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Current and future therapies for herpes simplex virus infections: mechanism of action and drug resistance

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Forty years after the discovery of acyclovir (ACV), it remains the mainstay of therapy for herpes simplex virus (HSV) infections. Since then, other antiviral agents have also been added to the armamentarium for these infections but ACV remains the therapy of choice. As the efficacy of ACV is reassessed, however, it is apparent that a therapy with increased efficacy, reduced potential for resistance, and improved pharmacokinetics would improve clinical outcome, particularly in high risk patients. Inhibitors of viral targets other than the DNA polymerase, such as the helicase primase complex, are of particular interest and will be valuable as new therapeutic approaches are conceived. This review focuses on currently approved HSV therapies as well as new systemic therapies in development.

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Introduction

Advances in therapies for human immunodeficiency virus (HIV) infection led to an enhanced appreciation of combination therapies with inhibitors of distinct viral targets. The recent characterization of genetic diversity among clinical isolates of the human herpesviruses suggested that a similar approach would likely be of value in the treatment of these infections, particularly in high-risk populations. New therapies for the herpesviruses are required not only to treat resistant infections, but also in combination therapies to improve efficacy and prevent resistance from arising in high-risk patients, as reviewed recently by Vere Hodge and Field [1•]. This review will discuss current and future therapies that may be considered in this search for novel therapeutic regimens (Figure 1).

One common theme of human herpesvirus infections, including those of herpes simplex virus (HSV), is the progression to severe disease in immunocompromised hosts. Resistance to the therapies of choice also arises readily in such hosts as the viruses continue to replicate notwithstanding sustained treatment with first line drugs [2]. Even in immunocompetent hosts, current therapies may fail to achieve adequate viral suppression, as evidenced by the finding that subclinical genital HSV shedding frequently occurs during the course of antiviral therapy [3]. Limitations of secondary therapies including lack of oral bioavailability, modest potency, and significant toxicities highlight the need for more effective therapies early in the course of treatment [4].

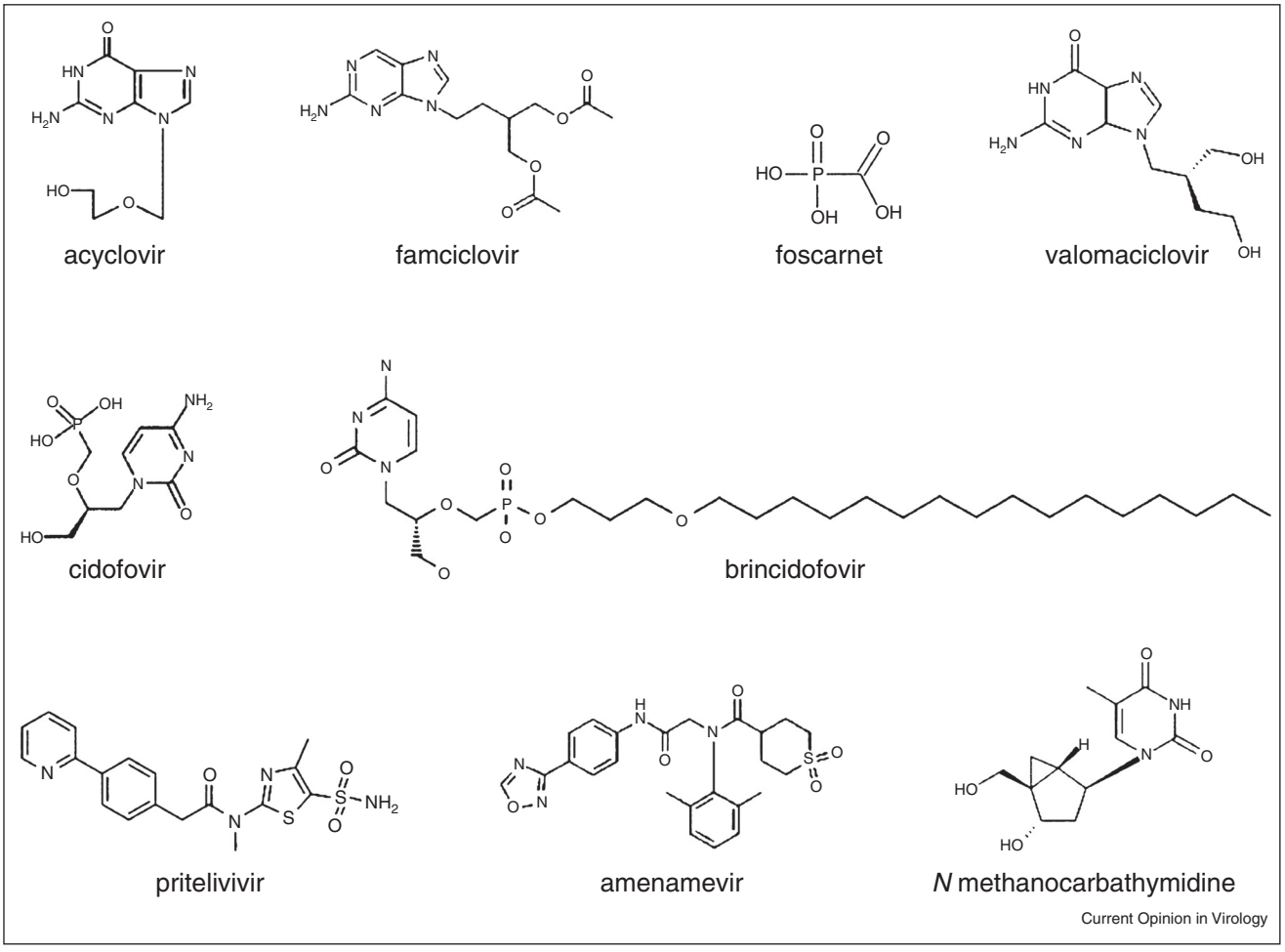
The search for new therapies for HSV has not only taken advantage of conventional targets, such as the DNA polymerase, but has resulted in the discovery of new molecular targets and improved our understanding of the biology of this virus (Figure 2). The development of new therapies, particularly those with novel molecular targets, will be important not only to treat resistant infections, but also to prevent their occurrence with combination chemotherapy [2,5,6]. In this review, a brief survey of the mechanism of action of existing drugs and that of novel therapies under development will be described together with a discussion of resistance pathways. These data presented together will help plot a path forward toward combined therapies with increased potency and decreased potential for treatment failure.

