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Patterns of Susceptibility to Acyclovir and Foscarnet in 209 Herpes Simplex Virus (HSV) Isolates. Safrin S, Elbaggari A, Mills J. San Francisco General Hospital, University of California, San Francisco, CA U.S.A.

We report results from a total of 209 clinical HSV isolates referred to our Research Virology Laboratory for susceptibility testing. The plaque reduction assay was performed for acyclovir and/or foscarnet susceptibilities. In addition, a "rapid screen" was performed, by observing the presence or absence of growth in 3 ug/ml acyclovir or 200 ug/ml foscarnet, respectively. The rapid screen correctly identified isolates as acyclovir-susceptible in 79.6%, and as acyclovir-resistant ($ID_{50} \geq$ 3 ug/ml) in 100% of 151 isolates when compared with results from the plaque reduction assay. Sixteen isolates were indeterminate on the rapid screen: 14 were susceptible and 2 resistant. Mean acyclovir ID_{50} was 15.3 $\pm$ 22.1 *u*g/ml, and distribution was bimodal. Acyclovir ID_{90} correlated closely with ID_{50} ($r=0.8$, $p=.0001$). In 4 of 58 patients in whom clinical information was available (1 who responded to acyclovir and 3 who did not), ID_{50} failed to correlate with *in vivo* response. In 2 such patients, ID_{90} closely correlated with ID_{50}, and therefore failed to yield data more predictive of response; in 2 however ID_{90} was substantially higher than the ID_{50} and might have been indicative of a mixed population. Median ID_{50} and ID_{90} were significantly greater in patients who failed to respond to acyclovir than in those who did not ($p=.0001$, $p=.0002$). In 164 isolates, the rapid screen correctly identified isolates as foscarnet susceptible in 95.7%. In 3 foscarnet-resistant isolates, rapid screen was accurate; however it incorrectly suggested resistance in 7 other isolates. Three isolates were of indeterminate susceptibility on the rapid screen; each was susceptible by ID_{50}. Median foscarnet ID_{50} was 25.6 $\pm$ 24 *u*g/ml, and did not differ in the 26 patients who had a complete response to foscarnet than in the 9 who had a partial response ($p=0.8$). Two of the 3 patients with foscarnet-resistant isolates had received 1 or more courses of foscarnet therapy for acyclovir-resistant HSV; in the third patient clinical data is missing. In all 3 patients, isolates with resistance to foscarnet showed concomitant susceptibility to acyclovir; in 1 a subsequent isolate showed susceptibility to foscarnet with resistance to acyclovir.

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Sequential Varicella Zoster Virus Isolates from an AIDS Patient: Phenotypic and Genetic Evidence for Evolution of Drug Resistance at the Thymidine Kinase and DNA Polymerase Loci. S. C. Stanat[1], C. L. Talarico[1], S. Safrin[2], and K. K. Biron[1]. [1]Burroughs Wellcome Co., Research Triangle Park, NC and [2]University of California, San Francisco, CA; USA.

AIDS patients are candidates for recurrent and recalcitrant infections with varicella zoster virus. Aggressive therapy with acyclovir (ACV) is generally the first approach in the management of zoster in these patients. Foscarnet (PFA) has been successfully used in the treatment of infections refractive to ACV therapy where the resistance to ACV could be correlated with the presence of thymidine kinase (TK) deficient virus (Safrin). We have previously reported *in vitro* ACV resistance of isolates from several AIDS patients after ACV clinical failure (Pahwa, Jacobson) and concomitant *in vitro* resistance to PFA in one of these patient isolates (Pahwa). In this study we will report on a set of serial isolates obtained from an AIDS patient with zoster who failed to respond to ACV and whose lesions were subsequently cleared after therapy with PFA. The first lesion isolate, obtained after 3 weeks of ACV treatment, demonstrated *in vitro* resistance to ACV but susceptibility to PFA. ACV resistance was attributable to a deficient viral TK by a plaque autoradiography assay. ACV therapy was discontinued after two months. Two weeks later, PFA therapy was initiated and a second isolate was recovered which exhibited wild type drug susceptibility patterns for both ACV and PFA. The patient responded to PFA therapy; however, two viruses isolated on days 6 and 10 of PFA therapy exhibited increasing resistance to PFA and slightly elevated ACV ED50s that could not be attributed to TK dysfunction. These drug susceptibilities indicated an increasing proportion of DNA polymerase-altered virus in the mixed populations. We will here describe the sequence alterations in the TK and polymerase genes which are responsible for these drug susceptibility phenotypes.

S. Safrin, et. al. Ann Intern Med. 1991; **115**: 19-21.
S. Pahwa, et. al. JAMA. 1988; **260**: 2879-2882.
M. Jacobson, et. al. Ann Intern Med. 1990; **112**: 187-191/