A Familiar Foe :
Beyond the Usual Approach

West Coast TID Society Conference

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Infectious Diseases Division

Keck School of Medicine of USC
Clinical Assistant Professor

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Disclosures

None

Chief Complaint/History of Present Illness

[redacted] **y/o** [redacted] with refractory myelodysplastic syndrome (MDS) presented for planned Azacitidine /Nivolumab (Aza/Nivo) therapy ([redacted]/[redacted]/26)

- Very painful lesion on [redacted] Rt upper lip, nose (initially thought to be from nasal cannula use), and Lt palate since around late [redacted] 2026.

Review of Systems

- (-) fever, (-) chills, (-) sweats, (+)15 pounds Wt loss in the past few months
- (-) headache, (-) vision changes, (-) eye pain, (-) facial numbness, (+) Rt nasal congestion, (-) rhinorrhea
- (-) shortness of breath, (-) nausea, (-) vomiting, (-) diarrhea, (-) abdominal pain, (-) pain elsewhere

The remainder of the review of systems was negative.

Relevant Medical History

- TP53 mutated myelodysplastic syndrome (MDS) diagnosed in [redacted] 2024
- [redacted] 2024-[redacted] 2025: Inqovi (Decitabine-Cedazuridine) C1-C4
- [redacted]/25: Haploidentical allogeneic HSCT (donor is CMV+ son) with fludarabine/FTBI conditioning followed by post-transplant cyclophosphamide, tacrolimus, and mycophenolate (CMV R+)
- [redacted]/2025 C. diff infection (toxin EIA positive)
- [redacted]/[redacted]/25: Relapsed MDS

Relevant Medical History

- Azacitidine+Venetoclax (Aza/Ven) ([redacted]/[redacted]/25 C1D1), f/b 2 cycles of Inqovi with Ven in [redacted] 2025 - [redacted] 2026, then CAV (Cladribine-cytArabine-Ven) in [redacted] 2026
- Methylprednisolone 60mg IV ~ 9 doses ([redacted]/[redacted]/26-[redacted]/[redacted]/26) prior to each PLT transfusion due to prior reaction
- "Lots of transfusion" in [redacted]

- Erythematous tender mobile nodules involving Rt ventral forearm, B/L inner thighs, shins and calves since [redacted] 2025 – diagnosed as panniculitis 2/2 Venetoclax by biopsy in [redacted] 2026 (vitD 100K x1 and PDS 5mg daily) → leukemia cutis in [redacted] 2026

- Late [redacted] 2026: Influenza A H1N1 c/b bacterial pneumonia requiring hospitalization at the OSH in [redacted]

Social and exposure history

- Born/raised in [redacted]. Resides in [redacted] alone with three dogs and a cat.
- Works as a pet groomer
- Remote history of methamphetamines and cocaine use, sober since [redacted]
- Smoked at age 15-25 intermittently
- No recent travel

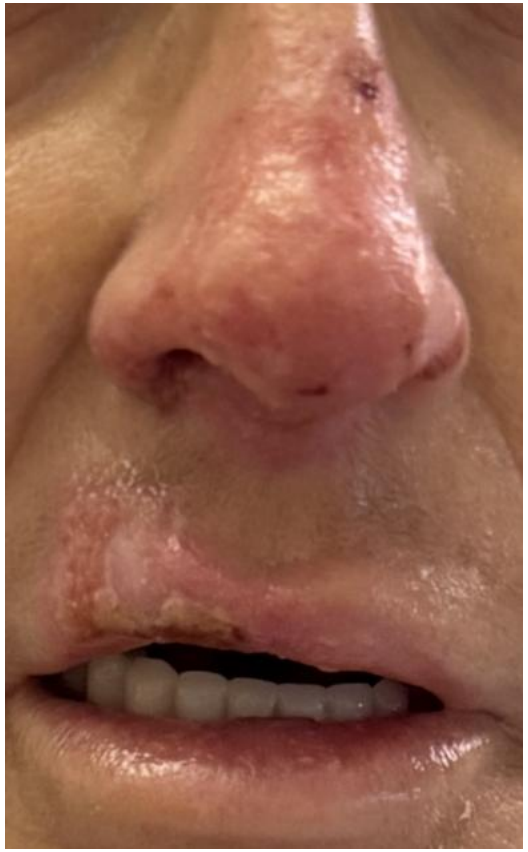
Drug allergies : none

Home medications

- Pantoprazole 400mg Q24hr; Prednisone 5mg daily
- Prophylaxis: Levaquin 500mg Q24hr; TMP-SMX 1tab three times weekly; ACV 800mg Q12hr → Valacyclovir 500mg Q12hr in Feb 2026; Voriconazole 200mg Q12hr
- As needed: hydromorphone 2gm Q8hr; zolpidem 5mg Q24hr

