49 (16.5)	−13.8 (−18.7 to −9.3)

Profilassi e Terapia CMV

Terapia	Profilassi
• **Ganciclovir/Valganciclovir**	• **Ganciclovir/Valganciclovir** • Sviluppo di resistenza (0.4-11.9%) • Leucopenia/Neutropenia (incidenza 30.5%) • **Letermovir** • Inibitore della terminasi virale non-inferiore a valganciclovir per profilassi • Minori effetti avversi (Leucopenia) • Bassa barriera genetica • **Cytomegalovirus immunoglobin** • Usate in D+/R- cuore e/o polmone • Non disponibili raccomandazioni specifiche



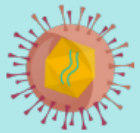
Fisher CE, *Clin Infect Dis*. 2017; Yadav DK, *Front Immunol*. 2022; Kotton, TID, 2023; Walti C, Transpl Int 2023
Hayes M, Am J Transplant. 2022; Kotton CN, Infect Dis Ther. 2023; A.P Limaye, JAMA, 2023; Yadav DK, Front Immunol. 2022

Resistant/Refractory CMV Infection

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES | Full Access
Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice
Raymund R. Razonable, Atul Humar
First published: 28 February 2019 | https://doi.org/10.1111/ctr.13512 | Citations: 259

Refractory CMV infection	CMV DNAemia or antigenemia increases (ie, >1 log10 increase in CMV DNA levels in blood between peak viral load within the first week and the peak viral load at 2 wk or more) after at least 2 wk of appropriately dosed antiviral therapy	Viral load persistence (at the same level or higher than the peak viral load within 1 wk but <1 log10 increase in CMV DNA titers) after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy	Lack of improvement in clinical signs and symptoms after at least 2 wk of appropriately dosed antiviral therapy
Resistant CMV	Presence of viral genetic alteration that confer reduced susceptibility to one or more antiviral drugs	

SOT CDST RESOURCE



Antiviral Medication Dosing for Resistant/Refractory CMV in Transplantation

Ganciclovir:

Full dose = 5 mg/kg IV every 12 hours, high dose = 10 mg/kg IV every 12 hours. Adjust doses for renal function and monitor for bone marrow suppression. Monitor CMV DNA levels and check again for resistance if patient does not respond to therapy. Frequently monitor immunosuppressant drug levels during treatment and adjust dose if needed.

Ganciclovir injection [package insert]. Exela Pharma Sciences. Lenoir, NC. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209347lbl.pdf

Foscarnet:

90 mg/kg IV every 12 hours or 60 mg/kg IV every 8 hours. Individualize dose for renal function, with careful monitoring for electrolyte abnormalities and renal toxicity. Monitor CMV DNA levels and check again for resistance if patient does not respond to therapy. Frequently monitor immunosuppressant drug levels during treatment and adjust dose if needed.

Foscavir (foscarnet sodium) injection [package insert]. Hospira, Inc. Lake Forest, IL. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020068s018lbl.pdf

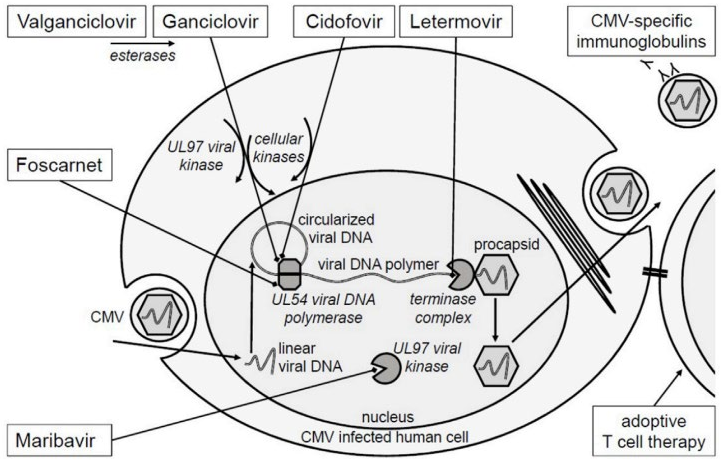
Maribavir:

400 mg PO twice daily. Coadministration with ganciclovir, valganciclovir, or strong CYP3A4 inducers is not recommended. Monitor CMV DNA levels and check again for resistance if patient does not respond to therapy. Frequently monitor immunosuppressant drug levels during treatment and adjust dose if needed.

