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# Drug Resistance in Herpes Simplex Virus: Challenges and Future Antiviral Strategies

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## ABSTRACT

The herpes simplex viruses (HSV 1 and 2) are among the most common infectious agents in the world causing recurrent mucocutaneous disease, neonatal infections, and serious infections in individuals with compromised immune systems. While nucleoside analogues including acyclovir are the mainstays of treatment, the emergence of drug-resistant HSV strains primarily caused by mutations in viral thymidine kinase and DNA polymerase has created a number of profound clinical challenges. Drug resistance results in prolonged disease durations, failed treatment courses, and increased costs to the healthcare system. This problem is especially significant for high-risk populations. Rapid detection of resistance mutations is possible through current advances in molecular diagnostics (e.g., PCR-based assays and next generation sequencing), thus facilitating personalized pharmacotherapy. In addition, novel therapeutic strategies (helicase-primase inhibitors, peptide entry inhibitors, CRISPR/Cas gene editing, RNA interference, nanotechnology-based drug delivery) represent promising potential solutions that may provide novel alternatives to current therapies.

**Keywords:** Molecular Diagnostics, Novel Antiviral Strategies, Gene Editing Therapies, Herpes Simplex Virus

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**Introduction**

Herpes simplex viruses are extremely common viral infections among humans. There are two major strains of these viruses: herpes simplex virus strain one (HSV-1) and herpes simplex virus strain two (HSV-2). Both strains (HSV-1 and HSV-2), are responsible for lifelong latent infections within the nervous system (sensory ganglia). These viruses can also reactivate on an intermittent basis, resulting in mucocutaneous lesions and invasive or systemic infections. The traditional association for HSV-1 has been orolabial lesions, while the traditional association for HSV-2 has been genital herpes. Both HSV types greatly contribute to the overall global burden of disease. It is estimated that in 2020 there were about 520 million people aged 15-49 infected with HSV-2, and an additional hundreds of millions of people infected with either genital or non-genital HSV-1, accounting for millions of genital ulcer disease-related episodes each year (1).

**Clinical significance and global burden**

Clinically, HSV infections demonstrate a wide range of effects ranging from self-limiting lesions in immunocompetent hosts to severe and widely spread infections in immunocompromised patients, newborns, and infected patients with mucosal or ocular involvement. The long-term, recurring nature of infection, reactivation of herpes simplex virus disease, and associated morbidity (specifically with manifestations such as encephalitis or keratitis) highlight the importance of HSV as a significant public health issue.

**Current antiviral therapies and treatment landscape**

Current pharmacologic therapies used to treat HSV are primarily based on the use of nucleoside analogs (including acyclovir, valacyclovir, and famciclovir) and, in cases of resistance to these agents, foscarnet and cidofovir. Both nucleoside analogs and non-nucleoside therapies exert their antiviral activity either by directly inhibiting viral DNA polymerase or by requiring activation by viral thymidine kinase. As such, although these antiviral agents improve clinical outcomes of acute HSV infections, they do not impact either the latent state of HSV or the transmission of the virus.

**Mechanisms of HSV Drug Resistance**

**Definition and clinical relevance**

Resistance of HSV to drugs is defined by patients who have become not to respond to the nucleoside antiviral agent, particularly among individuals who are immunocompromised and have been receiving prolonged treatment, resulting in continued lesions, slower than expected or no response to therapy, increased illness and significant difficulty for providers in managing these patients (e.g., transplant recipients, HIV/AIDS patients).

**Viral Genetic Mutations Leading to Drug Resistance**

Antiviral resistance for herpes Simplex virus (HSV) typically results from mutations in viral genes that code for proteins that either get targeted by a drug or factor into the activation of a drug. The majority of these mutations come from either the thymidine kinase (TK) gene or the DNA polymerase (POL) gene, which is referred to by two different loci on the viral genome, UL23 and UL30, respectively (2).

