randomized, controlled, double-blind study of 44 HIV-infected individuals with only CCR5 virus given subcutaneous administration of PRO 140, mean reductions in HIV viral load were observed of up to 1.65 $\log_{10}$ copies/ml compared to placebo In a single-arm, open-label, phase IIb extension study of HIV-infected individuals with only CCR5 HIV-1 and virologic suppression on antiretroviral therapy (ART), switching to weekly subcutaneous PRO 140 (350 mg) resulted in maintenance of virologic suppression in 8 of 11 subjects for approximately 56 weeks, with no development of antibodies against PRO 140. The 3 patients with virologic failure had no change in co-receptor tropism The company announced in April 2016 that 10 HIV-infected patients in the ongoing PRO 140 monotherapy extension study maintained complete viral load suppression for at least 18 months. As of July 2016 there were six active trials listed for PRO 140 at ClinicalTrials.gov, including a pivotal phase III trial (NCT02483078). PRO 140 does not appear to interfere with the normal immune function of CCR5, but there were some significant side effects (Li *et al.*, 2010; Pace and Markowitz, 2015; Tenorio, 2011).

2j. Ibalizumab

Ibalizumab (TMB-335, TNX-355, Hu5A8) is an anti-CD4 monoclonal antibody that blocks entry of HIV-1. It has broad and potent antiviral activity *in vitro* and *in vivo*. Median *in vitro* neutralization potency assessed by EC_{50} was 0.03 ug/ml. Early clinical trials of monotherapy resulted in a 10-fold reduction in HIV viral load. Preliminary results from current studies suggest efficacy with 82% of patients with multidrug-resistant HIV infection achieving the primary end point of a decrease of at least 0.5 $\log_{10}$ HIV RNA copies/ml after 7 days of treatment. Two phase III trials are under way (NCT02707861 and NCT02475629) (Mazor *et al.*, 2015; Pace and Markowitz, 2015).

2k. 3BNC117

The neutralizing antibody 3BNC117 targets the CD4 binding site on gp120, thus blocking HIV entry, with recent human studies. One dose of 3BNC117 given to HIV-infected subjects appeared to increase native neutralizing antibodies; no long-term or clinical data were available. In another study, when given to HIV-infected, viremic subjects, 3BNC117 cleared plasma virus and also killed HIV-infected cells by an Fc-dependent mechanism. As of July 2016, three phase I and phase II clinical trials listed at ClinicalTrials.gov are ongoing (Lu *et al.*, 2016; Schoofs *et al.*, 2016).

2l. Bictegravir

Bictegravir (GS-9883) is a novel integrase strand transfer inhibitor with low nM potency against wild-type HIV-1 that does not require boosting with ritonavir or cobicistat. It also displays an improved resistance profile relative to elvitegravir, raltegravir, and dolutegravir in patient isolates with high-level integrase inhibitor resistance, particularly for strains with mutations E92Q plus N155H or Q148R/H/K plus G140A/C/S. Bictegravir (in a dose of 50 mg) is being developed with emtricitabine (FTC) and TAF as a single-tablet regimen and is in several phase III clinical trials for the once-daily treatment of HIV-infected patients (NCT02397694, NCT02607930, and NCT02603107) (White *et al.*, 2016).

2m. Doravirine

Doravirine (MK-1439) is nonnucleoside reverse transcriptase inhibitor (NNRTI) under development for treatment of HIV infection. Doravirine has an EC_{50} of 9.7–12 nM against wild-type HIV and is active against many HIV strains with K103N, Y181C, E138K, Y181C, and K101E mutations, which mediate resistance of HIV to the NNRTIs nevirapine, etravirine, and rilpivirine. Pharmacokinetic studies of doravirine reveal it is mainly eliminated by oxidative metabolism (thus it unlikely to cause drug–drug interactions), and its profile supports once-daily dosing. Seven days of monotherapy resulted in a median 1.37 $\log_{10}$ reduction in HIV viral load. In a phase IIb dose-ranging study (25, 50, 100, and 200 mg daily, plus tenofovir and emtricitabine) in ART-naive individuals, potent antiviral activity was observed at week 24 in all arms. Patients were then switched to doravirine 100 mg once daily or 600 mg once daily of efavirenz, with the same backbone. Antiviral activity was retained at 48 weeks, and central nervous system side effects were less with doravirine than with efavirenz. Doravirine is currently in a phase III clinical trial (NCT02275780) that has not yet started recruiting; three other trials are active (Schurmann *et al.*, 2016; Gatell *et al.*, 2014; Anderson *et al.*, 2015).

2n. Dapivirine

Dapivirine (TMC120) is a diaryltriazine nonnucleoside reverse transcriptase inhibitor under development for topical use as a vaginal microbicide (cervical rings or vaginal coating) to prevent HIV infection in women. Dapivirine gel (0.05%) and film (1.25mg) deliver drug at concentrations that block HIV *ex vivo*. Although more difficult to insert than the gel, women find the film more comfortable with less leakage. The flexible ring is self-inserted every 4 weeks and slowly releases drug into the vaginal tissue. *In vitro*, it is well tolerated by T cells, epithelial cells, macrophages, and cervical explant cells and has potent and prolonged (up to 6 days) activity against a range of NNRTI-resistant HIV strains. It has a good safety profile in 17 phase I/II studies. A phase III, randomized, double-blind, placebo-controlled trial (MTN-020-ASPIRE) of a monthly vaginal ring containing 25 mg of dapivirine in 2629 women between the ages of 18 and 45 years was conducted in Malawi, South Africa, Uganda, and Zimbabwe. Overall 71 infections occurred in the dapivirine group and 97 in the placebo arm. The incidence of HIV-1 infection in the dapivirine group was lower by 37% (95% confidence interval [CI]: 12–56; $p = 0.007$) than that in the placebo group in an analysis that excluded two sites that had