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Clinical UPDATE

Herpes Simplex Virus in Immunocompromised Patients:

Exploring A New Paradigm in Diagnosis and Treatment of Refractory and Resistant Infections

TARGET AUDIENCE

The educational design of this activity addresses the needs of specialists in infectious disease, hematology/oncology, critical care, obstetrics/gynecology, dermatology, urology, microbiology, and transplant surgery; primary care providers; hospital/health-system/specialty pharmacists; nurse practitioners; and physician assistants involved in the treatment of patients with herpes simplex virus (HSV).

STATEMENT OF NEED

In immunocompromised patients, reactivation of HSV is frequently prolonged, atypical, and resistant to standard antiviral therapy. The only FDA-approved salvage agents require intravenous administration and carry substantial toxicity burdens that often limit their use. Clinicians face knowledge gaps in recognizing atypical presentations, applying current diagnostic definitions, and selecting appropriate salvage therapy. A novel oral helicase–primase inhibitor is under FDA Priority Review, underscoring the need for timely education on emerging treatment options for this vulnerable population.

GOAL

The goal of this activity is to educate clinicians about HSV infections in immunocompromised patients, including clinical presentation, use of diagnostic tests and clinical definitions, effective treatment strategies, the importance of considering resistance, the potential for atypical clinical presentations, and a new class of agents under regulatory review that may offer clinical advantages over existing salvage therapies.

LEARNING OBJECTIVES

After completing this activity, the participant should be better able to:

1. Discuss the risk factors and resistance mechanisms that may occur in immunocompromised patients with HSV.
2. Describe the presentation of HSV lesions in immunocompromised patients, highlighting variations in atypical cases.
3. Identify HSV reactivation in immunocompromised patients, using appropriate clinical definitions and recognizing the need for diagnostic testing.
4. Develop strategies to treat refractory HSV in immunocompromised patients, focusing on maximizing effectiveness, improving administration schedules, and minimizing toxicities.

FACULTY

Yeon Joo Lee, MD, MPH
Associate Attending Physician, Infectious Diseases and Allergy Service
Memorial Sloan Kettering Cancer Center
New York, NY

Jonathan Hand, MD
Section Head, Transplant Infectious Diseases
Associate Professor of Medicine
The University of Queensland School of Medicine
Ochsner Clinical School, Ochsner Health
New Orleans, LA

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Introduction

Herpes simplex virus (HSV) ranks among the most prevalent human infections worldwide. According to estimates from the World Health Organization, 3.8 billion individuals younger than 50 years are infected with HSV-1, and 520 million people aged 15 to 49 years are infected with HSV-2.[1] In the United States, more than half of adults are HSV-1–seropositive and nearly 1 in 6 are HSV-2–seropositive.[2] For most people, HSV is a manageable issue, involving periodic, self-limited outbreaks that respond reliably to a short course of oral antiviral therapy. For the growing population of patients living with immunocompromising conditions, however, the clinical picture is substantially more complex.

In immunocompromised hosts—including recipients of hematopoietic stem cell transplants (HSCT) or solid organ transplants (SOT), patients receiving intensive chemotherapy or immunosuppressive therapy, and individuals with advanced HIV—HSV reactivation can be frequent, prolonged, and severe. Lesions may be atypical, deep, or necrotizing; visceral or disseminated disease can occur; and standard antiviral therapy may fail.[3-5] The widespread use of prophylactic antivirals in these high-risk populations, although highly effective in preventing disease, has created sustained selection pressure that drives the emergence of resistant HSV strains, leaving clinicians with few options when first-line therapy loses efficacy.[3,6] The available salvage agents, foscarnet and cidofovir, require intravenous (IV) administration and are associated with significant renal and metabolic toxicity, which often restricts their use.[5,7]

Recent advances in the understanding of HSV resistance mechanisms and diagnostic definitions, as well as the development of a novel class of antiviral drugs targeting the viral helicase–primase complex, are reshaping how refractory and resistant HSV infections can be approached in immunocompromised patients. This activity summarizes the virology of resistance, the spectrum of clinical presentations, current diagnostic and treatment approaches, and emerging therapeutic options, including pritelivir, which has shown superior efficacy compared with investigator's choice of therapy (ICT) in a phase 3 trial and is currently under FDA Priority Review.[8-10]

Selection for Resistance

Role of Host Immunity and Antiviral Pressure

Because HSV-1 seroprevalence exceeds 50% among US adults, the majority of patients who undergo HSCT or SOT or who develop advanced HIV enter their period of immunosuppression already latently infected. This makes the risk for reactivation ever-present.[2,3,11] In immunocompetent patients, intact HSV-specific T-cell responses constrain viral replication and limit the severity of reactivation episodes, meaning that antiviral resistance is exceedingly rare outside of prolonged, high-dose exposure.[3,6] However, in immunocompromised patients, profound defects in cellular immunity permit sustained viral replication under antiviral pressure, creating conditions favorable for the emergence of resistant variants.

Nucleoside analogue prophylaxis is highly effective at preventing clinical reactivation, but it acts as a continuous selective filter on viral populations at mucosal sites. Although these regimens have substantially decreased the burden of acute HSV disease, they have shifted the clinical challenge toward the subset of patients who develop acyclovir-resistant or multidrug-resistant HSV during periods of sustained immune dysfunction and prolonged antiviral exposure.[3,5,6]

Table 1. Risk Factors for Acyclovir-Resistant HSV in Immunocompromised Patients[3,5,6,11,14]

Population	Reported Resistance Rate	Key Risk Factors
Allogeneic HSCT recipients[3,5]	≤14%	Prolonged neutropenia, GVHD, HLA-mismatched transplant, T-cell–depleting agents, corticosteroids, myeloid malignancy, extended antiviral exposure, relapsed underlying malignancy
Solid organ transplant recipients[5,14]	2%-3% (higher in heart, lung)	Intensive induction immunosuppression, treatment for rejection
Advanced HIV infection[5,6]	3%-7% (lower in ART era)	Low CD4 count, absence of effective ART, prolonged or repeated antiviral courses
All immunocompromised patients[3,11]	—	Sustained T-cell immunosuppression, high-level viral replication, subtherapeutic drug exposure (due to malabsorption, drug interactions, renal dose adjustment)

ART, antiretroviral therapy; **GVHD,** graft-vs-host disease; **HLA,** human leukocyte antigen; **HSCT,** hematopoietic stem cell transplantation.