**Cellular and Host Factors Contributing to Resistance**

Factors related to host and cellular biology affect the emergence of resistant herpes simplex virus (HSV) variants. Host factors such as the presence of immunosuppressive therapy/emergent/transplantation agents; prolonged exposure to antiviral agents; and high rates of viral replication are conducive to the selection of resistant strains. Also, continuing pressure (e.g., combination drugs) placed on the host from the immune system and viral heterogeneity are critical components for driving the evolution of minor resistant subpopulations that become dominant due to drug selection.

**Phenotypic vs. Genotypic Resistance Profiling**

The determination of HSV resistance is accomplished via phenotyping (measuring viral replication) and genotyping (detecting resistance mutations), both of which are more accurate when used in combination, although both methods will provide different timeframes for measurement.

**Laboratory Identification and Diagnostic Challenges**

Detection of HSV resistance in a laboratory is an issue because phenotypic approaches can be slow and labor intensive, while genotypic tests have not been completely validated for all possible mutations, cannot differentiate between polymorphisms, and may miss low-frequency resistant viruses. This combination of issues makes the interpretation of tests and the management of patients challenging.

**Clinical Impact of HSV Drug Resistance**

**Epidemiology and Prevalence Trends**

In the general population, there are few cases of drug-resistant HSV (<1%) among healthy people with intact immune systems; however, among patients who have compromised immune systems, drug resistance is much more common (≈3.5–10% or higher), resulting in severe lesions and increasing the difficulty of treating these patients. Because there are fewer studies in this area, the true frequency of drug-resistant HSV is unknown, but growing evidence indicates that it is an important clinical problem for HIV-positive persons and many other high-risk populations.

**Patient Populations at Higher Risk**

**Immunocompromised Individuals**

Immunocompromised patients, including those with depressed or absent cellular immune function as in patients with HIV/AIDS, hematological malignancies, solid organ transplants, and patients receiving hematopoietic stem cell transplantation, are particularly likely to experience ongoing infection with HSV and have increased risk of developing drug resistance with continued use of antiviral agents. Drug-resistant strain emergence among these patient populations is frequently associated with resistant lesions and frequent need for alternative treatments to effectively manage their HSV infections.

**Neonates**

Neonatal infection with HSV, usually obtained through the maternal infection period, is associated with a high level of morbidity and mortality.

Drug-resistant HSV is noted less often in the neonatal period than in adults, but the severity of the disease, prolonged replication times of the virus, and increased chance of therapy-resistant infection can be attributed to patient presentation due to the severity of the disease process.

**Current Antiviral Therapies and Their Limitations**

**Nucleoside Analogues**

The use of nucleoside analogues (e.g., acyclovir, valacyclovir, and famciclovir) for treatment of HSV infection is the mainstay of therapy. Each of these drugs is converted to the active form via viral thymidine kinase and inhibits viral DNA synthesis. Therefore, these medications shorten the length of time that lesions exist, decrease the amount of virus shed from lesions, and reduce how often patients experience recurrent lesions. Valacyclovir and famciclovir have higher oral bioavailability than acyclovir and therefore are more suitable options for outpatient management of HSV.

**Non-Nucleoside Antivirals**

Foscarnet and cidofovir can be utilized for the treatment of HSV infections that are resistant to nucleoside analogues. The advantages of both foscarnet and cidofovir are that they do not require activation by viral thymidine kinase, but they instead directly inhibit viral DNA polymerase. While both of these agents can be used to treat resistant HSV strains, their potential for nephrotoxicity and their requirement for parenteral administration limit their widespread clinical use.

**Limitations: Toxicity, Resistance, and Therapeutic Failure**

Antiviral therapy administered over an extended period (e.g., repeated treatment of patients with recurrent lesions) can lead to the selection of resistant viral strains, especially in immunocompromised patients. In addition, nucleoside analogues may not be effective in treating infections caused by TK-negative or viral strains that contain a mutation in DNP. Although non-nucleosides are effective, the adverse effects of non-nucleoside agents are significant; thus, their clinical usefulness is limited because of the risk that non-nucleoside agents can produce others suffered from renal toxicity, electrolyte imbalance, and hematologic complications.

