

HSV et CMV résistants aux antiviraux :

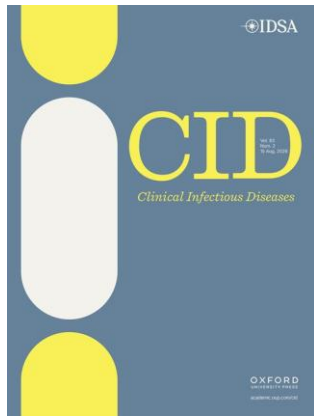
Quelles molécules pour quelles indications ?

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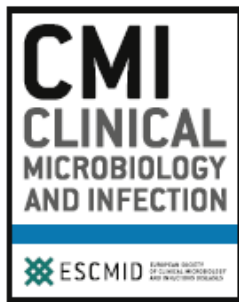


HSV



Refractory and Resistant Herpes Simplex Virus Mucocutaneous Infections in Immunocompromised Patients: Literature Review and Proposed Definitions for Use in Clinical Trials

Roy F. Chemaly,^{1,●} Tali Shafat,^{1,●} Anna Wald,^{2,●} Camille N. Kotton,^{3,●} Genovefa Papanicolaou,^{4,5,●} Michelle K. Yong,^{6,7,8} Veronica Miller,^{9,●} Takashi E. Komatsu,^{10,a,●} Charu Mullick,^{10,a} Aimee C. Hodowanec,^{10,a,●} Gabriel Westman,^{11,12,a} Fareed Khawaja,^{1,●} Alexander Birkmann,^{13,●} and Per Ljungman^{14,15,●}; HSV Resistance Working Group of the Transplant Associated Viral Infections Forum



How we diagnose and manage refractory and resistant herpes simplex virus mucocutaneous infection after haematopoietic cell transplantation

Tali Shafat*, Ella J. Ariza-Heredia, Marilyne Daher, Roy F. Chemaly

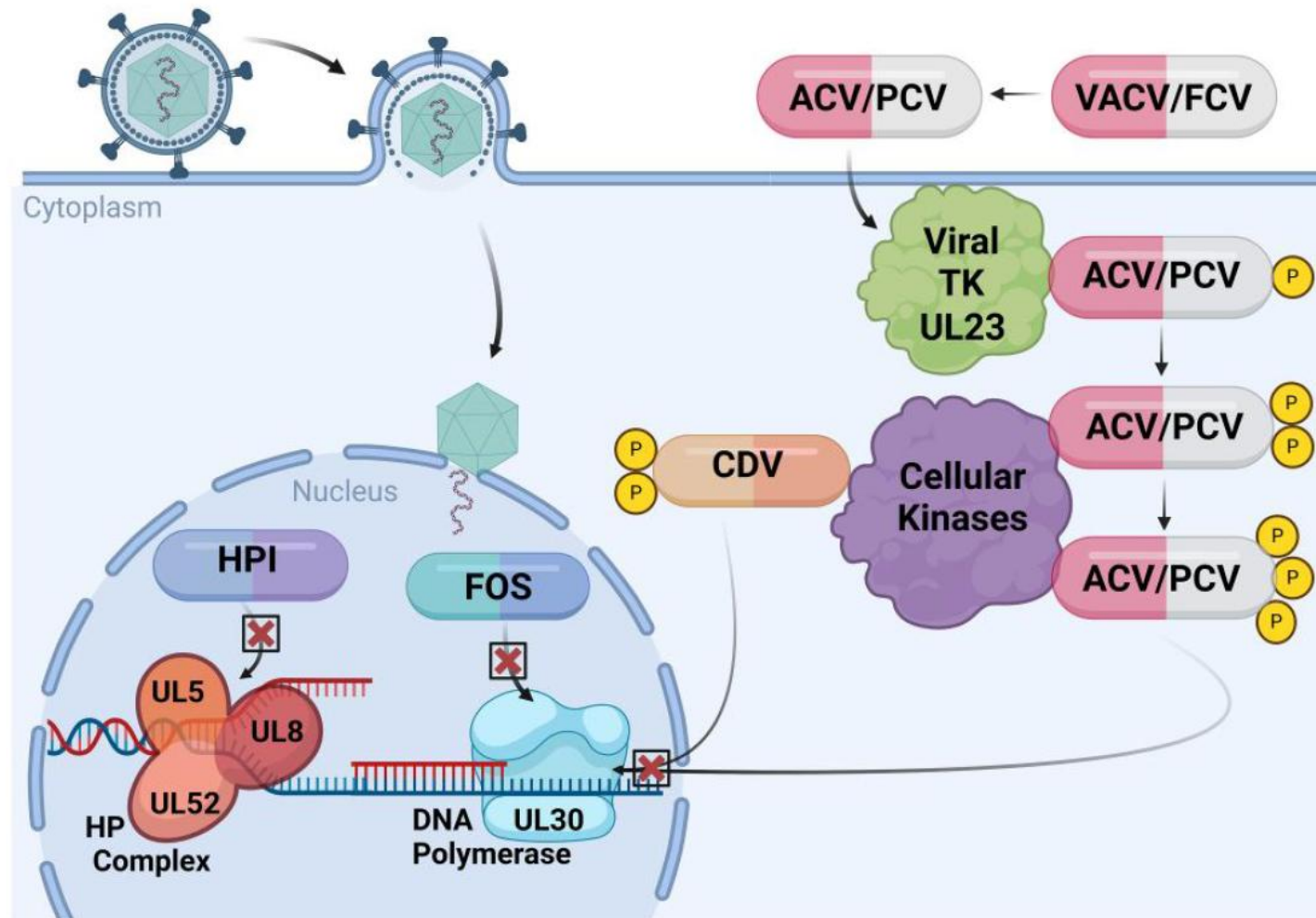
Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA



