Characterization of a new use for acyclovir and tenofovir using human cervico-vaginal tissue ex vivo

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Background: HSV-2, one of the most common HIV-1 copathogens, establishes a synergistic interaction with HIV-1. Several clinical trials have shown that the anti-herpetic drug acyclovir decreases HIV-1 viral load and delays HIV-1 disease progression. Similarly, CAPRISA004 reported that a vaginal gel containing 1% of the anti-HIV-1 drug tenofovir unexpectedly decreases the risk of HSV-2 acquisition by 51%. Using a system of cervico-vaginal tissue culture that reflects many of the in vivo tissue features, we evaluated the dual anti-HIV-1/HSV-2 activity of acyclovir and tenofovir.

Methods: Human tissues were infected ex vivo with HIV-1 (laboratory strains, primary isolates or NRTI-resistant HIV-1 variants), HSV-2 (HSV-2G, HSV-2MS) or with a combination of HIV-1 and HSV-2 variants and treated with acyclovir or tenofovir. HIV-1 and HSV-2 replication were respectively monitored by measuring HIV-1 p24 gag or HSV-2 DNA accumulated in culture media.

Results: Acyclovir suppressed the replication of the laboratory X4 LAI.04 HIV-1 with an EC50 of 3 µM (95% Confidence Interval (CI):1.85-5.24). No statistical difference between the inhibition of primary isolates and AZT-resistant variant was observed (n=5). In contrast, the EC50 for the 3TC-resistant virus (M184V) was four times higher than that of the parental HIV-1 isolate (n=5). Tenofovir suppressed HSV-2 replication with respective EC50s of 14 µg/ml (CI:10-163) for HSV-2G, and 19 µg/ml (CI:27-127) for HSV-2MS. Tenofovir 66 µg/ml reduced HSV-2G and HSV-2MS replication by 87±12% and 91.7±3.2%, respectively (p<0.01). Accordingly with the ex vivo results, we found in a cell-free system that the triphosphate form of acyclovir was a direct inhibitor of the HIV-1 reverse transcriptase and that tenofovir-diphosphate was a direct inhibitor of the HSV DNA polymerase.

Conclusion: Using human tissue culture ex vivo, we showed that (i) acyclovir inhibits HIV-1 at concentrations that are clinically relevant and commonly achieved in plasma of patients treated with acyclovir or valacyclovir; (ii) tenofovir, at the concentration achieved in topical vaginal application (which is substantially higher than achieved upon systemic administration) acts as a double-targeted antiviral agent as well. These data explain the inhibition of HIV-1 in clinical trials using acyclovir and the inhibition of HSV-2 observed in the clinical trial using tenofovir (CAPRISA004).