Physical exam

Vitals: T 36.9°C, BP 137/77, HR 75, RR 18, SpO_2 100% on room air



Nose and Rt upper lip



Lt palate

Crusted erythematous to violaceous plaques

Data

- Prolonged pancytopenia: WBC 0.79 (ANC 0.14), Hb 7.3, PLT 46
- CMP unremarkable
- IgG 677 mg/dL
- HIV Ab/Ag negative, immune to hepatitis B, Hepatitis C Ab negative
- Serum B-D glucan and galactomannan negative
- Serum CMV PCR and EBV PCR negative

- Blood cultures VRE E. faecium 2/2 sets

Question 1

What do you think is the cause of these orofacial lesions?

(a) Virus (HSV, CMV)

(b) Fungal infection (mucor, aspergillus, histoplasma, cryptococcus)

(c) Malignancy (oral squamous cell carcinoma, leukemia)

(d) Mycobacterial infection

(e) Inflammatory or immune-mediated (Sweet's syndrome, Behcet's syndrome)

(f) Drug-induced mucocutaneous lesions

Results

- OHNS (ENT) evaluation and results ([redacted]):
  - Nasal endoscopy –Normal nasal mucosa.
  - Frozen-section exam: no fungal elements. “nuclei atypia suggestive of viral etiology”
  - Lt palate and Rt external nare bx: viral cytopathic changes, IHC for HSV mix positive.
- Dermatology evaluation ([redacted])
  - Swabs from Rt upper lip: HSV culture positive, bacterial culture 1+ E. faecalis
- Viral swabs: HSV subtype PCR positive with type 1

Question 2

How would you treat a breakthrough mucocutaneous HSV infection?

(a) Valacyclovir standard treatment dose (1gm twice daily)

(b) High dose valacyclovir (1gm three times daily)

(c) High dose (≥ 10mg/kg IV Q8hr) or continuous acyclovir IV

(d) Foscarnet 40mg/kg IV Q8-12hr

(e) Cidofovir 5mg/kg IV weekly

(f) Investigational drug (e.g. pritelivir)

Question 3

How would you treat a refractory resistant (r/r) mucocutaneous HSV infection?

(a) High dose or continuous acyclovir IV (≥ 10mg/kg IV Q8hr)

(b) Foscarnet 40mg/kg IV Q8-12hr

(c) Cidofovir 5mg/kg IV weekly

(d) Combination of acyclovir IV and foscarnet IV

(e) Foscarnet IV with topical agent (cidofovir, imiquimod, or foscarnet)

(f) Investigational (e.g. pritelivir)

Clinical Course and Treatment Timeline

Day 1 (4/20) · Day 10 · Day 15 · Day 20 · Day 25 · Day 30 · Day 40 · Day 47 · Day 50 · Day 60 · Day 70 · Day 81 (7/9)

HSV ANTIVIRAL THERAPY

Systemic antiviral

- Days 1–15: ValACV 1 g q12h
- Days 16–24: ValACV 1 g q8h
- Days 25–46: Foscarnet
- IV cidofovir Day 47
- IV cidofovir Day 59
- IV cidofovir Day 73
- IV cidofovir Day 80

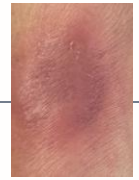
Topical antiviral

- Days 37–61: Oral (swish & spit) cidofovir 3%

Chemo / Immunosuppression

Chemo

- Days 17–23: AZA/VEN
- Days 24–37: VEN



Day 73
Donor lymphocyte infusion

Methylprednisolone

MethylPDS 60 mg — intermittent doses

MethylPDS 8 mg
Days 73–81

Day 1 (4/20) · Day 15 · Day 25 · Day 47 · Day 54 · Day 72 · Day 81 (7/9)