Antivirals for prophylactic or curative treatments of HSV infections

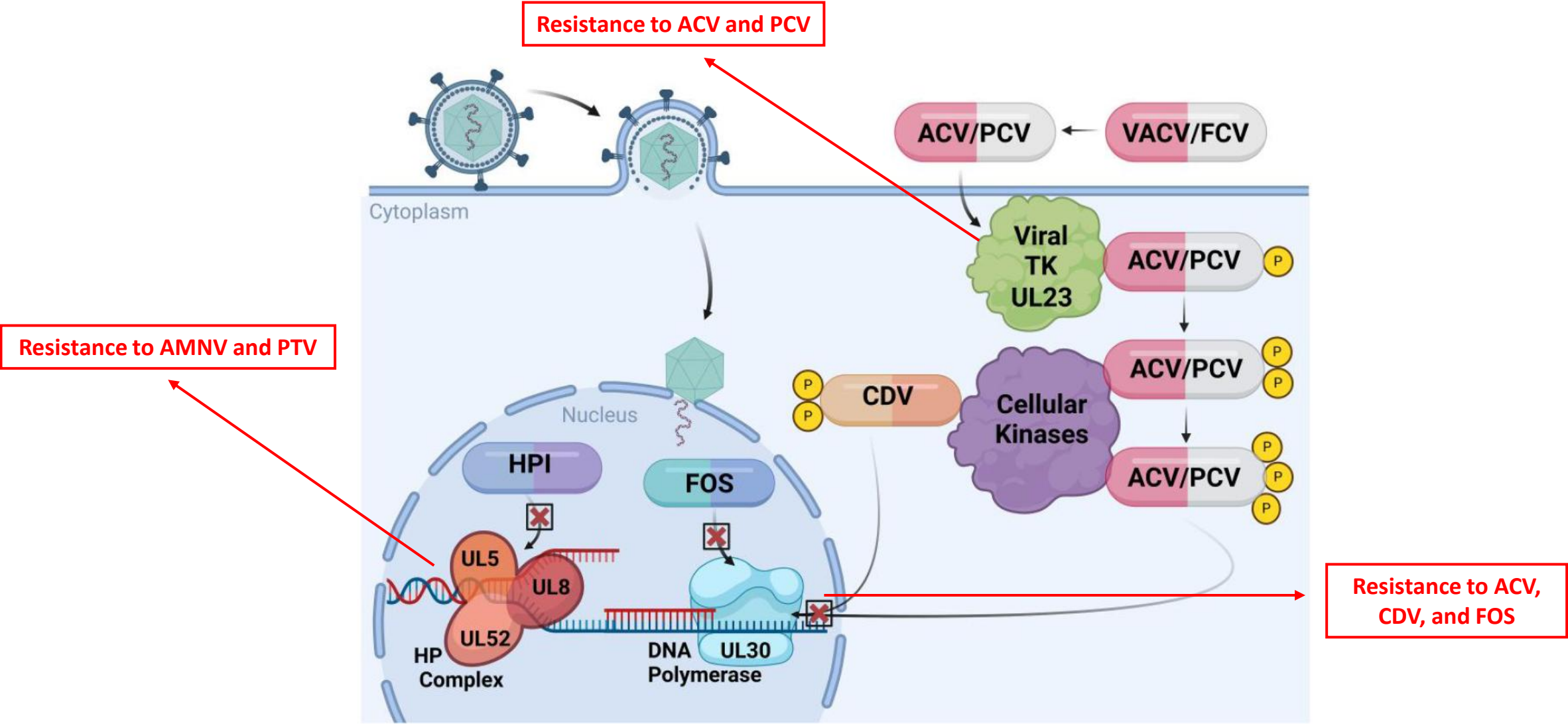
HSV target	Type	Antiviral	Administration	
DNA polymerase	Nucleoside analogues	Acyclovir (ACV)	IV, topical (oral)	1 st line
		Valacyclovir (VACV)	oral	
		Famciclovir (FCV)	oral	
		Ganciclovir (GCV)	Topical (keratitis)	
		Trifluridine (TFT)	Topical (keratitis)	
	Nucleotide analogue	Cidofovir (CDV)	IV	Off-label : compassionate use
	Pyrophosphate analogue	Foscarnet (FOS)	IV	2 nd line
Helicase-primase	Phenyloxadiazole derivative	Amenamevir (AMNV)	oral	Compassionate use
	Thiazolylamide derivative	Pritelivir (PTV)	oral	Compassionate use

Inhibition of viral DNA replication



HSV resistance to antivirals

Molecular mechanism: mutations in viral targets involved in the mechanism of action of antivirals



■ Frequency of HSV resistance to antivirals

- Immunocompromised patients: **3.5%** to **11%**
 - PLWHIV: **4.0%** to **8.0%** (higher among patients with AIDS)
 - SOT recipients: **2.0%** to **3.0%** (up to **10%**)
 - HSCT recipients: **16.0%** (up to **30%** to **40%**)
- Immunocompetent patients: **0.1%** to **0.7%**
 - Stable over time (unaffected by growing exposure to antivirals)
- Immunocompetent patients with recurrent herpetic keratitis: up to **8.0%**
 - Cornea: immunoprivileged site with reduced local immune responses
 - Decreased concentration of antiviral drugs

■ Virological diagnosis of HSV resistance to antivirals

- Genotypic resistance testing
- Sequencing HSV genes encoding enzymes implicated in mechanism of action of antivirals (UL23, UL30, UL5, UL52)

Thymidine kinase UL23

	51-63	83-88	162-164	168-176	216-222	284-289	376
1	HSV-1						
	HSV-2						
	ATP			Nucléoside			
	51-63	84-89	163-165	169-177	217-223	285-290	
HSV-1 UL23	R51W Y53D/H/stop D55N G56S/V P57H H58R/L G59R/V/W G61V/del K62N T63A/I/S	T64A/S E95stop T65N S74stop Y80N E83K P84S Y87N	E95stop T103P/stop Q104H/stop H/Q105P Q109stop S113L A117P M121R S123R A125E/L	M128A/L G129D P131S G144N A156V L157P D162A R163H/C A167V	A168T L170P Y172C/F P173L/R/del A174P A175V R176Q/stop/W	L 178R T201P Y248H L291R S181N/R G206R T183P A207P Q185R L208H R281stop C336Y/stop V187M R216H/C/S T287M Q342stop A189V R220C/H T354P V191M R222C L364stop I194del L227F Y239S/stop G200C/D T245M/P	
HSV-2 UL23	R34C D55N G56stop G59P	P85S Y88C N100H D163M	D137stop L158P D163M	Y173C R177W	S182D/N V192M P273V G201D D274R R217H T288M Q222stop R223H E226K Y240stop	C337Y	

DNA polymerase UL30

1	HSV-1									1235							
	HSV-2									1240							
		IV		A		II		VI		III		I		VII		V	
		437-479	577-637			694-736		772-791		805-845		881-896		938-946		953-963	
		D368A E370A G464V	E460D V462A K532T G464V	I529M K532T A542S E545D K552E Y557S P561S Q570R V573M	Y577H D581A L583V E597K/D A605V Q618H V621S	A657T	Y696H R700G/M L702H/P V714M V715G/M F716L A719V/T S724N/D/Q/E/A/K/T/H	E771Q L774F P797T V813M/A N815L/V/Y/E/S/Q/T Y818C T821M M880T G841S/C S889A F891C/Y V892M/S	L774F P797T V813M/A N815L/V/Y/E/S/Q/T Y818C T821M M880T G841S/C S889A F891C/Y V892M/S	E798K L802F	V813M/A N815L/V/Y/E/S/Q/T Y818C T821M M880T G841S/C S889A F891C/Y V892M/S		G901V D907V I922N Y941H		V958L R959H K960R N961K W998L L1007M I1028T D1070N H1228D		
	HSV-1 UL30																
		438-480	578-638			699-741		777-796		810-850		886-901		943-951		954-968	
		E250Q D307N	K533E	A606V D616G G617S C625R R628C/H	A606V D616G G617S C625R R628C/H	V718A A724T/V S725G S729N I731F/V Q732R	L779P L783M D785N L787M M789K			I815L V818A Y823C Q829R	A840T V842M R847C L850I		M910T D912V/A/N A915V F923L T934A		R964H		
	HSV-2 UL30					E678G Ins ED 684-685											

Definition and risk factors (2025)

Refractory and Resistant Herpes Simplex Virus Mucocutaneous Infections in Immunocompromised Patients: Literature Review and Proposed Definitions for Use in Clinical Trials

Roy F. Chemaly,^{1,●} Tali Shafat,^{1,●} Anna Wald,^{2,●} Camille N. Kotton,^{3,●} Genovefa Papanicolaou,^{4,5,●} Michelle K. Yong,^{6,7,8} Veronica Miller,^{9,●} Takashi E. Komatsu,^{10,a,●} Charu Mullick,^{10,a} Aimee C. Hodowanec,^{10,a,●} Gabriel Westman,^{11,12,a} Fareed Khawaja,^{1,●} Alexander Birkmann,^{13,●} and Per Ljungman^{14,15,●}; HSV Resistance Working Group of the Transplant Associated Viral Infections Forum

