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A missed point in deciphering the viral synergy between herpes simplex virus and HIV

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Philippe Van de Perre and colleagues¹ argue that herpes simplex virus (HSV) 2 and HIV infections are synergistic, since suppression of HSV2 decreases HIV load, while Rex G Cheng and Douglas F Nixon² insist that interactions between HSV2 and HIV-1 are more complex and that HSV2 coinfection might, in certain cases, be associated with elevated CD4+ T-cell counts.³ Both groups provide arguments on the basis of their own work and selected results of various clinical trials.^{4–7} Although there has been some criticism of the design and interpretation of results of some of these trials,^{8–10} all of them have one thing in common: they use aciclovir or its prodrug valaciclovir to suppress HSV2 replication and to investigate whether such suppression affects HIV replication and infection.

However, we have shown that aciclovir is not only a DNA polymerase inhibitor of herpes viruses, but also a direct HIV-1 reverse transcriptase inhibitor.¹¹ A group from the Johns Hopkins University¹² also reported on aciclovir inhibition of HIV-1 reverse transcriptase. So, the very drug that was used to suppress HSV2—to investigate whether HIV-1 infection is affected by this suppression—affects HIV-1 directly and therefore is obviously not appropriate to address this question.

The molecular mechanism of the aciclovir-mediated inhibition of HIV-1 reverse transcriptase involves the termination of the nascent HIV DNA chain by phosphorylated aciclovir accompanied by blockage of HIV-1 reverse transcriptase at the site of termination.^{11,12} Consequently, treatment of various herpesvirus-coinfected human tissues with aciclovir ex vivo reduces HIV replication, with a half maximum effective concentration of about 3 μ M.¹¹

This concentration is commonly found in the plasma of people treated with aciclovir (a single dose of 400 mg reaches a maximum plasma concentration of about 4 μ M)¹³ or valaciclovir (a single dose of 500 mg reaches a maximum plasma concentration of about 15 μ M).¹⁴

We are convinced that this previously unknown activity of aciclovir means that the trials mentioned need reconsideration. The direct effect of aciclovir on HIV-1 depends on the ability of HSV2, as well as of other herpesviruses, to produce amounts of phosphorylated aciclovir sufficient to suppress HIV reverse transcriptase. Also, host enzymes that have not yet been characterised can contribute to the amount of phosphorylated derivatives of aciclovir. These characteristics of aciclovir activity were not addressed in the clinical trials discussed in *The Lancet Infectious Diseases*. Moreover, the amounts of phosphorylated drugs should depend also on the doses of aciclovir or valaciclovir, which were different in

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different clinical trials. Such differences in the regimens adopted, as well as in the levels of adherence, might be less important for the suppression of HSV2 DNA polymerase, since it is generally very sensitive to aciclovir. By contrast, HIV-1 reverse transcriptase seems to be less sensitive to aciclovir, and plasma concentrations of the drug that suppress HSV2 might not be sufficient to suppress HIV. Therefore, the dose given might be crucial for the inhibition of HIV-1 reverse transcriptase, as well as whether it is aciclovir or valaciclovir that is given. Although aciclovir seems to be effective against HIV strains resistant to other tested nucleoside reverse transcriptase inhibitors,¹¹ it might affect the evolution of HIV-1 reverse transcriptase in patients infected with HIV, as reported for other HIV-1 reverse transcriptase inhibitors. The work of McMahon and colleagues¹² showed that aciclovir-resistant HIV-1 variants emerge upon selection in vitro, and suggested that the potential emergence of such variants in vivo might affect sensitivity to other reverse transcriptase inhibitors used at present. Although the evidence for HIV-1 reverse transcriptase evolution in people treated with aciclovir in vivo has never been reported, this possibility should be addressed.

We are convinced that, in view of the new data on aciclovir suppression of HIV reverse transcriptase, new studies and new targeted clinical trials are needed to understand these newly discovered features of the interaction between HSV and HIV, and of the herpes-suppressive drugs in patients infected with HIV-1. Also, acknowledgment of the necessity for such trials is a rare point upon which both of the teams engaged in this discussion in *The Lancet Infectious Diseases* agree.

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