Livtencity (maribavir) [package insert]. Takeda Pharmaceuticals America, Inc. Lexington, MA. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf

- Reducing the immunosuppressive therapy to the lowest feasible amount.
- **For asymptomatic or mildly symptomatic** disease: high dose GCV (from 7.5 to 10 mg/kg every 12 h)
- **For severe or life-threatening** disease: Foscarnet
- Maribavir

Avery RK, et al. Transplantation. 2016
Razonable, Clin Transpl, 2019
Kotton, C. Kamar N, Infect Dis Ther 2023
Clinical decision support tool for resistant/refractory CMV in transplantation. 2022.



New Treatment Options for Refractory/Resistant CMV Infection

Carla Simone Walti[1], Nina Khanna[1], Robin K. Avery[2] and Ilkka Helanterä[3]**

TABLE 1 | Advantages and limitations of new treatment options for refractory/resistant CMV in SOT.

	Mode of action	Advantages	Limitations
Maribavir	- Inhibition of viral UL97 kinase	- Well tolerated - Oral formulation - Efficacy demonstrated in a Phase 3 randomized controlled trial - Regulatory approval for this indication	- Dysgeusia in one-third of patients - No intravenous formulation - Reduced efficacy with high viral loads and in refractory CMV without resistance - Poor penetration to CNS/retina - Drug-drug interactions - Recurrences after successful treatment - Resistances
Letermovir	- Inhibition of viral terminase complex	- Well tolerated - Oral and intravenous formulation - Combination therapy with ganciclovir possible - Possible option as secondary prophylaxis	- No randomized controlled trials - Approved only for prophylaxis - Reduced efficacy with high viral loads - Relevant interaction with cyclosporine, sirolimus, tacrolimus - Recurrences after successful treatment - Resistances
CMV-specific adoptive T cell therapy	- Autologous or allogeneic *ex vivo* selected (and expanded) CMV-specific T cells to restore CMV-specific T cell immunity	- Mechanistic approach to restore immunity - Reported to be safe - Alternative in drug resistant CMV - Multi-virus specific commercial products under development	- No randomized controlled trials - Safety/efficacy await confirmation in Phase 3 trials - Complex donor selection - Not widespread available - Time/cost intensive laboratory protocols - Expansion and function limited by immunosuppressive drugs

Transplant International | Published by Frontiers
October 2023

Clinical Infectious Diseases
MAJOR ARTICLE

Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

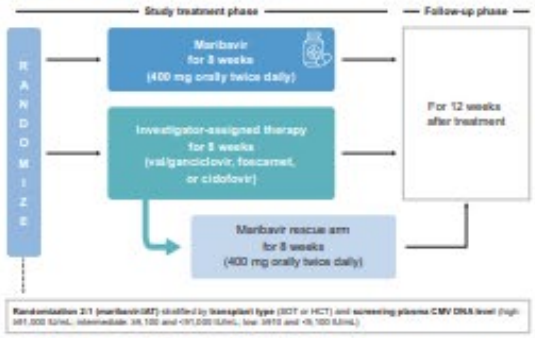
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,[1] Sophie Alain,[2] Barbara D. Alexander,[3] Emily A. Blumberg,[4] Roy F. Chemaly,[5] Catherine Cordonnier,[6] Rafael F. Duarte,[7] Diana F. Florescu,[8] Nassim Kamar,[9] Deepali Kumar,[10] Johan Maertens,[11] Francisco M. Marty,[12,a] Genovefa A. Papanicolaou,[13,14] Fernanda P. Silveira,[15] Oliver Witzke,[16] Jingyang Wu,[17] Aimee K. Sundberg,[18] and Martha Fournier[18]; for the SOLSTICE Trial Investigators[a]

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

STUDY DESIGN



STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

PRIMARY ENDPOINT (WEEK 8)

Adjusted difference (95% CI): 32.8 (22.80–42.74)

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)

Adjusted difference (95% CI): 9.5 (2.02–16.88)

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; TEAE, treatment-emergent adverse event.