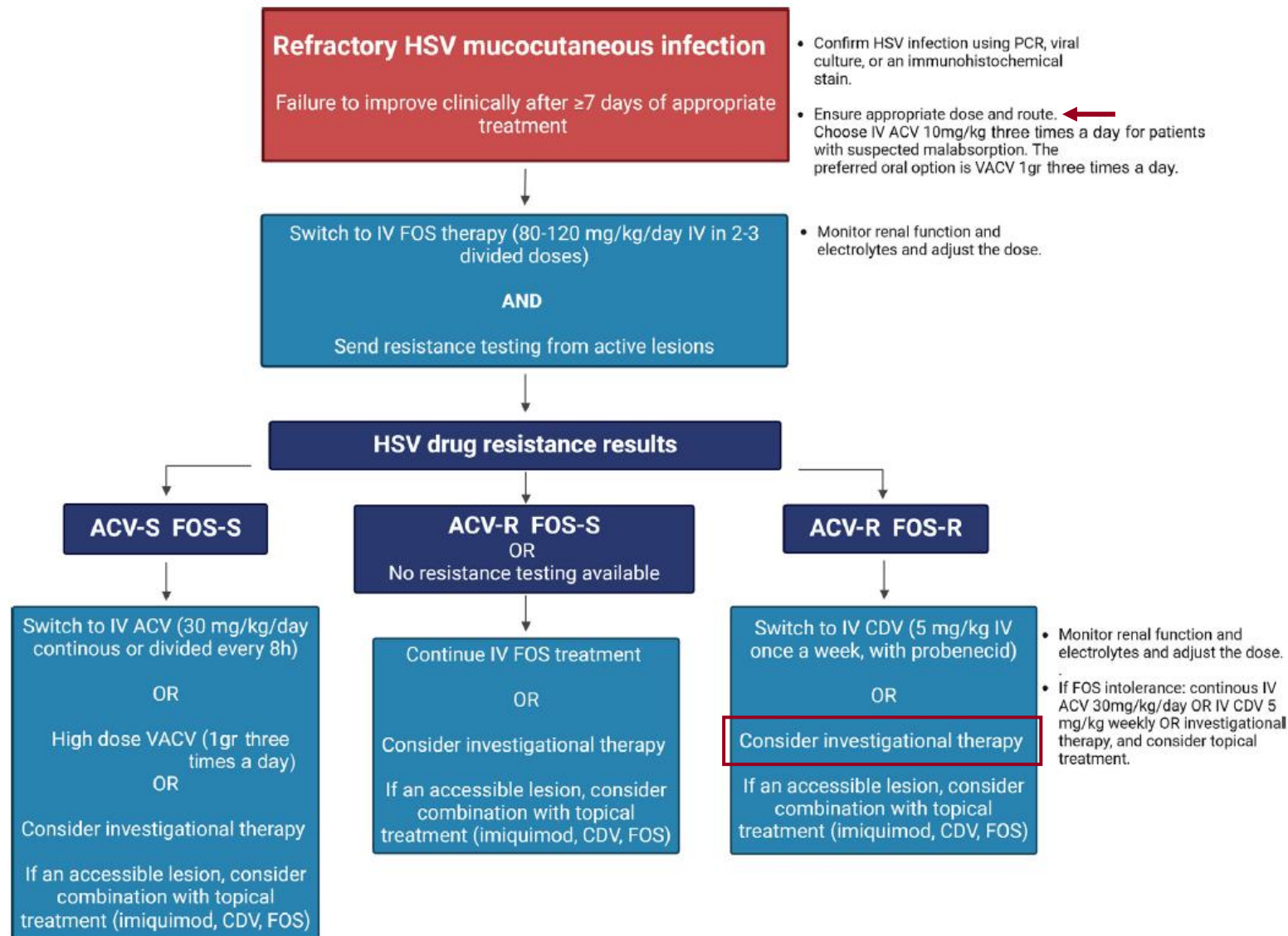
Table 2. Summary of the Definitions of Refractory Herpes Simplex Virus Mucocutaneous Infection and Antiviral Drug Resistance for Use in Clinical Trials

Term	Definition
Refractory HSV infection	<u>Failure of HSV-positive mucocutaneous lesion(s) to improve clinically after at least 7 d of appropriately dosed, directed anti-HSV therapy, in the absence of other causes of mucositis, such as recent high-dose chemotherapy, irradiation, oral GVHD, fungal or other viral infections, or the occurrence of a new HSV-positive mucocutaneous lesion(s) after receiving appropriately dosed, directed anti-HSV therapy for at least 7 d (excluding prophylaxis and suppressive antiviral therapy).</u>
Recurrent HSV infection	New HSV mucocutaneous lesion(s) occurring at least 1 wk after the total resolution of the prior episode of HSV infection while not receiving an antiviral drug effective against HSV.
Breakthrough HSV recurrence	The appearance of new HSV mucocutaneous lesion(s) while receiving prophylactic or suppressive antiviral drug effective against HSV.
Antiviral-resistant HSV infection	<u>Refractory HSV infection with viral genetic alteration(s) that decrease(s) susceptibility and/or phenotypic assay demonstrating increased EC₅₀ above the assay cutoffs to one or more antiviral drugs.</u>

Abbreviations: EC₅₀, half-maximal inhibitory concentration; GVHD, graft-versus-host disease; HSV, herpes simplex virus.

Management of refractory/resistant HSV infections

Algorithm for the management of refractory HSV infection (2025)



Amenamevir (AMNV)

Amenamevir, a novel helicase–primase inhibitor, for treatment of herpes zoster: A randomized, double-blind, valaciclovir-controlled phase 3 study

Makoto KAWASHIMA,¹ Osamu NEMOTO,² Mariko HONDA,³ Daisuke WATANABE,⁴ Juichiro NAKAYAMA,⁵ Shinichi IMAFUKU,⁶  Toshiyuki KATO,⁷ Tsuneo KATSURAMAKI,⁷  for the study investigators*

Single-Dose, Patient-Initiated Amenamevir Therapy for Recurrent Genital Herpes: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

Makoto Kawashima,¹ Shinichi Imafuku,² Kosuke Fujio,³ and Hiroshi Komazaki³

A phase 3, randomized, double-blind, placebo-controlled study evaluating a single, patient-initiated dose of amenamevir for recurrent herpes labialis

Makoto Kawashima¹  | Daisuke Watanabe² | Kosuke Fujio³ | Hiroshi Komazaki³

- **Amenamevir**
 - Efficacy for herpes zoster treatment
 - Efficacy for orolabial herpes treatment
 - Efficacy for genital herpes treatment
- **Japan**
 - AMNV approved for treatment of herpes zoster and recurrent labial or genital herpes (Amenalief®)
- **France**
 - Authorization of compassionate use for refractory/resistant HSV infections (200 to 400 mg/day)
- **Good tolerance** (thrombocytopenia)
- **No HSV resistance to AMNV described to date in patients**

Pritelivir (PTV)

Helicase–Primase Inhibitor Pritelivir for HSV-2 Infection

Anna Wald, M.D., M.P.H., Lawrence Corey, M.D., Burkhard Timmler, M.D., Amalia Magaret, Ph.D., Terri Warren, M.N., Stephen Tyring, M.D., Ph.D., Christine Johnston, M.D., M.P.H., John Kriesel, M.D., Kenneth Fife, M.D., Ph.D., Lawrence Galitz, M.D., Susanne Stoelben, M.D., M.P.H., Meei-Li Huang, Ph.D., Stacy Selke, M.A., Hans-Peter Stobernack, D.V.M., Helga Ruebsamen-Schaeff, Ph.D., and Alexander Birkmann, Ph.D.

Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

■ Pritelivir

- Efficacy for genital herpes treatment
- PTV > VACV for viral shedding

■ France

- Authorization of compassionate use for refractory/resistant HSV infections (400 mg/day on day 1, then 100 mg/day during 28 to 42 days)

■ Good tolerance

- Thrombocytopenia

Phase 3 clinical trial PRIOH-1 (NCT03073967) : Efficacy and safety of **Pritelivir** tablets for treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised subjects (vs foscarnet) (*completed*)



Results of PRIOH-1 presented at CROI 2026

Pritelivir (PTV): PRIOH-1 clinical trial

Phase 3 PRIOH-1 Study Design

Randomized, Open-label, Multicenter Trial

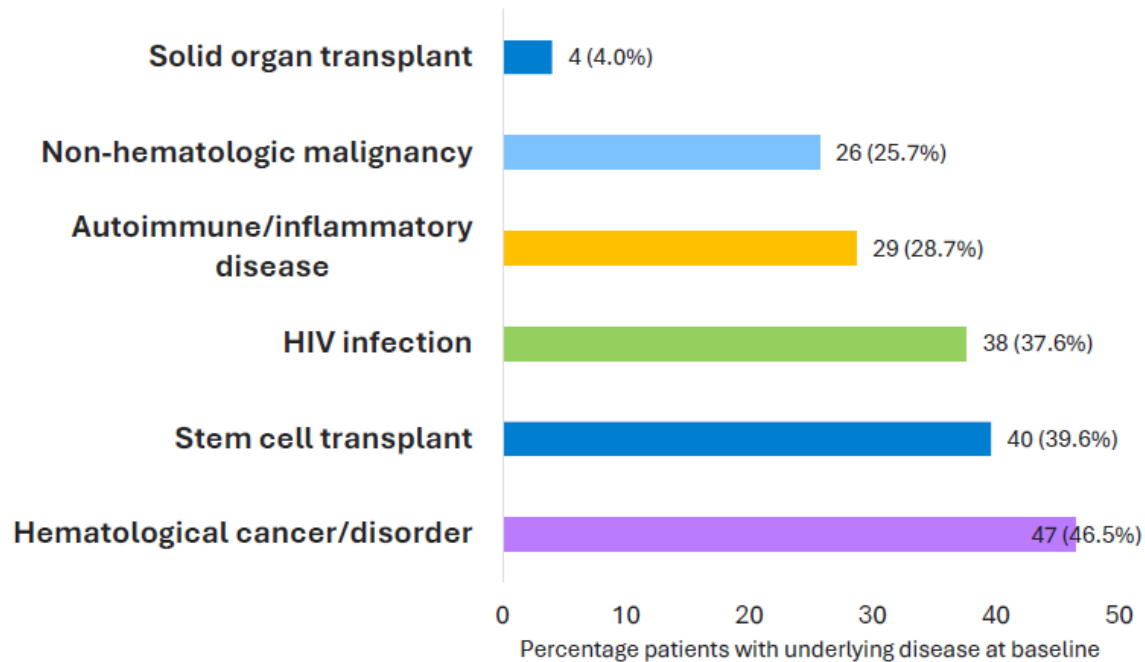
- **Study Aim:** To evaluate the efficacy and safety of pritelivir compared with Investigator's choice (ICT)
- **Primary endpoint:** % of patients with complete lesion healing up to 28 days of treatment
- **Secondary endpoints:** Include safety and tolerability
- **Key inclusion criteria:** Immunocompromised adults, ACV refractory $\pm$ resistant mucocutaneous HSV infection based on:
 - Refractory/Clinical Failure; No clinical improvement of HSV lesion(s) after ≥ 7 days with therapeutic doses of a NUC
 - OR
 - Resistance; Local laboratory confirmed genotypic/phenotypic ACV resistance testing for current lesion



Pritelivir (PTV): PRIOH-1 clinical trial

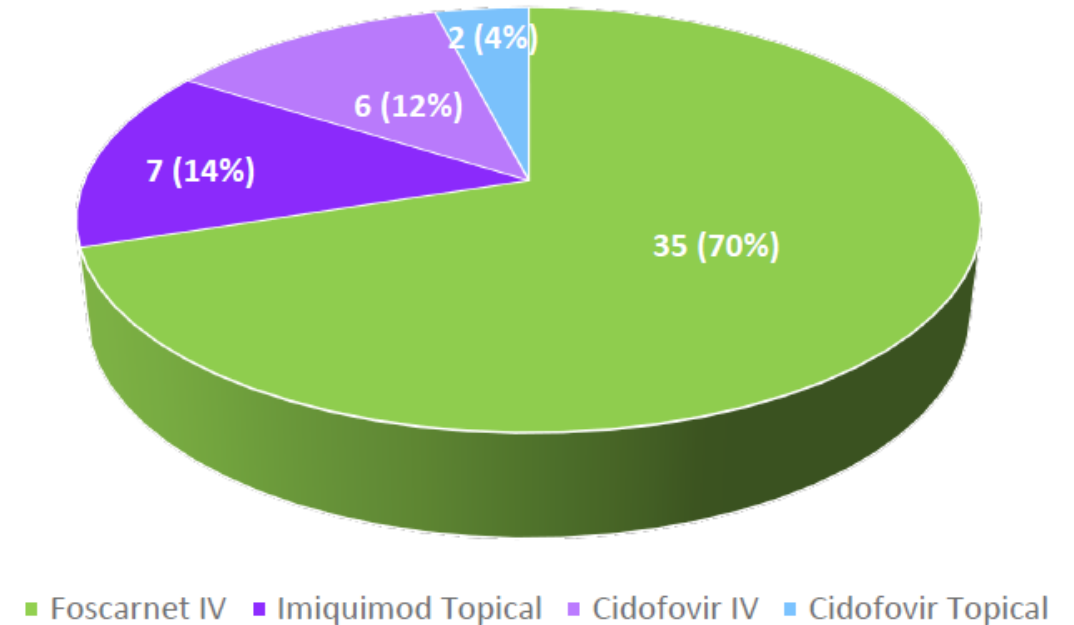
Underlying disease: Overall population*

(N=101) n (%)