Molecular Basis of Resistance Selection

Nucleoside analogs, such as acyclovir, valacyclovir, famciclovir, and penciclovir, require phosphorylation by the viral thymidine kinase (TK), which is encoded by the *UL23* gene, to become active forms that inhibit the *UL30* viral DNA polymerase. TK is critical for viral reactivation in neurons and is the obligate activation step for this drug class.[3,6] TK-deficient or TK-altered mutants account for approximately 95% of acyclovir-resistant strains observed in clinical practice and are typically cross-resistant to other nucleoside analogs; *UL30* DNA polymerase mutations account for most of the remaining resistance cases and can further diminish susceptibility to nucleotide analogs such as cidofovir and, through mutations at the pyrophosphate binding site, to foscarnet.[3,6]

In immunocompromised patients with persistent viral replication during prolonged therapy, these mutations can arise and be positively selected, with even modest fitness advantages leading to rapid outgrowth of resistant variants, particularly at mucosal sites where high viral loads and repeated reactivation cycles are common.[5,6]

The helicase–primase complex, which is encoded by the *UL5*, *UL52*, and *UL8* genes, defines the target for a mechanistically distinct class of antivirals. Helicase–primase inhibitors, such as pritelivir and amenamevir, do not require TK activation and retain activity against TK-deficient strains and many DNA polymerase-mutant strains.[12,13]

Resistance Rates and Risk Factors

Acyclovir resistance rates are consistently higher in immunocompromised vs immunocompetent hosts. Among HSCT recipients, resistance has been documented in as many as 14% of patients, particularly in those with prolonged neutropenia, graft-vs-host disease (GVHD), or extended antiviral exposure.[3,5] In SOT recipients, resistance rates are lower but still clinically significant, typically ranging from 2% to 3%, with higher rates seen in heart and lung transplant recipients. Individuals with advanced HIV show resistance rates of 3% to 7%, although this prevalence is lower in the context of effective antiretroviral therapy.[5,6,14]

Risk factors for resistant HSV reflect the interplay of immune suppression depth and antiviral exposure to antiviral medications (**Table 1**).[3,5,6,11,14] Key contributors include prolonged T-cell immunosuppression, sustained high-level viral replication, repeated or extended courses of antiviral treatment, and subtherapeutic drug exposure due to malabsorption or drug interactions.[3,11] In HSCT recipients, additional risk factors include human leukocyte antigen-mismatched transplants, the use of T-cell–depleting agents, corticosteroid therapy, myeloid malignancies, relapsed underlying malignancy, and GVHD.[3] As prophylactic strategies have become more widespread, cumulative exposure to TK-dependent drugs in high-risk populations has increased, raising concern that resistance may become more prevalent in centers where prolonged antiviral prophylaxis is standard practice.[3,5]

These observations highlight the importance of balancing the clear benefits of prophylaxis against the potential risk for selecting resistant strains in patients with sustained immune dysfunction.

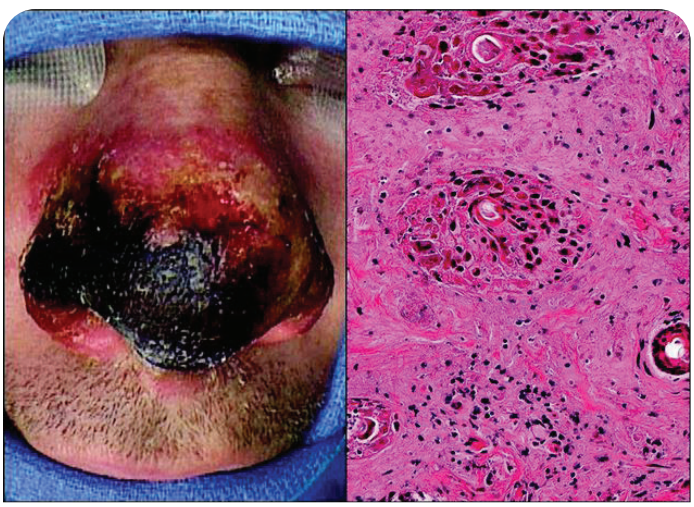

Figure 1. Reactivation of herpes simplex virus involving the nose.[17]

Left: Photograph of the patient's nasal lesion caused by HSV reactivation mimicking necrotizing fasciitis.

Right: Photomicrograph of the nasal tissue (hematoxylin–eosin stain; original magnification, ×200) obtained by surgical debridement revealing the effects of infection with HSV.

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Clinical Presentation

Typical HSV Lesions

In immunocompetent hosts, HSV classically presents with grouped, fluid-filled vesicles on an erythematous base involving the orolabial or anogenital regions. In contrast, immunocompromised patients may experience HSV outbreaks that are more extensive, deeper, and slower to heal, with larger areas of confluence and a higher risk for superinfection.[3,15] Mucosal involvement of the oral cavity, pharynx, and anogenital region is common in HSCT recipients and individuals with advanced HIV, in whom HSV reactivation can significantly impair oral intake and quality of life.[3,15]

Atypical Cutaneous and Mucocutaneous Manifestations

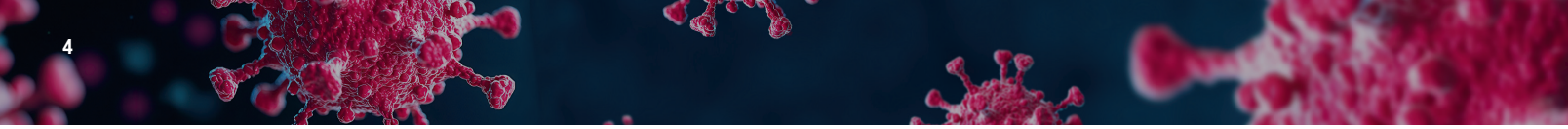
Profound or prolonged immunosuppression can lead to atypical HSV lesions that deviate substantially from the classic grouped vesicle pattern. HSV may present as necrotizing skin lesions with ulceration, eschar formation, and tissue destruction mimicking bacterial necrotizing infections or other ulcerative dermatoses (**Figure 1**).[4,16,17] Other atypical morphologies include hypertrophic, wart-like, or verrucous lesions, and deep ulcerative plaques that resemble malignancy, chronic bacterial or fungal infection, or pyoderma gangrenosum.[4,15]

HSV infection may also manifest as herpes vegetans or eczema-like eruptions, particularly in patients with underlying dermatoses or widespread skin barrier disruptions.[4,15] Case reports have described granulomatous vasculitis associated with HSV, which appears as persistent, painful papular or nodular lesions in the anogenital region. The histologic features may be misattributed to autoimmune vasculitis if HSV is not considered in the differential diagnosis.[18] A high index of suspicion and broad differential diagnosis are essential when evaluating unusual or refractory cutaneous lesions in immunocompromised patients.

Visceral and Systemic Involvement

Although HSV remains predominantly a mucocutaneous pathogen, immunocompromised individuals are at increased risk for visceral and systemic disease. HSV can involve the liver, lungs, adrenal glands, and central nervous system (CNS), presenting as hepatitis, pneumonitis, adrenalitis, or encephalitis.[15,19] These manifestations can occur in the absence of any visible mucocutaneous lesions, delaying diagnosis.