ClinicalTrials.gov: NCT02931539
This study was funded by Takeda Development Center Americas, Inc., Lexington, MA

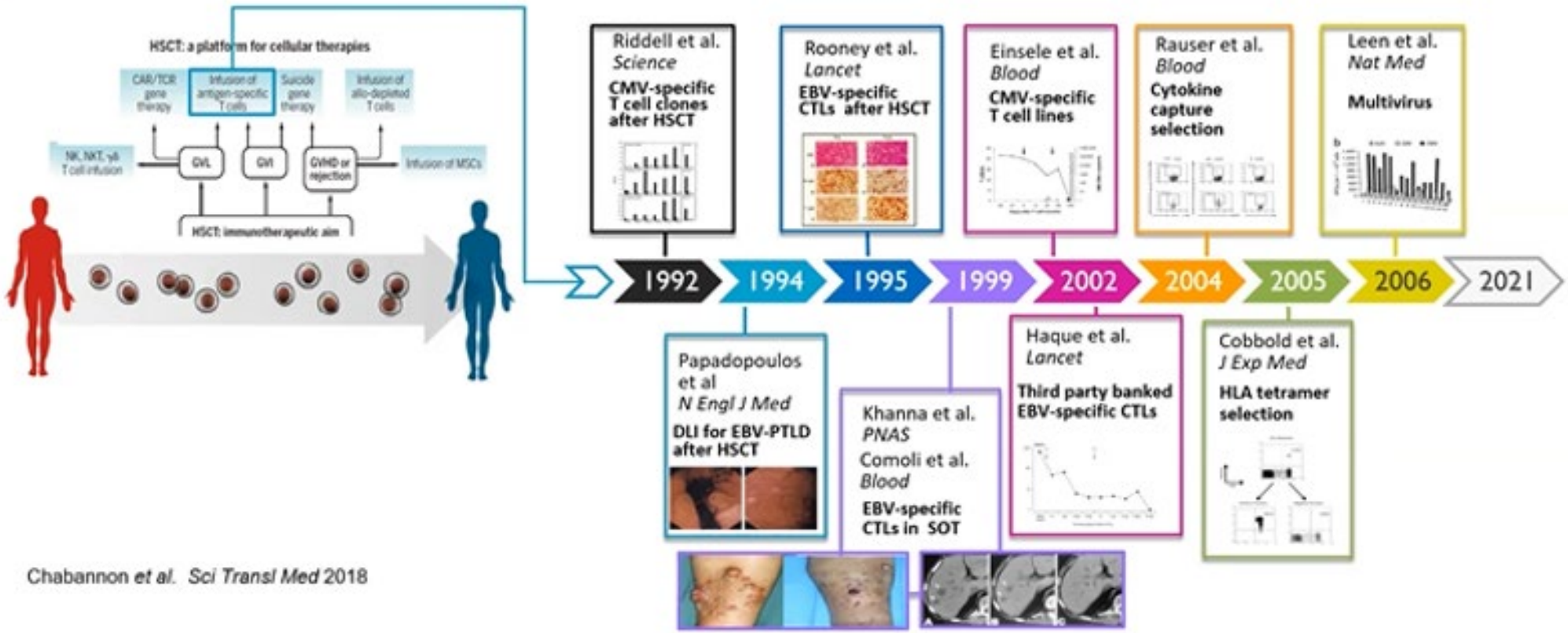
CMV-specific T-cell response

- Cell mediated Immunity CMI assays (ELISA/QuantiFERON-CMV, ELISpot, Flow cytometry) misurano il rilascio di IFNγ o altre citochine in risposta a stimolazione antigenica: informazioni quantitative e funzionali sui Linfociti T CMV specifici.
- Utile per stratificare il rischio di CMV e guidare decisioni su pre-emptive e profilassi
- SCOPO: gestione personalizzata, ridurre eccessi di trattamento e prevenire tossicità
- Maggiori evidenze necessarie per: standardizzare cutoff, dimostrare efficacia costo/beneficio
- Applicando lo stesso principio di stimolazione cellulare → Immunoterapia Adottiva con Linfociti T Citotossici (CTL) terapia che si fonda sulla ricostituzione della immunità protettiva del paziente.

