Of 64 women, 30 who received boosted darunavir 800/100 mg once daily and 43 who received 600/100 mg twice daily, who underwent pharmacokinetic analyses during second and third trimesters as well as postpartum, the median darunavir AUC and maximum concentration were significantly reduced during pregnancy with both dosing regimens; 38% and 39% reduction in AUC in the second and third trimesters with once-daily darunavir, and 26% and 26% with twice-daily dosing (Stek *et al.,* 2015). While these authors suggested that an increased, twice-daily dose may be needed there is no recommendation for an altered dose in pregnancy by the manufacturers.

Darunavir maximum concentration ($C_{max)}$ and AUC were also decreased in 24 pregnant women receiving ritonavir-boosted darunavir (600/100 mg) twice daily or 800/100 mg once daily. The unbound (active) fraction of darunavir did not differ during pregnancy; 12% during pregnancy and 10% postpartum (Colbers *et al.,* 2015).

4d. Those requiring altered dosages

PATIENTS WITH IMPAIRED RENAL FUNCTION

There are no pharmacokinetic data available for the use of darunavir in HIV-infected patients with severe or end-stage renal impairment. However, due to its limited renal clearance, a significant decrease in total drug excretion would not be expected. Moreover, both darunavir and ritonavir are highly protein bound in plasma and, therefore, unlikely to be significantly cleared by dialysis. Population pharmacokinetic data demonstrate that darunavir is not significantly affected by the presence of mild to moderate renal impairment (creatinine clearance [CrCl]: 30–60 ml/minute) and no dose adjustment is required (Janssen, 2015a).

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

As darunavir is primarily metabolized by the liver, darunavir should be prescribed with caution in patients with hepatic dysfunction. Patients co-infected with hepatitis B and/or C were included in trials of both treatment-naive and -experienced patients. Limited data are available regarding the use of darunavir in patients with severe hepatic impairment and its use is not recommended in this setting.

In a subgroup of patients with co-existent viral hepatitis, darunavir was associated with lower rates of transaminase derangement than in the lopinavir-containing comparator arm (Orkin *et al.,* 2013). In a treatment-experienced cohort, there were similar rates of grade 2–4 transaminase elevations in darunavir-treated patients versus the lopinavir comparator arm (Madruga *et al.*, 2007). A substudy of the TITAN cohort showed no significant pharmacokinetic changes in patients with mild to moderate hepatic impairment and therefore no dosing adjustments are recommended in this group (Sekar *et al.,* 2010). In the subset of 68 patients with active hepatitis C co-infection and receiving ritonavir-boosted darunavir who were enrolled within the ICONA trial no severe (grade 3 or 4) elevation in liver enzymes was found (Di Biagio *et al.,* 2014).

ELDERLY PATIENTS

Clinical trials of darunavir have not included sufficient numbers of elderly patients to draw any strong inferences about this group. The manufacturer recommends caution in using this agent in patients aged > 65 years (Janssen, 2015a).

5. PHARMACOKINETICS AND PHARMACODYNAMICS

5a. Bioavailability

Absorption of darunavir is rapid after oral administration, with the C_{max} being achieved 2.5–4 hours after a ritonavir -boosted dose (Sekar *et al.,* 2007). Bioavailability after a single 600 mg dose of darunavir alone is 37%, whereas boosting with ritonavir yields a bioavailability of 82% (Janssen, 2015a). Bioequivalence has been demonstrated between the 800 mg darunavir tablet and two 400 mg tablets, in both fed and fasted conditions (Kakuda *et al.,* 2014a). Comparable bioavailability has also been demonstrated for the fixed-dose combination darunavir–cobicistat (800/150 mg) once daily and darunavir–ritonavir (800/100 mg) once daily (Kakuda *et al.,* 2014b).

When healthy volunteers were administered darunavir at 600 mg twice daily with ritonavir, C_{max} in the nonfasted state ranged from 5.33 to 5.91 µg/ml (Sekar *et al.*, 2007). Once-daily ritonavir-boosted darunavir (at 800/100 mg) yielded a C_{max} in healthy controls of 7.46 µg/ml (± 20.3%). Reported AUC_{24} was 80 µg·h/ml (± 34%) (Kakuda *et al.,* 2014c) with once-daily dosing of darunavir. In contrast, median AUC24 values of 109.4–123.3 µg.h/ml (range 48.9, 355.4 µg·h/ml) were reported in an analysis of groups of participants receiving twice-daily dosing (Janssen, 2015a).

Cobicistat, a potent inhibitor of CYP3A4 with no intrinsic antiviral activity, yields a comparable pharmacokinetic profile to boosting ritonavir. When cobicistat (150 mg) was co-administered with 800 mg of darunavir, C_{max} was 7.74 µg/ml (± 21.8%), and estimated AUC_{24} was 81.1 µg/h/ml (± 31%) (Kakuda *et al.,* 2014b).

In vivo data suggest that an active transport mechanism is involved in intestinal absorption, with darunavir being a known substrate of the ATP-dependent P-glycoprotein efflux transporter on intestinal cells. Ritonavir inhibits P-glycoprotein-mediated efflux, thereby leading to increased absorption of darunavir (Fujimoto *et al.*, 2009). C_{max} is increased by up to 30% when darunavir is ingested with food, although the type of food appears to make no difference (Sekar *et al.*, 2007). This effect has also been demonstrated when cobicistat is used as a pharmacological enhancer (Kakuda *et al.,* 2014b).

The estimated drug exposure after once- or twice-daily boosted darunavir has been reported as median population pharmacokinetic estimates in both adults and children (Janssen, 2015a). Estimates in adolescents receiving once-daily dosing (800/100 mg) were comparable with the reported AUC_{24} geometric mean 80.7 µg/h/ml (± 23.6) (Flynn *et al.,* 2014). Children receiving twice-daily dosing at 20 mg/kg of darunavir with concomitant 3 mg/kg ritonavir had a reported AUC_{24} of 157 µg/h/ml (± 50.2) (Violari *et al.,* 2015).