Disseminated HSV may present with fever, sepsis-like physiology, multiorgan dysfunction, or neurologic symptoms, particularly in patients with advanced HIV, profound lymphopenia after HSCT, or those undergoing intensive immunosuppression for GVHD or organ rejection.[3,19] Therefore, unexplained cases of hepatitis, pneumonitis,



or neurologic syndromes in profoundly immunosuppressed patients warrant evaluation for HSV even in the absence of obvious mucocutaneous disease.

Diagnostic Testing and Definitions

Confirmatory Diagnosis of HSV Reactivation

When HSV reactivation is suspected in an immunocompromised patient, confirmatory diagnostic testing of lesion material is essential, both to establish the diagnosis and to provide a specimen for subsequent resistance testing if needed. Polymerase chain reaction (PCR) testing of lesion swab material is the preferred method, offering high sensitivity and specificity for both HSV-1 and HSV-2. Optimal specimens are obtained by unroofing an intact vesicle or firmly swabbing the base of an ulcer or erosion.[5,16]

In settings where PCR is not immediately available, direct fluorescent antibody testing of lesion scrapings can provide rapid results, but sensitivity is lower than with PCR, particularly in partially healed or crusted lesions.[16] Viral culture, although less sensitive than PCR, can yield an isolate suitable for phenotypic susceptibility testing, making it a useful adjunct when resistance testing is anticipated.[5,7] Serology is not useful for diagnosing active reactivation in immunocompromised patients and should not be relied upon to confirm an acute episode.

Table 2. Definitions of Refractory and Resistant HSV (HSV Resistance Working Group of the TAVI Forum Consensus)[5,7,20]

Term	Definition	Notes
Refractory mucocutaneous HSV[5]	Lack of clinical improvement in HSV-positive lesions after ≥7 d of appropriately dosed directed antiviral therapy,[a] in the absence of other plausible causes; OR Appearance of new HSV-positive lesions after ≥7 d of appropriately dosed directed therapy[a]	Excludes prophylaxis and suppressive regimens; HSV-positive status must be confirmed by PCR or culture
Resistant HSV[5,7]	Refractory clinical disease (as above); PLUS Confirmed decreased antiviral susceptibility on phenotypic or genotypic testing	Resistance testing often pursued in parallel with treatment escalation due to prolonged turnaround times
Practical implication[5,7,20]	Treatment escalation (eg, to foscarnet) is typically initiated based on clinical refractory criteria before resistance testing results are available	Laboratory confirmation informs future management and clinical trial eligibility rather than directing the immediate therapeutic switch

[a]Appropriately dosed directed therapy refers to treatment-dose (not prophylactic or suppressive-dose) antiviral therapy prescribed specifically for active HSV disease.

HSV, herpes simplex virus; **PCR,** polymerase chain reaction; **TAVI,** Transplant Associated Viral Infections.

Phenotypic and Genotypic Resistance Testing

Phenotypic antiviral susceptibility testing for HSV is typically performed using plaque reduction assays, in which a viral isolate is exposed to serial dilutions of antiviral drugs to determine the drug concentration required to inhibit 50% of viral replication (EC50) for agents such as acyclovir, foscarnet, and cidofovir.[3,5] These assays provide a functional measure of susceptibility and can detect complex resistance patterns, but they require viable virus and specialized laboratory infrastructure, with turnaround times that typically exceed 2 to 3 weeks.[6,7] No FDA-cleared commercial HSV phenotypic resistance assays exist. Currently available methods are laboratory-developed tests with limited standardization and complicated interpretation across centers due to inter-laboratory variability in EC50 cutoffs.[3,5]

Genotypic resistance testing detects mutations in HSV genes that are known to confer antiviral resistance, most commonly *UL23* (TK) and *UL30* (DNA polymerase).[5,6] Sanger sequencing of these loci can identify frameshifts, nonsense mutations, and key amino acid substitutions more rapidly than plaque reduction assays, but this method is available at only a limited number of centers and may yield indeterminate results when viral loads are low or in the presence of novel variants of uncertain significance.[3,7]

Next-generation sequencing methods offer the potential to detect minority resistant variants at lower frequencies and to characterize resistance across multiple loci simultaneously, but these methods remain largely confined to research or highly specialized settings, and standardized interpretation frameworks are still evolving.[5,7]

In routine clinical practice, both phenotypic and genotypic testing are typically reserved for patients with strong clinical suspicion of resistance in whom the result would meaningfully influence management, such as confirming TK-deficient resistance that predicts failure of all TK-dependent agents or identifying polymerase mutations with implications for foscarnet or cidofovir response.[5,6] Given the prolonged turnaround times, treatment decisions often must be made empirically, with testing pursued in parallel to confirm the diagnosis and inform future management rather than to direct the immediate therapeutic switch.[5,7]

Definitions of Refractory and Resistant HSV

Historically, the lack of universally accepted clinical definitions for refractory HSV has complicated both patient management and clinical trial design.[5] To address this issue, the HSV Resistance Working Group of the Transplant Associated Viral Infections (TAVI) Forum has proposed standardized definitions for immunocompromised patients (**Table 2**).[5,7,20] Refractory mucocutaneous HSV infection is defined as either (1) lack of clinical improvement in HSV-positive lesions after at least 7 days of appropriately dosed directed antiviral therapy, in the absence of other plausible causes; or (2) the appearance of new HSV-positive lesions after at least 7 days of appropriately dosed directed

Table 3. Antiviral Agents for Refractory HSV in Immunocompromised Patients[5,6,10-13,16,21-32]