HSV2



Clinical Course and Treatment Timeline — antiviral (Pritelivir) therapy

Day 82 7/10 · Day 89 · Day 91 · Day 96 · Day 99 · Day 102 · Day 104 · Day 109 · Day 112 8/9

HSV ANTIVIRAL

Pritelivir

MAJOR EVENTS

Day 91
Hypoxic respiratory failure/shock
IRS/GVHD → 2nd HLH,
AKI

Day 94
Dusky purpuric changes of hands

Day 99
CRRT initiated

Day 102
Lt frontal SAH • **TA-TMA**
Hand biopsy: hypoperfusion injury

Day 104
C. glabrata
blood stream infection

Day 112 — DEATH
Multiorgan failure
Multifactorial encephalopathy
Unresolved complications

IMMUNOSUPPRESSION

Cyclophosphamide d 100-101

Methylprednisolone 8mg (d 82-85)–dexamethasone (d 92-99) • Jakafi (d 93-112) • tacrolimus (d 93-94, d 100-102) –sirolimus (d 106-112)

Tocilizumab d 92; d 104

Eculizumab d 103; d 110

methylprednisolone 1gm d 102–104 → 40mg d 105-112

Day 82



Day 89



Day 96



Day 102



Day 109



HSV phenotypic resistance test results (ARUP)

- [redacted]/26 facial/oral HSV 1 (day 1 of therapeutic ACV) resistant to both ACV and FOS !¡
  - Acyclovir IC50 = 6.2 µg/mL (resistance ≥2 µg/mL)
  - Foscarnet IC50 = 400 µg/mL (resistance ≥ 100 µg/mL) – **the patient never received foscarnet !**

HSV phenotypic resistance test results (ARUP)

- [redacted]/26 Lt buttock ulcer with HSV 2 (day 72 of therapeutic antiviral; 47 days after D/C of acyclovir, 25 days after D/C of foscarnet).

  Susceptible to both ACV and FOS

  - Acyclovir IC50 = 0.5 µg/mL (resistance ≥2 µg/mL)
  - Foscarnet IC50 = 42.6 µg/mL (resistance ≥ 100 µg/mL)

HSV Resistance Working Group of the Transplant Associated Viral Infections Forum for clinical trial use

Chemaly et al. CID 2025:81

Refractory HSV mucocutaneous infection

- **No clinical improvement after ≥7 days of appropriately dosed, directed anti-HSV therapy**, after excluding other plausible causes of the lesion/mucositis; **OR**
- Development of a **new HSV-positive mucocutaneous lesion after ≥7 days** of appropriately dosed directed therapy

Resistant HSV

- Refractory HSV **plus laboratory evidence of reduced antiviral susceptibility**:
  - Resistance-associated genetic alteration and/or
  - Phenotypic evidence of increased EC50 above the assay cutoff to 1 or more antiviral drugs.

