Update on herpesvirus infections

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This review will attempt to summarise recent developments in herpes virology, with an emphasis on understanding pathogenesis and implications for diagnosis and treatment.

Pathogenesis

The eight human herpesviruses (HHV) have features in common, yet are also distinct (see Tables 1 and 2). Each herpesvirus causes more than one disease by interacting in multiple ways with the host. They have also evolved multiple ways of impairing cell-mediated immune responses by down-regulating display of HLA molecules on the surface of infected cells.

The herpesviruses are divided into three subfamilies: alpha, beta and gamma. This classification was originally based upon biological criteria, in that alpha-herpesviruses establish latency in neural cells, beta-herpesviruses grow slowly in fibroblasts, while gamma-herpesviruses are lymphotropic and oncogenic. The classification has more recently been supported by molecular biological techniques demonstrating the genetic relatedness of viruses within each subfamily.

Disease is both more common and more severe in patients with T cell immunodeficiency, emphasising the importance of this arm of the immune response for controlling herpes replication. As well as being major pathogens in transplant and AIDS patients, there is evidence that herpesviruses can interact with HIV using a variety of mechanisms to accelerate the rate at which AIDS progresses (reviewed in Ref 1). In addition, HHV-8 causes cytomegalovirus (CMV) and Epstein-Barr virus (EBV) causes oncogene activation by genome translocations, and EBV and cytomegalovirus (CMV) trigger immunopathologically-mediated effects (infectious mononucleosis and pneumonitis, respectively). The use of prophylactic antiviral drugs may potentially prevent some of these diseases, but there is a risk of antiviral resistance in the profoundly immunocompromised.

### Treatment

Herpesvirus replication employs several essential virus-encoded enzymes. Specific inhibitors are potential antiviral agents.

**Aciclovir**

The first, aciclovir, remains the 'gold standard' because it is effective without exhibiting significant side effects. It is specific because phosphorylation to an active form occurs only in cells infected with herpesviruses (see Fig 1). In the alpha- and gamma-herpesviruses, the viral enzyme thymidine kinase (TK) phosphorylates aciclovir. The beta-herpesviruses do not have a TK, but a gene, UL97 (the 97th gene in the unique long region of CMV), performs the same function. Aciclovir monophosphate is further phosphorylated to the triphosphate by cellular enzymes. It then inhibits the DNA polymerase of all herpesviruses both directly and by becoming incorporated into the growing DNA chain and acting as an obligate chain terminator.

**Ganciclovir and penciclovir**

Ganciclovir and penciclovir are activated in a similar way, but their triphosphates have important differences in safety profiles because they are not obligate chain terminators.

### Table 1. Characteristics of herpesviruses.

| Characteristic | Description |
|---------------|-------------|
| Characteristic appearance in the electron microscope | |
| Large, double-stranded DNA genome: | |
| - many genes conserved in all viruses | |
| - many genes specific to individual members | |
| Initial infection often asymptomatic | |
| Establish latency, persist for life of individual | |
| Reactivate from latency | |
| Most reactivations asymptomatic | |
| Reinfecions also occur | |
| Most herpesviruses cause more than one disease | |
| Diseases particularly severe in the immunocompromised | |

### Table 2. The human herpesviruses (HHV).

| Virus | Systematic nomenclature |
|-------|-------------------------|
| **Alpha-herpesviruses:** | |
| Herpes simplex virus type 1 (HSV-1) | HHV-1 |
| Herpes simplex virus type 2 (HSV-2) | HHV-2 |
| Varicella zoster virus (VZV) | HHV-3 |
| **Beta-herpesviruses:** | |
| Cytomegalovirus (CMV) | HHV-5 |
| Human herpesvirus type 6 | HHV-6 |
| Human herpesvirus type 7 | HHV-7 |
| **Gamma-herpesviruses:** | |
| Epstein-Barr virus (EBV) | HHV-4 |
| Human herpesvirus type 8 | HHV-8 |
Ganciclovir can be incorporated into host DNA; it is carcinogenic and teratogenic in animals, causing clinically significant bone marrow suppression. It is licensed only for life- or sight-threatening CMV infections. Penciclovir shows animal carcinogenicity only after lifelong exposure at high dosage and, in contrast to ganciclovir, is well tolerated clinically.