Agent	Mechanism	Route	FDA Approval for Resistant HSV	Dosing	Key Toxicities
Foscarnet[6,11,21,22]	Pyrophosphate analog; direct DNA polymerase inhibitor; TK-independent	IV	Yes	40 mg/kg q8-12 h for 14-21 d; adjusted for renal function	Renal impairment, seizures (boxed warnings); electrolyte disturbances (hypocalcemia, hypomagnesemia, hypokalemia, hyperphosphatemia), genital/mucous membrane irritation
Cidofovir[5,11,23]	Nucleotide analog; DNA polymerase inhibitor; TK-independent	IV (topical: compounded)	No	5 mg/kg/wk for 2 doses, then q2wk; requires prehydration and probenecid	Nephrotoxicity (boxed warning), neutropenia; contraindicated with preexisting renal dysfunction
Brincidofovir[24-26]	Lipid-conjugated nucleotide analog prodrug of cidofovir; DNA polymerase inhibitor; TK-independent	Oral	No; FDA-approved for smallpox only; efficacy may be reduced in immunocompromised patients	Not established for HSV; emergency use cases used 2 mg/kg q2wk (pediatric) or 200 mg biw (adult)	Diarrhea, nausea, vomiting, abdominal pain; no nephrotoxicity
High-dose acyclovir infusion[27-29]	Nucleoside analog; DNA polymerase inhibitor (TK-dependent)	IV	No	30-45 mg/kg/d as continuous infusion	Nephrotoxicity, neurotoxicity
Topical cidofovir[11,16]	Nucleotide analog; DNA polymerase inhibitor; TK-independent	Topical (compounded)	No (compounded)	1% gel (compounded) bid-qid	Local irritation; limited systemic absorption
Topical imiquimod[11,30]	Immune response modifier; not directly antiviral	Topical	No	Variable; no standard regimen	Local irritation, erythema
Pritelivir[10,12,13,31,a]	Helicase–primase complex inhibitor; TK-independent	Oral	Under FDA Priority Review	400-mg loading dose on day 1, then 100 mg/d for ≤28 d (extendable to 42 d)	Headache, diarrhea, nausea, decreased appetite, vomiting, dizziness

[a]Under FDA Priority Review; not yet approved. Available through expanded access protocol NCT05844436 for eligible immunocompromised patients.[32]

bid, twice daily; **biw,** twice weekly; **HSV,** herpes simplex virus; **IV,** intravenous; **q2wk,** every 2 weeks; **qid,** 4 times daily; **TK,** thymidine kinase.

therapy, excluding prophylaxis and suppressive regimens.[5] Resistant HSV is then defined by the presence of refractory clinical disease plus confirmed decreased antiviral susceptibility based on phenotypic or genotypic testing.[5]

In practice, many treatment decisions are made before the results of resistance testing are available. Clinicians typically rely on clinical criteria, such as failure to respond to an adequate course of first-line therapy in a high-risk patient, to make a working diagnosis of refractory infection, with laboratory confirmation pursued in parallel when feasible.[5,7] The decision to escalate to second-line agents, such as foscarnet or IV cidofovir, is guided by degree of immunosuppression, renal function, and severity of disease.[3,7] As access to rapid molecular and sequencing-based resistance testing improves, these definitions and the diagnostic algorithms that incorporate them are likely to be refined further.

Current Treatment Options and Their Limitations

Management of refractory HSV infection in immunocompromised patients remains challenging given the limited number of available agents, their substantial toxicity, and the logistical burdens of administration (**Table 3**).[5,6,10-13,16,21-32] Treatment decisions must often be made empirically once refractory disease is suspected, with resistance testing performed concurrently.[5]

IV Foscarnet

IV foscarnet is the only FDA-approved therapy for acyclovir-resistant mucocutaneous HSV infection.[21,22] A pyrophosphate analog that directly inhibits viral DNA polymerase without requiring TK activation, foscarnet retains activity against most TK-deficient HSV strains.[6,11] Recommended dosing for resistant mucocutaneous HSV generally ranges from 40 mg/kg every 8 to 12 hours for 14 to 21 days, adjusted for renal function.[11,21]

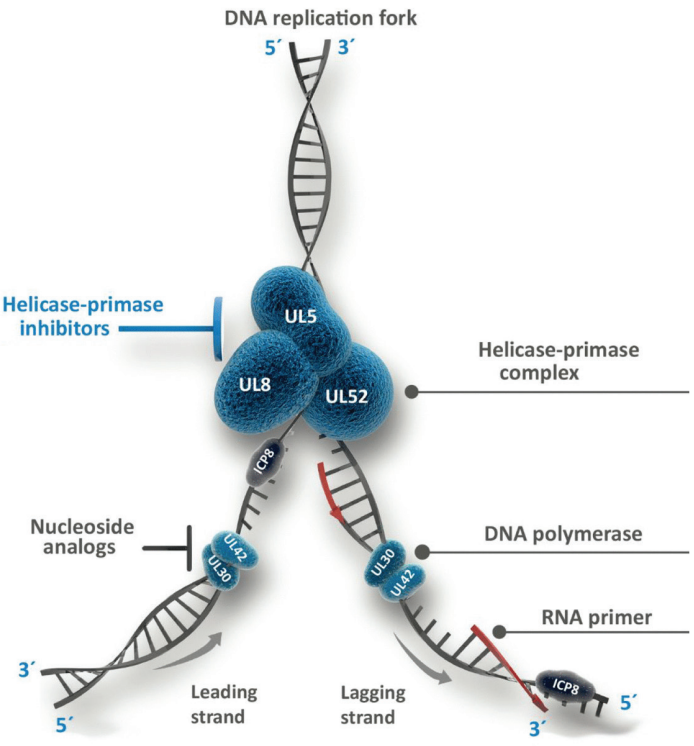


Figure 2. Mechanism of action of pritelivir vs standard antivirals.[12]

Pritelivir targets the viral helicase–primase complex (*UL5, UL52, UL8*), blocking viral DNA unwinding upstream of DNA polymerase. In contrast to nucleoside analogs and foscarnet, it does not require activation by viral TK. Because it bypasses this activation step and uses a distinct molecular target, pritelivir retains full clinical activity against both TK-deficient and foscarnet-resistant viral strains.

TK, thymidine kinase.

Nephrotoxicity is a common adverse event (AE) of foscarnet and may be exacerbated by dehydration, concomitant nephrotoxins, and pre-existing renal impairment, requiring close monitoring and aggressive hydration.[21] Electrolyte disturbances, including hypocalcemia, hypomagnesemia, hypokalemia, and hyperphosphatemia, can contribute to seizures and other serious complications if not corrected promptly.[21]

Frequent IV dosing and the need for laboratory monitoring often necessitate hospitalization or highly coordinated outpatient infusion support.[7,11] Real-world data underscore these limitations: in a multicenter retrospective study of immunocompromised patients treated with foscarnet for acyclovir-resistant mucocutaneous HSV, complete lesion healing was achieved in fewer than half of treated episodes (48%), and treatment was discontinued due to AEs in 32% of cases.[33] In a recent multicenter study involving 125 HSCT recipients with refractory HSV, foscarnet was the primary second-line therapy.[20] Complete lesion healing occurred in only 55.2% of patients, with a median time to healing of 38 days, and foscarnet carried significant toxicity, with nephrotoxicity in 40.4% of courses.

