Good news on the HSV-2 front

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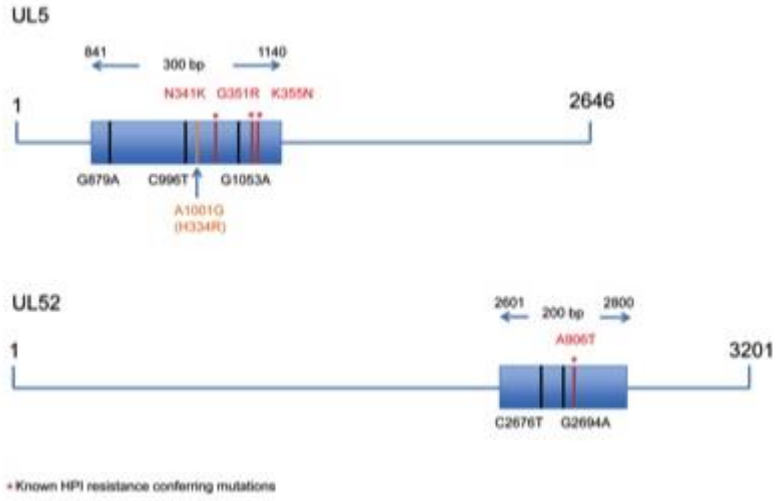

Venn diagrams indicating co-occurrence of variations from the consensus in UL5 (left) and UL52 (right).

Figure adapted from publication.

Herpes simplex virus-2 (HSV-2), the etiological agent of genital herpes, is a double-stranded DNA virus able to establish lytic as well as latent infections. In the lytic cycle, the virus infects epithelial cells and replicates, therefore inducing cell death that manifests in form of blisters and ulcers typical of this infection. So far, treatment for these symptoms relies on the use of nucleoside analogues that, upon phosphorylation by the viral thymidine kinase, inhibit viral DNA polymerase activity, blocking viral DNA synthesis. These compounds, although able to ameliorate the clinical disease, do not abrogate viral shedding and only partially reduce the transmission to sexual partners. Moreover, resistance develops occasionally in immunocompromised subjects, such as transplant recipients or HIV-infected subjects.

The thiazolylamide pritelivir is the first in a new class of antiviral agents that inhibit HSV replication by targeting the viral helicase-primase enzyme complex. Pritelivir binds to a complex composed of the HSV-2 gene products of UL5, UL8 and UL52. Unlike nucleoside analogues, it does not need activation by phosphorylation and is active in uninfected cells, opening the possibility of its use for both prevention and therapy. Pritelivir has been shown to be efficacious against HSV-2 in vitro and in animal preclinical studies. Moreover, a recent trial, whose results have been published in The New England Journal of Medicine (Wald A. et al., 2014; 370: 201-210) showed that pritelivir administration reduced the rates of shedding and days with lesions in a dose-dependent manner in otherwise healthy men and women with genital herpes.

In the aforementioned *in vitro* studies, it was possible to generate resistance-mediating mutations, located at either a single amino acid in the viral UL52 primase (AA906) or within/downstream the 4th functional motif of the UL5 helicase (AA341-355). Dr. Paul Edlefsen from the Vaccine and Infectious Disease Division at Fred Hutch and Dr. Alexander Birkmann from Aicuris investigated whether such mutations could be induced in humans. The results have been recently published in the *Journal of Infectious Diseases*.

Using samples obtained from the pritelivir clinical trial, the previously identified resistance regions of HVS-2 primase and helicase were sequenced. While the majority of mutations were synonymous (did not change the amino acid sequence in the protein), one mutation caused an amino acid substitution. This mutation evidently was not induced by the drug, however, since it was present even before the start of the treatment; nor did it induce resistance to the virus. Moreover, a whole-gene sequencing approach was used to test if there were any sequence differences between the last on-treatment positive swab and the pre-treatment, or the first on-treatment positive sample. For both UL5 and UL52 genes, two participants had one sequence variation between the first and last sample. Since both subjects were found to be dually infected, the mutation was likely a polymorphism reflecting pre-existing sequence variation and not a mutation induced by pritelivir treatment.

This study reduces concerns about potential of pritelivir to generate a high frequency of resistance mutations, since none were observed in this study which analyzed more than 800 samples.

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Edlefsen PT,Birkmann A,Huang ML,Magaret CA,Kee JJ,Diem K,Goldner T,Timmler B,Stoelben S,Ruebsamen-Schaeff H,Zimmermann H,Warren T,Wald A,Corey L. 2016. No evidence of resistance of HSV-2 to pritelivir following four weeks of daily therapy. *J Infect Dis.* [Epub ahead of print.]