**Clinical Challenges**

Delay in detecting resistance; however, alternative therapies are limited. Patient adherence to antiviral therapy is often poor, and antiviral agents that specifically attack latent infections remain unavailable. These factors lead to increases in either recurrent disease, prolonged viral shedding, or increased healthcare burden, all of which support the urgent need for the development of new antiviral medications and personalized approaches to treatment (3).

**Table 1: Current and Emerging Antiviral Strategies Against**

| Antiviral Class / Strategy | Examples | Target / Mechanism of Action | Resistance Mechanism | Key Limitations |
|---|---|---|---|---|
| **Nucleoside Analogues** | Acyclovir, Valacyclovir, Famciclovir | Inhibit viral DNA synthesis after activation by viral thymidine kinase | Mutations in the thymidine kinase (UL23) gene or DNA polymerase (UL30) | Resistance in immunocompromised patients does not eliminate the latent virus |
| **Non-Nucleoside Antivirals** | Foscarnet, Cidofovir | Direct inhibition of viral DNA polymerase without TK activation | DNA polymerase mutations | Nephrotoxicity, intravenous administration |
| **Helicase–Primase Inhibitors** | Pritelivir, Amenamevir | Inhibit viral helicase–primase complex required for DNA replication | Mutations in helicase-primase complex proteins | Limited clinical availability; still under evaluation |
| **Peptide Therapeutics / Entry Inhibitors** | Experimental peptide inhibitors | Block viral attachment or fusion with host cell membranes | Potential viral envelope glycoprotein mutations | Early research stage |
| **cGene Editing Approaches** | CRISPR/Cas systems | Target and disrupt latent HSV genome within host cells | Possible viral escape mutations | Delivery challenges and safety concerns |
| **RNA Interference** | siRNA, antisense oligonucleotides | Silence viral gene expression at mRNA level | Viral sequence variation affecting targeting | Stability and delivery limitations |
| **Nanotechnology-Based Drug Delivery** | Nanoparticle antiviral formulations | Improve drug delivery, stability, and targeted tissue penetration | Not resistance-based; enhances existing drugs | Limited clinical translation |

**Existing Diagnostic Techniques**

There are two types of diagnostic technologies that provide high-speed, highly sensitive detection of HSV drug resistance in addition to slower, phenotypic assays.

**PCR-Based Assays**

Detection of resistance mutations associated with viral thymidine kinase (TK) or DNA polymerase is performed using PCR-based assays. PCR-based assays have the advantage of being able to provide highly sensitive detection from clinical specimens without having to growth/propagate the virus in culture (4).

**Sequencing (Sanger & NGS)**

Sanger sequencing can be used to provide information regarding whether a patient's virus has a specific targeted mutation, whereas NGS sequencing can be used to comprehensively identify both genetically diverse major and minor populations of viruses that include low-frequency resistant mutations that may impact patient treatment.

**Resistance Testing Procedures**

A general procedure for assessing mutations will involve sample acquisition, nucleic acid extraction, PCR amplification of the target gene, and sequencing of the target gene for mutation identification. Mutation results can be interpreted by comparison against a database of mutations that have been evaluated for clinical relevance versus an acceptable variant.

**Advantages, Limitations and Future Diagnostic Tools**

Molecular diagnostics provide fast, accurate identification/characterization of genomic alterations. Their utility is diminished due to mutations not being adequately characterized due to database limitations, misinterpretation of novel/rare mutations, and the inability to characterize functional resistance. New technologies (CRISPR-based diagnostics, multiplex assays, and point of care sequencing) provide assurances for faster, clearer identification/characterization of antiviral resistance.

