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Narrative review

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

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ABSTRACT

*Background:* Herpes simplex virus (HSV) infection is a clinically significant complication in haematopoietic cell transplant (HCT) recipients. Refractory and resistant (R/R) HSV infections may occur in this patient population, particularly after prolonged exposure to anti-HSV agents.
*Objectives:* This study aims to provide a comprehensive review of the diagnostic approach and the treatment options for R/R HSV mucocutaneous infections in HCT recipients and to highlight future treatment strategies.
*Sources:* We searched the PubMed Central Database and Embase to identify published studies on R/R HSV infections in HCT recipients. We used the search terms "herpes simplex virus," "resistant*," OR "refractory," "immunocompromised," "immunosuppress*," and "immunodeficien*," and screened the results for articles reporting R/R HSV infections among HCT recipients. We chose an HCT recipient with a complicated refractory HSV infection as a representative clinical case.
*Content:* A clear clinical definition of refractory HSV infection is currently not available, which can lead to delays in diagnosis and treatment, negatively impacting patient care. Apart from two small randomized controlled trials in the 1990s that looked at treatment with systemic foscarnet and topical cidofovir in patients living with human immunodeficiency virus, all treatment recommendations for R/R HSV infections are based on observational studies and case reports. The use of alternative treatment options often comes with serious side effects, such as kidney toxicity. This underscores the urgent need for safer and more effective treatment options. Pritelivir, a new oral antiviral medication, is currently being studied in a phase 3 trial for R/R HSV infections in immunocompromised patients. Limited data from the Early Access Program, which allows compassionate use, suggest that pritelivir holds promise as a treatment option for HCT recipients with R/R HSV infections.
*Implications:* The proposed R/R HSV mucocutaneous infection diagnostic and treatment algorithm guides the appropriate management of these difficult-to-treat infections, potentially improving patient outcomes. **Tali Shafat, Clin Microbiol Infect 2025;31:761**


## Introduction

Herpes simplex virus (HSV) infection may pose a significant clinical challenge for haematopoietic cell transplant (HCT) recipients [1]. The prevalent use of nucleoside inhibitors, such as acyclovir (ACV) and valacyclovir (VACV), for the treatment or prolonged prophylaxis of HSV may lead to the development of drug-resistant HSV strains [2].

The prevalence of refractory and resistant (R/R) HSV infections in HCT recipients mostly ranges from 0% to 14%, with few studies of small sample sizes reporting a prevalence of up to 46% [1,3,4]. Identified risk factors include relapsed haematological malignancy, graft-versus-host disease (GVHD), transplant type, and HSV seropositivity mismatch [1,2,5–14]. HCT recipients are most prone to R/R HSV infections during the pre-engraftment period, GVHD flares

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concomitant with steroid therapy, and during periods of enhanced chemotherapy owing to relapse of the underlying malignancy [10,15]. Typically, these infections manifest as mucocutaneous lesions [16], possibly with atypical presentations [5], and rarely with systemic dissemination or end-organ disease [17,18]. Notably, for HCT recipients, R/R HSV infections are associated with adverse outcomes such as prolonged antiviral therapy and increased rates of recurrent infections, renal failure, hospitalization risk, and mortality [3,5,9,12,15].

The management of R/R HSV infection is particularly challenging owing to limited treatment options (systemic foscarnet [FOS] or cidofovir [CDV] and topical agents), which are associated with severe toxicity, including renal injury, electrolyte disturbances, myelosuppression, and treatment-induced genital lesions [19]. Investigational agents such as pritelivir, an oral antiviral agent in the helicase-primase complex inhibitors (HPI) family, are showing promise in a phase 3 clinical trial conducted in immunocompromised patients (NCT03073967) [20,21].

Herein, we describe a case study of an allogeneic HCT recipient treated with multiple agents, including pritelivir, within the Expanded Access Program during two episodes of refractory HSV infection. Furthermore, we present a literature review summarizing the diagnostic complexities and available treatment options for R/R HSV infections in HCT recipients. Lastly, we propose an algorithm for optimally managing R/R HSV mucocutaneous infections in HCT recipients.

## Case presentation

The patient consented to using his data and images for publication (Fig. 1 and Table 1).

### *First episode*

A 59-year-old man with chronic lymphocytic leukaemia/small lymphocytic lymphoma with Richter's transformation underwent matched unrelated donor allogeneic HCT on February 3, 2021. He received rituximab, gemcitabine, clofarabine, busulfan, and antithymocyte globulin for conditioning while in complete remission. Because of suspected acute upper gastrointestinal GVHD on endoscopy on D+19, he began systemic steroid treatment up to D+37. He received HSV infection prophylaxis with VACV at 500 mg orally twice a day. On D+29, the patient was diagnosed with an oral PCR-confirmed HSV-1 infection, which presented as a large ulcer on the tongue and a few small ulcers on the palate, buccal mucosa, and lips (Fig. 1(a)). On D+30, he began antiherpetic treatment with 1 g of oral VACV taken three times a day. Because of a lack of clinical improvement, on D+54, the treatment was changed to 10 mg/kg intravenous (i.v.) ACV three times a day, and on D+56, to i.v. FOS (90 mg/kg/day). Phenotypic testing results for HSV resistance on D+55 demonstrated no apparent resistance to ACV or FOS (ACV inhibitory concentration 50% [$IC_{50}$] = 1.01 μg/mL [sensitive: <2 μg/mL], FOS $IC_{50}$ = 5.40 μg/mL [sensitive: <150 μg/mL]) [22], and no genotypic testing was performed. FOS was discontinued before the healing of his oral lesions because of renal toxicity. Imiquimod (5% cream) and CDV (1% oral solution) were used as adjuvant treatments. On D+104, compassionate treatment with pritelivir was initiated for a 42-day course (400 mg loading dose and 100 mg daily afterwards), resulting in a complete response with no apparent side effects identified.

### *Second episode*

Two years later, on 9 February 2023, the patient was diagnosed with relapsed large B cell lymphoma and treated with combined pirtobrutinib, venetoclax, and obinutuzumab. A second allogeneic HCT from a mismatched unrelated donor was performed on February 9, 2024, after conditioning with fludarabine, melphalan, total body irradiation, and posttransplant cyclophosphamide while the patient was in complete remission. He received an HSV prophylaxis regimen of 500 mg of oral VACV administered once daily (renally adjusted) until D+17 and then 500 mg administered twice a day. On D+48, the patient was diagnosed with HSV-1 oral infection, which presented as small ulcers on the lips, buccal mucosa, and palate (Fig. 1(b)) and treated with 1000 mg of oral VACV taken twice a day (renally adjusted). Phenotypic resistance testing results demonstrated no apparent resistance to ACV or FOS (ACV $IC_{50}$ = 0.36 μg/mL, FOS $IC_{50}$ = 11.36 μg/mL), and no genotypic testing was performed. Because of a lack of clinical improvement, his treatment was replaced with 10 mg/kg i.v. ACV administered twice a day (renally adjusted). Meanwhile, the patient was started on systemic steroid treatment at 1–2 mg/kg/day for suspected lower gastrointestinal GVHD and later for suspected diffuse alveolar haemorrhage. Because of renal failure and the imperilling use of FOS or CDV, compassionate use of pritelivir was initiated for 6 weeks (400 mg loading dose and 100 mg daily afterwards). Pritelivir treatment resulted in significant improvement after 1 week, complete resolution, with no apparent adverse effects.

## Diagnostic challenges

Diagnosing R/R HSV infections in HCT recipients poses unique challenges, primarily owing to the varied clinical criteria for suspecting a refractory infection, the turnaround time of resistance testing, and the availability of drug-resistance assays.

### *Resistance mechanisms*

The primary mechanism of HSV resistance to nucleoside analogues involves mutations in the viral thymidine kinase gene (*UL23*) in 95% of cases, with a smaller percentage (5%) involving mutations in the viral DNA polymerase gene (*UL30*) [12,23]. Specific DNA polymerase mutations may confer cross-resistance to nucleoside analogues, FOS, and CDV [1,24].

### *Diagnostic approaches*

#### *Defining refractory HSV mucocutaneous infection*

The diagnosis of refractory infection is based on the clinical failure of lesions to improve with anti-HSV therapy, mainly with nucleoside inhibitors. Previously used criteria are varied and include the duration of the failing treatment with antiviral agents (ranging from 5 to 14 days), the extent of the lesions, microbiological failure with documented prolonged viral shedding, and recurrences. These criteria lack standardization across centres and providers [2,10,25–27]. Recently, the HSV Resistance Working Group of the Transplant Associated Viral Infections Forum published consensus definitions for R/R HSV infections for clinical trial use ([28] in press). According to these definitions, refractory mucocutaneous HSV infection is “the failure of HSV-positive mucocutaneous lesion(s) to improve clinically after at least 7 days 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 days (excluding prophylaxis and suppressive antiviral therapy)”. Although this definition was originally designed for clinical trials, we advocate for its relevance in clinical practice as well.