S. Calarota, J. Clin. Virol., 2015.
M. Ritta, New Microbiol. 2015
D. Trivedi,, Blood , 2005
Tzannou I, Blood Adv. 2019;

CELL THERAPY FOR VIRAL INFECTIONS:
origin of adoptive cellular therapy: the era of HSCT

Courtesy of Prof. Patrizia Comoli



Chabannon *et al. Sci Transl Med* 2018

Clinical Infectious Diseases
MAJOR ARTICLE

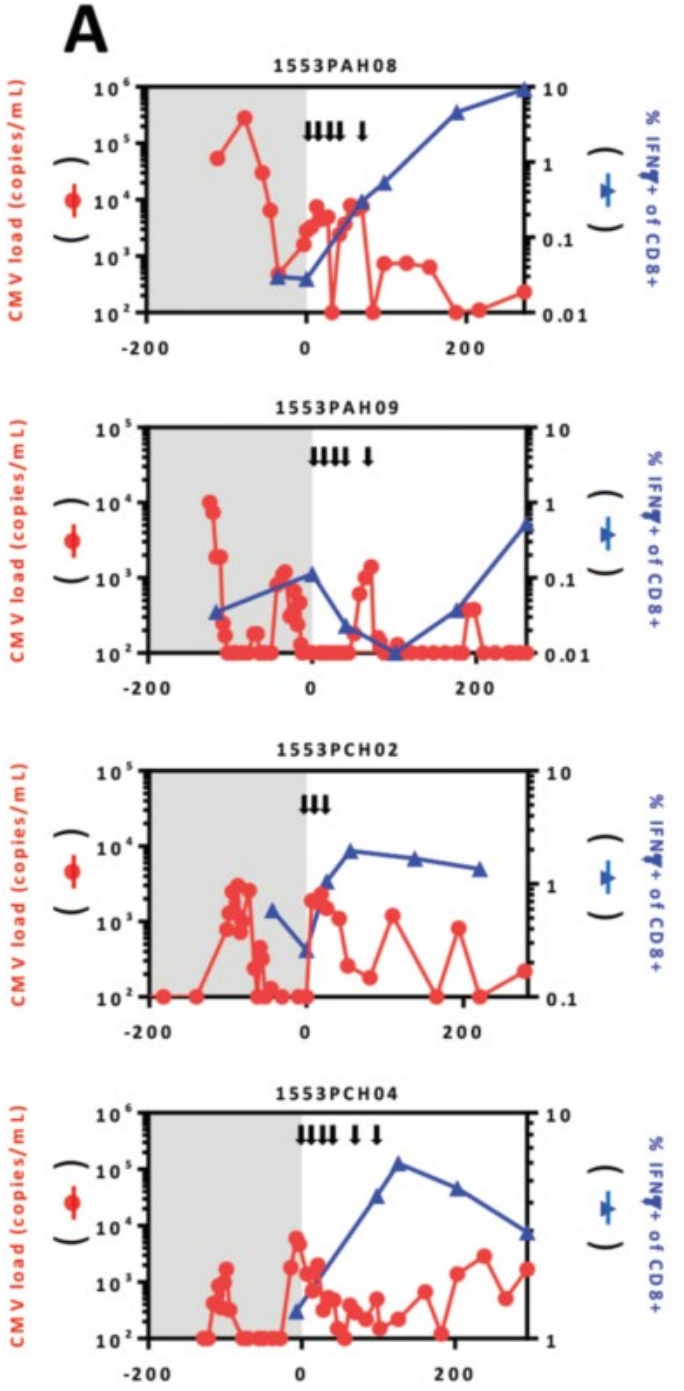
Autologous Adoptive T-cell Therapy for Recurrent or Drug-resistant Cytomegalovirus Complications in Solid Organ Transplant Recipients: A Single-arm Open-label Phase I Clinical Trial

