National AIDS Treatment Advocacy Project

MUTATIONS IN HIV-1 PROTEASE ASSOCIATED WITH DRUG RESISTANCE

Please be advised that our current knowledge on viral resistance to protease inhibitors is based largely on **laboratory experiments** using many different biochemical techniques. As with all approved and experimental antiretroviral drugs, the demonstration of viral resistance to a particular drug and its subsequent cross-resistance to other drugs *in vitro* (in cell culture) **may not** necessarily predict the presence or absence of viral resistance *in vivo* (humans). **Some of the mutations listed for each of the drugs below contribute more towards actual resistance than others.**

The clinical impact of viral resistance to protease inhibitors in individuals undergoing protease inhibitor treatment is yet to be determined. Viral resistance to antiretroviral drugs, including protease inhibitors, is a natural consequence of antiretroviral therapy. The generation of drug resistant HIV strains is a function of the viral reproduction rate. Therefore, effective and durable inhibition of HIV reproduction with a safe and potent antiretroviral treatment regimen should delay the emergence of drug-resistant viruses in favor of the individual undergoing such treatment.

As illustrated in the table below, many pieces of the viral-resistance-to-protease-inhibitor puzzle have been discovered. However, more pieces are needed before anyone could attempt to put this complex puzzle together. **Much of the information below is reported from the manufacturer's own research and is open to interpretation.** It is believed that shutting down HIV reproduction for as long as possible with safe and potent treatment regimen is an effective way of delaying viral resistance, thus optimizing the benefits of such treatment for people living with HIV/AIDS.

Compound	Amino Acid Change	In Vitro	In Vivo	Resistance (in vitro or in vivo)	Cross-Resistance to Other Protease Inhibitors (in vitro or in vivo)

Saquinavir	L10I/V/R M46I/L G48V I54V L63P A71V/T V82A/F/T I84V L90M	No No Yes Yes Yes Yes No Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes	® G48V+I84V+L90M (30-fold increase _ ® G48V+L90M (20-fold increase in viral resistance to saquinavir in vitro). ® G48V+L90M less common in vivo. ® L90M frequent in vivo. ® Majority of patients on saquinavir monotherapy or combination therapy have no G48V and/or L90M mutations after 1 year of treatment. ® Analysis of 4 patients on saquinavir (from studies ACTG229 and NV 14256) have found virus carrying L90M or G48V+L90M (<4- to 44-fold increase in viral resistance to saquinavir. ® Mutations at 10, 36,63,71 correlate with development of L90M mutation	Clinical isolates from majority of patients treated with saquinavir alone or in combination with AZT and/or ddC after 1 year retain full sensitivity to both saquinavir and indinavir. Clinical isolates from 4 patients treated with saquinavir (from studies ACTG229 and NV 14256) had a 4-fold increase in viral resistance to indinavir. Similarly, 2 of the 4 isolates had a 4-fold increase in viral resistance to 141W94. And 1 of the 4 isolates had a 9-fold increase in viral resistance to ritonavir. 13-22% with previous saquinavir experience develop varying degrees of cross-resistance to indinavir ranging from low to high level.

Ritonavir	K20R L33F M36I M46I/L I54V L63P A71V/T V82F V82A V82T I84V L90M	No No No Yes No Yes Yes Yes No No Yes No	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	® Mutations associated with ritonavir resistance in isolates taken from 41 ritonavir-treated patients appeared to occur in a stepwise and ordered fashion. ® V82T (2.5-fold increase in viral resistance to ritonavir in vitro). ® V82T+I54V (9-fold increase in viral resistance to ritonavir in vitro). V82T+I54V+A71V+M36I (17-fold increase in viral resistance in vitro).	® Clinical isolates taken from two ritonavir-treated patients had an 8-fold increase in viral resistance to indinavir. One isolate had K20R+ M36I+I54V+ A71V+ V82T and another had M36I+I54V+ V82S/F/A/T. ® Clinical isolates taken from two ritonavir-treated patients had a 10-fold increase in viral resistance to nelfinavir. One isolate had K20R+M36I+I54V +V82A and another had 20R+M36I+ I54V+A71V+V82T.

Indinavir	L10I/V/R K20M/R/I/L L24I V32I M46I/L I54V L63P I64V A71V/T V82A/F/T I84V L90M	No No No Yes Yes No No No Yes Yes No No	Yes Yes Yes Yes No Yes Yes Yes Yes Yes Yes Yes	® None of the mutations leads to phenotypic changes alone or in pairs. ® M46I+L63P+V82T (4-fold increase in viral resistance to indinavir in vitro). ® M46I+L63P+V82T+I84V (8-fold increase in viral resistance to indinavir in vitro).	® Indinavir resistant virus (M46I+L63P+V82T+I84V) had reduced sensitivity to saquinavir, ritonavir, and 141W94. ® Two-thirds of indinavir resistant clinical isolates are resistant to saquinavir and 141W94. ® All indinavir resistant isolates had a 4- to 30-fold increase in viral resistance to ritonavir.
Nelfinavir	D30N M36I M46I A71V V77I I84V N880	Yes No Yes Yes No Yes No	Yes Yes Yes Yes Unknown Yes	® M46I+I84V (30-fold increase in viral resistance to nelfinavir in vitro). ® D30N+A71V in vitro was resistant (8-fold increase) after 22 passages, but not cross-resistant to RTN, SQV or IDV. ® In vivo, D30N is thought to be pre-dominant cause of resistance. ® Also seen in vivo: N88D/S,E35N,M36I,M46I,	® Cross-resistance studies with clinical isolates are ongoing. ® In vitro, after 28 passages, M46I/I84V double mutant was cross-resistant to RTN, IDV & SQV.

				A71T/V,V77I	
141W94 (VX-478)	M46I/L I47V I50V	Yes Yes Yes	Unknown Unknown Unknown	® I50V (3-fold increase in viral resistance to 141W94). ® I50V+M46I/L+I47V (20-fold increase in viral resistance to 141W94).	® Clinical isolates taken from 5 ritonavir-treated patients remained fully sensitive to 141W94.