less than 50 HIV-1 RNA copies/ml at week 48. Noninferiority was demonstrated in the 48-week analysis, with a virologic response of 72.1% in the once-daily arm, versus 70.9% in the twice-daily arm. The rates of virologic failure did not significantly differ between the two treatment regimens (Cahn *et al.,* 2011). In a subanalysis, nearly 50% of patients had non-B HIV subtypes, and 46% were NNRTI experienced but protease inhibitor naive. In this report the efficacy data at week 48 are reported differently (Geretti *et al.,* 2015).

PROTEA

In the PROTEA study patients were randomized to assess efficacy and safety of ritonavir-boosted darunavir (800/100 mg) once daily as monotherapy versus darunavir plus two NRTIs as triple therapy in patients with suppressed VL. At 48 weeks boosted-darunavir monotherapy was less effective in maintaining virologic suppression than triple therapy (Antinori *et al.,* 2015). In the intent-to-treat analysis, virologic suppression to < 50 copies/ml at week 96 remained lower in the monotherapy arm (103 of 137 patients, 75%) than with triple therapy (116 of 136 patients, 85%), particularly those with a CD4 of < 200 cells/μl (Girard *et al.,* 2016). There was no difference in neurocognitive function, although 2 patients with CD4 nadir of < 200 cells/μl and who were receiving darunavir monotherapy had detectable viral load in plasma and CSF, and one patient was hospitalized with HIV encephalomyelitis (Clarke *et al.,* 2014).

INROADS

INROADS was a phase IIb, single-arm, open-label, multicenter study that examined a nucleoside sparing regimen of etravirine 400 mg plus darunavir boosted with ritonavir (800/100 mg) once daily in treatment-experienced patients or -naive patients with transmitted drug resistance. Of the 54 participants in the study, 7 experienced virological failure; and 74% of the intention to treat population had virological suppression at week 48. The most common reported adverse events were diarrhea (15%) and rash (15%).

7c. Use in salvage regimens

The ANRS 139 TRIO trial, a phase II, noncomparative study, examined the use of darunavir in combination with etravirine and raltegravir, with or without a background regimen of either an NRTI or enfuvirtide (Fagard *et al.,* 2012; Yazdanpanah *et al.,* 2009). This study was conducted in a highly treatment experienced cohort, with resistance to multiple antiretroviral agents and few remaining treatment options. At baseline, patients had a median of four primary protease inhibitor mutations, one NNRTI mutation, and six NRTI mutations, but were naive to the investigational drugs being used in the study. The primary end point was virologic suppression with a viral load < 50 copies/ml at 24 weeks, with followup to 96 weeks also reported. At 24 weeks, 90% of patients had achieved virologic suppression. The effect was durable, with 88% remaining suppressed at 96 weeks.

7d. Use with cobicistat

Darunavir–cobicistat is the first boosted protease inhibitor in a fixed-dose combination (Rezolsta). It may reduce pill burden and thus improve adherence. It has been included as an alternative regimen in the 2015 US treatment guidelines.

The use of darunavir with an alternate pharmacokinetic enhancer cobicistat, a cytochrome P-450 3A inhibitor, was investigated in a phase IIIb, open-label, noncomparative, single-arm study (Tashima *et al.,* 2014; Crutchley *et al.,* 2016). Participants were either treatment naive or experienced, but had no darunavir RAMs on genotypic testing. The primary end point was safety and tolerability; however, virologic responses were high (81% overall and 83% in treatment-naive subjects), consistent with previous studies. Cobicistat inhibits transporters of creatinine in renal tubules and thus exerts a reversible reduction in estimated glomerular filtration rate. Consistent with this, in this study a rise in serum creatinine was observed, with a mean change of 0.09 mg/dl.

7e. Use in pregnancy and lactation

There have been no controlled studies on the use of darunavir in human pregnancy. Animal studies in mice, rats, and rabbits exposed to up to 100 0mg/kg/day of darunavir, with or without ritonavir, showed no evidence of teratogenicity (Janssen, 2015a). However, due to limited bioavailability in animals as well as dosing limitations, the plasma exposure to darunavir was approximately 50% in rodents and 5% in rabbits of those seen in humans. The Antiretroviral Pregnancy Registry in its interim report with data up to July 31, 2015, had 333 registered pregnancies with first trimester exposure to darunavir. The overall rate of birth defects in this group was 2.7%, which was not significantly higher than the rate in the CDC's birth defects surveillance system (APRegistry, 2015). The registry has sufficient numbers of pregnancy outcomes from first trimester exposure to darunavir to exclude at least a twofold increase in the risk of birth defects. Darunavir is listed as a category B2 drug in pregnancy.

The DHHS (2015c) guidelines on the perinatal management of HIV lists darunavir as one of the preferred protease inhibitors in this setting, particularly in women who may elect to stop therapy postpartum. Several small studies have investigated the pharmacokinetics of darunavir in pregnancy, with mixed findings. Studies measuring total darunavir concentrations in pregnancy have found low plasma levels in the second and third trimester in women provided once-daily dosing, with AUC_{24} levels reduced by up to 39% (Stek *et al.*, 2015). Where the unbound, active fraction of darunavir has been measured, studies have shown this parameter to be either unchanged during pregnancy (Colbers *et al.,* 2015) or lower when compared to plasma exposures postpartum (Zorrilla *et al.*, 2014). The DHHS recommend twice-daily dosing of darunavir with ritonavir in pregnancy.

There are currently no available safety or pharmacokinetic data for darunavir in combination with cobicistat in pregnancy, and it is not recommended in this patient group.