This agent's prescribing information includes boxed warnings for renal impairment and seizures/electrolyte abnormalities.[21]

IV Cidofovir

IV cidofovir is generally reserved for patients who are intolerant of or have disease refractory to foscarnet.[7,11] A nucleotide analog that inhibits viral DNA polymerase without TK activation, cidofovir retains activity against many TK-mutant HSV isolates; however, its use for resistant HSV is off-label and supported primarily by case reports and small case series.[5,11]

The principal limitation of cidofovir is toxicity. The prescribing information carries boxed warnings for dose-limiting nephrotoxicity and neutropenia, and its use requires strict adherence to renal monitoring, prehydration, and coadministration of probenecid to reduce tubular injury.[23] In clinical practice, cidofovir is contraindicated in patients with preexisting renal dysfunction or significant proteinuria, and dose modification is necessary with even modest increases in serum creatinine.[11,23] Although the longer dosing interval (5 mg/kg weekly for 2 doses, then every 2 weeks) may make cidofovir more feasible than foscarnet in some outpatient settings, this advantage is offset by its risk for nephrotoxicity and the limited quality of supporting evidence.[7,11,20]

Brincidofovir

Brincidofovir is an oral lipid-conjugated nucleotide analog prodrug of cidofovir that inhibits viral DNA polymerase without requiring TK activation, retaining activity against TK-deficient HSV strains and without the nephrotoxicity associated with parenteral cidofovir.[24,25] Brincidofovir is FDA-approved for smallpox only and is not indicated for HSV.[26] The prescribing information includes a caution that efficacy may be reduced in immunocompromised patients, based on studies in immune-deficient animals.[26]

Published experience in HSV is limited to isolated case reports in which the drug was obtained through emergency use authorization; clinical and microbiological responses have been reported in immunocompromised patients with confirmed acyclovir-resistant HSV who had exhausted other salvage options, including one pediatric HSCT recipient and one adult with aplastic anemia.[24,25] Brincidofovir is not commercially available for HSV, and no established access pathway exists outside of emergency authorization.

High-Dose Continuous Acyclovir Infusion

High-dose acyclovir administered as a continuous IV infusion has been proposed as an alternative salvage strategy for selected patients. This approach may be particularly effective in cases where high serum drug exposures can help overcome low-level TK-mediated resistance, when other treatment options are poorly tolerated, or when foscarnet is considered too risky.[27,28]

Published reports have generally recommended total daily doses of 30 to 45 mg/kg, with some patients achieving clinical and virologic responses.[27,28] Although home infusion services with portable pump support can facilitate outpatient administration, the evidence base

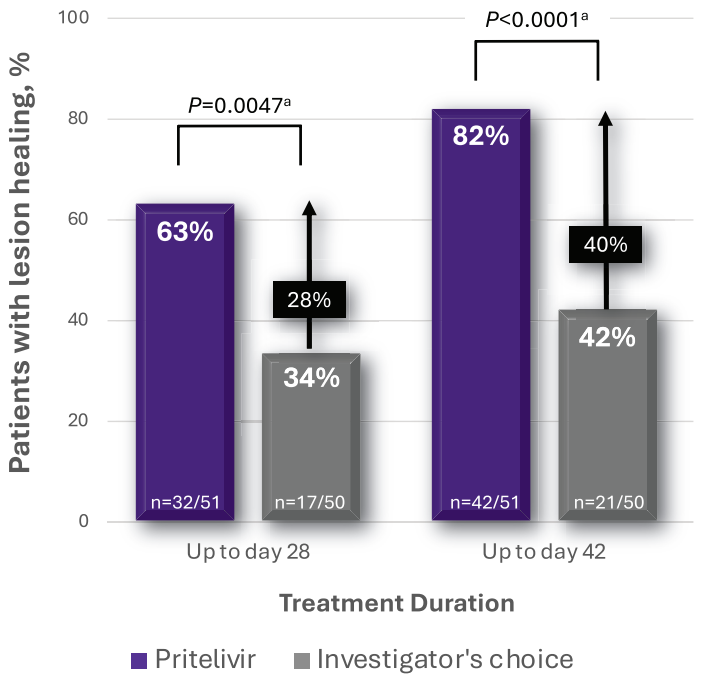


Figure 3. Complete lesion healing rates in PRIOH-1 at day 28 (primary end point) and day 42 (secondary end point).[39]

Pritelivir demonstrated statistically superior complete lesion healing compared with investigator's choice therapy at both time points.

[a]Stratified Cochran Mantel Haensel test adjusted for protocol versions (4.0 and earlier, 5.0 and later).

is limited to small case series, and concerns for nephrotoxicity and neurotoxicity at high systemic exposures remain.[27,29]

Topical and Adjunctive Therapies

Topical therapies have been used as adjuncts for localized mucocutaneous disease when systemic therapy has failed or cannot be tolerated. Topical cidofovir has been reported in patients with orofacial and perianal lesions but is not commercially available in the United States and requires compounding, limiting access and standardization.[11] Topical imiquimod, which enhances local innate and cell-mediated immune responses rather than acting directly on the virus, has been described in cases of acyclovir-resistant HSV, with some reports of complete lesion resolution.[11,30] The evidence for both agents remains anecdotal, and these therapies are best considered as individualized options for selected patients rather than definitive treatment.

IV Immunoglobulin

IV immunoglobulin (IVIG) has been used adjunctively for some immunocompromised patients with refractory HSV, particularly those with concurrent hypogammaglobulinemia, but its role is not established.[34,35] Available data are limited to small case series in which IVIG was administered alongside antiviral therapy, and routine use is not recommended.[34,35]

Real-World Context

The clinical limitations of existing salvage therapies are reflected in real-world practice patterns. A retrospective cohort study using linked US electronic health record and administrative claims data from 2022 to 2024 identified 152,835 patients with HSV infection who had at least 1 antiviral claim; among them, 6.8% had an underlying immunocompromising condition.[36] Treatment-modification patterns used as proxies for refractory disease, including first-line agent switching, upward dose titration, route-of-administration changes, and escalation to second-line therapy, were observed in 20.3% of immunocompromised patients overall, with the highest rates among HSCT recipients, 72.5% of whom required switching between first-line agents. AE rates increased with treatment escalation: 7% of patients initiating first-line oral therapy experienced an AE within 30 days, compared with 14% of those receiving second-line therapy and 40% of those receiving IV therapy, with electrolyte disturbances (52%) and renal events (36%) predominating in the IV-treated group.[36]

Limits of the Current Treatment Landscape

The collective evidence from controlled studies and real-world analyses underscores the inadequacy of the current salvage armamentarium for refractory HSV in immunocompromised patients. Foscarnet remains the only FDA-approved option but is constrained by nephrotoxicity, electrolyte disturbances, and the requirement for IV administration.[20,21,33] Cidofovir offers a mechanistically plausible alternative but is used off-label, carries significant risk for nephrotoxicity, and is supported by limited evidence.[11,20,23] Brincidofovir is an oral agent with activity against TK-deficient HSV but is approved for smallpox only and is not accessible for the treatment of HSV.[24-26] Continuous-infusion acyclovir and topical agents have roles in selected patients but rest on small case series or anecdotal reports rather than prospective data.[27,30] The absence of an oral, well-tolerated agent with activity against TK-deficient HSV represents a clear gap in the therapeutic landscape.