**Prodrugs**

The poor bioavailability of these antiviral compounds has been improved by the development of prodrugs which are absorbed and then metabolised in the intestinal wall and/or liver to produce high plasma levels of the parent compound. Valaciclovir is the prodrug of aciclovir, while famciclovir is the prodrug of penciclovir. These prodrugs will probably replace aciclovir for some indications and also introduce new indications (see Table 3).

**Resistance**

Treatment can select for resistant strains. Most have lost the ability to make TK and fortunately are metabolically debilitated, with a decreased ability to establish latency and inability to reactivate from the latent state. As a result, herpes simplex virus (HSV) resistance to aciclovir is not a clinical problem in patients with normal immunity. However, in patients who are profoundly and chronically immunocompromised following bone marrow transplantation or AIDS, these debilitated viruses can nevertheless cause disease and require treatment with drugs such as foscarin intravenously. The same rules apply to CMV in that UL97 mutations appear first, followed by mutations in DNA polymerase if the selective pressure of ganciclovir is continued.

**Alpha-herpesviruses**

*Herpes simplex virus types 1 and 2*

Asymptomatic reactivations of HSV are clearly a source of infection, which suggests that prophylaxis with antiviral agents should be evaluated for its ability to decrease transmission in the community (which is continuing despite advice about ‘safer sex’).

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**Figure 1. Mechanism of activation of aciclovir (ACV) in a cell infected with alpha-herpesviruses.** To increase the availability of precursors required for DNA synthesis, herpes simplex virus (HSV) DNA contains a gene for an enzyme (thymidine kinase (TK)) that phosphorylates nucleosides (Nuc) (this enzyme is distinct from the TK of the uninfected cell). Aciclovir is an alternative substrate for HSV TK which phosphorylates it to aciclovir monophosphate (ACV-P). Cellular enzymes then convert it to aciclovir triphosphate (ACV-3P), a potent inhibitor of HSV-encoded DNA polymerase (ACV-3P has little effect on the cellular DNA polymerase in the uninfected cell). The pathway for ganciclovir or penciclovir is identical. In cells infected with beta-herpesviruses, ganciclovir or aciclovir is activated by another enzyme, UL97.
Varicella zoster virus

Chickenpox. Controlled trials demonstrated that oral aciclovir significantly hastens recovery from chickenpox, but it is questionable whether the modest clinical benefit is justified on a cost-benefit basis. The subgroups of patients with a high risk of complications warrant early therapy as a matter of policy because complications, once established, do not respond well to therapy. Thus, aciclovir, 800 mg five times a day, should be offered to all immunocompromised patients (given intravenously if a patient is profoundly immunocompromised), to all adults, including all pregnant women. (Aciclovir is not licensed for use during pregnancy, and all exposed cases should be reported to the International Registry.)

Shingles. Although shingles is a disease of the peripheral nervous system, many doctors consider only its dermatological features, describing phases of prodrome (pain before the onset of rash), herpetic (vesicles on the skin), and post-herpetic neuralgia (pain after the vesicles have healed). A better classification is zoster-associated pain (ZAP), which measures pain as a continuum and emphasises the need to deliver antiviral chemotherapy to the dorsal root ganglia. The pathogenesis of chronic pain involves the central as well as the peripheral nervous system. Varicella zoster virus (VZV) reactivation in the dorsal root ganglia results in chronic stimulation of the central nervous system which resets homeostatic mechanisms controlling pain, so that the patient perceives chronic pain, severe pain from minor stimuli, and allodynia (abnormal sensations).

Early therapy can reduce the incidence and severity of future chronic pain, but only if given within 72 hours of rash onset. Thus, as a matter of policy, all patients at risk of chronic pain should be treated promptly (eg, patients over 50 years, those with severe pain at presentation and/or ophthalmic zoster). Three drugs are now licensed for VZV:

- aciclovir, 800 mg five times a day
- famciclovir, 250 mg three times a day
- valaciclovir, 1 g three times a day.

The data currently available from controlled trials demonstrate that, with ZAP as the end-point, famciclovir and aciclovir have similar efficacy, and valaciclovir is superior to aciclovir. A formal comparison of famciclovir and valaciclovir is in progress.

Beta-herpesviruses

Cytomegalovirus

Congenital CMV causes progressive mental retardation and hearing loss. No antiviral chemotherapy is licensed for its treatment but this is under evaluation.