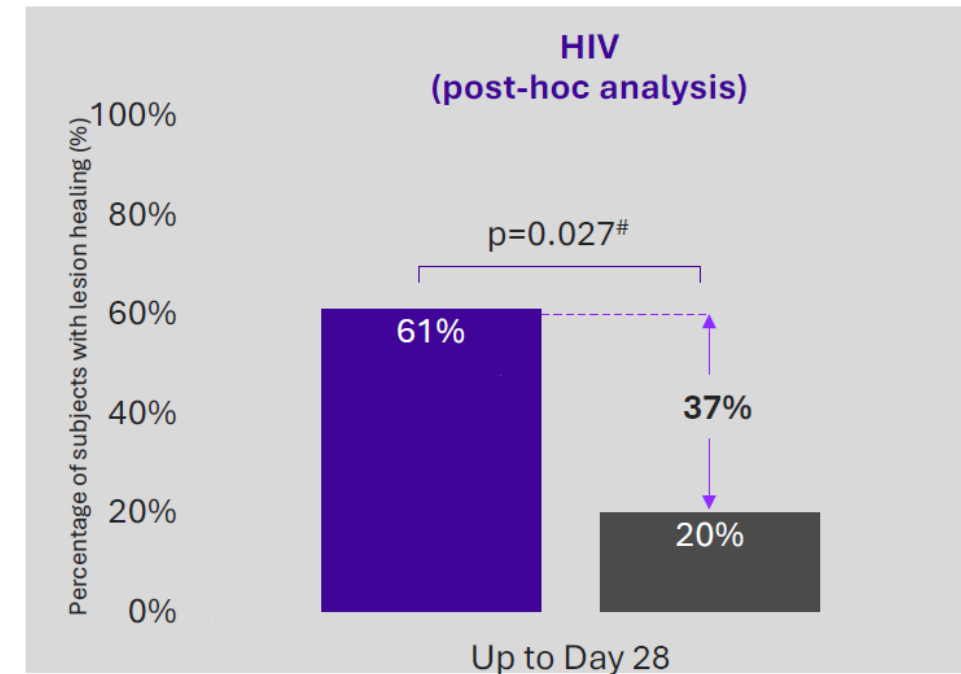
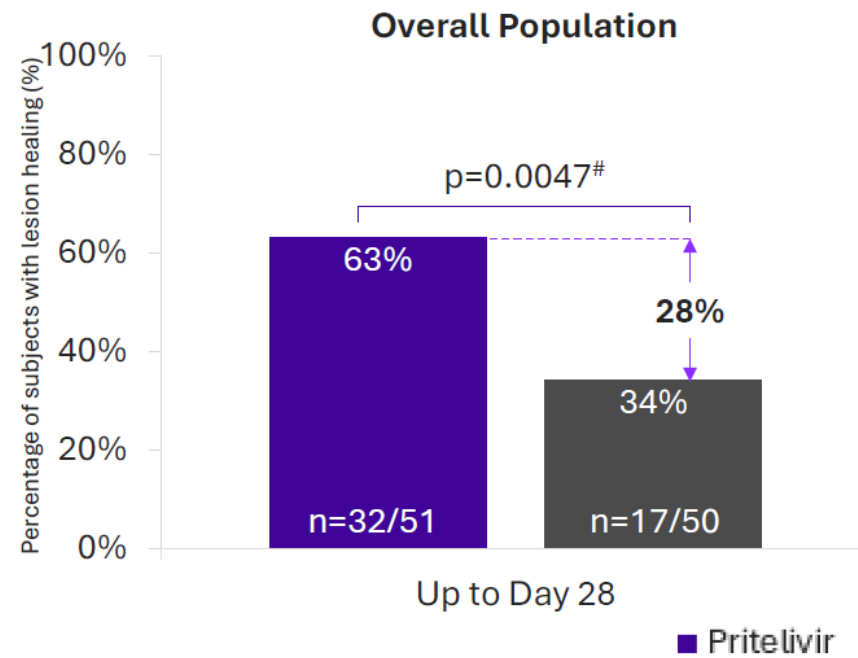
■ Hematological cancer/disorder ■ Stem cell transplant
■ HIV infection ■ Autoimmune/inflammatory disease
■ Non-hematologic malignancy ■ Solid organ transplant

Investigator's Choice Treatment: Overall Population (N=50) n (%)



Pritelivir (PTV): PRIOH-1 clinical trial

PRIOH-1: Pritelivir Demonstrated Superior Lesion Healing over Investigator's Choice Treatment, Including in the HIV subgroup*



Use of HPIs in patients

Orolabial herpes (HSV-1) in HSCTx (PTV)

Salvage Treatment of Refractory HSV Oral Lesions with Pritelivir in Allogeneic Hematopoietic Cell Transplant Recipients

David Bosetti,^a Chiara Bernardi,^b Marie Maulini,^b Federica Giannotti,^b Anne-Claire Mamez,^b Stavroula Masouridi-Levrat,^b Yves Chalandon,^b Dionysios Neofytos^a

Orolabial herpes (HSV-1) in HSCTx (AMNV)



Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Amenamivir for treating acyclovir-resistant or refractory herpes simplex virus infection in allogeneic hematopoietic stem cell transplantation recipients: Two case reports



Sallée L, Souchet L,
Boutolleau D, Nguyen S

Genital herpes (HSV-2) in HSCTx (PTV)

Pritelivir for recurrent aciclovir-resistant herpes simplex virus 2 infections in immunocompromised patients

Alexandra Serris¹, Anne Pouvaret¹, Clémence Loiseau², Hanene Abid³, Sonia Burrell^{4,5}, Jacques Fourgeaud^{3,6,7}, Claire Rouzaud¹, Fanny Lanternier¹, David Boutolleau^{4,5} and Pierre Frange^{3,7*}

Genital herpes (HSV-2) in PLWHIV (AMNV)

Amenamivir for acyclovir-resistant genital HSV-2 infection in people living with HIV

Destoop J, Boutolleau D, Jary A, Bleibtreu A, Cordel H, Ouedraogo E, Pourcher V, Monsel G

Herpetic keratitis (HSV-1) (AMNV)

Efficacy and Safety of Amenamivir, a Helicase-Primase Inhibitor for the Treatment of Acyclovir-Resistant Herpes Simplex Virus 1 Keratitis

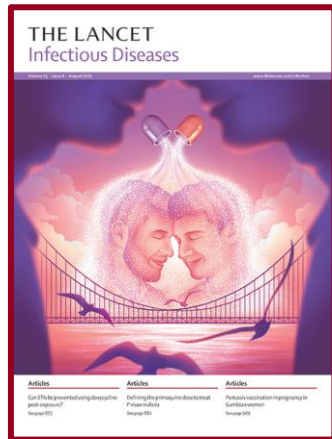
Rafael Boucher, MD,*† David Boutolleau, PharmD, PhD,‡§ Sonia Burrell, PharmD, PhD,‡¶ Oscar Haigh, PhD,† José Fernandez,‡ Christelle Vauloup-Fellous, MD, PhD,|| Emmanuel Barreau, MD,* Antoine Rousseau, MD, PhD,*†**†† and Marc Labetoulle, MD, PhD*†**††

CMV



The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,¹ Deepali Kumar, MD,² Oriol Manuel, MD,³ Sunwen Chou, MD,⁴ Randall T. Hayden, MD,⁵ Lara Danziger-Isakov, MD, MPH,⁶ Anders Asberg, PhD,⁷ Helio Tedesco-Silva, MD,⁸ and Atul Humar, MD²; on behalf of The Transplantation Society International CMV Consensus Group*



Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies

Per Ljungman, Sophie Alain, Roy F Chemaly, Hermann Einsele, Federica Galaverna, Hans H Hirsch, Alicja Sadowska-Klasa, David Navarro, Jan Styczynski, Rafael de la Camara