**Emerging Antiviral Strategies**

Current advancements in antiviral therapies for herpes simplex virus include new generations of enzyme inhibitors, helicase–primase inhibitors, peptide entry blockers, as well as gene-based therapies (CRISPR/Cas, RNA interference and antisense oligonucleotides). The use of nanotechnology to develop drug delivery systems has increased the targeting, bioavailability and effectiveness of these drugs against strains of herpes simplex that have developed resistance to the existing antiviral therapies.

**Future Antiviral Development Framework**

**Rational Design and Computer-Assisted Drug Development**

The combination of rational drug design, structural biology, and computer-aided modeling will enable researchers to efficiently design antivirals with optimized binding to viral proteins responsible for the herpes virus infection with a minimal risk of affecting non-target proteins, thereby having an increased potential for antiviral activity. In addition, the use of computer-aided technologies (i.e. in silico) will speed up the selection of antiviral candidates prior to a requirement for in vitro and in vivo validation.

**High Throughput Screening Platforms for Antiviral Activity**

Utilizing high-throughput screening (HTS) to rapidly evaluate thousands of potential active compounds for antiviral activity (and with the use of automated phenotypic assays) can lead to the identification of numerous novel candidates in the development of potential antivirals, including those which are effective against drug resistant herpes simplex viruses. High-throughput screening methods streamline the early-stage drug discovery processes.

**Personalized Medicine and Resistance Profiling**

Combining genomic information and phenotypic resistance data can provide important information for providers to assist in the selection of the most appropriate therapies for their individual patients. Providers are encouraged to develop an individualized treatment approach for patients

who are immunocompromised and who may have the potential for failing to respond to treatment or who may develop further resistance to antiviral therapy.

**Regulatory Considerations and Clinical Trial Design**

Use of robust pre-clinical data, standardized resistance endpoints, and adaptation of clinical trial design are required to meet regulatory approval requirements. Early engagement with regulatory agencies can facilitate an efficient process in the assessment of the safety, effectiveness, and novel mechanism of action of potential new antiviral agents.

**Conclusion**

Drug-resistant HSV infection is an increasing problem in immunocompromised individuals, as well as in neonates and those who have received long-term antiviral therapy. Although current therapies may still be effective, they are severely limited due to drug-resistance, toxicity, and inability to eliminate latent viruses. In addition, new antiviral strategies have been developed such as next-generation inhibitors, gene editing approaches, immunotherapies, and nanotechnology-based delivery systems that may help overcome these issues. In order to manage the growing threat posed by drug-resistant HSV, a multidisciplinary approach will be required that utilizes molecular diagnostics, personalized therapies, high-throughput drug discovery, and global surveillance of drug resistance. It is also critical that researchers work together and provide equitable access to diagnostic testing and therapeutic options to alleviate the burden of drug-resistant HSV infections and improve long-term clinical outcomes.

**References**

[1] Harfouche M, AlMukdad S, Alareeki A, Osman AMM, Gottlieb S, Rowley J, et al. Estimated global and regional incidence and prevalence of herpes simplex virus infections and genital ulcer disease in 2020: mathematical modelling analyses. 2025;101(4):214-23.

[2] Sauerbrei A, Deinhardt S, Zell R, Wutzler P. Phenotypic and genotypic characterization of acyclovir-resistant clinical isolates of herpes simplex virus. Antiviral Research. 2010;86(3):246-52.

[3] Bhatia N, Kumari A, Thakur N, Sharma G, Singh RR, Sharma R. Phytochemically stabilized chitosan encapsulated Cu and Ag nanocomposites to remove cefuroxime axetil and pathogens from the environment. International journal of biological macromolecules. 2022; 212:451-64.

[4] Sauerbrei A, Bohn-Wippert K. Phenotypic and Genotypic Testing of HSV-1 and HSV-2 Resistance to Antivirals. Methods in molecular biology (Clifton, NJ). 2020; 2060:241-61.