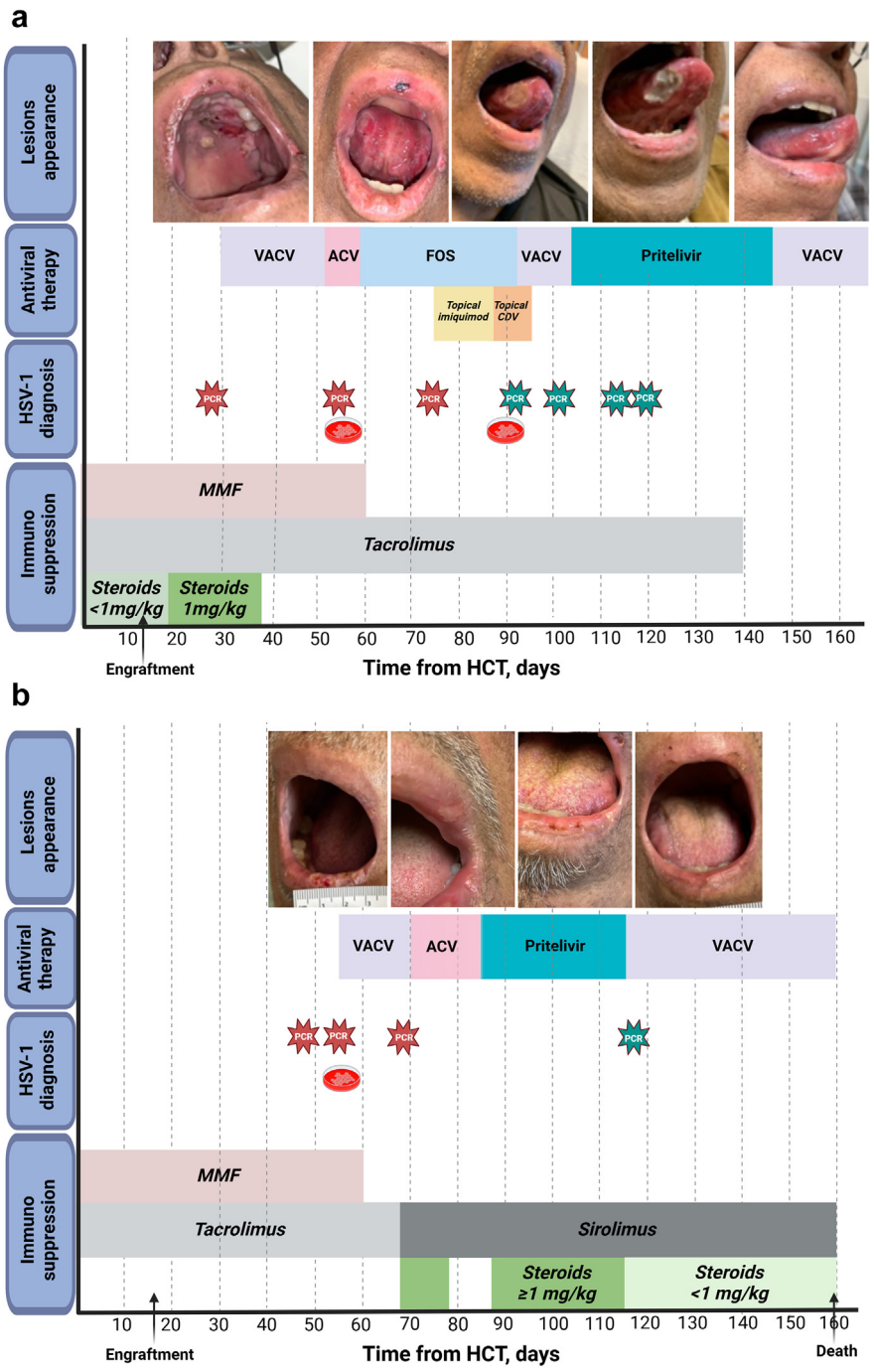


**Fig. 1.** HSV infection diagnosis, immunosuppressive therapy, and antiviral treatment characteristics over time. (a) first episode, (b) second episode. Red star, positive lesion PCR test result; green star, negative lesion PCR test result; Petri dish, viral culture and resistance testing. Created in https://BioRender.com. ACV, acyclovir; CDV, cidofovir; FOS, foscarnet; HCT, haematopoietic cell transplant; HSV, herpes simplex virus; MMF, mycophenolate mofetil; VACV, valacyclovir.

*Antiviral-resistant HSV*

The definition of antiviral-resistant HSV infection according to the HSV Resistance Working Group of the Transplant Associated Viral Infections Forum ((28], in press) is "a refractory HSV infection with viral genetic alteration(s) that decrease(s) susceptibility and/or phenotypic assay demonstrating increased $IC_{50}$ above the assay cutoffs to one or more antiviral drugs" [29]. The primary phenotypic testing method is the plaque reduction assay [29]; however, the turnaround time for this method, typically 21–24 days, the difficulty in defining resistance breakpoints and reproducibility are of concern [5,15,22]. The genotypic assay has been increasingly used and allows for the rapid detection of specific mutations in particular genes, *UL23* and *UL30,* that confer resistance to nucleoside analogues, but no software for interpreting UL23 and UL30 sequences exists to our knowledge. In addition, the most commonly used sequencing method (Sanger) lacks sensitivity to detect low-frequency resistant variants, interpreting unknown mutations is challenging, and, most importantly, commercially

**Table 1**
Summary of the characteristics and outcomes of the presented clinical case

| Episode | Background haematological malignancy | Immunosuppression before HSV infection | GVHD status upon HSV infection | HSV infection | Standard-of-care treatment | Standard-of-care treatment adverse events | Pritelivir administration | Outcome |
|---|---|---|---|---|---|---|---|---|
| The first episode | CLL/SLL with Richter's transformation s/p first allogeneic HCT (MUD) | Conditioning: rituximab, gemcitabine, clofarabine, busulfan, anti-thymocyte globulin<br>GVHD prophylaxis: tacrolimus (until D+139), MMF (until D+60) | Suspected upper GI GVHD treated with systemic steroids 1 mg/kg/day between D+24 and D+37 | Large ulcer on the tongue and a few small ulcers on the palate, buccal mucosa, and lips.<br>Phenotypic resistance test results were ACV and FOS sensitive. | High-dose VACV<br>High-dose i.v. ACV i.v. FOS<br>Topical imiquimod<br>Topical CDV | FOS-induced renal injury and penile lesion. | 42 days. 400 mg loading dose, 100 mg daily | Partial resolution on FOS.<br>Complete resolution on pritelivir. |
| The second episode | Large B cell lymphoma relapse in bone marrow, mediastinum and retroperitoneum, s/p second allogeneic HCT (MMUD) | Conditioning: fludarabine, melphalan, total body irradiation, and posttransplant cyclophosphamide<br>GVHD prophylaxis: tacrolimus (until D+69), sirolimus (until end of follow-up), MMF (until D+60) | On D+68, suspected GI GVHD was treated with systemic steroids at 1 mg/kg/day and on D+89 at 2 mg/kg/day. | Small ulcers on the lips, buccal mucosa, and palate.<br>Phenotypic resistance test results were ACV and FOS sensitive. | High-dose VACV<br>High-dose i.v. ACV<br>Because of renal failure, FOS and CDV were not administered. | None | 42 days. 400 mg loading dose, 100 mg daily | No response to VACV and i.v. ACV.<br>Complete resolution on pritelivir.<br>The patients expired on D+160 secondary to multiple organ failure. |

ACV, acyclovir; CDV, cidofovir; CLL, chronic lymphocytic leukaemia; D+, posttransplant day; FOS, foscarnet; GI, gastrointestinal; GVHD, *graft-versus-host disease*; HCT, haematopoietic *cell* transplant; HSV, herpes simplex virus; i.v., intravenous; MMF, mycophenolate mofetil; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; s/p, status post; SLL, small lymphocytic lymphoma; VACV, valacyclovir.

available genotypic assays are not readily available, requiring specialized labs with sequencing capabilities [24,30].

Considering these challenges, our proposed diagnostic approach (Fig. 2) underscores a comprehensive clinical and microbiological evaluation to ensure timely and accurate identification of R/R HSV mucocutaneous infections in HCT recipients.

## Current treatment options for R/R HSV infection

According to many national and international guidelines [31–35] i.v. FOS is the recommended alternative therapy for HSV resistant to nucleoside analogues. i.v. CDV is the alternative therapy when FOS resistance is suspected. Topical therapy is recommended in some of these guidelines in combination or as monotherapy for accessible lesions (Table 2) [5,15,16,31,32,34–52].

### *Intravenous FOS*

FOS is the only FDA-approved medication for R/R HSV infections to date. FOS is associated with significant adverse events, foremost nephrotoxicity, secondary to interstitial nephritis and acute renal tubular necrosis, electrolyte imbalances, and skin ulcerations, mainly in the genital areas [53,54]. Resistance to FOS emerges through mutations along the DNA polymerase gene, potentially also conferring resistance to nucleoside analogues and CDV [19,24]. In a pivotal randomized controlled trial, FOS demonstrated superiority over vidarabine for unresponsive mucocutaneous herpetic lesions in people living with HIV [25]. However, data on using FOS for R/R HSV infections in HCT recipients are based on observational studies and case series [5,15], owing to the lack of randomized clinical trials in this patient population.

