Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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letter to editor

Therapeutic Concern: HSV-2 Resistance Following Long-Term Antiviral Use

Running Title: HSV-2 Antiviral Resistance: A Growing Therapeutic Concern

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ARTICLEINFO

Received: 08/26/2025
Accepted: 08/27/2025

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Dear Editor

Herpes simplex viruses (HSV) are clinically significant pathogens that establish latent infections in humans. HSV-2 is a double-stranded DNA virus that commonly causes anogenital infections. HSV-2, sexually transmitted virus, can establish latency in ganglionic neurons and subsequently reactivating. Consequently, Genital herpes recurrences are common, usually milder than initial infections, but can significantly affect quality of life and mental well-being (1). Primary HSV infection can present with a wide range of symptoms including genital sores, itching, painful urination, urinary retention, vaginal or urethral discharge, headache, fever, and other systemic manifestations (2). Moreover, HSV-2 infection significantly elevates the risk of acquiring HIV, with those affected being around three times more likely to contract HIV than uninfected individuals. Genital HSV infections often goes asymptomatic or undiagnosed, as shown in a National Health and Nutrition Examination Survey, where only 13% of individuals with HSV-2 antibodies had received a genital herpes diagnosis. When genital lesions are present, HSV can be accurately diagnosed using type-specific molecular or virologic assays; in asymptomatic cases, serologic testing is useful for detecting type-specific antibodies. Antiviral therapy is advised for all patients experiencing a primary HSV infection. Management of recurrent genital herpes consists of episodic antiviral therapy, which involves taking medication during outbreaks, and suppressive therapy, which includes daily antiviral treatment to prevent recurrences, reduce viral shedding, and lower the risk of HSV transmission during sexual contact.(2, 3).

Keywords: Herpes Symplex 2, Antiviral Drug, Antiviral Resistance

Citation: Behnezhad F, Astani A. Therapeutic Concern: HSV-2 Resistance Following Long-Term Antiviral Use. Adv Pharmacol Ther J. 2025;5(2): 106-109.

Introduction

Herpes simplex viruses (HSV) are clinically significant pathogens that establish latent infections in humans. HSV-2 is a double-stranded DNA virus that commonly causes anogenital infections. HSV-2, a sexually transmitted virus, can establish latency in ganglionic neurons and subsequently reactivate. Consequently, Genital herpes recurrences are common, usually milder than initial infections, but can significantly affect quality of life and mental well-being (1).

Primary HSV infection can present with a wide range of symptoms, including genital sores, itching, painful urination, urinary retention, vaginal or urethral discharge, headache, fever, and other systemic manifestations (2). Moreover, HSV-2 infection significantly elevates the risk of acquiring HIV, with those affected being around three times more likely to contract HIV than uninfected individuals. Genital HSV infections often go asymptomatic or undiagnosed, as shown in a National Health and Nutrition Examination Survey, where only 13% of individuals with HSV-2 antibodies had received a genital herpes diagnosis. When genital lesions are present, HSV can be accurately diagnosed using type-specific molecular or virologic assays; in asymptomatic cases, serologic testing helps detect type-specific antibodies. Antiviral therapy is advised for all patients experiencing a primary HSV infection. Management of recurrent genital herpes consists of episodic antiviral therapy, which involves taking medication during outbreaks, and suppressive therapy, which includes daily antiviral treatment to prevent recurrences, reduce viral shedding, and lower the risk of HSV transmission during sexual contact (2, 3).

The development of an effective HSV vaccine remains a significant challenge due to the Viral mechanisms of immune evasion, and previous efforts have not been successful. Non-pharmaceutical interventions can eliminate HSV from the host (4). Commonly prescribed antiviral medications for treating HSV-2 include acyclovir (oral prodrug valacyclovir), Penciclovir (prodrug famciclovir), cidofovir, and foscarnet. These antiviral agents ultimately target the HSV DNA polymerase, encoded by the UL30 gene, to inhibit viral DNA replication (5). Acyclovir and its prodrug, valaciclovir, are established as the first-line therapies for the treatment of HSV infections. Penciclovir or its prodrug, famciclovir, represent effective alternatives for its treatment. Acyclovir and famciclovir are nucleoside analogs that undergo initial phosphorylation to the monophosphate form by viral thymidine kinase (TK), encoded by the UL23 gene, and are subsequently phosphorylated by host cellular kinases to become active and incorporated into viral DNA during replication. The triphosphate form of acyclovir incorporates into DNA and halts DNA chain elongation because it lacks the 3′ hydroxyl group necessary for adding additional nucleotides. As a result, this frontline therapy targets only actively replicating HSV and depends on functional thymidine kinase to be effective (4, 6).

Antiviral resistance to HSV-2 has been reported substantially in immunocompromised cases (3.5–10%), including HIV-positive people, cancer chemotherapy, hematopoietic stem cell transplantation, and organ

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transplantation, although drug resistance is rare among immunocompetent individuals (0.1–0.6%). Prolonged use of acyclovir prophylaxis can increase the risk of resistant strains, such as in the treatment of herpes keratitis. Also, Acyclovir-resistant HSV is especially more common in immunocompromised individuals, particularly those with HIV infection. Cell-mediated suppression hinders HSV clearance, increasing viral replication and causing more severe ulcerative lesions. Hence, in approximately 95% of cases, reduced susceptibility to acyclovir results from mutations in the UL23 gene (5, 6).

There are alternative antiviral treatments available for managing HSV strains that are resistant to acyclovir. Only a few antivirals have been approved for their treatment. Foscarnet is indeed recognized as a valuable second-line therapeutic option for HSV strains resistant to acyclovir. Foscarnet effectively inhibits viral DNA polymerase without needing activation by viral enzymes, which makes it effective against strains with thymidine kinase mutations. DNA polymerase mutations may give rise to strains resistant to both foscarnet and acyclovir, which have been documented in immunocompromised as well as immunocompetent patients. These viral strains resistant to both acyclovir and foscarnet can be managed with cidofovir, a drug primarily used to treat cytomegalovirus infections in immunocompromised patients. Due to its significant side effects, particularly nephrotoxicity, cidofovir is reserved for cases where other treatments have failed and therapy is essential (7, 8).

As a result, the emergence of HSV-2 resistance during prolonged antiviral prophylaxis raises significant concerns for clinical management. Given the limited range of currently approved drugs—most targeting viral DNA polymerase—monitoring resistance trends is essential. There is a pressing need to develop alternative therapies with novel mechanisms to ensure continued treatment success. Recognizing resistance early and adjusting therapeutic strategies accordingly will be crucial for improving patient care in both immunocompromised and immunocompetent populations.

Conflict of interest: The authors declare no conflicts of interest related to this publication.

Funding: This research received no external funding.

Acknowledgment: The authors have no acknowledgments to declare.

Authors' contribution: Authors contributed equally to the preparation of this manuscript and approved its final submission.

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