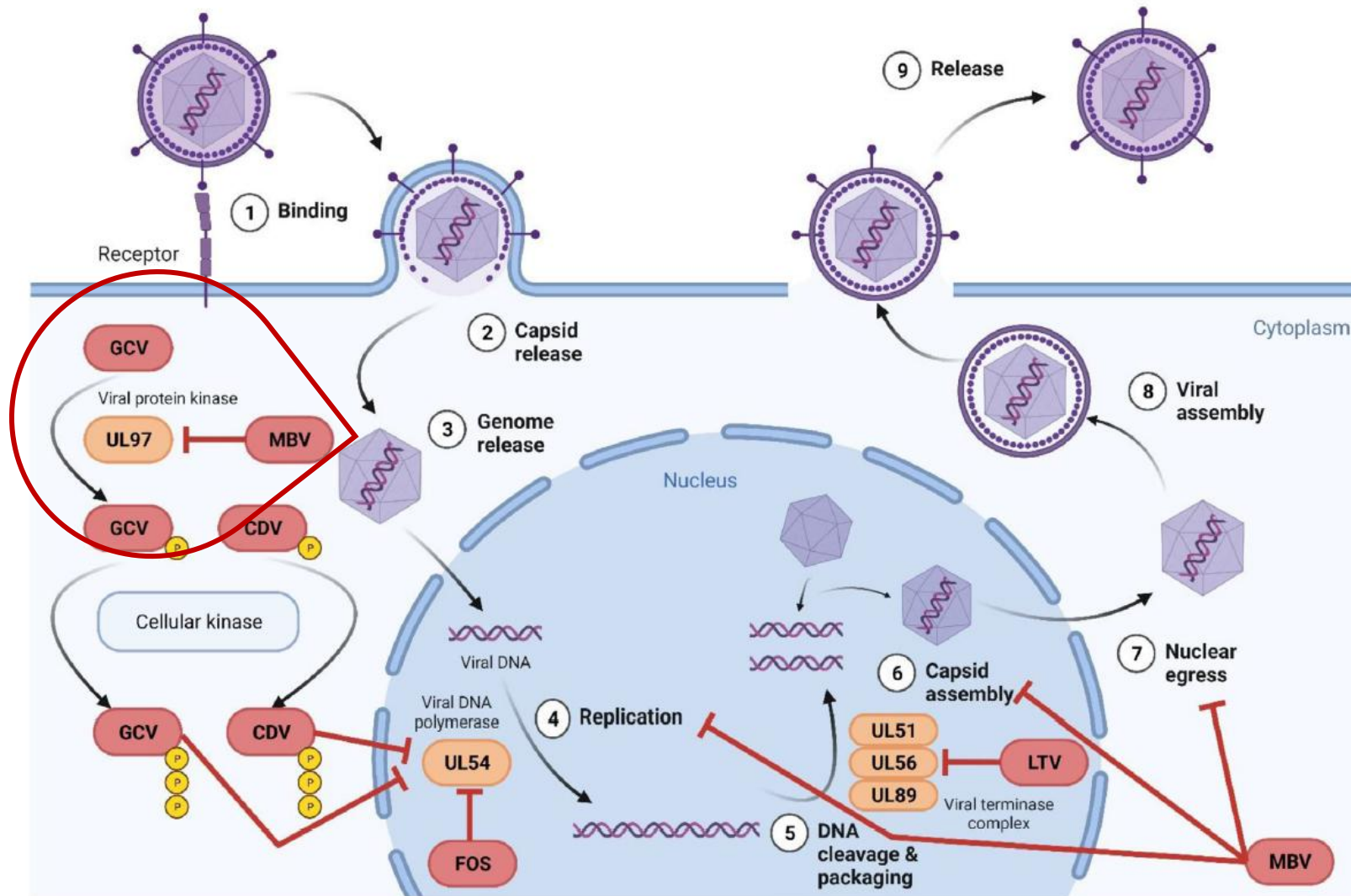


Antivirals for prophylactic or curative treatments of CMV infections

CMV target	Type	Antiviral	Administration	
DNA polymerase	Nucleoside analogues	Ganciclovir (GCV)	IV	1st line
		Valganciclovir (VGCV)	oral	
		Ganciclovir (GCV)	Topical (keratitis)	
	Nucleotide analogue	Cidofovir (CDV)	IV	<i>Off-label : compassionate use</i> (2nd line)
	Pyrophosphate analogue	Foscarnet (FOS)	IV	
Terminase	Dihydroquinazoline	Letermovir (LMV)	Oral / IV	<u>Prophylaxis</u> (PREVYMIS®)
Phosphotransferase	Benzimidazole	Maribavir (MBV)	Oral	2nd line

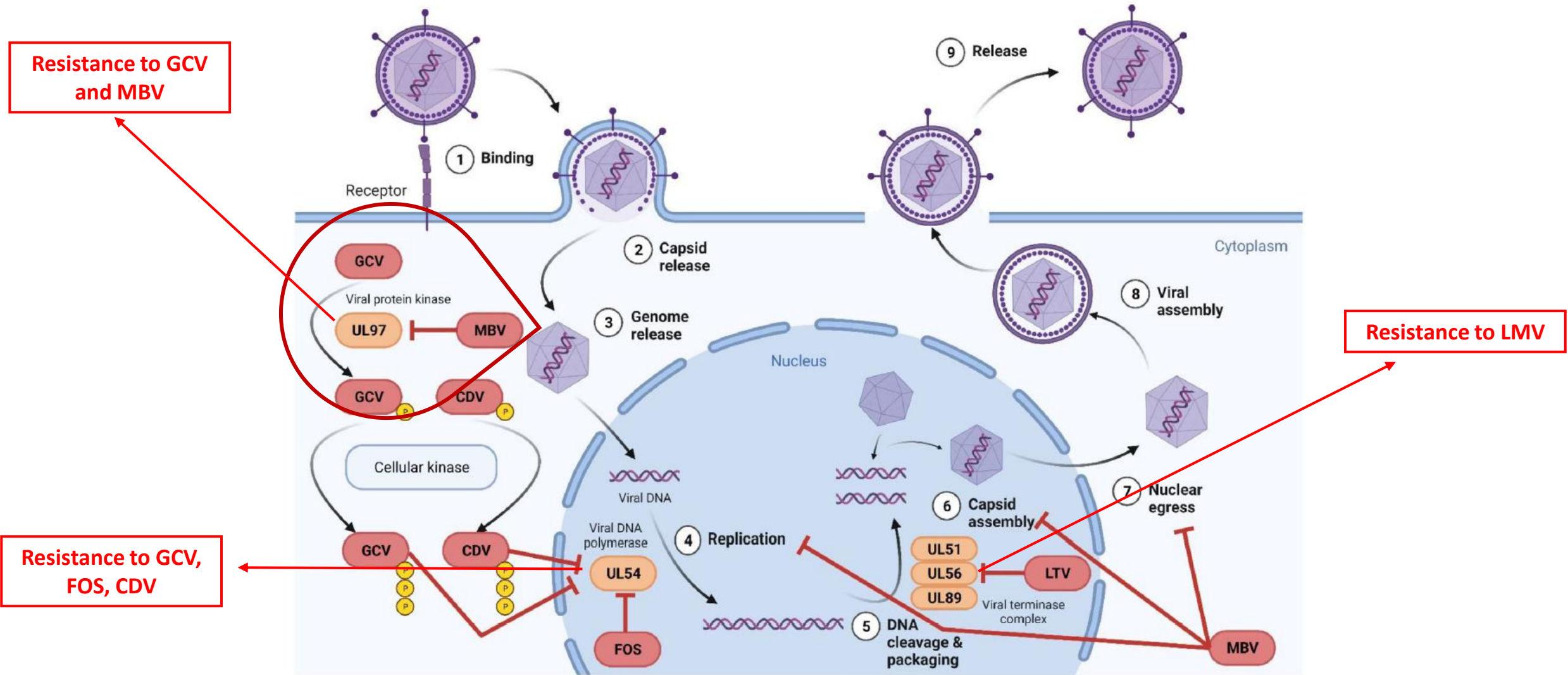
Mechanism of action of antivirals

Inhibition of viral DNA replication, viral DNA encapsidation, viral capsid nuclear egress



CMV resistance to antivirals

Molecular mechanism: mutations in viral targets involved in the mechanism of action of antivirals