In one of the largest retrospective studies of 18 allogeneic HCT recipients with R/R HSV infections (11 with oral, six with genital/perianal, and one with mixed infections), 11 out of 16 patients who received i.v. FOS experienced renal toxicity [15]. Four out of five patients who received i.v. FOS and i.v. CDV required haemodialysis. Across all 18 patients, only five responded to treatment within 2 weeks [15]. Interestingly, a recently published multicentre study that includes 16 HCT recipients with ACV-resistant HSV infections questioned the efficacy of FOS [54].

### *Intravenous CDV*

Off-label CDV use for R/R HSV infection has been described in observational studies and case series [15,39,40,55], mainly for patients with FOS intolerance or suspected FOS resistance. Nephrotoxicity is the most common side effect of CDV [56], even when administered with probenecid; myelosuppression, including neutropenia, is also of concern [19]. Resistance to CDV may arise from mutations in the DNA polymerase gene (*UL30*) [41,57]. In a cohort of 18 HCT recipients with R/R HSV infections [15], five patients received i.v. CDV, and four of them experienced renal toxicity (concurrently exposed to FOS). The limited available data and the severe toxicity of CDV underscore the need for further investigation into the optimal conditions and patient profiles for successful CDV intervention for HCT recipients with R/R HSV infections.

### *High-dose Intravenous ACV*

Higher doses of ACV administered through continuous i.v. infusion were previously used to overcome ACV resistance in HCT recipients [42–44]. A case series [42] described six allogeneic HCT recipients with severe mucocutaneous ACV-resistant HSV infections, as determined by high $IC_{50}$ on phenotypic assays, four with oral HSV-1, and two with genital HSV-2 infections. Three of

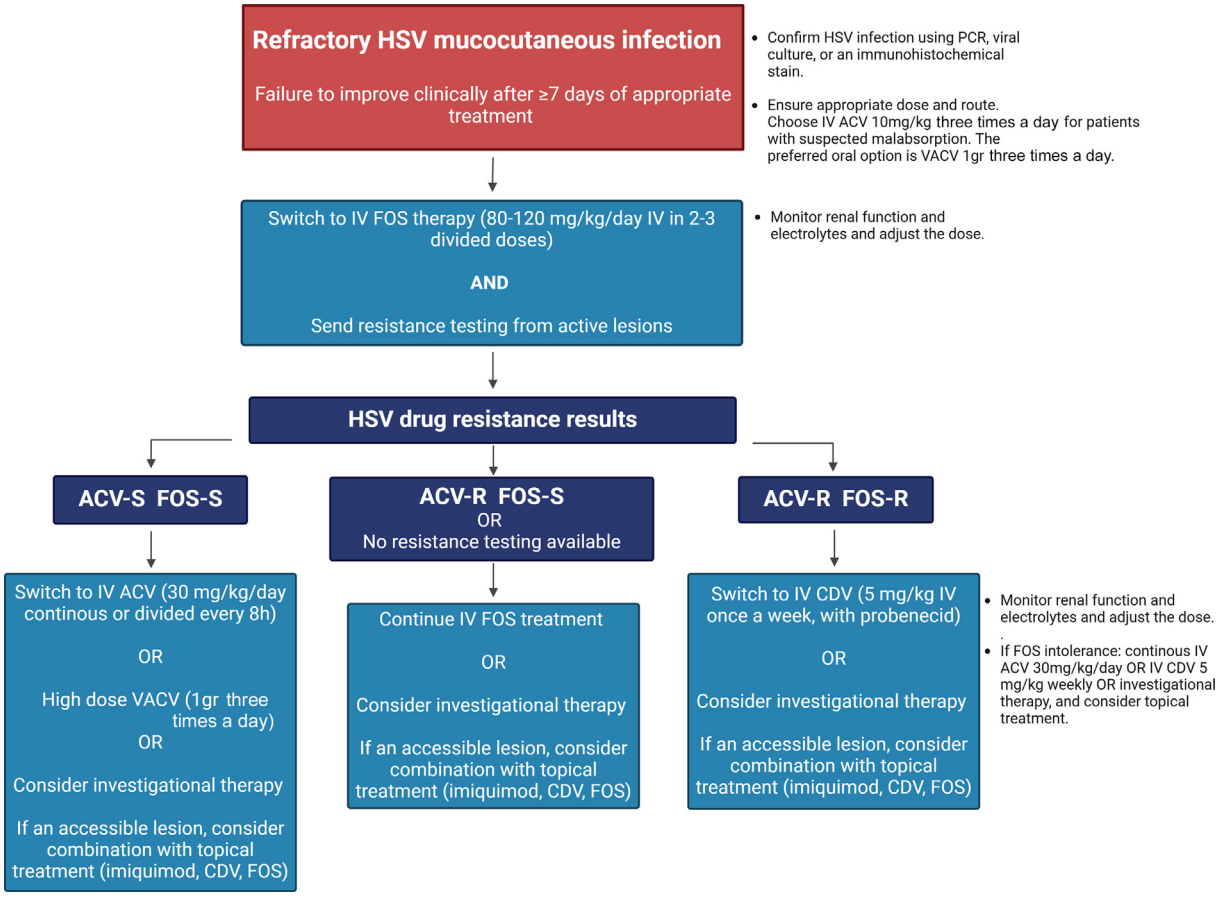


**Fig. 2.** Proposed algorithm for management of refractory and/or resistance HSV infections in HCT recipients. Created in https://BioRender.com. ACV, acyclovir; ACV-R, acyclovir-resistant; ACV-S, acyclovir-sensitive; CDV, cidofovir; FOS, foscarnet; FOS-R, foscarnet-resistant; FOS-S, foscarnet-sensitive; HSV, herpes simplex virus; i.v., intravenous; VACV, valacyclovir.

the strains were also resistant to FOS. High-dose continuous i.v. ACV was administered at 30 mg/kg/day for four patients and up to 45 or 50 mg/kg/day for two patients. Positive clinical responses were reported in five patients within 72 hours of therapy. Importantly, high-dose ACV was well tolerated without notable reported renal dysfunction. The role of continuous i.v. ACV as a proper therapeutic strategy for patients with R/R HSV infections is worth exploring.

*Topical therapy*

*Topical CDV*

The Infectious Diseases Society of America (IDSA) recommends applying 1% CDV cream or gel (not commercially available) once daily or oral rinse up to four times daily for ACV-resistant mucocutaneous HSV infections [58]. In HCT recipients, the use of topical CDV (1–5%) has produced mixed results (Table 3) [5,15,16,41,45–49,51,52] and could lead to acute kidney injury and glycosuria, suggesting proximal tubule injury, as reported in one patient [46].

*Topical FOS*

FOS cream at a concentration of 1.0–2.5% (not commercially available) applied five times a day is another recommended option for ACV-resistant mucocutaneous HSV infections [34,58], based on a few reported cases [16] (Table 3).

*Topical imiquimod*

Imiquimod is used for external anogenital warts, superficial basal cell carcinoma, and actinic keratoses treatment [59]. Its antiproliferative action may contribute to its effectiveness in treating R/R HSV genital ulcers [58,60,61]. Imiquimod use has been described in a case series of HCT recipients, often as part of a combination regimen, for patients with genital and/or perianal lesions in particular [15] (Table 3).

*Ophthalmic trifluridine solution*

Trifluridine is mainly recommended as a treatment for HSV keratitis [50,62–64]. Some guidelines suggest the off-label use of topical 1–5% trifluridine (not commercially available) three times a day as an alternative option for R/R HSV mucocutaneous lesions [34,38,58], based on a few reported cases of patients with HIV and refractory HSV-2 hypertrophic lesions [65].

## Combination therapy

Topical therapy with CDV or imiquimod cream has been used in addition to systemic treatment for R/R HSV infections despite no supporting clinical trials. Ariza-Heredia et al. [15] reported mixed results and thus an undetermined added value of this topical therapy for 12 patients undergoing therapy with i.v. FOS combined with topical treatment (either CDV or imiquimod [$n = 5$] or topical ACV [$n = 2$]) or i.v. CDV combined with topical CDV in ($n = 2$) [15].

Combination treatment with a nucleoside analogue and another systemic agent was reported in an oral refractory HSV-1 infection immediately after HCT. The patient was given i.v. ACV at 10 mg/kg three times a day and i.v. FOS, and his symptoms improved but returned 2 weeks later [51].