Helicase–Primase Complex Inhibitors: A New Paradigm

Rationale and Mechanism of Action

Traditional anti-HSV therapies such as acyclovir, valacyclovir, and famciclovir depend on viral TK for initial phosphorylation and ultimately inhibit viral DNA polymerase, which makes them vulnerable to resistance mediated by *UL23* (TK) and *UL30* (polymerase) gene mutations.[3,6] Helicase–primase inhibitors represent a distinct anti-viral class that targets the HSV helicase–primase complex (*UL5, UL52,* and *UL8*), which is essential for unwinding the viral DNA template and synthesizing RNA primers during replication (**Figure 2**).[12] By inhibiting this complex, these agents block viral DNA synthesis upstream of DNA polymerase and do not require viral TK for activation, thereby retaining activity against many TK-deficient and nucleoside analog-resistant strains.[12,13]

Pritelivir is an oral small-molecule helicase–primase inhibitor with potent activity against HSV-1 and HSV-2 in vitro and in animal models, including strains with resistance to acyclovir and related nucleoside

Table 4. PRIOH-1 Phase 3 Trial: Key Efficacy and Safety Outcomes[8,31,38,39]

Outcome	Pritelivir	Investigator's Choice Therapy	Treatment Difference	*P* value
Primary end point				
Complete lesion healing, day 28, %[8,38]	62.7	34.0	28.4	*P*=0.0047
Extended treatment				
Complete lesion healing, day 42, %[39]	82.4	42.0	40.2	*P*<0.0001
Virologic response				
HSV DNA undetectable in lesions, %[39]	73.7	48.7	25.0	*P*=0.0251
Median time to undetectable HSV, d[39]	9	21	—	*P*=0.0581
Predefined subgroup: day 28				
Oncology/other (nontransplant), %[31]	68.4	26.7	41.8 (95% CI, 6.7-69.0)	—
Transplant, %[31,a]	50.0	39.3	CI crosses 0[a]	—
HIV (post hoc), %[31]	68.8	28.6	40.2 (95% CI, −7.5 to 73.7)	—
Predefined subgroup: day 42				
Oncology/other (nontransplant), %[31]	89.5	33.3	56.1 (95% CI, 20.3-80.0)	—
Transplant, %[31,a]	75.0	50.0	CI crosses 0[a]	—
HIV (post hoc), %[31]	81.3	28.6	52.7 (95% CI, 6.4-83.1)	—
Safety				
TEAEs leading to discontinuation, %[8]	2.0	20.0	—	—
Drug-related TEAEs, %[31]	21.6	54.0	—	—
Serious TEAEs, %[31]	19.6	30.0	—	—

[a]CIs wide and crossing 0 at both day 28 and day 42, likely reflecting smaller sample size (n=44).[31]

CI, confidence interval; **TEAE,** treatment-emergent adverse event.

analogs.[12] Preclinical pharmacokinetic and pharmacodynamic studies demonstrated favorable oral bioavailability, sustained plasma concentrations above antiviral target thresholds at clinically achievable doses, and suppression of HSV replication and lesion formation in murine models of systemic and mucocutaneous infection.[12] These characteristics, together with its TK-independent mechanism, provided the rationale for developing pritelivir specifically for the treatment of immunocompromised patients with refractory HSV infection.

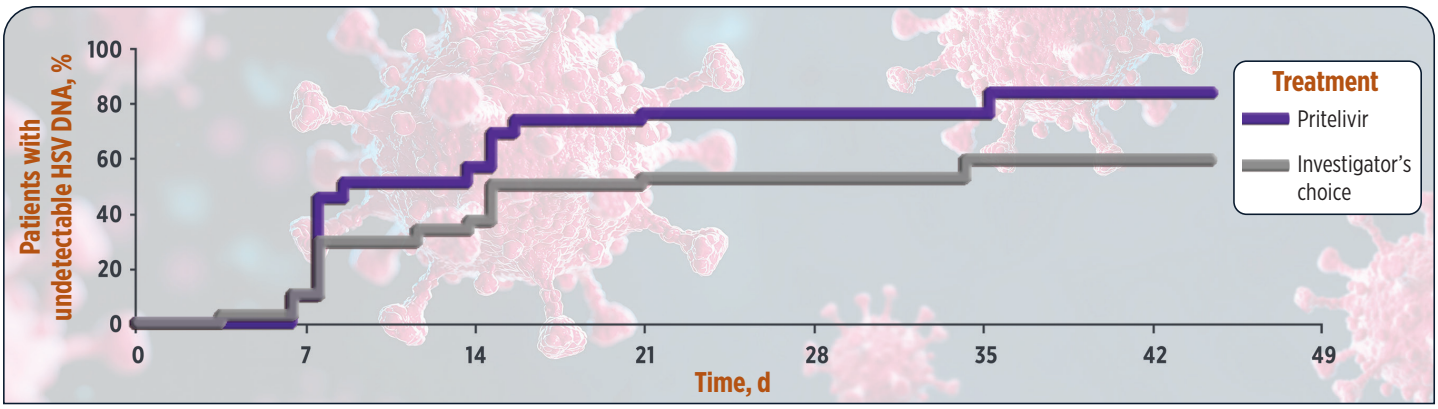
Phase 2 Clinical Data

Early-phase clinical data established proof of concept for pritelivir in the immunocompromised setting. In a randomized, open-label phase 2 trial, immunocompromised patients with acyclovir-refractory or resistant HSV infection were assigned to pritelivir (400-mg loading dose on day 1, then 100 mg once daily for ≤28 days) or IV foscarnet (Part A), with a separate single-arm cohort for patients who were acyclovir- and foscarnet-refractory or foscarnet-intolerant (Part B).[37]

In Part A, complete lesion healing at day 28 occurred in 14 of 15 patients (93%) receiving pritelivir and 4 of 7 patients (57%) receiving foscarnet. Treatment-emergent AEs (TEAEs) leading to drug discontinuation were less common with pritelivir (4%) than with foscarnet (43%).[37] In Part B, 5 of 8 patients (63%) with foscarnet-refractory or -intolerant HSV achieved complete healing with pritelivir.[37] Although the phase 2 study was small and not powered for formal statistical testing, the results were directionally consistent with subsequent phase 3 findings.