Corey Smith,[1] Leone Beagley,[1] Sweera Rehan,[1] Michelle A. Neller,[1] Pauline Crooks,[1] Matthew Solomon,[1] Chien-Li Holmes-Liew,[2,3] Mark Holmes,[2,3] Scott C. McKenzie,[4,7] Peter Hopkins,[5,7] Scott Campbell,[6,7] Ross S. Francis,[6,7] Daniel C. Chambers,[5,7] and Rajiv Khanna[1,7]

itute, Brisbane, Australia, [2]South Australian Lung Transplant Unit, Department of Thoracic Medicine, Australia, [4]Advanced Heart Failure and Cardiac Transplant Unit and [5]Queenland Lung Transplant ital, Brisbane, Australia, and [7]School of Medicine, University of Queensland, Brisbane, Australia

CID 2019:68 (15 February) • Smith et al

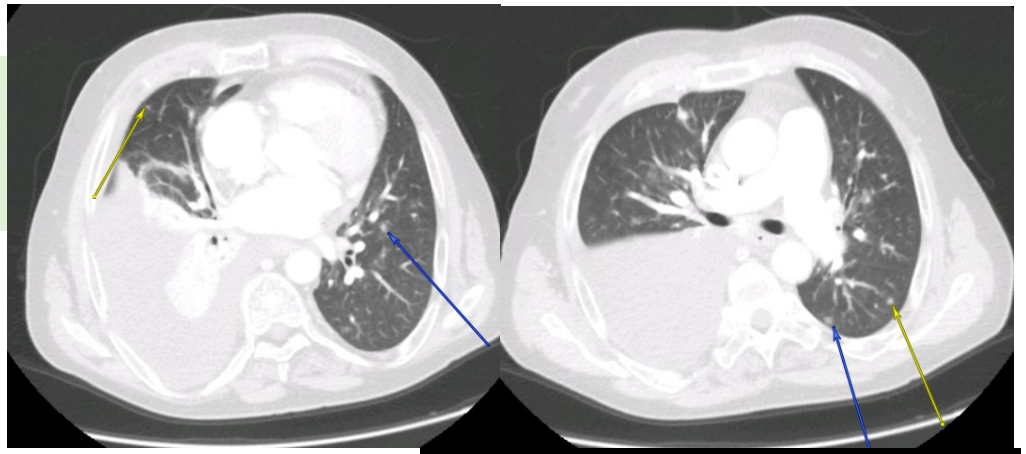
PBMC samples from patients before and after T-cell therapy were assessed for interferon (IFN) γ–producing cytomegalovirus (CMV)–specific T cells after stimulation with the CMV peptide pool.

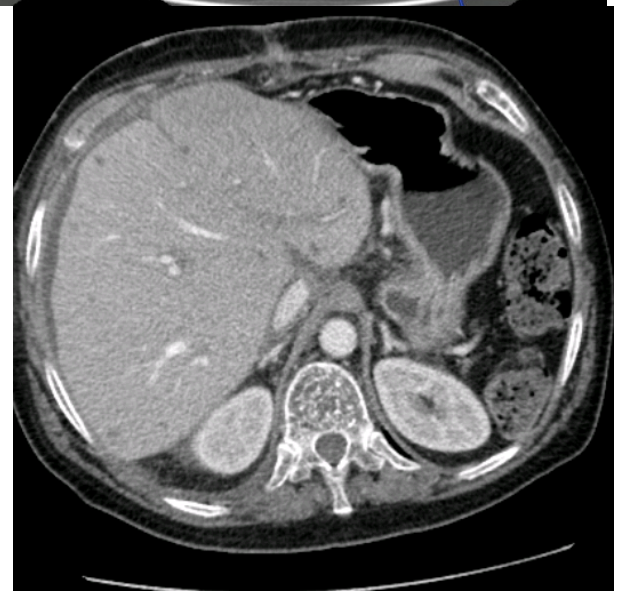


- 22 SOT recipients (13 kidney, 8 lung and 1 heart) con infezione ricorrente o resistente a ganciclovir.
- 13 sono stati trattati con infusione di Linfociti T autologhi CMV specifici espansi in vitro