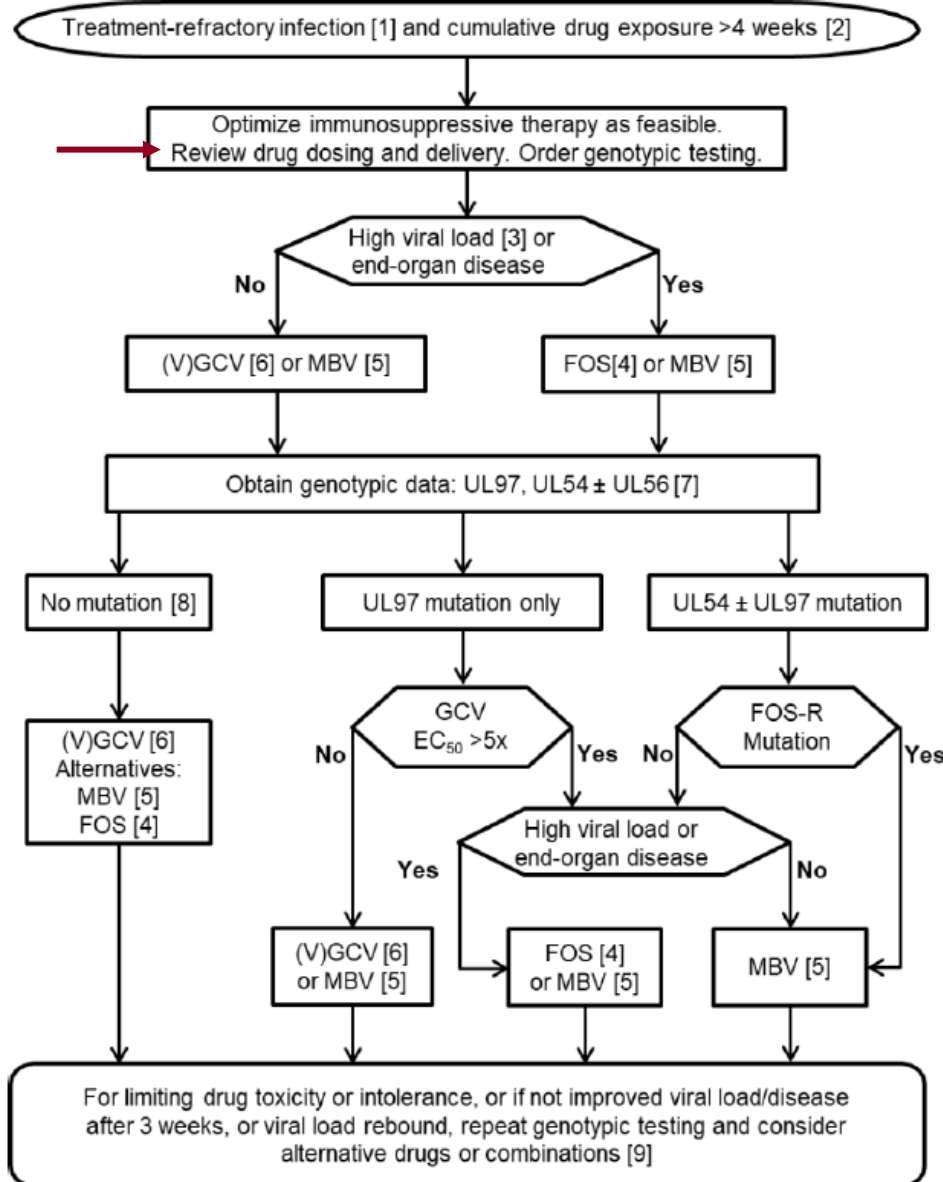
- **Frequency of CMV resistance to antivirals**
 - Solid organ transplant recipients:
 - **GCV: 2% to 12%**
 - **MBV: 26%** (clinical trial) / **10%** (real-world)
 - Hematopoietic stem cell transplant recipients:
 - **GCV: 2% to 15%**
 - **LMV: <2%** (primary prophylaxis)
- **Virological diagnosis of CMV resistance to antivirals**
 - **Genotypic** resistance testing
 - **Sequencing CMV genes** encoding enzymes implicated in mechanism of action of antivirals (UL97, UL54, UL51, UL56, UL89)

Kotton et al., 2025



Management of refractory/resistant CMV infections

Algorithm for the management of refractory CMV infection in SOTx



Legend:

[1] Treatment-refractory $\leq 1 \log_{10}$ decrease in plasma or blood viral load after ≥ 2 weeks of therapy, new or worsening CMV disease.

[2] GCV resistance is rare with drug exposure <6 weeks.

[3] High viral load: $\geq 50,000$ IU/mL (plasma).

[4] Avoid FOS if renal dysfunction or metabolic intolerance. FOS is suggested for high viral loads in clinically unwell patients.

[5] Avoid MBV for CNS disease or retinitis. Treatment-emergent resistance to MBV may limit efficacy. Do not use if any MBV resistance mutations are detected. MBV works better with lower viral loads, see text. M460I/V as sole UL97 mutation favors use of MBV.

[6] GCV dose 5 mg/kg bid IV, optionally 10 mg/kg bid (high dose), or VGCV dose 900 mg bid, optionally 1800 mg bid (high adult dose) (adjusted for renal function).

[7] UL56 genotyping If previous exposure to letermovir.

[8] Includes sequence variants conferring <2-fold EC_{50} change. Repeat genotyping with tissue-specific sample for end-organ disease, if available.

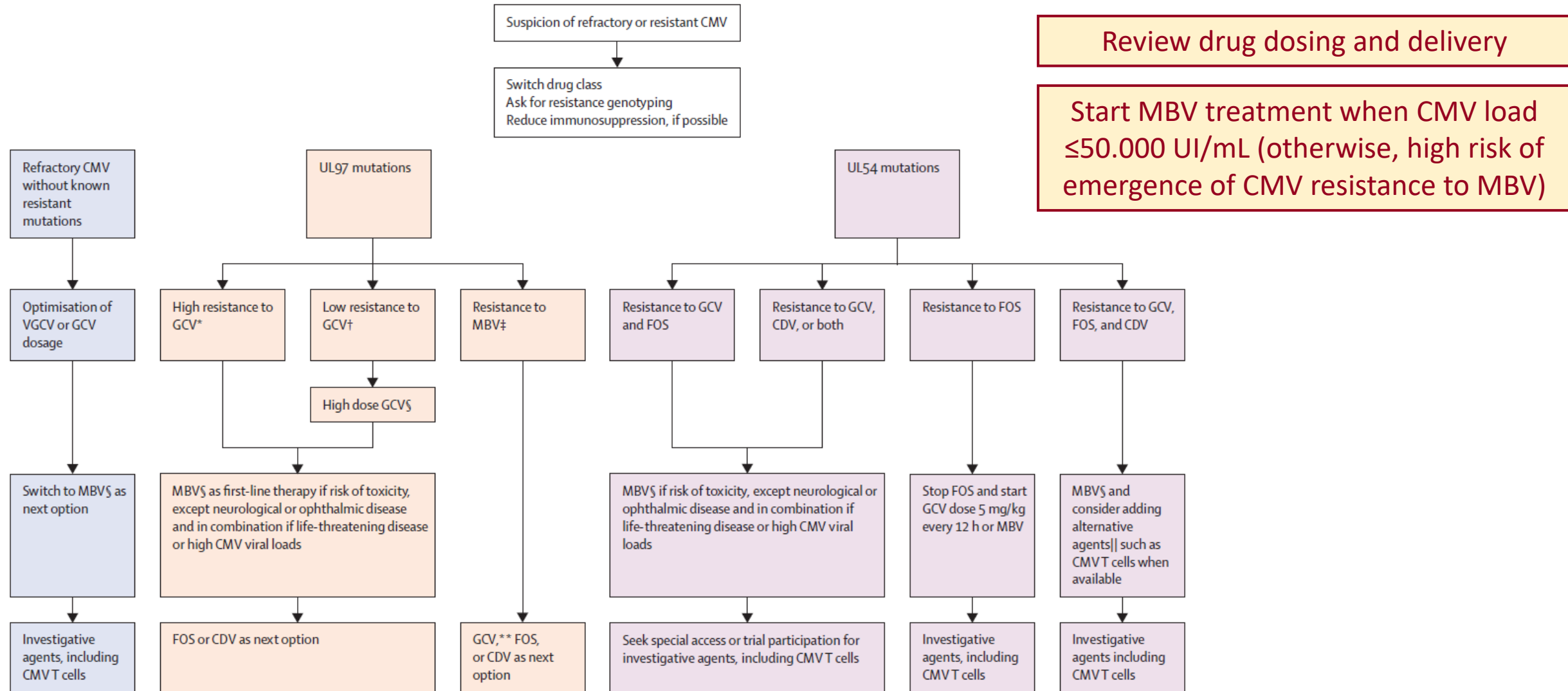
[9] Consider combination therapy as tolerated. MBV-GCV combination is antagonistic, do not use. MBV may be suitable as step-down treatment after initial response to FOS when viral load <5000 IU/mL Cidofovir performed poorly in a clinical trial, see text. Letermovir has no clinical trial evidence for efficacy in treating refractory/resistant infection, see text. Emergent MBV and letermovir resistance is often high grade and requires genotypic monitoring. Other unapproved therapies (weak evidence) include mTOR inhibitors, augmentation of host immunity using adoptive T-cell transfers and CMV immunoglobulins.