Breakthrough HSV

- New HSV mucocutaneous lesions while on prophylactic or suppressive therapy

ACV drug-resistant HSV Prevalence

Chemaly et al. CID 2025:81

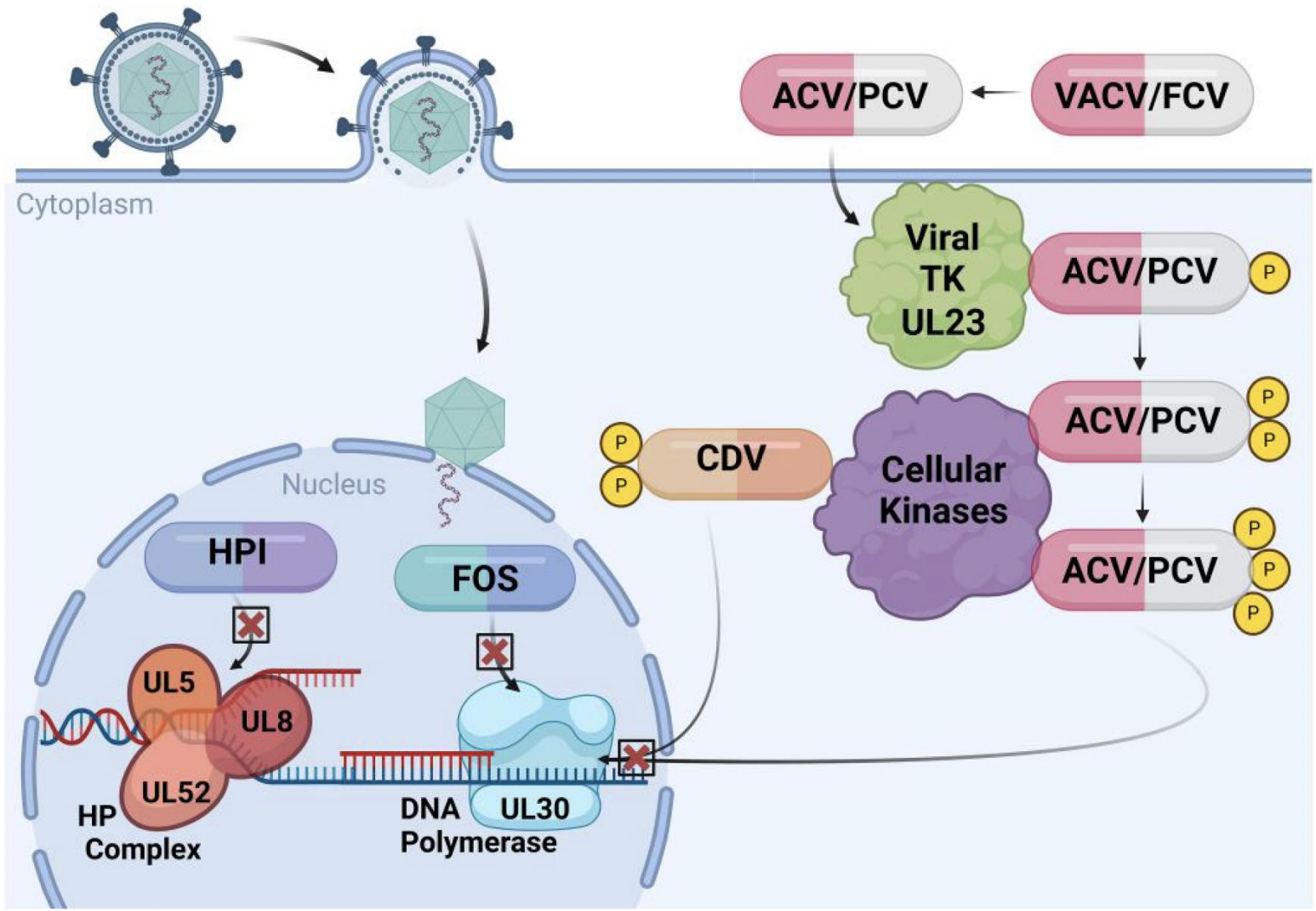
Immunocompetent ACV resistance **<1%**	HCT recipients **0–14%**
SOT recipients **0–3%**	Advanced HIV **3–7%**

Median prevalence among allo HCT 16.1% (2.4–100%)

Sallée et al. Reviews in Medical Virology, 2024; 34

Antiviral mechanisms of antiherpetic medications

Chemaly et al. CID 2025:81



UL23 — Thymidine Kinase

≈95%

of ACV resistance

insertion/deletion in G/C homopolymer runs leading to frame shits (most common) or amino-acid substitutions in ATP-/nucleoside-binding sites

UL30 — DNA Polymerase

≈5%

of ACV resistance

Amino-acid substitutions in conserved regions; roughly half can confer foscarnet cross-resistance, rarely cidofovir

Wang, J Clin Microbiol 2024

Testing Methods: Phenotypic vs. Genotypic

Wang, J Clin Microbiol 2024 (62); Dähne et al. Clin Microbiol Infect. 2025;31

PHENOTYPIC

- Plaque reduction assay (PRA): gold standard; virus grown on cell monolayer with increasing drug concentrations; IC50/EC50 calculated. **TAT ~ 3 weeks**
- **Lack of standardization**
- More available as HSV can grow rapidly in culture (swab, fluid, tissue)
- Historic outcomes data link elevated IC50 to treatment failure.
  - Failure to heal on acyclovir therapy when isolate IC50 is ≥2 µg/mL (95%) vs. IC50 is <2 µg/mL (38%)
  - Failure to heal on foscarnet therapy when isolate IC50 is ≥100 µg/mL (88%) vs. IC50 <100 µg/mL (0%)
- Not always correlate with clinical response

