Study shows genital herpes can reactivate even during high dose antiviral therapy

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A study combining three trials of antiviral therapy to treat genital herpes (herpes simplex virus type 2/HSV-2) has shown that the virus can reactivate in 'breakthrough episodes' even when doses of antiviral therapy are high. Thus new therapies are needed to successfully prevent onward transmission of this common infection that affects some one in five of the general population. These are the conclusions of an Article published Online First by the *Lancet*, written by Dr Christine Johnston, University of Washington Virology Research Clinic, Seattle, WA, USA, and colleagues.

Symptoms of HSV-2 infection include ulcers in the skin or mucus membranes of the mouth, lips, or genitals. However, most people with this infection do not have obvious symptoms, but even so, can shed the virus and transmit it to sexual partners. Once someone is infected, HSV-2 is able to hide in the nervous system of the host, enabling it to reactivate periodically in those infected. During re-activation, the virus in a nerve cell is transported along the nerve to the skin, where new replication and 'shedding' occur and cause new sores. Intensive genital secretion collection shows that HSV shedding episodes are three-times more frequent than was previously realised.

In this study, three separate but complementary open-label cross-over studies involving 113 patients were carried out, comparing no medication with aciclovir 400 mg twice daily (standard-dose aciclovir); valaciclovir 500 mg daily (standard-dose valaciclovir) with aciclovir 800 mg three times daily (high-dose aciclovir); and standard-dose

valaciclovir with valaciclovir 1 g three times daily (high-dose valaciclovir).

The results showed that short episodes of subclinical (symptom free) shedding persist with both standard-dose and high-dose aciclovir and valaciclovir. Although HSV shedding was reduced by 50% with the highest doses of valaciclovir (1 g, three times daily) compared with standard dose valaciclovir (500 mg daily), the rate of breakthrough shedding episodes did not change—about 16 episodes per year.

The authors say: "Our finding that high-dose valaciclovir increases the kinetics of viral clearance, but not expansion, supports the hypothesis that these antiviral drugs do not suppress the release of virions into the genital tract."

They add: "That we could not eliminate or even alter the frequency of shedding episodes with high-dose valaciclovir suggests that the maximum benefit of shedding reduction has probably been reached for currently available antiviral drugs."

They conclude: "Although currently available anti-HSV therapy benefits patients by preventing clinical HSV recurrences, suppressive therapies with greater potency, including antiviral drugs or immunotherapy in the form of therapeutic vaccines, are needed to provide substantial public health benefits, such as prevention of HSV-2 transmission and HIV-1 acquisition and transmission."

In a linked Comment, Dr Philippe Van de Perre and Dr Nicolas Nagot INSERM U 1058, Montpellier, France, and Université Montpellier 1, Montpellier, France, say that development of new classes of antiviral drug such as helicase-primase inhibitors is important but such drugs would need good long-term coverage and adherence to successfully prevent shedding and onward transmission of HSV-2. They add: "These

needs are unlikely to be met because about 20% of the general population is infected with HSV-2 in the USA and Europe, most of whom have no clinical need for antiherpetic therapy."

They conclude: "Alternative control tools, such as immunotherapeutic strategies (therapeutic vaccines), are in preclinical development, but they are hampered by the absence of an adequate animal model and the lack of commitment from pharmaceutical companies and the public sector."

More information: paper online: www.thelancet.com/journals/lan … (11)61750-9/abstract

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