- **Outcome**
- Undici (84%) dei 13 pazienti trattati hanno avuto miglioramento dei sintomi, risoluzione/riduzione della viremia, malattia, sospensione dell'antivirale.
- L'utilizzo della immunoterapia adottiva non si è associato a effetti avversi severi

Malattia da EBV





Forme Cliniche

- Faringite, Epatite, Noduli polmonari, linfoadenopatia, epatosplenomegalia, localizzazione SNC e malattia gastroenterica. Predilizione per il graft
- PTLD: Proliferazione Linfoide → Linfoma B

Terapia

- Riduzione della immunosoppressione in caso di viremia crescente
- Acyclovir e Ganciclovir non attivi su virus latente (forma predominante nella PTLD)
- Rituximab
- Chemioterapia in caso di Linfoma
- Immunoterapia adottiva con Linfociti T EBV specifici

Allen UD, Clin Transplant. 2019

Off-the-shelf EBV-specific T cell immunotherapy

Patients with T Cell Deficiency are at High Risk for Devastating Viral Infections

Virus-infected cells

Treated with Current Care Options

Deficient T Cell Immunity Fails to Control Viral Infections, Resulting in Devastating Consequences

Deficient T cells

Treated with Off-the-Shelf VSTs

Expanded Off-the-Shelf VSTs

Restored T Cell Immunity with Expanded Off-the-Shelf VSTs Controls Viral Infections

CD4+ T cells in patients
CD8+ T cells in patients
CD4+ Off-the-Shelf VSTs
CD8+ Off-the-Shelf VSTs

Prockop et al. J Clin Invest. 2020

Polyoma: BKV e JCV

- BKPyV Virus BK causa nefropatia e ematuria nel trapianto di rene.
- Terapia: riduzione della immunosoppressione
- Nessuna terapia efficace ad oggi
- *Since its discovery in 1971, an effective prophylaxis or therapy is yet to be devised, with unmitigated disease frequently resulting in allograft loss.*
- JCV è agente eziologico di PML (progressive multifocal leukoencephalopathy)
- Terapia: riduzione della immunosoppressione
- Immunoterapia Adottiva

Hamad Y, J Heart Lung Transplant 2017
Hirsch HH, Clin Transplant. 2019

CASE ANECDOTES, COMMENTS AND OPINIONS

Successful JC virus-targeted T-cell therapy for progressive multifocal leukoencephalopathy in a lung transplant recipient

Maddalena Peghin, MD, PhD,[a,b] Nadia Castaldo, MD,[a,c]

The Journal of Heart and Lung Transplantation

The Journal of Heart and Lung Transplantation, Vol 41, No 7, July 2022

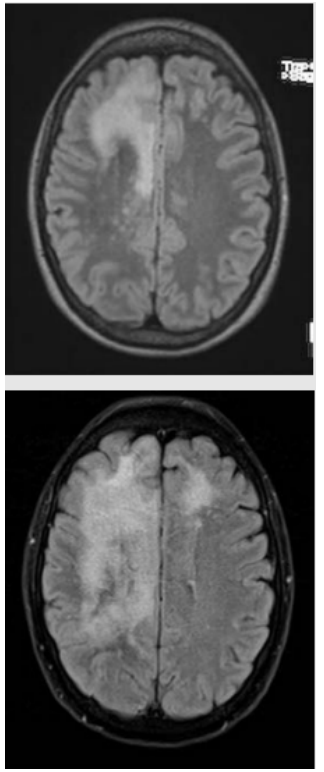
- 30 year-old woman
- Cystic Fibrosis
- 2015 Lung Transplant
  - Complications
  - Chronic lung allograft disfunction
  - Infections:
    - Chronic cavitary Aspergillosis
    - Lung colonization with
    - *Pseudomonas aeruginosa* XDR
- **2019 re- transplantation**
- Thymoglobulin and Steroid boluses
- IS: MMF, Tacrolimus, PDN