Clinically available testing in the US (2024)

- **ACV : Plaque reduction/viral replication assay**
- **Foscarnet: Plaque reduction/viral replication assay**

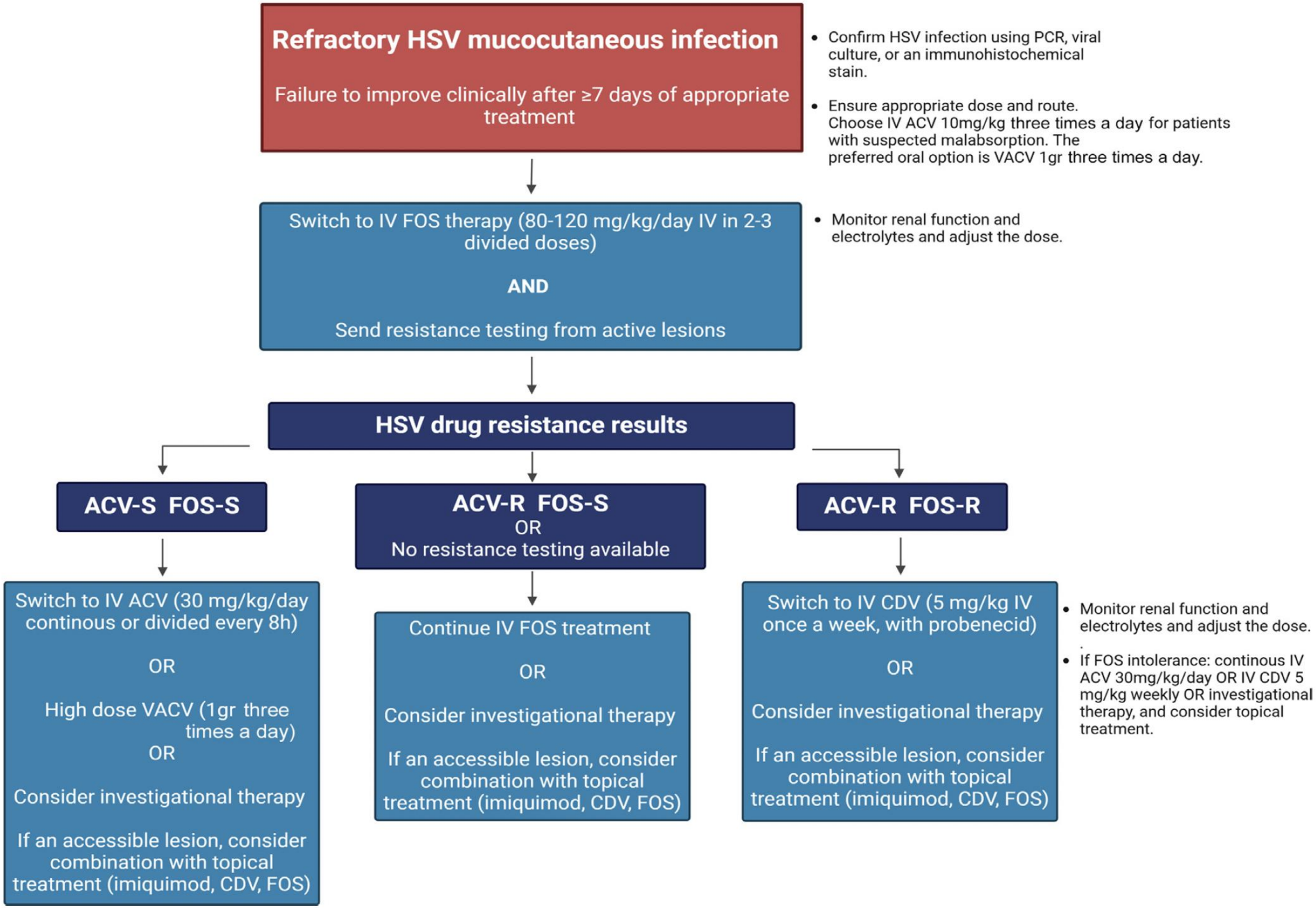
GENOTYPIC

- Sanger sequencing of **UL23 (thymidine kinase) for ACV** is the only clinically available genotypic HSV assay in the US, through reference labs, UW (2024).
  - Misses a mutation if a minor viral population.
  - Uncharacterized mutation – antiviral resistance vs. natural polymorphism