**Table 2**
Current treatment options for refractory and/or resistant HSV infections

| Medication | Mechanism of action | Dose | Clinically significant adverse reactions | Monitoring | FDA approval or off-label use | Reference |
|---|---|---|---|---|---|---|
| **Systemic treatment** | | | | | | |
| Foscarnet i.v. | Pyrophosphate analogue inhibits the viral DNA polymerase and viral DNA elongation. | 80–120 mg/kg/day i.v. in 2–3 divided doses. i.v. hydration with each dose. | GI toxicity: nausea, vomiting, diarrhoea. Nephrotoxicity: renal insufficiency Electrolyte imbalances: hypokalaemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia. | Serum creatinine Electrolytes Electrocardiogram Signs of volume overload | FDA-approved | [5,15] |
| Cidofovir i.v. | Deoxycytidine diphosphate analogue is incorporated into the replicating viral DNA by the viral DNA polymerase and inhibits viral DNA elongation. | 5 mg/kg i.v. weekly for 3 weeks and then once every 2 weeks for 3 doses. Co-administered with probenecid and i.v. hydration. | Nephrotoxicity: renal insufficiency. (U.S. boxed warning). Contraindicated if serum creatinine >1.5 mg/dL, CrCl ≤55 mL/min, or urine protein ≥100 mg/dL. Haematological toxicity: neutropenia (U.S. boxed warning) | Serum creatinine Electrolytes Urine protein Complete blood count | Off-label use | [39,40] |
| Continuous high-dose acyclovir i.v. | Deoxyguanosine triphosphate analogue is incorporated into the replicating viral DNA by the viral DNA polymerase and inhibits viral DNA elongation. | 30–50 mg/kg daily continuous infusion | Nephrotoxicity: interstitial nephritis or renal tubular necrosis Neurotoxicity: agitation, confusion, dysarthria, hallucination, and impaired consciousness | Serum creatinine | Off-label use | [42–44] |
| **Topical treatment** | | | | | | |
| Cidofovir 0.3–5.0% cream | Deoxycytidine diphosphate analogue is incorporated into the replicating viral DNA by the viral DNA polymerase and inhibits viral DNA elongation. | 1–4 times daily | Nephrotoxicity: renal insufficiency | Serum creatinine Electrolytes | Off-label use | [5,15,16,45–49] |
| Cidofovir 3% oral rinse | Deoxycytidine diphosphate analogue is incorporated into the replicating viral DNA by the viral DNA polymerase and inhibits viral DNA elongation. | Swish and spit 2–4 times daily | Nephrotoxicity: renal insufficiency | Serum creatinine Electrolytes | Off-label use | [5,41,45] |
| Foscarnet 1.0–2.5% cream or mouthwash | Pyrophosphate analogue inhibits the viral DNA polymerase and viral DNA elongation. | 4–6 times daily | Dermatologic: local skin/mucosal reactions | Local reaction | Off-label use | [16,52] |
| Imiquimod 5% | Toll-like receptor 7 agonist that activates immune cells | Three times a week | Dermatologic: localized erythema, xeroderma, crusted skin, and dermal ulcer Systemic and flu-like reactions. | Local reaction | Off-label use | [15,51] |
| Trifluridine 1–5% ophthalmic solution | Deoxyuridine monophosphate analogue inhibits thymidylate synthase, and deoxyuridine triphosphate analogue is incorporated into the replicating viral DNA by the viral DNA polymerase, resulting in aberrant viral DNA production. | Three times daily | Dermatologic/ ophthalmic: local skin and eye reactions | Local reaction | Off-label use | [50] |

FDA, U.S. Food and Drug Administration; CrCl, creatinine clearance; GI, gastrointestinal; HSV, herpes simplex virus; i.v., intravenous.

**Table 3**
Topical therapy for refractory and/or resistant HSV infections in HCT recipients

| Reference | Age/sex | Background haematological malignancy | Immunosuppression before HSV infection | GVHD status on HSV infection diagnosis | Antiviral prophylaxis | HSV infection | Resistance diagnosis | Topical treatment regimen | Systemic concurrent therapy | Topical treatment adverse effects | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Topical CDV** | | | | | | | | | | | |
| Anton-Vazquez et al. [5], 2020 | Unspecified | s/p allogeneic HCT | Unspecified | Unspecified | Unspecified | HSV-1, oral | Unspecified | CDV 1% mouthwash for 3 months and topical cream for 2 months | None | None | No resolution |
| Epstein et al. [45], 2016 | 67/M | Myelofibrosis s/p MMUD allogeneic HCT | Anti-thymocyte globulin, methotrexate, and cyclosporin | Chronic GI GVHD | ACV | HSV-1, oral | Phenotypic assay: ACV-R FOS-S | CDV rinse (3%/15 $cm^3$ swish and spit four times a day) | i.v. FOS in the first episode | None | Improvement with concurrent i.v. FOS. In the next episode, a resolution on CDV rinses monotherapy. |
| Saunders et al. [46], 2016 | 58/M | MDS s/p second MUD allogeneic HCT | Busulfan, fludarabine, and anti-thymocyte globulin | Acute skin GVHD grade 4 | On oral VGCV (for CMV reactivation) | Unspecified, oral | Unspecified | CDV 5% oral gel twice a day | i.v. ACV 5 mg/kg three times a day | AKI, glucosuria | No resolution |
| Saunders et al. [46], 2016 | 52/M | SLL s/p MUD allogeneic HCT | Fludarabine, cyclophosphamide, rituximab, anti-thymocyte globulin, and steroids | Acute skin GVHD grade 3 | VACV | Perianal | Unspecified | CDV cream 3–5% 2–4 times daily | i.v. FOS, oral VACV | AKI, glucosuria haemodialysis, and kidney biopsy revealed ATN | Improvement |
| Evans et al. [47], 2011 | 66/M | Mantle cell lymphoma s/p allogeneic HCT | Mycophenolate, cyclosporin, and steroids | Yes | ACV | HSV-2, perianal | Unspecified | CDV 2%, ointment twice a day for 3 weeks | None | None | Resolution |
| Sims et al. [41], 2007 | 48/F | AML MDS s/p MSD allogeneic HCT | Busulfan and fludarabine | No | ACV | HSV-1, oral | Phenotypic assay: ACV-R FOS-S | CDV 3% rinse solution twice a day for 5 days | None | None | Resolution |
| Stránská et al. [49], 2004 | 7/M | CML s/p allogeneic HCT | Cyclophosphamide ATG TBI, fludarabine, methylprednisolone, anti-T-cell monoclonal antibody, and thiotepa | No | Unspecified | HSV-1, oral | Phenotypic assay: ACV-R FOS-R. R163H in UL23 gene and S724N in UL30 gene | CDV 1% cream | None | None | Partial healing |
| Heidenreich et al. [16], 2020 | 6 patients | AML s/p allogeneic HCT | Variable | No (excluded) | ACV in 5 of 6 patients | HSV-1, oral | Clinical refractory and phenotyping | CDV 3% oral rinse solution twice a day and 1% CDV gel twice a day | i.v. ACV (2 patients) and i.v. FOS (1 patient) | None | Response in 4/6 and resolution in 3/6 |
| Muluneh et al. [48], (2013) | 34/F | CML s/p MUD allogeneic HCT | TBI, cyclophosphamide, methotrexate, tacrolimus, and steroids | Skin and GI grade 2 GVHD | Unspecified | HSV-1, perianal | Phenotypic assay | CDV 1% gel every 6 hours | i.v. FOS | None | Resolution |
| Ariza-Heredia et al. [15], 2018 | 9 of 18 patients | s/p allogeneic HCT | Variable | 12 of 18 had GVHD | VACV or ACV | Five oral infections, three genital/anal infections, and one mixed infection | Phenotypic assay | CDV 1–3% once daily | i.v. FOS, oral VACV or i.v. CDV | AKI (concurrent i.v. FOS or CDV) | Unspecified |
| **Topical Imiquimod** | | | | | | | | | | | |
| Cannon et al. [51], 2021 | 72/F | MDS with RSAS s/p allogeneic HCT | Cyclosporin, steroids, and ECP | Skin GVHD | Unspecified | HSV-2, genital and buttock | H214HR mutation (ACV-R) | Imiquimod 5% cream | None | It was not specified, but it resulted in treatment cessation. | Imiquimod was not tolerated after a week of use. |
| Ariza-Heredia et al. [15], 2018 | 3 of the 18 patients | s/p allogeneic HCT | Variable | 12 of 18 had GVHD | VACV or ACV | One oral infection, one genital/anal | Phenotypic assay | Imiquimod 5% cream | i.v. FOS, oral VACV, or i.v. CDV | AKI (concurrent i.v. FOS or CDV) | Unspecified |

(*continued on next page*)

**Table 3** (*continued*)

| Reference | Age/sex | Background haematological malignancy | Immunosuppression before HSV infection | GVHD status on HSV infection diagnosis | Antiviral prophylaxis | HSV infection | Resistance diagnosis | Topical treatment regimen | Systemic concurrent therapy | Topical treatment adverse effects | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | infection, and one mixed infection | | | | | |
| **Topical FOS** | | | | | | | | | | | |
| Bosetti et al. [52], 2023 | 35 | ALL *s/p* allogeneic HCT | Steroids, tacrolimus, ciclosporin, MMF, ruxolitinib, etanercept, ECP, tocilizumab, and ibrutinib | Acute Skin GVHD grade 4, severe chronic GVHD | VACV | HSV-1, oral | Deletion of a base in position 1060 (ACV-R) | FOS mouthwash daily for 20 days | i.v. CDV | Not specified | Not specified |
| Heidenreich et al. [16], 2020 | Two patients, aged 45 and 61 | Relapse AML *s/p* allogeneic HCT | First patient: FLAG-Ida, 5-azacytidine/ venetoclax; second patient: sorafenib | No (excluded) | ACV | HSV-1, oral | Clinical refractory, phenotyping | FOS 2% cream | None | None | Response in 2/2, resolution in 1/2 |

ACV, acyclovir; ACV-R, acyclovir-resistant; AKI, acute kidney injury; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; ATN, acute tubular necrosis; CDV, cidofovir; CML, chronic myeloid leukaemia; CMV, cytomegalovirus; ECP, extracorporeal photopheresis; F, female; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; FOS, foscarnet; FOS-R, foscarnet-resistant; FOS-S, foscarnet-sensitive; GI, gastrointestinal; GVHD, graft-versus-host disease; HCT, haematopoietic cell transplant; HSV, herpes simplex virus; i.v., intravenous; M, male; MDS, myelodysplastic syndrome; mg, milligram; MMF, mycophenolate mofetil; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; MSD, matched sibling donor; RSAS, refractory anemia with ring sideroblasts; SLL, small lymphocytic lymphoma; s/p, status post; TBI, total body irradiation; VACV, valacyclovir; VGCV, valganciclovir.

