

Herpes Group Viruses

What are herpes infections?

There are eight known human herpes viruses, classified into three groups. Cold sores, which affect the majority of us, are caused by *herpes simplex* (HSV) *Type-1*; genital herpes, one of the most common sexually transmitted diseases, is usually the result of infection by HSV-2 (although some cases are due to HSV-1), and chicken pox and shingles are manifestations of *varicella zoster* infection.

Apart from the fact that their genomes consist of double-stranded DNA or deoxyribonucleic acid, the group of herpes viruses share the property that, following primary infection, they persist in one or more body cells (nerve cells in the case of HSV-1, -2 and -3) in a dormant form and may be reactivated, either spontaneously or when the immune system is depressed, possibly with more severe consequences than during the primary infection. Herpes viruses of the gamma type have been implicated in the development of various cancers.

Who does herpes affect?

Most human beings are exposed to HSV-1, and those who have a sore often become carriers and have recurrences. Cold sores are usually trivial, but in people undergoing immunosuppressive therapy, or who have cancer or AIDS, they can be life-threatening. Similarly, in a newborn baby, infection arising from a vaginal sore can be very serious. Of newborns who survive neonatal herpes, 50 per cent have prolonged, permanent neurological consequences.

Until vaccines against *varicella* became available, chicken pox was a common childhood infection and shingles, frequent in older people, is often accompanied by severe, long-lasting neuropathic pain. In kidney transplant patients, infection with *cytomegalovirus* can result in rejection of the graft. Immunosuppressive treatment due to chemotherapy or transplantation can cause chicken pox to develop into an overwhelming general infection with a potentially fatal outcome.



Serological studies indicate that human herpes virus 6 (HHV-6) infects 90 percent of children by two years of age. Symptoms of HHV-6 infection include fever, dizziness, diarrhoea, rash and roseola. Febrile seizures are infrequently associated with primary HHV-6 infection. Older siblings appear to be a source of HHV-6 transmission.

Present treatments

While latent, herpes virus is concealed inside cells where it is invisible to the immune system. In cold sores, the cells are nerves in the head and neck, while in genital herpes the virus lodges in the nerves in the lower spine.

Milder outbreaks of oral or genital herpes are often treated with non-prescription topical preparations, but more serious or frequently recurring cases require systemic medication. Anti-herpes preparations that are available include a series of nucleoside

Infections by herpes viruses cause a lot of misery – including cold sores, genital herpes, chicken pox and shingles. While there have been extraordinary advances in medicines, research continues into vaccines and other ways to combat these common viruses.

The Human Herpes Viruses and the Diseases they Cause

	Type	Common name	Disease associated with virus
HHV-1	Alpha	Herpes simplex, type 1	Cold sores
HHV-2	Alpha	Herpes simplex, type 2	Genital sores
HHV-3	Alpha	Varicella zoster (VZV)	Chicken pox, shingles
HHV-4	Gamma	Epstein-Barr (EBV)	Infectious mononucleosis, Burkitt's lymphoma
HHV-5	Beta	Cytomegalovirus (CMV)	Retinitis, pneumonia (immunocompromised)
HHV-6	Beta	Human herpes virus 6	Roseola infantum, exanthema subitum
HHV-7	Beta	Human herpes virus 7	Not known
HHV-8	Gamma	Human herpes virus 8	Kaposi's sarcoma (immunocompromised)

analogues and work by blocking replication of the viral DNA, preventing the formation of infectious particles. There are tablets and a topical preparation, also available is an infusion form for use in serious systemic infections.

Varicella zoster (VZV), which causes chicken pox, hides in clusters of nerves alongside the spine or in ganglia. Medical treatment deals with the symptoms, but does not eradicate the latent virus infection. After reactivation in adulthood, the disease manifests as herpes zoster at various parts of the human body, often along the trigeminal nerve in the face or following the neural dermatomes of the lower back. Treatment of this neuropathic pain syndrome is difficult and often disappointing.