No genotypic assay for foscarnet resistance is available

- Faster turnaround; can be performed directly on specimens that culture poorly (plasma, CSF)
- Low viral load prevents sequencing
- Misses the ~5% of resistance caused by UL30 mutations — negative result does not rule out resistance

Based on retrospective/observational data and expert opinion, not a randomized-trial-derived algorithm.



Refractory Mucocutaneous HSV in HCT Recipients: Key Findings

Retrospective analysis across **7 US centers** · 125 adults with mucocutaneous HSV failing ≥7 d of appropriately dosed anti-HSV therapy · Transplants 2009–2024

Papanicolaou et al. Open Forum Infect Dis 2026 Vol. 13

Patient characteristics

- All patients developed HSV **on prophylaxis**
- Median onset **101 days** post-HCT
- 24% on prednisone ≥20 mg/day · 27% neutropenic
- 35% relapsed/progressive malignancy

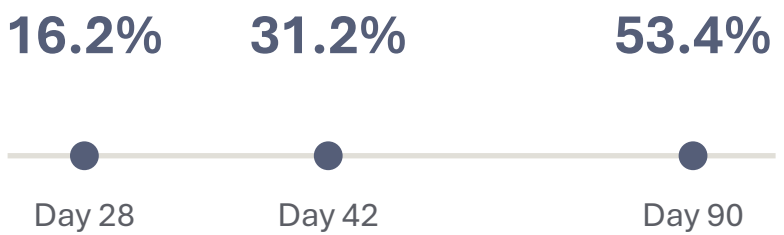
Infection Profile

- **82%** orofacial , 18% genital/perianal
- **HSV-1** predominated (71%)
- **12%** had systemic involvement (GI, respiratory, corneal, 1 CNS case)

Resistance

- **81.7%** (85/104) confirmed acyclovir-resistant (98 phenotypic vs. 6 genotypic assays)
- Only **5.2% (4/77)** foscarnet-resistant among those tested (3/4 median 25d foscarnet therapy; 1 with a remote hx of FOS exposure)

Cumulative incidence of complete healing



Median time to complete healing: 38 days

Overall complete healing: 69/125 (55.2%)

- *Patients (4) who received pritelivir were excluded*
- *Lost to follow-up or discontinued therapy before censored (12)*

Retrospective analysis across **7 US centers** · 125 adults with mucocutaneous HSV failing ≥7 d of appropriately dosed anti-HSV therapy · Transplants 2009–2024

Papanicolaou et al. Open Forum Infect Dis 2026 Vol. 13

Treatment sequencing

- 80% (100/125) started with a nucleoside analogue; 20% with foscarnet
- 88% (110/125) ultimately received second-line therapy
- 1/3 (43/125) received high-dose IV acyclovir; 77% (33/43) of these escalated to foscarnet

Foscarnet

- 94 patients (75%)
- Median start 12 days from the treatment initiation
- Mean course: 21.8 days • Renal abnormalities: 40.4%
- 30.3% of courses discontinued because of toxicity

Cidofovir

IV cidofovir: 6 patients; mean 20.3 days; renal abnormalities in 3/6 courses (50%), with 1 discontinuation.

Topical antivirals: 21 patients; often used in combination with systemic therapy.

32.0% **died while still receiving anti-HSV therapy (40/125)**

39.1% of patients who healed had ≥1 recurrence (median to first recurrence: 61 days)

Among the 69 who healed, **31.9% died** during the subsequent 1-year follow-up.

62 of 125 patients **(49.6%)** died during the study's observation period (1 year)

Treatment burden: 75.3% (52 /69) of patients who ultimately healed did so during 2nd - 4th antiviral course.

