darunavir resistance associated mutations increased from 77.6% in 2006 to 92.8% in 2012 (Lathouwers *et al.,* 2015). The UK HIV Drug Resistance Database identified 306 patients who underwent genotype analysis before or during darunavir treatment or within 30 days of ceasing the drug. Darunavir-associated RAMs developed in 3 (1.9%) and 7 (4.7%) protease inhibitor–naive and –experienced patients, respectively. Of the 7 protease inhibitor–experienced patients, 3 had darunavir RAMs at baseline (El Bouzidi *et al.,* 2014).

In regard to cross-resistance, HIV isolates resistant to darunavir in cell culture usually test resistant to other protease inhibitors, including atazanavir, lopinavir, amprenavir, saquinavir, and indinavir. However, the majority of these isolates demonstrated a less than threefold reduction in EC_{50} to tipranavir, suggesting limited cross-resistance to this agent (Janssen, 2015a).

In clinical studies of treatment-experienced patients, minimal cross-resistance was observed between darunavir and tipranavir. Patients who experienced virological rebound on darunavir treatment retained tipranavir susceptibility on testing (Arasteh *et al.,* 2009).

The current IAS-USA guidelines describe 11 major mutations associated with reduced darunavir susceptibility. These are outlined in Table 245.1.

3. MECHANISM OF ACTION

Similar to other protease inhibitors, darunavir is a competitive inhibitor for the active site of the protease enzyme.

Darunavir is a peptidomimetic inhibitor of the HIV protease, inhibiting proteolytic activity as well as the first step of HIV-1 protease dimerization (Koh *et al.,* 2007; Hayashi *et al.,* 2014). Dimerization of the subunits of the HIV-1 protease are required for proteolytic activity of the protease.

Darunavir acts predominantly within the substrate envelope, displaying a high affinity for its target, with a binding constant of 4.5×10^{-12} M, approximately 100-fold higher than that of its structural analog amprenavir (King *et al.,* 2004).

X-ray crystallographic analysis has shown that the compound's P1 and P1′ groups form van der Waals interactions with protease residues Leu-23, Gly-49, Ile-50, Pro-81, Val-82, and Ile-84 from both protease subunits, with additional interactions between the P2 and P2′ groups and residues Ala-28, Asp-29, Asp-30, Val-32, Ile-47, and Ile-50 (Koh *et al.,* 2003; Tie *et al.,* 2004). The crystal structure of HIV-1 protease has demonstrated a unique curling conformation at the flap regions that are important for darunavir binding (Nakashima *et al.,* 2016).

The terminal bis-tetrahydrofuran group is of major importance to the potency of the agent, due to formation of hydrogen bonds between the two oxygen atoms of this moiety and the amide groups of the Asp-29 and Asp-30 residues on the protease backbone (Surleraux *et al.,* 2005). Conformational analysis studies have demonstrated that darunavir exhibits both rigid and flexible docking within the active site of a range of both wild-type and mutant proteases, forming highly stable complexes (Nivesanond *et al.,* 2008).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

Darunavir is approved for use in both treatment-naive and -experienced adults and children aged 3 years and older. It must always be administered together with a cytochrome

Table 245.1. Major mutations associated with reduced susceptibility to darunavir.

Mutation	Selecting antiviral agent	Effect on DRV susceptibility	Cross-resistance
V11I/L	DRV	Minimal reduction	Minimally reduced susceptibility to FPV
V32I	IDV, FPV, LPV, DRV	Reduced	All protease inhibitors except SQV
L33F	All protease inhibitors except ATV, IDV, SQV	Reduced when occurs with other protease inhibitor mutations	Reduced susceptibility to DRV, FPV, LVP, TPV ± NFV in combination with other protease inhibitor mutations
I47V	IDV, FPV, LPV, DRV; usually occurs in combination with V32I	Reduced	Reduced susceptibility to all protease inhibitors except SQV and ATV
I50V	I50V selected by FPV, LPV, DRV	Reduced	Reduced susceptibility to FPV, LPV; increased susceptibility to TPV
I54M/L	FPV, LPV, DRV	Reduced	Reduced susceptibility to FPV, LPV, NFV, IDV, ATV (I54M/L), TPV (I54M); increased susceptibility to TPV (I54L)
G73S/T/C/A	SQV, ATV, IDV, NFV	Reduced	All protease inhibitors, except TPV
L76V	IDV, LPV, DRV	Reduced	Reduced susceptibility to IDV, LPV, FPV; increased susceptibility to ATV, SQV, TPV
V82F	IDV or previous treatment with multiple protease inhibitors	Reduced	Reduced susceptibility to IDV, FPV, LPV, NFV
I84V	Selected by all protease inhibitors, most frequently IDV, LPV, DRV, SQV, TPV	Reduced	Reduced susceptibility to all protease inhibitors
L89V	IDV, NFV, FPV, LPV, DRV	Reduced	Reduced susceptibility to IDV, NFV, LPV, FPV

Abbreviations: DRV: darunavir; FPV: fosamprenavir; IDV: indinavir; LPV: lopinavir; SQV: saquinavir; ATV: atazanavir; TPV: tipranivir; NFV: nelfinavir.
Sources: Data compiled from de Meyer (2008) and Stanford University 2014 database (Rhee, 2003).