FOS, foscarnet; MBV, maribavir; GCV, ganciclovir, VGCV, valganciclovir; (V)GCV, valganciclovir or ganciclovir; EC_{50} , drug concentration required to reduce viral growth by 50% (stated as fold-change from baseline); R, resistance.

Start MBV treatment when CMV load $\leq 50,000$ UI/mL (otherwise, high risk of emergence of CMV resistance to MBV)

Management of refractory/resistant CMV infections

Algorithm for the management of refractory CMV infection in HSCTx



Clinical Infectious Diseases

MAJOR ARTICLE

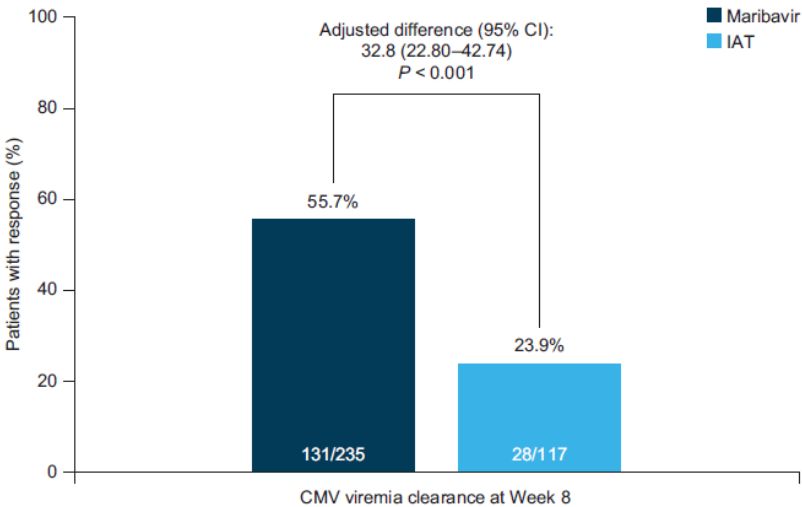


Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,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 Fournier¹⁸; for the SOLSTICE Trial Investigators^b

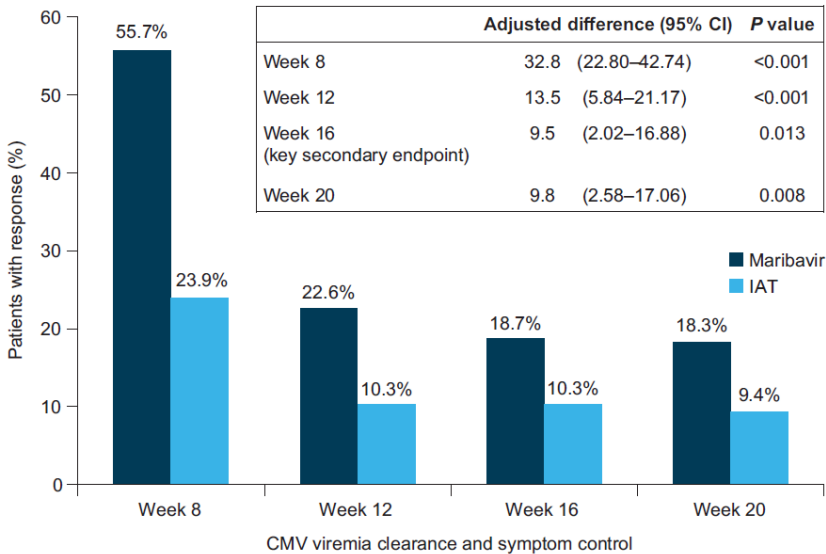
Primary endpoint

CMV viremia clearance at week 8



Secondary endpoints

Confirmed viremia clearance and symptom control at week 8 and maintained through week 12, week 16 (key secondary endpoint), and week 20



■ Indications

- Treatment of refractory CMV infection or CMV disease (with or without resistance mutations) to previous antivirals (ganciclovir, valganciclovir, cidofovir or foscarnet) in adult solid organ transplant recipients and adult hematopoietic stem cell transplant recipients

■ Dose

- 800 mg/day during 8 weeks (oral administration)

■ Adverse effect

- Taste disturbance

■ Warning

- No association GCV + MBV
- CMV load in blood < 50.000 UI/mL (risk of emergence of resistance)
- Poor penetration in the CSF and brain: not recommended for CNS and ocular infections

- **Use of combination of antiviral therapy**
 - **CMV:** GCV + FOS; MBV + FOS; LMV + GCV (LUCY clinical trial); **no association of GCV+ MBV (antagonism)**
 - **HSV:** ACV + FOS; in vitro synergistic activity: **ACV + AMNV; ACV + PTV**
- **mTOR inhibitors (everolimus)**
 - **CMV** prevention
 - Refractory **CMV** infection
- **Adoptive T-cell therapy**
 - Multiple case reports and phase I/II trials have demonstrated use of **CMV-specific T cells for resistant/refractory CMV infection in transplant recipients**
- **Vaccine**
 - To date: no CMV and no HSV vaccine

- HSV and CMV infections are **common**, **potentially serious**, and **sometimes life-threatening** in immunocompromised patients (SOT or HSCT recipients)
- **Definition of HSV refractory infection**: failure to improve lesions or to prevent new lesions after **7 days of an appropriate route and dosage of antiviral therapy**
- **Definition of CMV refractory infection**: $\leq 1 \log_{10}$ decrease in plasma or blood CMV load after **2 weeks of well-conducted antiviral therapy**, new or worsening CMV disease
- Frequency of **HSV/CMV resistance to antivirals** varies from **2% to 15%**
- **Genotypic diagnosis of HSV/CMV resistance to antivirals**
- **Therapeutic management of antiviral-resistant HSV/CMV infections** may be **very complicated/challenging**
- Novel antivirals: **AMNV** and **PTV** for **HSV**; **LMV** and **MBV** for **CMV**
- What about anti-HSV and anti-CMV **vaccination**?

A photograph of the interior of a grand, ornate theater. The stage is framed by a highly decorative, gilded archway. The stage itself is covered by a large, draped red curtain. The theater's architecture features multiple tiers of balconies with intricate carvings and gold leaf accents. The ceiling is also highly decorated with circular motifs. The foreground shows rows of dark, upholstered seats facing the stage.

Thank you for your attention

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