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Lopinavir

A Viewpoint by Martin Markowitz

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Lopinavir, a potent, specific inhibitor of HIV-1 protease, represents yet another advance in the drug armamentarium now available to treat HIV-1/AIDS. Though protease inhibitors (PIs) have been available since 1996, there are features of this drug which merit highlighting.

Interestingly, lopinavir is available as a fixed coformulated combination with ritonavir (133mg/33mg). The addition of ritonavir alters the pharmacokinetics of lopinavir such that, when dosed at 400mg/100mg, the combination results in trough plasma levels that are more than 75-fold in excess of the antiviral 50% effective concentration (EC_{50}) for lopinavir (when corrected for protein binding). Such drug concentrations have been previously unobtainable with single PI-based combination therapies.

Ritonavir boosting of PIs has come to the fore in designing effective combinations of available HIV-1 PIs. Ritonavir has potent inhibitory effects on the cytochrome P450 isoenzyme 3A4 that inhibits the metabolism of lopinavir, as well as that of other PIs. Ritonavir is also a potent inhibitor of p-glycoprotein and probably increases both the absorption and intracellular concentrations of p-glycoprotein substrates (which PIs have been identified as).

In a series of well designed clinical trials, lopinavir coformulated with ritonavir has demonstrated potent antiviral activity *in vivo* when tested in combination in 3 distinct patient populations; those naive to all antiretroviral drugs, first PI treatment failures who are naive to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and multiple PI treatment failures also naive to NNRTIs. It is worth noting that the population that still requires study is the multiple PI- and NNRTI-experienced patient, particularly the subset with high HIV-1 RNA levels and low levels of CD4 T cells.

Lopinavir use also challenges our current methods of resistance testing. Given the ability to achieve drug concentrations in marked excess of the EC_{50} value for both wild-type and multi-PI resistant viruses, it is not yet clear how to predict whether an individual patient will respond to a lopinavir-based regimen. Current estimates suggest that lopinavir may remain active against isolates that are up to 40-fold less susceptible to the drug as demonstrated by recombinant phenotypic assays. This seeming contradiction raises the issue of the importance of both resistance testing and therapeutic drug monitoring, especially in the setting of salvage therapies.

Lopinavir is a welcome addition to the current drugs available to treat HIV-1. However, as with all antiviral agents, it is unclear when it is best to use this agent. Well designed clinical trials to test effectiveness in challenged populations, as well as considerations of sequencing therapies in the event of failure, will better define the future use of lopinavir. ▲