## Treatment options for R/R HSV infections under investigation

### *Helicase-primase complex inhibitors*

The helicase-primase complex consists of three proteins: *UL5* (helicase), *UL52* (primase), and *UL8* (an accessory protein). The helicase subunit unwinds and separates the duplex DNA into the two individual DNA strands. The primase synthesizes short RNA primers as substrates for DNA polymerase, and the subunit UL8 is essential for coordination between UL5 and UL52 [21].

Pritelivir (BAY 57-1293 and AIC316) is a novel oral HPI [66]. It is currently being studied in PRIOH-1, a phase 3 randomized, open-label, multicentre comparative trial (NCT03073967), to evaluate its efficacy and safety compared with FOS for ACV-resistant mucocutaneous HSV infections in immunocompromised patients. Previously reported resistance to pritelivir was secondary to mutations of *UL5* and *UL52* [21,67,68].

Table 4 [18,51,52,69] depicts previously published data for HCT recipients with R/R HSV infections treated with pritelivir in the Expanded Access Program [18,51,52,69].

A short report describing the phase 2 PRIOH-1 study results encompassed 23 patients with R/R HSV infections with diverse underlying immunocompromised conditions, including 12 patients with underlying cancers after transplantation and autoimmune diseases. Nineteen patients had complete resolution of their mucocutaneous infections after 28 days of pritelivir administration without significant side effects, and four patients had partial resolution. One patient with HIV and HSV-2 genital infection had an isolate at the end of treatment that was resistant to pritelivir secondary to a mutation on UL5 [20,68]. In non-immunocompromised patients, pritelivir was more effective in reducing HSV viral shedding in healthy patients with herpes genitalis than placebo [70] and VACV [71], with reported adverse events of headache, nausea, diarrhoea, dizziness, fatigue, elevated lipase, elevated alanine aminotransferase, and migraine. In a non-clinical toxicity study performed in monkeys, identified adverse effects included dry skin, crusty skin lesions, alopecia, and anaemia [71]. On the basis of these findings, patients with myelosuppression are excluded from the ongoing clinical trial for immunocompromised patients with R/R HSV infections (NCT03073967).

Amenamevir (ASP2151), another HPI, has been found effective and safe for the treatment of recurrent oral [72] and genital herpes [73,74] in three clinical trials conducted among immunocompetent patients. It has received approval in Japan for these indications [75]. A recent report detailed two patients with acute myeloid leukaemia post HCT who had R/R ACV HSV-1 infections. Both patients experienced FOS-related renal toxicity and were successfully treated with amenamevir with no apparent adverse events [76]. Another case from Japan involved a patient with T-cell prolymphocytic leukaemia post-cord HCT and oral ACV-resistant HSV infection; the lesions improved within 1 week of amenamevir treatment [77].

### *Brincidofovir*

Brincidofovir is a pro-drug comprising CDV conjugated to a lipid molecule. Two case reports described using oral brincidofovir to treat R/R HSV infections in patients with haematological malignancies with good responses [78,79]. Of note, the oral formulation of brincidofovir is no longer under investigation because of its association with significant gastrointestinal toxicity in HCT recipients, as reported in clinical trials for cytomegalovirus prophylaxis [80,81]. However, an i.v. formulation of brincidofovir is currently under investigation and being studied in phase 2 trials for adenovirus or cytomegalovirus infection (NCT04706923) and BK virus infection after kidney transplantation (NCT05511779).

**Table 4**
Pritelivir-based therapy for refractory and/or resistant HSV infections in HCT recipients

| Reference | Age /sex | Background haematological malignancy | Immunosuppression before HSV infection | GVHD status on HSV infection diagnosis | HSV infection episode | Antiviral prophylaxis | HSV infection | Resistance diagnosis | Treatment | Treatment adverse effects | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Serris et al. [69], 2022 | F | Sickle-cell disease s/p allogeneic HCT | Sirolimus | None | The first episode | VACV | HSV-2, anogenital | L228Stop frameshift mutation in *UL23* (ACV-R) | FOS (14 d)<br>Pritelivir (42 d) | FOS-induced severe electrolyte disturbances | Complete resolution on pritelivir. |
| | | | | | The second episode, after 4 w | None | HSV-2, anogenital | | FOS (7 d)<br>Pritelivir (42 d) | FOS-induced severe electrolyte disturbances | Complete resolution on pritelivir. Another relapse after 2 w was treated with pritelivir. |
| Serris et al. [69], 2022 | F | AML s/p allogeneic HCT | Ciclosporin steroids, vedolizumab, ruxolitinib | Yes | The first episode | VACV | HSV-2, genital | L263Stop frameshift mutation in the *UL23* (ACV-R) | FOS (10 d) | None | Complete resolution |
| | | Relapsed AML s/p allogeneic HCT | Cytarabine, gemtuzumab, ozogamicin | Yes | The second episode | VACV | HSV-2, genital | D229Stop frameshift mutation in *UL23* (ACV-R) | FOS (21 d)<br>Pritelivir (28 d) | None | Complete resolution. Three more ACV-R episodes (after 12 d, 56 d, and 70 d), one treated with pritelivir, and two resolved without treatment. |
| Cannon et al. [51], 2021 | 72/F | MDS with RSAS s/p allogeneic HCT | Cyclosporin, steroids, ECP | Skin | The first episode | Unspecified | HSV-2, genital and buttock | H214HR mutation (ACV-R) | i.v. ACV (7 w)<br>Topical imiquimod<br>FOS<br>CDV<br>Pritelivir (4 w) | FOS-induced severe electrolyte disturbances, seizure, ICU admission | On pritelivir improvement after 2 w with healing after 4 w. The patient died of hospital-acquired pneumonia. |
| Huntjens et al. [18], 2023 | 37/F | Refractory AML s/p allogeneic HCT | Steroids, ruxolitinib, vedolizumab | Acute GI GvHD grade 4 | The first episode | VACV | HSV-1, oral, viraemia | | i.v. ACV (7 d)<br>FOS (14 d) | None | Clinical improvement and resolution of viraemia. |
| | | | | | The second episode, after 5 d | VACV | HSV-1, oral | A605V mutation UL30 (ACV-R and FOS-R) | FOS (4 w)<br>CDV (2 w) | FOS- and CDV-induced renal toxicity | Partial resolution |
| | | | | | The third episode, after 5 w | ACV | HSV-1, oral | | Pritelivir (4 w) | None | Resolution |
| Huntjens et al. [18], 2023 | 61/F | CMML s/p allogeneic HCT | Steroids | None | The first episode | VACV | HSV-1, oral, viraemia and pneumonitis | Phenotypic—oral ACV-R FOS-S, BAL ACV-S FOS-R, mutations in UL30 (ACV-R and FOS-R) | ACV (14 d)<br>FOS (14 d)<br>ACV + FOS (2 −3 d)<br>Pritelivir (4 w) | FOS-induced renal toxicity | On pritelivir, there was a resolution of BAL shedding, but the patient developed multiorgan failure and died. |
| Bosetti et al. [52], 2023 | 35 | ALL s/p allogeneic HCT | Steroids, tacrolimus, ciclosporin, MMF, ruxolitinib, etanercept, ECP, tocilizumab, ibrutinib | Acute skin GVHD grade 4, severe chronic GVHD | The first episode | VACV | HSV-1, oral | Deletion of a base in position 1060 (ACV-R) | FOS (21 d) | None | Resolution. |
| | | | | | The second episode, after 20 d | VACV | HSV-1, oral | | FOS (5 d)<br>CDV (3 w)<br>FOS mouthwash | FOS-induced genital ulcerations | Resolution |

(*continued on next page*)