Clinical Development: PRIOH-1

The pivotal PRIOH-1 trial (NCT03073967) was a randomized, open-label, multicenter, comparative study evaluating oral pritelivir in 101 immunocompromised patients with refractory HSV infection, with or without documented antiviral resistance (**Table 4**).[8,31,38,39] Patients were randomized 1:1 to receive either pritelivir or ICT, which could include IV foscarnet, IV or topical cidofovir, or topical imiquimod. Pritelivir was given as a 400-mg loading dose on day 1 followed by 100 mg orally once daily for up to 28 days, with extension to 42 days permitted



Number at risk

Pritelivir	38	37	17	8	3	3	1	0
Investigator's choice	39	33	21	14	11	6	4	0

Figure 4. Kaplan-Meier plot of time to undetectable HSV DNA in mucocutaneous lesions.[39]

Median time to undetectable HSV DNA was 9 days with pritelivir vs 21 days with investigator's choice therapy (hazard ratio, 1.76; 95% CI, 0.98-3.16; *P*=0.0581).

Analysis performed on subgroup of patients who had a positive HSV DNA PCR result at baseline. Patients who had positive HSV DNA PCR result at the post-treatment visit were censored at that visit. Patients who had no post-baseline HSV DNA PCR evaluation were censored at the date of first dose. HSV DNA limit of detection ≥150 copies/mL + censored observation.

HSV, herpes simplex virus; **PCR,** polymerase chain reaction.

in patients with ongoing clinical improvement.[31] Enrolled patients represented the full spectrum of immunocompromising conditions, including hematologic malignancies, HSCT, HIV infection, autoimmune and inflammatory diseases, and SOT.[8] Data for this trial are from conference presentations; full peer-reviewed publications are pending.

The trial met its primary end point: complete lesion healing by day 28 occurred in 62.7% of patients receiving pritelivir compared with 34.0% of those receiving ICT, corresponding to an adjusted treatment difference of 28.4% (*P*=0.0047; **Figure 3**).[8,38] Among patients who continued therapy, complete lesion healing at day 42 was achieved in 82.4% of pritelivir-treated patients compared with 42.0% of those receiving ICT, an adjusted treatment difference of 40.2% (*P*<0.0001).[39]

HSV DNA became undetectable in lesions during the treatment period in 73.7% of patients in the pritelivir group compared with 48.7% in the ICT group (treatment difference, 25%; *P*=0.0251).[39] Pritelivir also shortened the median time to undetectable HSV in lesions to 9 days compared with 21 days for ICT (*P*=0.0581; **Figure 4**).[39]

HIV Subgroup

In a post-hoc subgroup analysis of people living with HIV enrolled in PRIOH-1 (n=38, representing 37.6% of the randomized population), pritelivir demonstrated superior lesion healing compared with ICT among evaluable patients: 68.8% (11/16) vs 28.6% (2/7), a treatment difference of 40.2% (95% CI, −7.5 to 73.7).[31] The remaining 15 baseline participants were excluded from this end point analysis due to missing or nonevaluable lesion data at the primary assessment window.

Complete lesion healing at day 42 was achieved in 81.3% (13/16) of patients in the pritelivir arm vs 28.6% (2/7) in the ICT arm (95% CI, 6.4-83.1),[31] and 96% of patients in the pritelivir arm completed treatment compared with 60% in the ICT arm.[39]

Other Immunocompromised Subgroups

Predefined subgroup analyses from PRIOH-1 examined treatment response across the 3 major immunocompromising conditions represented in the trial.[31] In the oncology/other (nontransplant) subgroup, complete lesion healing rates were 68.4% vs 26.7% at day 28 (treatment difference, 41.8%; 95% CI, 6.7-69.0) and 89.5% vs 33.3% at day 42 (treatment difference, 56.1%; 95% CI, 20.3-80.0). In the transplant subgroup, complete healing rates were numerically higher with pritelivir at both day 28 (50.0% vs 39.3%) and day 42 (75.0% vs 50.0%), although confidence intervals were wide and crossed zero, likely reflecting the smaller sample size in this subgroup (n=44).[31]

Across all 3 predefined subgroups, including HIV, the direction of effect consistently favored pritelivir. Prospective data are needed.

Safety and Tolerability

TEAEs leading to discontinuation occurred in 2.0% of patients receiving pritelivir and 20.0% of those receiving ICT in PRIOH-1.[8] Drug-related TEAEs occurred in 21.6% of the pritelivir group vs 54.0% of the ICT group, and serious TEAEs occurred in 19.6% vs 30.0%, respectively.[31] TEAEs of special interest, including electrolyte abnormalities, renal and urinary disorders, skin disorders, and hematologic events, all occurred at lower rates

with pritelivir than with ICT.[31] The most common AEs reported with pritelivir (each occurring in ≥5% of patients) were headache, diarrhea, nausea, decreased appetite, vomiting, and dizziness.[8]

Drug Interactions and Use With Calcineurin Inhibitors

Clinical pharmacokinetic studies have evaluated the effects of pritelivir on various cytochrome P450 (CYP) enzymes, specifically CYP3A4, CYP2B6, CYP2C9, CYP2C8, as well as on the intestinal transporters, including the organic anion transporting polypeptide 2B1 and the breast cancer resistance transporter protein (BCRP). These studies demonstrated no clinically relevant effects on CYP enzyme substrates, with only weak inhibition of the intestinal efflux transporter BCRP.[12,40] Because calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are metabolized primarily by CYP3A4, pritelivir is not expected to meaningfully alter CNI exposure. Thus, there is no evidence from the available data suggesting that a dose adjustment of CNIs is needed due to a pharmacokinetic interaction with pritelivir.[40] Nonetheless, CNI levels should continue to be monitored per standard practice in transplant recipients receiving any new concomitant therapy.

Pediatric Considerations

Prospective efficacy and safety data for pritelivir in pediatric patients are not yet available. The European Medicines Agency approved a Pediatric Investigation Plan for pritelivir in 2021, with pediatric studies deferred pending completion of adult development.[41]

Regulatory and Expanded-Access Context

Pritelivir received FDA Breakthrough Therapy designation in 2020 based on phase 2 efficacy and safety data. After submission of the New Drug Application in early 2026, the FDA granted Priority Review for the treatment of refractory HSV infection, with or without resistance, in immunocompromised patients, with a target action date in the fourth quarter of 2026.[10]

In parallel, an expanded access intermediate-size treatment protocol (NCT05844436) has been established in the United States for immunocompromised patients with refractory HSV-1 or HSV-2 who cannot participate in a clinical trial and for whom no approved treatment option is available.[32]

Amenamevir: Additional Helicase–Primase Inhibitor Experience

Amenamevir is a helicase–primase complex inhibitor approved in Japan for the treatment of herpes zoster and recurrent HSV but not commercially available outside that country.[13] Experience with amenamevir in treating HSV, particularly in immunocompromised patients, is limited. Case reports describe successful use in acyclovir-resistant HSV infections after allogeneic HSCT, including in patients with renal dysfunction, for whom foscarnet presented considerable risk.[13,42] However, worsening of symptoms and development of CNS infections have also been reported in some patients receiving amenamevir in the immunocompromised setting, and the risk–benefit profile in this population is not yet fully characterized.[13] Prospective data are lacking, and pritelivir remains the only helicase–primase inhibitor with prospective phase 3 data in immunocompromised patients with refractory HSV infections.

