5b. Drug distribution

Darunavir is highly protein bound (95%), binding predominantly to alpha$_1$-acid glycoprotein (AAG) in plasma and, to a lesser extent, albumin (Kakuda, *et al.,* 2014c). The volume of distribution after intravenous administration is 88.1 l when administered alone and 130.8 l when co-administered with ritonavir (Rittweger and Arasteh, 2007).

Darunavir achieves clinically significant levels in cerebrospinal fluid (CSF), semen, and cervicovaginal fluid (Patterson *et al.*, 2011; Taylor *et al.*, 2010; Yilmaz *et al.*, 2009). Limited data demonstrate that darunavir can cross the placenta (McCormack *et al.,* 2014).

Median CSF concentration of darunavir was 34.2 ng/ml (range: 15.9–212) with twice-daily dosing, with the majority (93.5%) being free drug rather than protein bound (Croteau *et al.*, 2013). In this study fractional penetrance of darunavir into the CSF compartment was found to be 1.4% of the median total plasma concentration; however, this correlated with unbound CSF darunavir levels that exceeded the IC_{90} for wild-type virus by a median of 20.6-fold. Of note, CSF levels appear to be lower with once-daily dosing, with trough concentrations measured at 10.7 ng/ml (range: 6.7–23) versus 38.2 ng/ml (range: 30.2–52.3) in patients receiving twice-daily dosing (Calcagno *et al.*, 2012).

In two studies in which maternal and cord plasma trough darunavir levels were available in pregnant women receiving darunavir boosted with ritonavir, 800/100 mg once daily, the median cord/maternal blood ratio in the two studies was similar: 0.11 (range: 0.06–0.49) (Lambert *et al.,* 2014) and 0.13 (0.08–0.35) (Colbers *et al.,* 2015). However, another recent study has reported a median darunavir CSF concentration of 13.2 (range: 3.5–33.0) ng/ml with a CSF: plasma ratio of 0.008 (0.004–0.0.017) in patients receiving darunavir boosted with ritonavir 800/100 mg once daily (Di Yacovo *et al.,* 2015).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Findings from a prospective observational study where 150 patients with virologic suppression were switched from triple therapy to receive ritonavir-boosted darunavir monotherapy (800 mg darunavir/100 mg ritonavir) once daily have demonstrated that the darunavir C_{min} correlated with virological control, with higher C_{min} present during undetectable viremia. No precise cut-off value could be defined (Nishijima *et al.,* 2014).

5d. Excretion

Darunavir is extensively metabolized in the liver, predominantly by CYP3A4. In addition to being a CYP3A4 substrate, darunavir is also an inhibitor of the cytochrome enzyme, with a reported inhibitory constant (K_i) of 0.22 µg/l (Rittweger and Arasteh, 2007). *In vitro* studies involving human liver microsomes showed darunavir has three primary metabolites: M19 by carbamate hydrolysis, M23 by aliphatic hydroxylation, and M29 by aromatic hydroxylation. All three primary metabolites are at least 10-fold less potent than darunavir itself. Three minor metabolites M27, M28, and M6 have also been elucidated (Rittweger and Arasteh, 2007). The terminal half-life of ritonavir-boosted darunavir is approximately 15 hours. Studies using radiolabeled drug have demonstrated that excretion is primarily in feces (79.5%) and urine (13.9%) (Janssen, 2015a).

5e. Drug interactions

Darunavir is metabolized by the CYP3A; therefore, drugs that either inhibit or induce this enzyme can lead to altered levels of darunavir. When used concomitantly with ritonavir, darunavir acts as an inhibitor of the hepatic cytochrome enzymes CYP3A and CYP2D6, in addition to the transporter P-glycoprotein, leading to the prolonged therapeutic effect of medications that are metabolized or transported by these enzymes or transporter.

For details of interactions with specific drugs, see Table 245.4, Table 245.5, and Table 245.6. For updated information see the most recent package insert.

6. ADVERSE REACTIONS AND TOXICITY

The most commonly reported adverse drug reactions reported with darunavir are diarrhea (up to 14.4%), headache (up to 8.8%), nausea (up to 7%), abdominal pain (up to 6.4%), and skin rash (11%) (Janssen, 2015a; Nishijima *et al.,* 2014).

6a. Hepatotoxicity

During clinical development involving a large cohort of > 3000 participants exposed to darunavir, hepatotoxicity developed in 0.5% of participants. Patients with preexisting liver disease, including chronic viral hepatitis, were at higher risk (Janssen, 2015a). In treatment-naive participants, the incidence of grade 3 or 4 elevations in transaminase levels was low, being 1.2% in ARTEMIS (Orkin *et al.*, 2013) and 3% in FLAMINGO (Molina *et al.*, 2015). Similarly, in treatment-experienced cohorts, rates of grade 3 or 4 transaminase rises were low, reported at 2–3% in the darunavir arm of POWER (Arasteh *et al.,* 2009; Clotet *et al.*, 2007); 7–9% in TITAN (Madruga *et al.,* 2007), which was similar to the lopinavir comparator arm; and 1.7–3.5% in ODIN (Cahn *et al.,* 2011).

Postmarketing cases of severe liver injury, including fulminant hepatitis leading to death, have been reported, although a causal relationship to darunavir was not established (Janssen, 2015a). These cases were associated with advanced HIV infection, use of concomitant medications, concurrent viral hepatitis, and/or the development of the immune reconstitution inflammatory syndrome. More frequent monitoring of liver function tests is recommended by the manufacturer and the FDA in patients with underlying liver disease.