Live, attenuated (weakened) vaccines are already available to protect against primary infection with the *varicella zoster* virus, and so prevent chickenpox. Cases of chickenpox have fallen dramatically in communities since the vaccine was introduced in 1995. Immunisation against VZV has reduced infections in every age group, including among babies less than one year old, who are too young to be vaccinated but become protected by "herd immunity". It has also been shown that the vaccine prevents 95 per cent of severe sequelae which include VZV pneumonia and encephalitis.

Three DNA polymerase inhibitors are used for the treatment of *cytomegalovirus* infections in AIDS and immuno-compromised patients. The drawbacks of all of these anti-herpes preparations are the regularity with which they have to be applied, and the fact that they do not eliminate the latent virus.

What's in the development pipeline?

Development projects for herpes virus infections are mainly aimed at *herpes simplex*, *varicella zoster* and *cytomegalovirus*. The growing frequency of sexually transmitted diseases has increased the need for effective prevention of HSV infections, and this is where much current development work is focused. One of the antivirals mentioned has also received approval to prevent transmission of HSV infections among heterosexual, monogamous couples.

Scientists have developed a topical treatment which could stop HSV-2 from replicating in a new host. The therapeutic principle uses a technique called RNA interference (RNAi) that disables key genes needed for transmission of the virus and is targeted against a molecule called nectin-1.

One research group has a vaccine in Phase 3 trial for the prevention of genital herpes and another group has a vaccine in Phase 1 study for treating HSV-2 infections. This vaccine produces an immune response which may enable the virus to be eliminated, or help prevent the viral reactivation that leads to the recurrence of symptoms.

Other scientists have a therapeutic vaccine in Phase 1 trial that is intended to activate both helper and killer T-lymphocytes. Another research group has isolated a lipopeptide from a marine fungus that appears to be at least as effective as the existing DNA nucleoside analogues in inhibiting HSV-1 and HSV-2, and this compound is now being tested in the clinic.

Further vaccines against *varicella zoster* virus are in development for primary prevention. New antiviral compounds in cream formulations are being tested for the treatment of shingles eruptions. Other institutions are developing new molecules for the treatment of the painful post-herpetic nerve pain (neuralgia) that often follows shingles.

CMV infections are mainly a problem in those with an impaired immune system. One research group is studying a DNA-based vaccine against CMV for the prevention of infection after blood cell transplants and this has reached Phase 2.

Another vaccine against CMV is being tested for prevention of maternal–foetal transmission. Lastly, scientists are developing a new type of antiviral for the prevention of CMV reactivation following bone marrow transplantation.

Currently, there is no effective intervention for a primary CMV infection during pregnancy. According to preliminary findings of clinical studies in pregnant women with a primary CMV infection, hyper-immune globulin therapy was associated with a significantly lower risk of congenital CMV infection. The outcome suggests that passive immunisation may be effective in the treatment and prevention of congenital CMV infection. Further trials of this agent are needed to confirm the results.

The longer-term future

Removal of the virus from inside nerves remains the ultimate goal for new treatments in herpes virus infections, but is still tantalisingly out of reach. Meanwhile, more effective prevention and the development of less toxic antiviral compounds that can increase symptom-free periods would seem to be more realistic goals.

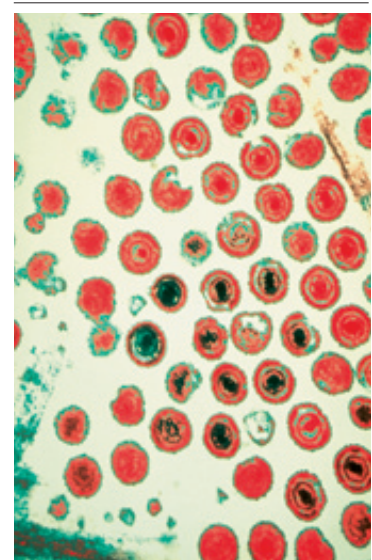


FIGURE 1: Electron-microscopic picture of Herpes simplex (HSV) Type-1

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