**Table 4** (*continued*)

| Reference | Age /sex | Background haematological malignancy | Immunosuppression before HSV infection | GVHD status on HSV infection diagnosis | HSV infection episode | Antiviral prophylaxis | HSV infection | Resistance diagnosis | Treatment | Treatment adverse effects | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | The third episode, after 25 d | CDV | HSV-1, oral | | FOS (15 d) | None | Resolution |
| | | | | | The fourth episode, after 87 d | CDV | HSV-1, oral | | CDV (15 d) | None | Resolution |
| | | | | | The fifth episode, after 15 d | CDV | HSV-1, oral | | Pritelivir (34 d) | None | Resolution. Another recurrence, after 84 days without prophylaxis, was treated successfully with CDV. |
| Bosetti et al. [52], 2023 | 42 | MDS s/p haploidentical allogeneic HCT | Steroids | Acute GVHD GI grade 2 | The first episode | VACV | HSV-1, oral | R281STOP TK (ACV-R) | VACV (7 d) FOS (10 d) | None | Resolution |
| | | | | | The second episode, after 11 d | CDV | HSV-1, oral | | CDV (14 d) | None | Resolution |
| | | | | | The third episode, after 9 d | CDV | HSV-1, oral | | Pritelivir (30 d) | None | Resolution |

ACV, acyclovir; ACV-R, acyclovir-resistant; ACV-S, acyclovir-sensitive; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; BAL, bronchoalveolar lavage; CDV, cidofovir; CMML, chronic myelomonocytic leukaemia; ECP, extracorporeal photopheresis; F, female; FOS, foscarnet; FOS-R, foscarnet-resistant; FOS-S, foscarnet-sensitive; GI, gastrointestinal; GVHD, graft-versus-host disease; HCT, haematopoietic cell transplant; HSV, herpes simplex virus; ICU, intensive care unit; i.v., intravenous; M, male; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; RSAS, refractory anemia with ring sideroblasts; s/p, status post; TK, thymidine kinase; VACV, valacyclovir.

## Proposed management algorithm

Navigating the complexities of R/R HSV infections requires an individualized approach. Our proposed algorithm (Fig. 2) serves as a guide and offers considerations for clinicians managing R/R HSV mucocutaneous infections in HCT recipients. The recommendations outlined in this algorithm are not based on findings from randomized controlled clinical trials but rather on retrospective or observational studies, expert opinion, and clinical experience.

### *Summary*

This review summarizes published data and clinical experience for diagnosing and treating R/R HSV infections in HCT recipients. The main advantage of HPI over the standard of care is the mechanism of action that does not confer cross-resistance with other anti-HSV agents. However, data on its efficacy, safety, and longer follow-up periods to characterize recurrences are still limited. This review proposes a diagnostic and treatment algorithm for R/R HSV mucocutaneous infections in HCT recipients to guide clinicians in promptly diagnosing and implementing appropriate therapy. Future trials will determine whether this approach leads to improved patient outcomes.

## Author contributions

T.S. and R.F.C. contributed to conceptualization. T.S. contributed to writing (original draft). E.J.A.-H., M.D., and R.F.C. contributed to writing (review and editing). T.S. contributed visualization.

## Transparency declaration

### *Potential conflict of interest*

R.F.C. reports as consultant/speaker/adviser for ADMA Biologics, Janssen, Merck/MSD, Takeda, Shinogi, AiCuris, Roche/Genentech, Astellas, Tether, Oxford Immunotec, Karius, Moderna, InflaRX, and Ansun Pharmaceuticals. He received research grants paid to his institution from Merck/MSD, Karius, AiCuris, Ansun Pharmaceuticals, Takeda, Genentech, Oxford Immunotec, and Eurofins-Viracor. He also serves as a Data Safety and Monitoring Committee (DSMC) member for AstraZeneca. T.S., E.J.A.-H., and M.D. declare that they have no conflicts of interest.

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## References

[1] Schalkwijk HH, Snoeck R, Andrei G. Acyclovir resistance in herpes simplex viruses: prevalence and therapeutic alternatives. Biochem Pharmacol 2022;206:115322. https://doi.org/10.1016/j.bcp.2022.115322.
[2] Piperi E, Papadopoulou E, Georgaki M, Dovrat S, Bar Illan M, Nikitakis NG, et al. Management of oral herpes simplex virus infections: the problem of resistance. A narrative review. Oral Dis 2024;30:877–94. https://doi.org/10.1111/odi.14635.
[3] Sallée L, Boutolleau D. Management of refractory/resistant herpes simplex virus infections in haematopoietic stem cell transplantation recipients: a literature review. Rev Med Virol 2024 Sep;34:e2574. https://doi.org/10.1002/rmv.2574.
[4] Schmidt S, Bohn-Wippert K, Schlattmann P, Zell R, Sauerbrei A. Sequence analysis of herpes simplex virus 1 thymidine kinase and DNA polymerase genes from over 300 clinical isolates from 1973 to 2014 finds novel mutations

