regimens. In the RADAR study, the combination of darunavir and raltegravir was found to be inferior in terms of virologic response at 48 weeks when compared to tenofovir plus emtricitabine plus darunavir, although this was largely due to higher rates of discontinuation in the raltegravir arm (Bedimo *et al.,* 2014).

Similarly, in ACTG A25262, an open-label, single-arm study investigating darunavir and raltegravir in treatment-naive patients, the rate of virologic failure at 48 weeks was 16% (Taiwo *et al.,* 2011).

Studies using darunavir in combination with the CCR5 antagonist maraviroc have demonstrated inferior rates of virologic efficacy to tenofovir plus emtricitabine also with boosted darunavir (Stellbrink e*t al*., 2016), with lack of efficacy not associated with non-R5 tropism or resistance, leading to early termination of the study in the case of the MODERN study.

7b. Treatment-experienced adults

POWER

The use of darunavir was initially studied in highly treatment experienced adults. In POWER 1, 2, and 3, the licensing studies (Clotet *et al.,* 2007; Katlama *et al.,* 2007), ritonavir-boosted darunavir was studied in a heavily pretreated cohort. Inclusion criteria for this study required at least one preexisting protease inhibitor mutation. The majority of patients (> 90%) in both arms had previous treatment with multiple classes of drugs, with prior exposure to a mean of four protease inhibitors, five NRTIs and one NNRTI in the darunavir arm versus four protease inhibitors, six NRTIs, and one NNRTI in the comparator arm. The primary outcome, virologic response, was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 $\log_{10}$ versus baseline. Patients were randomized to receive either ritonavir-boosted darunavir with an investigator-selected optimized background regimen (OBR), or a control arm receiving an investigator-selected protease inhibitor(s) regimen plus an OBR. Selected protease inhibitors in the control arm included lopinavir–ritonavir in 36%, fosamprenavir in 34%, saquinavir in 35%, atazanavir in 17%, and dual-boosted protease inhibitors in 23%. The choice of protease inhibitors was guided by genotypic resistance testing and treatment history. After 24-week dose-finding phases and primary efficacy analyses, participants continued in the assigned treatment arm to the longer term open-label phase.

Overall, 47% of patients in the study were also treated with enfuvirtide, with similar rates of use between the two arms. At 48 weeks, 61% of patients in the darunavir arm, versus 15% in the control arm, had viral load reductions of 1 $\log_{10}$ copies/ml or greater from baseline. At this time point, 45% of participants in the darunavir arm, versus 11.3% in control protease inhibitor arm had a viral load of < 50 copies/ml. At 96 and 144 weeks, the darunavir-containing regimen remained superior to the control protease inhibitor arm in terms of virologic suppression. It is important that rates of discontinuation were high in the study (21% in darunavir arm versus 81% in control protease inhibitor arm at 48 weeks), particularly in the control arm, with virologic failure being the primary reason for cessation in both groups. However, virologic responses were significantly better in the darunavir arm at the earlier time points of 12 and 24 weeks, suggesting that the high rate of treatment discontinuation in the control arm was not the primary driver of differences between the groups.

TITAN

The TITAN study also investigated the use of darunavir in a treatment-experienced cohort (Banhegyi *et al.,* 2012; Madruga *et al.,* 2007). Patients were randomized to receive darunavir and ritonavir at 600/100 mg twice daily versus lopinavir and ritonavir at 400/100 mg twice daily. Both arms used an OBR made up of two different antiretrovirals (NRTIs with or without an NNRTI). Again, this was a highly pretreated cohort, with previous exposure to NRTIs in > 50% and NNRTIs in > 75% of patients in both arms. The primary end point was viral load < 400 copies/ml at 48 weeks. Patients with previous exposure to lopinavir were excluded. Darunavir, in combination with the NRTI-based OBR, demonstrated significantly better rates of virologic suppression, compared to lopinavir at both 48 and 96 weeks. At 48 weeks, 71% of patients in the darunavir arm, versus 60% in the lopinavir arm, were virologically suppressed with an HIV-1 RNA < 50 copies/ml. At 96 weeks, 60.4% in the darunavir arm, versus 55.2% of patients treated with lopinavir were virologically suppressed. Predetermined criteria for noninferiority was met at both 48 and 96 weeks. Subsequent testing for superiority demonstrated that significantly more patients in the darunavir arm achieved a viral load < 400 copies/ml at both 48 and 96 weeks.

MONET

Patients with stable virologic suppression on ART were switched to darunavir boosted with ritonavir (800/100 mg) once daily either monotherapy or with two NRTIs. At week 48, 86.2% and 87.8% of patients receiving monotherapy or triple therapy had virologic suppression, respectively, showing noninferiority with boosted darunavir monotherapy (Arribas *et al.,* 2010). These data extended to 144 weeks showed noninferior efficacy in a strict intent-to-treat analysis where switches were not considered failures, but not in a time to loss of virologic response (TLOVR) analysis in which switch equals failure (Arribas *et al.,* 2012).

ODIN

The use of once-daily darunavir in treatment-experienced patients was investigated in ODIN, a randomized, open-label trial comparing darunavir–ritonavir 800/100 mg once daily to darunavir–ritonavir 600/100 mg twice daily in 590 patients with no darunavir-associated mutations on baseline genotypic testing. The background regimen consisted of at least two NRTIs. The primary objective was to demonstrate noninferiority of virologic response in the once-daily dosing arm. Virologic response was defined as a plasma viral load of