CMV causes systemic infection in the immunocompromised, with involvement of multiple organs including lungs, retina, liver and gastroin-

### Table 3. 1998 recommendations for licensed antiherpes drugs.

| Virus               | Disease                          | Recommended treatment         |
|---------------------|----------------------------------|--------------------------------|
|                     |                                  | First-line                     |
| Herpes simplex      | Immunocompromised patients       | Aciclovir iv                   |
|                     | Encephalitis                     | Aciclovir iv                   |
|                     | Initial genital                  | Aciclovir oral                 |
|                     | Recurrent genital                | Aciclovir oral                 |
|                     | Prophylaxis genital              | Aciclovir oral                 |
| Varicella zoster    | Immunocompromised patients       | Aciclovir iv                   |
|                     | Chickenpox                       | Aciclovir iv                   |
|                     | Zoster:                          | Valaciclovir                   |
|                     | ophthalmic                       | Aciclovir oral                 |
|                     | elsewhere                        | Valaciclovir                   |
| Cytomegalovirus     | Immunocompromised patients       | Ganciclovir iv                 |
|                     | Prophylaxis:                     | Foscarnet iv                   |
|                     | bone marrow T_x                  |                                |
|                     | liver T_x                        |                                |
|                     | renal T_x                        |                                |
|                     | Retinitis in AIDS                |                                |
| iv = intravenous    | T_x = transplant                 |                                |

### Key Points

- Offer aciclovir or valaciclovir to all adult patients with chickenpox
- If aciclovir is prescribed during pregnancy, report the case to the International Registry (Fax: 001 919 315 8981)
- Treat elderly patients early with valaciclovir, famciclovir or aciclovir for zoster to reduce zoster-associated pain
- Consider screening AIDS patients regularly for the viraemia that precedes cytomegalovirus retinitis
- Suspect underlying herpes simplex virus if an AIDS patient develops a 'bed sore'
testinal tract. Monitoring of patients to detect asymptomatic viraemia with institution of pre-emptive therapy is established in transplant patients\(^8\) and becoming adopted for AIDS patients\(^9\). The quantity of viraemia 'viral load' correlates strongly with the development of CMV disease, explaining the previously identified risk factors of donor/recipient serostatus\(^10\).

**Human herpesvirus type 6**

HHV-6 was identified in 1986. It causes exanthema subitum in infants, as well as a forme fruste presenting with fever without the typical rash, with or without febrile fits\(^11\). It is clearly neurotropic\(^12\) and is a possible candidate for the aetiology of multiple sclerosis\(^13\). HHV-6 probably causes some cases of encephalopathy, bone marrow suppression or pneumonitis in immunocompromised patients in whom the full range of pathological consequences remains to be defined.

**Human herpesvirus type 7**

Some cases of exanthema subitum are caused by HHV-7. This virus was described only in 1991 and has been less extensively studied than HHV-6. It uses CD4 as a cellular receptor, and so may potentially interfere with HIV replication (reviewed in Ref 1).

**Gamma-herpesviruses**

**Epstein-Barr virus**

Acyclovir inhibits EBV replication, but has no clear effect on the symptoms of infectious mononucleosis\(^14\). EBV also causes genotypic rearrangements, leading to Burkitt's lymphoma in Africa among children with malaria and to lymphomas in the immunocompromised. It is mitogenic, activating several cellular genes (see Table 4).

**Human herpesvirus type 8**

HHV-8 was described in 1994, and is a strong candidate for causing KS in AIDS patients and all other groups. The virus encodes several genes which can influence the cell cycle, and shows striking similarities with the requirements of EBV (see Table 4). The human gamma-herpesviruses may be oncogenic because they activate cellular genes (EBV) or contain viral homologues of these genes (HHV-8). The incidence of KS is reduced among AIDS patients receiving ganciclovir or foscarin\(^15\).

### Table 4. Gene functions required by human herpesvirus-8 (HHV-8) and Epstein-Barr virus (EBV). (Adapted from Ref 16.)

| HHV-8 ORF | HVS | EBV |
|-----------|-----|-----|
| 1         | ✓   | ✓+  |
| 72        | ✓   | +   |
| 4         | ✓   | +   |
| 74        | ✓   | +   |
| K2        | ✓   | +   |
| K14       | ✓   | +   |
| 2         | ✓   | ✓   |
| X         | ✓   | ✓   |

**Function**

- Bcl-2
- Cyclin-D
- Complement binding
- Chemokine receptor
- Interleukin-6
- Adhesion molecule
- Dihydrofolate reductase
- Transforming

ORF = open reading frame

✓ = present in herpes virus salmin (HVS) or EBV
+ = cellular gene activated by EBV

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