that may be relevant for development of antiviral resistance. Antimicrob Agents Chemother 2015;59:4938–45. https://doi.org/10.1128/AAC.00977-15.
[5] Anton-Vazquez V, Mehra V, Mbisa JL, Bradshaw D, Basu TN, Daly ML, et al. Challenges of aciclovir-resistant HSV infection in allogeneic bone marrow transplant recipients. J Clin Virol 2020;128:104421. https://doi.org/10.1016/j.jcv.2020.104421.
[6] Frobert E, Burrel S, Ducastelle-Lepretre S, Billaud G, Ader F, Casalegno JS, et al. Resistance of herpes simplex viruses to acyclovir: an update from a ten-year survey in France. Antivir Res 2014;111:36–41. https://doi.org/10.1016/j.antiviral.2014.08.013.
[7] Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. Antimicrob Agents Chemother 2011;55:459–72. https://doi.org/10.1128/AAC.00615-10.
[8] Langston AA, Redei I, Caliendo AM, Somani J, Hutcherson D, Lonial S, et al. Development of drug-resistant herpes simplex virus infection after haploidentical hematopoietic progenitor cell transplantation. Blood 2002;99:1085–8. https://doi.org/10.1182/blood.v99.3.1085.
[9] Patel D, Marchaim D, Marcus G, Gayathri R, Lephart PR, Lazarovitch T, et al. Predictors and outcomes of acyclovir-resistant herpes simplex virus infection among hematopoietic cell transplant recipients: case-case-control investigation. Clin Transplant 2014;28:1–5. https://doi.org/10.1111/ctr.12227.
[10] Chakrabarti S, Pillay D, Ratcliffe D, Cane PA, Collingham KE, Milligan DW. Resistance to antiviral drugs in herpes simplex virus infections among allogeneic stem cell transplant recipients: risk factors and prognostic significance. J Infect Dis 2000;181:2055–8. https://doi.org/10.1086/315524.
[11] Nichols WG, Boeckh M, Carter RA, Wald A, Corey L. Transferred herpes simplex virus immunity after stem-cell transplantation: clinical implications. J Infect Dis 2003;187:801–8. https://doi.org/10.1086/367894.
[12] Kakiuchi S, Tsuji M, Nishimura H, Yoshikawa T, Wang L, Takayama-Ito M, et al. Association of the emergence of acyclovir-resistant herpes simplex virus type 1 with prognosis in hematopoietic stem cell transplantation patients. J Infect Dis 2017;215:865–73. https://doi.org/10.1093/infdis/jix042.
[13] Kotton BD, Kotton CN. Resistant herpes simplex virus infections—who, when, and what's new? Curr Opin Infect Dis 2022;35:530–5. https://doi.org/10.1097/QCO.0000000000000889.
[14] Erard V, Wald A, Corey L, Leisenring WM, Boeckh M. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. J Infect Dis 2007;196:266–70. https://doi.org/10.1086/518938.
[15] Ariza-Heredia EJ, Chemaly RF, Shahani LR, Jang Y, Champlin RE, Mulanovich VE. Delay of alternative antiviral therapy and poor outcomes of acyclovir-resistant herpes simplex virus infections in recipients of allogeneic stem cell transplant—a retrospective study. Transpl Int 2018;31:639–48. https://doi.org/10.1111/tri.13142.
[16] Heidenreich D, Kreil S, Mueller N, Jawhar M, Nolte F, Hofmann WK, et al. Topical treatment of acyclovir-resistant herpes simplex virus stomatitis after allogeneic hematopoietic cell transplantation. Oncol Res Treat 2020;43:672–8. https://doi.org/10.1159/000510988.
[17] Frangoul H, Wills M, Crossno C, Engel M, Domm J. Acyclovir-resistant herpes simplex virus pneumonia post-unrelated stem cell transplantation: a word of caution. Pediatr Transplant 2007;11:942–4. https://doi.org/10.1111/j.1399-3046.2007.00822.x.
[18] Huntjens DW, Dijkstra JA, Verwiel LN, Slijkhuis M, Elbers P, Welkers MRA, et al. Optimizing antiviral dosing for HSV and CMV treatment in immunocompromised patients. Pharmaceutics 2023;15:163. https://doi.org/10.3390/pharmaceutics15010163.
[19] Majewska A, Mlynarczyk-Bonikowska B. 40 years after the registration of acyclovir: do we need new anti-herpetic drugs? Int J Mol Sci 2022;23:3431. https://doi.org/10.3390/ijms23073431.
[20] Albrecht KW, Avery RK, Avery RK, Chandrasekar P, Chemaly RF, Issa NC, et al. 1060. Pritelivir in immunocompromised patients with mucocutaneous acyclovir-resistant herpes simplex virus-infections—first case series. Open Forum Infect Dis 2021;8:S622–3. https://doi.org/10.1093/ofid/ofab466.1254.
[21] Birkmann A, Bonsmann S, Kropeit D, Pfaff T, Rangaraju M, Sumner M, et al. Discovery, chemistry, and preclinical development of pritelivir, a novel treatment option for acyclovir-resistant herpes simplex virus infections. J Med Chem 2022;65:13614–28. https://doi.org/10.1021/acs.jmedchem.2c00668.
[22] Labcorp. Labcorp acyclovir and foscarnet resistance HSV testing (phenotype) [Internet]. Available from: https://www.labcorp.com/tests/138370/herpes-simplex-virus-hsv-types-1-2-phenotyping-for-acyclovir-drug-resistance. https://www.labcorp.com/tests/138362/foscarnet-resistance-hsv-phenotype. [Accessed 17 February 2025].
[23] Morfin F, Souillet G, Bilger K, Ooka T, Aymard M, Thouvenot D. Genetic characterization of thymidine kinase from acyclovir-resistant and -susceptible herpes simplex virus type 1 isolated from bone marrow transplant recipients. J Infect Dis 2000;182:290–3. https://doi.org/10.1086/315696.
[24] Sauerbrei A, Bohn-Wippert K, Kaspar M, Krumbholz A, Karrasch M, Zell R. Database on natural polymorphisms and resistance-related non-synonymous mutations in thymidine kinase and DNA polymerase genes of herpes simplex virus types 1 and 2. J Antimicrob Chemother 2016;71:6–16. https://doi.org/10.1093/jac/dkv285.
[25] Safrin S, Crumpacker C, Chatis P, Davis R, Hafner R, Rush J, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. The AIDS Clinical Trials Group. N Engl J Med 1991;325:551–5. https://doi.org/10.1056/NEJM199108223250805.
[26] Danve-Szatanek C, Aymard M, Thouvenot D, Morfin F, Agius G, Bertin I, et al. Surveillance network for herpes simplex virus resistance to antiviral drugs: 3-year follow-up. J Clin Microbiol 2004;42:242–9. https://doi.org/10.1128/JCM.42.1.242-249.2004.
[27] Fajfr M, Pliskova L, Bolehovská R, Uhlířová Z, Vrbacký F. Herpes simplex virus resistant to acyclovir: a single-centre experience from the Czech Republic. J Glob Antimicrob Resist 2019;19:269–73. https://doi.org/10.1016/j.jgar.2019.05.004.
[28] Chemaly RF, Shafat T, Wald A, Kotton CN, Papanicolaou GA, Yong MK, et al. Refractory and resistant herpes simplex virus mucocutaneous infections in immunocompromised patients: literature review and proposed definitions for use in clinical trials. Clin Infect Dis 2025:ciae638. https://doi.org/10.1093/cid/ciae638.
[29] Afshar B, Bibby DF, Piorkowska R, Ohemeng-Kumi N, Snoeck R, Andrei G, et al. A European multi-centre External Quality Assessment (EQA) study on phenotypic and genotypic methods used for herpes simplex virus (HSV) drug resistance testing. J Clin Virol 2017;96:89–93. https://doi.org/10.1016/j.jcv.2017.10.002.
[30] Burrel S, Deback C, Agut H, Boutolleau D. Genotypic characterization of UL23 thymidine kinase and UL30 DNA polymerase of clinical isolates of herpes simplex virus: natural polymorphism and mutations associated with resistance to antivirals. Antimicrob Agents Chemother 2010;54:4833–42. https://doi.org/10.1128/AAC.00669-10.
[31] Mofenson LM, Brady MT, Danner SP, Dominguez KL, Hazra R, Handelsman E, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the national institutes of health, the HIV medicine association of the infectious diseases society of America, the pediatric infectious diseases society, and the American academy of pediatrics. MMWR Recomm Rep 2009;58:1–166.
[32] Styczynski J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, et al. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the second European conference on infections in leukemia. Bone Marrow Transplant 2009;43:757–70. https://doi.org/10.1038/bmt.2008.386.
[33] Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the national institutes of health, and the HIV medicine association of the infectious diseases society of America. MMWR Recomm Rep 2009;58:1–207 [quiz CE1-4].
[34] Lee DH, Zuckerman RA. AST Infectious Diseases Community of Practice. Herpes simplex virus infections in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019;33:e13526. https://doi.org/10.1111/ctr.13526.
[35] Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep 2021;70:1–187. https://doi.org/10.15585/mmwr.rr7004a1.
[36] Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143–238. https://doi.org/10.1016/j.bbmt.2009.06.019.
[37] Patel R, Alderson S, Geretti A, Nilsen A, Foley E, Lautenschlager S, et al. European guideline for the management of genital herpes, 2010. Int J STD AIDS 2011;22:1–10. https://doi.org/10.1258/ijsa.2010.010278.
[38] Patel R, Kennedy OJ, Clarke E, Geretti A, Nilsen A, Lautenschlager S, et al. 2017 European guidelines for the management of genital herpes. Int J STD AIDS 2017;28:1366–79. https://doi.org/10.1177/0956462417727194.
[39] Andrei G, Fiten P, Goubau P, van Landuyt H, Gordts B, Selleslag D, et al. Dual infection with polyomavirus BK and acyclovir-resistant herpes simplex virus successfully treated with cidofovir in a bone marrow transplant recipient. Transpl Infect Dis 2007;9:126–31. https://doi.org/10.1111/j.1399-3062.2006.00186.x.
[40] Blot N, Schneider P, Young P, Janvresse C, Dehesdin D, Tron P, et al. Treatment of an acyclovir and foscarnet-resistant herpes simplex virus infection with cidofovir in a child after an unrelated bone marrow transplant. Bone Marrow Transplant 2000;26:903–5. https://doi.org/10.1038/sj.bmt.1702591.
[41] Sims CR, Thompson K, Chemaly RF, Shpall EJ, Champlin RE, Safdar A. Oral topical cidofovir: novel route of drug delivery in a severely immunosuppressed patient with refractory multidrug-resistant herpes simplex virus infection. Transpl Infect Dis 2007;9:256–9. https://doi.org/10.1111/j.1399-3062.2007.00261.x.
[42] Kim JH, Schaenman JM, Ho DY, Brown JM. Treatment of acyclovir-resistant herpes simplex virus with continuous infusion of high-dose acyclovir in hematopoietic cell transplant patients. Biol Blood Marrow Transplant 2011;17:259–64. https://doi.org/10.1016/j.bbmt.2010.06.020.
[43] Ikawa Y, Fujiki T, Nishimura R, Noguchi K, Koshino E, Fujiki A, et al. Improvement of refractory acyclovir-resistant herpes simplex virus type 1 infection by continuous acyclovir administration. J Infect Chemother 2019;25:65–7. https://doi.org/10.1016/j.jiac.2018.07.004.
[44] Englund JA, Zimmerman ME, Swierkosz EM, Goodman JL, Scholl DR, Balfour Jr HH. Herpes simplex virus resistant to acyclovir. A study in a tertiary care center. Ann Intern Med 1990;112:416–22. https://doi.org/10.7326/0003-4819-76-3-112-6-416.