Case Study: Connie, Refractory Oropharyngeal HSV in an Allogeneic HSCT Recipient

Connie, a 57-year-old woman, presents with a 10-day history of painful, grouped, and coalescent erosions affecting her tongue, hard palate, and buccal mucosa. She underwent allogeneic HSCT 8 months earlier for acute myeloid leukemia and is currently receiving tacrolimus and systemic corticosteroids for chronic GVHD. Connie is HSV-seropositive and has a history of prior mucocutaneous episodes.

Despite escalation of her valacyclovir dosage to 1 g 3 times daily 9 days ago, her lesions have enlarged, becoming more ulcerative, and she is experiencing significant odynophagia with poor oral intake. Lesion PCR confirms the presence of HSV-1, and her renal function is preserved (serum creatinine, 0.8 mg/dL).

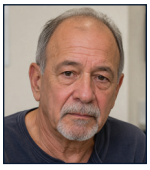
Having failed at least 7 days of appropriately dosed nucleoside analog therapy, this case meets the consensus definition of refractory mucocutaneous HSV.[5] The medical team transitions Connie to IV foscarnet and sends specimens for phenotypic resistance testing. She is hospitalized for central venous access, aggressive hydration, and monitoring. However, by day 10 of foscarnet treatment, her serum creatinine rises to 1.6 mg/dL, prompting a dose reduction, and she develops symptomatic hypocalcemia necessitating supplementation. Resistance testing results, available on day 12, confirm acyclovir-resistant HSV-1, with preserved foscarnet susceptibility. Lesion healing is incomplete at day 14.

Considering her foscarnet intolerance and persistent disease, the team enrolls her in the pritelivir expanded access program. She transitions to oral pritelivir 400 mg on day 1, followed by 100 mg daily thereafter, and achieves complete lesion healing by day 21.

Key Points

- Persistent HSV lesions despite 7 or more days of appropriately dosed nucleoside analog therapy meets the proposed consensus definition of refractory HSV and warrants escalated antiviral therapy.[5]
- Resistance testing should be sent at the time of escalation; however, results typically require 2 to 3 weeks, and treatment decisions must be made empirically while awaiting confirmation.[5,7]
- Foscarnet remains the standard salvage option, but nephrotoxicity and electrolyte disturbances are common, frequently requiring dose modification or early discontinuation, and hospitalization is necessary.[20,21,33]
- Oral helicase–primase inhibitors represent a mechanistically distinct option that does not require viral TK activation and retains activity against TK-deficient strains.[12]
- At the time of this publication (August 2026), patients who are intolerant of or have disease refractory to acyclovir or foscarnet may be candidates for the pritelivir expanded access program, which is available for immunocompromised patients with refractory HSV who have no approved alternatives.[32]

Case Study: Barney, Necrotizing Anogenital HSV in a Patient With Renal Dysfunction



Barney is a 72-year-old man with advanced HIV infection (CD4 count, 50 cells/mm^3) who presents with a 3-week history of painful necrotizing ulcers in the perianal and anogenital regions, resembling lymphogranuloma venereum. He has a history of genital HSV and has been intermittently adherent to valacyclovir suppressive therapy. He also has a history of acute kidney injury.

Bacterial cultures are negative but biopsy and PCR testing confirm the presence of HSV-2. Despite treatment with high-dose oral valacyclovir for 10 days and IV acyclovir for 7 days, Barney's condition does not improve. Phenotypic testing confirms acyclovir resistance. The foscarnet EC50 is within the susceptible range, and baseline estimated glomerular filtration rate (eGFR) is 40 mL/min/1.73 m^2.

Cidofovir is contraindicated given Barney's renal dysfunction,[23] and topical agents are insufficient for disease of this extent. The medical team initiates renal dose-adjusted IV foscarnet with aggressive hydration and close monitoring. By day 7, Barney's eGFR falls to 28 mL/min/1.73 m^2, requiring further reduction in foscarnet dosage. Lesions show only partial improvement at day 14 and foscarnet is discontinued at day 17 due to progressive nephrotoxicity. Residual ulcerations persist. Recognizing the need for additional treatment options, the team identifies Barney as a candidate for the pritelivir expanded access program and pursues enrollment, while continuing topical compounded cidofovir as a temporizing measure.

Key points

- Atypical, necrotizing anogenital lesions in an immunocompromised patient should prompt HSV in the differential diagnosis, particularly when refractory to antibiotics.[4,15]
- Confirmed acyclovir resistance with documented treatment failure meets criteria for refractory HSV; foscarnet remains the only FDA-approved salvage option but is frequently limited by nephrotoxicity, especially in patients with preexisting renal dysfunction.[20,21,33]
- Chronic kidney disease significantly narrows the therapeutic window for all currently available salvage agents, often forcing early discontinuation and leaving patients with incompletely treated disease.
- This case illustrates the critical unmet need for an oral, TK-independent agent with a renal-sparing profile. Pritelivir, if approved, would represent a meaningful option for patients like Barney who cannot safely complete a full course of foscarnet or cidofovir.[12]

Conclusion

HSV infection in immunocompromised patients carries a substantial burden of disease, driven by frequent reactivation, atypical and severe clinical presentations, and a heightened risk for antiviral resistance. Prolonged antiviral exposure and impaired cellular immunity create conditions that favor the emergence of resistant strains, while current diagnostic tools remain slow, specialized, and incompletely standardized. Foscarnet remains the only FDA-approved therapy for acyclovir-resistant mucocutaneous HSV but is constrained by nephrotoxicity, electrolyte disturbances, and the requirement for IV administration; complete lesion healing is achieved in fewer than half of treated episodes, and treatment discontinuation due to AEs is common. Cidofovir and other salvage approaches carry comparable toxicity profiles and are supported by evidence that extends little beyond case reports and small retrospective series. Pritelivir, an oral helicase–primase inhibitor active against TK-deficient and foscarnet-resistant strains, demonstrated superior lesion healing and a substantially more favorable tolerability profile than ICT in the phase 3 PRIOH-1 trial, and represents the most significant advance in the management of refractory HSV in immunocompromised patients in decades. Broader access to resistance testing, continued refinement of diagnostic frameworks, and timely integration of emerging therapies into clinical practice will be essential to translating these advances into improved outcomes for a population defined by immunologic vulnerability and limited therapeutic recourse.

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