Current HSV therapies

The mainstay agents currently licensed to treat HSV infections all share a common mechanism of action in that, although they may have differing metabolic pathways to their target, they each ultimately act to prevent the synthesis of viral DNA through inhibition of the DNA polymerase. The development of acyclovir (ACV) and the related compounds penciclovir, valacyclovir, and famciclovir proved a great improvement over their antiviral predecessors, idoxuridine and vidarabine. With the advent of these acyclic nucleoside analogs, management of HSV infections became more efficacious as well as less toxic. Beyond these, current second-line antiviral therapies for treatment-resistant HSV infections consist of the pyrophosphate analog, foscarnet, and the acyclic nucleoside phosphonate analog, cidofovir.

ACV is a deoxyguanosine analog that must undergo phosphorylation to the triphosphate within the HSV-infected

Figure 1



Inhibitors of herpes simplex virus replication. Most drugs used to treat herpes simplex virus infections target the viral DNA polymerase. Two new molecules in clinical development target the helicase–primase complex (pritelivir and amenamevir).

cell prior to its competitive inhibition of the viral DNA polymerase [7]. Within an infected cell, the first phosphorylation of ACV occurs through the virally encoded thymidine kinase (TK), while the second and third phosphorylation steps are carried out by cellular kinases. ACV-triphosphate competes with naturally occurring nucleoside triphosphates and is incorporated into the elongating DNA chain as it replicates, resulting in chain termination. Valacyclovir is the L-valyl ester oral prodrug of ACV that offers improved bioavailability. Penciclovir is similar to ACV in that it is an acyclic guanosine analog that acts through a TK dependent phosphorylation pathway. The active form of the agent, penciclovir-triphosphate, also competitively inhibits the replicative function of the viral DNA polymerase, but unlike ACV, penciclovir is not considered an obligate DNA chain terminator, owing to the presence of a 3′ hydroxyl group on its acyclic side chain, which can allow for a limited amount of continued chain elongation [2]. Penciclovir has very poor oral bioavailability and so famciclovir was designed as its diacetylester prodrug.

In patients with HSV infections that are failing first-line therapy, alternative therapy with foscarnet or cidofovir can be considered. The clinical utility of foscarnet and cidofovir is somewhat limited by their toxicity profiles, however. Foscarnet is a pyrophosphate analog that reversibly inhibits DNA polymerase in many herpesviruses by binding to and blocking the viral polymerase's pyrophosphate binding site, which interferes with pyrophosphate cleavage from incoming deoxynucleoside triphosphates and impedes viral replication [8]. Foscarnet acts directly on viral DNA polymerase without requiring activation *via* either viral or host phosphorylation. Cidofovir is a deoxycytidine acyclic nucleotide phosphonate analog with antiviral activity against a broad range of DNA viruses, including herpesviruses [9]. Because it is a monophosphate analog, cidofovir does not require initial