[45] Epstein JB, Gharapetian S, Rejali AR, Zabner R, Lill M, Tzachanis D. Complex management of resistant oral herpes simplex virus infection following hematopoietic stem cell transplantation: potential role of topical cidofovir. Support Care Cancer 2016;24:3603–6. https://doi.org/10.1007/s00520-016-3264-5.
[46] Saunders IM, Lahoti A, Chemaly RF, Trevino C, Westmoreland M, Hosing C. Topical cidofovir-induced acute kidney injury in two severely immunocompromised patients with refractory multidrug-resistant herpes simplex virus infections. J Oncol Pharm Pract 2016;22:325–31. https://doi.org/10.1177/1078155214560921.
[47] Evans KG, Morrissey KA, Goldstein SC, Vittorio CC, Rook AH, Kim EJ. Chronic acyclovir-resistant HSV-2 ulcer in an immunosuppressed patient treated with topical cidofovir. Arch Dermatol 2011;147:1462–3. https://doi.org/10.1001/archderm.147.12.1462.
[48] Muluneh B, Dean A, Armistead P, Khan T. Successful clearance of cutaneous acyclovir-resistant, foscarnet-refractory herpes virus lesions with topical cidofovir in an allogeneic hematopoietic stem cell transplant patient. J Oncol Pharm Pract 2013;19:181–5. https://doi.org/10.1177/1078155212448408.
[49] Stránská R, van Loon AM, Bredius RG, Polman M, Nienhuis E, Beersma MF, et al. Sequential switching of DNA polymerase and thymidine kinase-mediated HSV-1 drug resistance in an immunocompromised child. Antivir Ther 2004;9:97–104.
[50] Rousseau A, Pharm SB, Gueudry J, Deback C, Haigh O, Schweitzer C, et al. Acyclovir-resistant herpes simplex virus 1 keratitis: a concerning and emerging clinical challenge. Am J Ophthalmol 2022;238:110–9. https://doi.org/10.1016/j.ajo.2022.01.010.
[51] Cannon L, Tholouli E, Ward C, Farooq H, Kingston M. Use of pritelivir in refractory aciclovir-resistant herpes simplex virus type 2. Int J STD AIDS 2021;32:978–80. https://doi.org/10.1177/09564624211006568.
[52] Bosetti D, Bernardi C, Maulini M, Giannotti F, Mamez AC, Masouridi-Levrat S, et al. Salvage treatment of refractory HSV oral lesions with pritelivir in allogeneic hematopoietic cell transplant recipients. Antimicrob Agents Chemother 2023;67:e0173222. https://doi.org/10.1128/aac.01732-22.
[53] He D, Kong D, Zeng Y, Han M, Zhang S, Li Z. Differences in safety profiles of anti-herpesvirus medications: a real-world pharmacovigilance study based on the FAERS database. Expert Opin Drug Saf 2024:1–10. https://doi.org/10.1080/14740338.2024.2412235.
[54] Hammond SP, Rangaraju M, Sumner M, Timmler B, Chandrasekar P, Avery RK. A multicenter assessment of the outcomes and toxicities of foscarnet for treatment of acyclovir-resistant mucocutaneous herpes simplex in immunocompromised patients. Open Forum Infect Dis 2024;11:ofae046. https://doi.org/10.1093/ofid/ofae046.
[55] Bryant P, Sasadeusz J, Carapetis J, Waters K, Curtis N. Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. Pediatr Infect Dis J 2001;20:1083–6. https://doi.org/10.1097/00006454-200111000-00016.
[56] Stern A, Alonso CD, Garcia-Vidal C, Cardozo C, Slavin M, Yong MK, et al. Safety and efficacy of intravenously administered cidofovir in adult haematopoietic cell transplant recipients: a retrospective multicentre cohort study. J Antimicrob Chemother 2021;76:3020–8. https://doi.org/10.1093/jac/dkab259.
[57] Lalezari J, Schacker T, Feinberg J, Gathe J, Lee S, Cheung T, et al. A randomized, double-blind, placebo-controlled trial of cidofovir gel for the treatment of acyclovir-unresponsive mucocutaneous herpes simplex virus infection in patients with AIDS. J Infect Dis 1997;176:892–8. https://doi.org/10.1086/516542.
[58] Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the centers for disease control and prevention, the national institutes of health, and the HIV medicine association of the infectious diseases society of America [Internet]. 2020. [Accessed at 02/17/2025]. Available from: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/herpes-simplex?view=full.
[59] Wagstaff AJ, Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. Drugs 2007;67:2187–210. https://doi.org/10.2165/00003495-200767150-00006.
[60] Oliveira SR, Assoni AS, Vargas TJS, Daxbacher E. Acyclovir-resistant chronic mucocutaneous herpes with good response to the association with imiquimod in an AIDS patient: case report. Bras Dermatol 2022;97:264–6. https://doi.org/10.1016/j.abd.2020.10.019.
[61] Hengge UR, Benninghoff B, Ruzicka T, Goos M. Topical immunomodulators—progress towards treating inflammation, infection, and cancer. Lancet Infect Dis 2001;1:189–98. https://doi.org/10.1016/s1473-3099(01)00095-0.
[62] Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. Drugs 1982;23:329–53. https://doi.org/10.2165/00003495-198223050-00001.
[63] Moshirfar M, Kelkar N, Peterson T, Bradshaw J, Parker L, Ronquillo YC, et al. The impact of antiviral resistance on herpetic keratitis. Eye Contact Lens 2023;49:127–34. https://doi.org/10.1097/ICL.0000000000000952.
[64] Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev 2015;1:CD002898. https://doi.org/10.1002/14651858.CD002898.pub5.
[65] Yudin MH, Kaul R. Progressive hypertrophic genital herpes in an HIV-infected woman despite immune recovery on antiretroviral therapy. Infect Dis Obstet Gynecol 2008;2008:592532. https://doi.org/10.1155/2008/592532.
[66] Sadowski LA, Upadhyay R, Greeley ZW, Margulies BJ. Current drugs to treat infections with herpes simplex viruses-1 and -2. Viruses 2021;13:1228. https://doi.org/10.3390/v13071228.
[67] Field HJ, Biswas S. Antiviral drug resistance and helicase-primase inhibitors of herpes simplex virus. Drug Resist Updat 2011;14:45–51. https://doi.org/10.1016/j.drup.2010.11.002.
[68] Spengler JR, Welch SR, Deval J, Gentry BG, Brancale A, Carter K, et al. Meeting report: 35th international conference on antiviral research in Seattle, Washington, USA—March 21-25, 2022. Antivir Res 2023;211:105521. https://doi.org/10.1016/j.antiviral.2022.105521.
[69] Serris A, Pouvaret A, Loiseau C, Abid H, Burrel S, Fourgeaud J, et al. Pritelivir for recurrent aciclovir-resistant herpes simplex virus 2 infections in immunocompromised patients. J Antimicrob Chemother 2022;77:2303–5. https://doi.org/10.1093/jac/dkac165.
[70] Wald A, Corey L, Timmler B, Magaret A, Warren T, Tyring S, et al. Helicase-primase inhibitor pritelivir for HSV-2 infection. N Engl J Med 2014;370:201–10. https://doi.org/10.1056/NEJMoa1301150.
[71] Wald A, Timmler B, Magaret A, Warren T, Tyring S, Johnston C, et al. Effect of pritelivir compared with valacyclovir on genital HSV-2 shedding in patients with frequent recurrences: a randomized clinical trial. JAMA 2016;316:2495–503. https://doi.org/10.1001/jama.2016.18189.
[72] Kawashima M, Watanabe D, Fujio K, Komazaki H. A phase 3, randomized, double-blind, placebo-controlled study evaluating a single, patient-initiated dose of amenamevir for recurrent herpes labialis. J Dermatol 2023;50:311–8. https://doi.org/10.1111/1346-8138.16608.
[73] Tyring S, Wald A, Zadeikis N, Dhadda S, Takenouchi K, Rorig R. ASP2151 for the treatment of genital herpes: a randomized, double-blind, placebo- and valacyclovir-controlled, dose-finding study. J Infect Dis 2012;205:1100–10. https://doi.org/10.1093/infdis/jis019.
[74] Kawashima M, Imafuku S, Fujio K, Komazaki H. Single-dose, patient-initiated amenamevir therapy for recurrent genital herpes: a phase 3, randomized, double-blind, placebo-controlled study. Open Forum Infect Dis 2022;9:ofac494. https://doi.org/10.1093/ofid/ofac494.
[75] Maruho. Maruho receives manufacturing and marketing approval for a partial change of the indication and dosage/administration for anti-herpes virus agent “Amenalief Tab. 200 mg” for the treatment of recurrent herpes simplex in Japan. 2023 [Internet]. Available from: https://www.maruho.co.jp/english/information/20230224.html. [Accessed 17 February 2025].
[76] Sallée L, Souchet L, Boutolleau D, Nguyen S. Amenamevir for treating acyclovir-resistant or refractory herpes simplex virus infection in allogeneic hematopoietic stem cell transplantation recipients: two case reports. Int J Antimicrob Agents 2024;63:107169. https://doi.org/10.1016/j.ijantimicag.2024.107169.
[77] Kawamura Y, Uchibori N, Arakawa T, Fujii T, Negishi S, Morikawa S, et al. Successful treatment of acyclovir-resistant herpes simplex virus infection with amenamevir in a patient who received umbilical cord blood transplantation for T-cell prolymphocytic leukemia. EJHaem 2024;5:616–9. https://doi.org/10.1002/jha2.899.
[78] El-Haddad D, El Chaer F, Vanichanan J, Shah DP, Ariza-Heredia EJ, Mulanovich VE, et al. Brincidofovir (CMX-001) for refractory and resistant CMV and HSV infections in immunocompromised cancer patients: a single-center experience. Antivir Res 2016;134:58–62. https://doi.org/10.1016/j.antiviral.2016.08.024.
[79] Voigt S, Hofmann J, Edelmann A, Sauerbrei A, Kühl JS. Brincidofovir clearance of acyclovir-resistant herpes simplex virus-1 and adenovirus infection after stem cell transplantation. Transpl Infect Dis 2016;18:791–4. https://doi.org/10.1111/tid.12582.
[80] Marty FM, Winston DJ, Chemaly RF, Mullane KM, Shore TB, Papanicolaou GA, et al. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:369–81. https://doi.org/10.1016/j.bbmt.2018.09.038.
[81] Marty FM, Winston DJ, Rowley SD, Vance E, Papanicolaou GA, Mullane KM, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med 2013;369:1227–36. https://doi.org/10.1056/NEJMoa1303688.