Table 1. Simulated Percentage of Patients With Higher-Than-Target Steady-State C_{24} hr for a Representative HIV-1 Patient Population Assuming Full Compliance

Dose, mg QD	Concentration, nM Median (90% PI)	Wild Type 78 nM	K103N 117 nM	Y181C 195 nM	G190A 211 nM	K103N/ Y181C 335 nM
25	228 (77, 580)	94.9	86.9	61.8	56.2	26.6
50	453 (156, 1051)	99.3	97.7	90.5	88.5	69.5
100	831 (276, 1993)	99.9	99.7	98.2	97.5	92.3
200	1467 (479, 3442)	100	100	99.5	99.4	98.3

QD, once daily; 90% PI, 90% prediction interval.
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analysis confirmed that there is no relationship between doravirine plasma levels and both efficacy and AE rates. Based on these results and the superior coverage of dual mutant HIV-1 strains [K103N/Y181C], the 100 mg dose of doravirine was selected for Part 2 of the study (with additional enrollment at 100 mg doravirine vs efavirez) and for study in Phase 3.

No Resistance and Improved Renal and Bone Profiles With a Single-Table Regimen of D/C/F/TAF

Written by Toni Rizzo

Tenofovir disoproxil fumarate (TDF) is a safe and potent prodrug of the nucleotide reverse transcriptase inhibitor tenofovir; it is available as a single-tablet regimen; and it can be taken in combination with 3 of the 4 guideline-recommended third agents. Tenofovir alafenamide (TAF) is a novel tenofovir prodrug that provides higher intracellular tenofovir diphosphate levels and lower plasma tenofovir levels than TDF. Darunavir is a protease inhibitor (PI) dosed as a single daily tablet. PIs have a high genetic barrier to resistance, but a PI-based single-tablet regimen has not been available.

Anthony Mills, MD, Southern California Men's Medical Group, Los Angeles, California, USA, presented the results of the week 48 analysis of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-Boosted Darunavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment Naïve Adults [GS-US-299-0102; NCT01565850]. This phase 2 trial compared the combination of darunavir/cobicistat/emtricitabine/TAF (D/C/F/TAF) versus darunavir (DRV) boosted by cobicistat (COBI) and F/TDF in treatment-naïve HIV-infected adults.

A total of 150 treatment-naïve patients with HIV RNA ≥5000 copies/mL, CD4 >50, estimated glomerular filtration rate >70 mL/min, and a screening genotype with sensitivity to darunavir, TDF, and emtricitabine (F) were randomized to D/C/F/TAF (n=100) or DRV+COBI+F/TDF (n=50) once daily with matched placebos. The primary end point was HIV-1 RNA <50 copies/mL (virologic success) at week 24.

At week 24, there were similar proportions of patients in the D/C/F/TAF and DRV+COBI+F/TDF groups that achieved virologic success (75% vs 74%; weighted difference, 3.3; 95% CI, −11.4 to 18.1). At week 48, 77% of patients in the D/C/F/TAF group versus 84% in the DRV+COBI+F/TDF group had achieved virologic success (weighted difference −6.2; 95% CI, −19.9 to 7.4).

Of 8 patients meeting the criteria for resistance analysis due to virologic rebound, none tested resistant to TDF, emtricitabine, or darunavir. The study drug was discontinued by 18% of D/C/F/TAF patients and 16% of DRV+COBI+F/TDF patients, but none of the discontinuations were efficacy related. Two patients in each arm discontinued due to adverse events (AEs). AEs in the D/C/F/TAF versus the DRV+COBI+F/TDF group were as follows: diarrhea (21% vs 26%), upper respiratory tract infection (16% vs 14%), fatigue (14% vs 18%), nausea (13% vs 10%), and rash (12% vs 8%).

The mean change in serum creatinine at week 48 was +0.06 mg/dL in the D/C/F/TAF group and +0.09 mg/dL in the DRV+COBI+F/TDF group ($P=.053$). Renal tubular proteinuria rates were significantly lower in the D/C/F/TAF group (retinol binding protein:creatinine ratio, $P=.003$; β-2 microglobulin:creatinine ratio, $P=.002$).

At week 48, in the D/C/F/TAF group versus the DRV+COBI+F/TDF group, the median changes in fasting metabolic assessments were as follows: total cholesterol (40 vs 5 mg/dL, $P<.001$), low-density lipoprotein (26 vs 4 mg/dL, $P<.001$), high-density lipoprotein (7 vs 3 mg/dL, $P=.009$); total cholesterol:high-density lipoprotein ratio (0.0 vs −0.2, $P=.15$), triglycerides (29 vs −5 mg/dL, $P=.007$), and serum glucose (5 vs 2 mg/dL, $P=.33$). Patients in the D/C/F/TAF group had a significantly lower mean percentage change in bone mineral density of the hip ($P\leq.001$) and spine ($P=.003$) at week 48.

At week 48, viral suppression rates were the same in both study groups, and no patients had developed drug resistance. Both regimens were well tolerated, with similarly low rates of AE-related discontinuation. Dr Mills concluded that the improved renal and bone profiles of TAF and the high-resistance barrier of darunavir warrant a phase 3 study of a single-tablet regimen of D/C/F/TAF.