CORRESPONDENCE

HSV Therapy and HIV-1 Reduction

TO THE EDITOR: Nagot et al. (Feb. 22 issue)[1] report that treatment with valacyclovir (1 g per day) to suppress herpes simplex virus (HSV) reduced human immunodeficiency virus type 1 (HIV-1) RNA levels in patients in Burkina Faso. This finding raises important questions regarding the clinical management of HSV infection in poor countries. Of the 68 patients receiving valacyclovir, 3 (4%) had at least one episode of vesicular or genital ulceration during the study period. In another trial,[2] which showed a reduction of recurrences of HSV type 2 (HSV-2) with valacyclovir (1 g per day) in HIV-infected patients, 3 (6%) of the 50 HSV-2 isolates collected were resistant to acyclovir. In Western countries, 5 to 6% of the HSV-2 isolates from patients with immunosuppression are resistant to acyclovir.[3] Treatment of such patients is challenging and may require intravenous foscarnet or cidofovir. However, none of these drugs are routinely available in poor countries such as Burkina Faso. The risk of emergence of resistant HSV strains raises important questions that must be considered.

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2. DeJesus A, Wald T, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. J Infect Dis 2003;188:1009-16. [Erratum, J Infect Dis 2003;188:1404.]
3. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. J Infect Dis 2002;186:Suppl 1: S40-S46.

TO THE EDITOR: In the study by Nagot et al., which showed that treatment with valacyclovir for HSV infection was associated with a reduction in HIV viral load in plasma and the genital tract, the viral load at baseline was higher in the placebo group, and the statistical analysis accounted for this factor. However, there was also an increase in the HIV viral load in the placebo group during the study, and most of the evolving difference in viral load between the study groups during treatment may have been due to the increase in the placebo group. This increase, in turn, may have been due to other (e.g., gastrointestinal) infections and HIV-unrelated gastrointestinal disorders. (Diarrhea, vomiting, dysphagia, and constipation were reported in 26 patients in the placebo group vs. 13 in the valacyclovir group; P=0.02.) Breach of the gastrointestinal epithelial barrier with the associated translocation of products of enteric bacteria such as lipopolysaccharide and butyrate[1,2] has been associated with systemic immune activation, which amplifies replication of HIV through nuclear factor-κB–mediated stimulation of long terminal repeats induced by tumor necrosis factor. In future studies, investigators will need to consider adjusting analyses for other concomitant

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infections, such as those affecting the gastrointestinal tract, that fuel HIV replication.

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1. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365-71.
2. Stein TP, Koerner B, Schluter MD, et al. Weight loss, the gut and the inflammatory response in AIDS patients. Cytokine 1997;9:143-7.

THE AUTHORS REPLY: Our study was a proof-of-concept trial and so did not allow prediction of the effect of HSV suppressive therapy as a public health intervention to prevent the transmission of HIV. Available data regarding resistance to acyclovir are reassuring. The occurrence of acyclovir-resistant HSV-2 strains in HIV-infected patients (4 to 7%) has not increased during the past two decades in Western countries, despite the frequent use of acyclovir and valacyclovir.[1] Instead, resistance to acyclovir could be declining, since the use of highly active antiretroviral therapy has become widespread.[2] When such resistance occurs, it is not predictive of clinical failure.[3] In addition, the occurrence of genital ulceration during the course of HSV suppressive therapy does not necessarily mean that the causative strain is resistant to acyclovir. We agree that in the absence of second-line therapy in resource-constrained countries (and considering the paucity of data available to date), the importance of resistance to acyclovir should be investigated further. However, even if such resistance is confirmed, it is unlikely to counterbalance the potential positive effect of HSV suppressive therapy on HIV-1 disease progression and transmission.

The HIV-1 plasma viral load in the placebo group increased slightly during our study, but we doubt this rise was due to HIV-unrelated gastrointestinal diseases. Several women reported having more than one symptom, so the P value calculated by Dr. Eisenhut needs modification. In fact, the proportion of women who reported at least one gastrointestinal symptom tended to be higher in the placebo group (38.2%) than in the valacyclovir group (25.0%) but without reaching statistical significance (P=0.10). Valacyclovir and acyclovir have been used for decades with a safety profile similar to that of placebo.[4] The hypothesis by Brenchley et al.[5] that a sustained systemic immune activation is fueled by intestinal bacteria through a translocation mechanism is based on the commensal enteric flora and not on pathogens. It is unlikely that this mechanism could be altered or enhanced by the intake of valacyclovir. It should also be noted that our primary outcome was genital HIV viral load, and there was little difference in this outcome in the placebo group before randomization and after randomization (mean number of $\log_{10}$ copies per milliliter, 2.97 and 3.02, respectively).

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Coronary Microvascular Dysfunction

TO THE EDITOR: Camici and Crea (Feb. 22 issue)[1] review the different causes and mechanisms of coronary microvascular dysfunction. However, coronary microvascular dysfunction due to aging deserves further comment. Age is a recognized risk factor for cardiovascular disease, and senescence is associated with morphologic and functional changes in the coronary microvasculature.[2] Studies in animals have shown that coronary flow reserve and the endothelium-dependent dilatation