Foscarnet for Treatment of R/R Mucocutaneous HSV in Immunocompromised

Hammond et al., Open Forum Infect Dis 2024 Vol. 11

Multicenter retrospective study (5 centers, Jan 2012-Dec 2017)

- **29 immunocompromised patients**

- **Clinical outcomes**
  Complete lesion resolution: **48% (15/31)**
  Only **23% healed within 28 days**

- Median time to healing: **38 days** (range 9–1088)
- **53% of healed episodes recurred**
- **Toxicity (**Any adverse event: **84% ;** Electrolyte disturbances: **65%;** Kidney dysfunction: **42%)**
  Foscarnet discontinued because of toxicity: **32%**

Foscarnet remains a preferred therapy for r/r HSV, but efficacy is limited and renal/electrolyte toxicities are substantial

Pritelivir

Phase 2 randomized trial (*Wald et al. JAMA. 2016;316*)

- HSV-2 genital shedding in immunocompetent adults with recurrent genital herpes: 2.4% pritelivir group vs. 5.3% valacyclovir group ($P = 0.01$).
- FDA placed the trial on hold based on findings in a long-term monkey toxicology study (very high daily doses of pritelivir were administered for prolonged periods)

Immunocompromised Patients with Mucocutaneous Acyclovir- Resistant Herpes Simplex Virus-Infections (OFID 2021:8 (Suppl 1) abstract) - Open-label case series from a phase 2 portion of PRIOH-1

- 19 of 23 immunocompromised patients (83%) achieved complete lesion resolution within 28 days of pritelivir treatment
- 4 improved (3 later resolved, 1 on foscarnet for CMV).

Expanded access (early access): ~ 4 weeks to obtain

- ACV-resistant and foscarnet-resistant/intolerant mucocutaneous HSV infection (immunocompromised patients)

Feb 2026

TANDEM MEETINGS
Transplantation & Cellular Therapy Meetings
of ASTCT® and CIBMTR®
ASTCT® American Society for Transplantation and Cellular Therapy
CIBMTR® A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Pritelivir demonstrated superior efficacy compared to investigator's choice treatment for refractory herpes simplex virus infections in immunocompromised patients: PRIOH-1, phase 3 safety and efficacy

Genovefa A. Papanicolaou[1], Robin Avery[2], Kimberly Workowski[3], Karl S. Peggs[4], Yeon Joo Lee[1], Jean-Michel Molina[5], Anum Abbas[6], Alma Perez-Rios[7], Jana Dickter[8], Sanjeet Dadwal[8], Stuart Cohen[9], Nicolas Issa[10], Palash Samanta[11], Alexander Birkmann[12], Cynthia Wat[12], Dilruwan Chaminda Herath[12], Alessandra Marini[12], Bernadette Surujbally[12], Melanie Sumner[12], Anna Wald[13], Roy Chemaly[14]

A Randomized, Open Label, Multi-center, Comparative Trial, to Assess the Efficacy and Safety of Pritelivir for the Treatment of Acyclovir-resistant Mucocutaneous HSV Infections in Immunocompromised Subjects (PRIOH-1): pritelivir (n=51) vs. ICT (n=51)

- Healing: Pritelivir 62.7% vs. ICT 34.0%. Adjusted treatment difference of 28.4% (*P* = 0.0047)
- Treatment emergent adverse events: Pritelivir 21.6% vs. ICT 54%
- Discontinuations due to adverse events: Pritelivir 2.0% vs. ICT 20%

Takeaways: Challenges in Managing R/R Mucocutaneous HSV

- "Failure to improve" is quite vague or difficult to determine. Quantitative clinical responses could not be captured because of a lack of standardized assessments or measurements
  - Oral HSV: mucositis-related, impaired tissue healing, GVHD vs. HSV replication: complete healing can be difficult to assess
  - Genital ulcer associated with irritation from foscarnet excreted in urine
- Heavily immunocompromised patients with High mortality (~50% mortality)
- Breakthrough infection is very rare (0.6%, 23/3,749), but almost half (47.8%,11/23) with R/R HSV. *Fischer MD, et al. medRxiv [Preprint]. 2026*

  Should resistance testing be sent as soon as breakthrough infection is identified? Consider Pritelivir EAP sooner?

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