- January 2020: acute mild left arm hyposthenia, followed by complete left body hemiparesis, dysphagia and seizures

- **PML**
- JCV-DNA in CSF: 208,567 cp/mL
- MRI: right frontal lobe cerebritis

Reduction of IS + adjuvant treatement

- Worsening of Respiratory function and rejection
- Steroid boluses



The Journal of Heart and Lung Transplantation, Vol 41, No 7, July 2022

CASE ANECDOTES, COMMENTS AND OPINIONS

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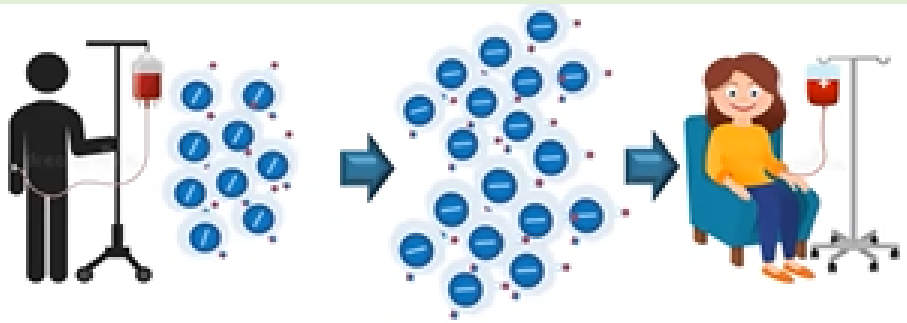
The Journal of Heart and Lung Transplantation

Blood lymphocytes from HLA haploidentical family donor were collected and specific JCV T-cells were successfully generated



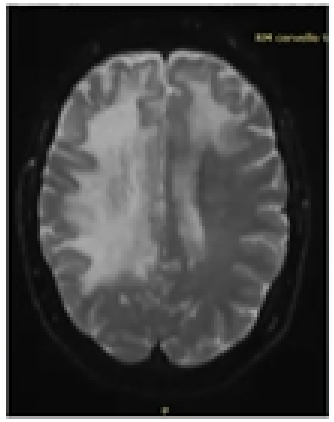
Month +2

- Intensive rehabilitative therapy → ability to sit without support
- VII nerve palsy disappeared
- EEG: reduction in epilectic spikes

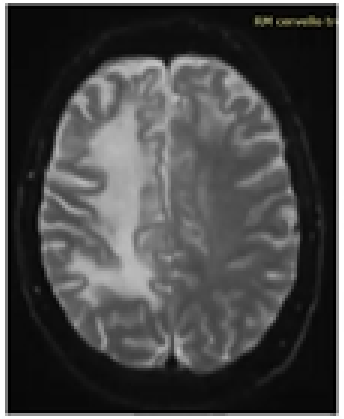
Month +4

- Slowly re-gaining ability to walk with support
- Left arm persistently paralized
- EEG: no more epilectic spikes

Before treatment



After treatment



What about the organ?

- Good lung function
- IS: Tac restarted + everolimus + PDN

JCV-CTL immunotherapy may be promising for management of PML in SOT recipients

Courtesy of Prof. Patrizia Comoli

Take Home Messages

- Complesse interazioni tra virus e l'ospite immunocompromesso
- CMV: nuovi antivirali efficaci disponibili per la profilassi e la terapia del CMV refrattario
- Per molte infezioni virali non sono disponibili antivirali efficaci (Adenovirus, HHV8, BK, JC, EBV)
- E' importante elevato sospetto clinico per la diagnosi precoce di Sindromi infiammatorie (ad.es Sindrome KICS correlata ad HHV8)
- Promettente la immunoterapia adottiva per le infezioni virali refrattarie o per le quali non è disponibile una terapia

Grazie per l'attenzione

amularoni@ismett.edu

ISMETT Istituto di Ricovero e Cura a Carattere Scientifico

UPMC LIFE CHANGING MEDICINE