Supplemental digital content 1

No pharmacokinetic (PK) analysis was originally planned for Study A4001095 and, therefore, no specific PK samples or dose times relative to sample collection were collected. Institutional review boards or independent ethics committees were approached for permission to use stored samples, originally intended for potentially additional virology analysis, for a post hoc PK analysis.

Week 4 samples (or next available sample if a Week 4 sample was not available) for all maraviroc (MVC) subjects, for whom permission was obtained, were assessed for MVC, darunavir (DRV), and ritonavir (RTV) concentrations. For those subjects who were not virologically suppressed at Week 48 (Categories 2, 3, and 4 below), the Week 48 sample or a sample taken just prior to failure/discontinuation was also assessed. Plasma samples were analyzed for MVC (Tandem Laboratories, West Trenton, NJ) and DRV and RTV (Tandem Laboratories, Salt Lake City, UT) using validated liquid chromatography–tandem mass spectrometry analytical methods.

For the purpose of the analysis, subjects were categorized as described below and virologic successes were compared with virologic failures.

- Category 1–virologic success: HIV-1 RNA <50 copies/mL at Week 48
- Category 2–virologic failure: HIV-1 RNA ≥50 copies/mL at Week 48
- Category 3–no HIV-1 RNA data at Week 48 but discontinued for any reason (excluding adverse event or death) prior to Week 48 with HIV-1 ≥50 copies/mL or switched background drugs after Week 4
- Category 4–no HIV-1 RNA data at Week 48 but not discontinued from the study, or discontinued for adverse event or death irrespective of HIV-1 RNA, or

discontinued for any other reason prior to Week 48 with HIV-1 RNA <50 copies/mL

Graphical data analysis and summaries were performed using R scripts (version 3.0.2) in R Studio™.

Supplemental digital content 2

Pharmacokinetic analysis

Post hoc pharmacokinetic (PK) analysis to determine maraviroc (MVC), darunavir (DRV), and ritonavir (RTV) concentrations at Week 4 (Week 8 for 5 subjects) was performed for 313 of 396 patients in the MVC treatment arm. Of these subjects 255 (81.5%) had HIV-1 RNA <50 copies/mL at Week 48 and were thus considered to be virologic successes. For the 58 "non-successes," 15 (4.8%) had HIV-1 RNA ≥50 copies/mL at Week 48; 21 (6.7%) discontinued mainly due to lack of efficacy prior to Week 48; and 22 (7.0%) had no HIV-1 RNA data at Week 48 and were not discontinued or had discontinued prior to Week 48 with HIV-1 RNA <50 copies/mL, some because of adverse events. For 54 of the 58 non-successful subjects, a Week 48 sample or one taken just prior to the point of virologic failure was also assessed.

For the analysis of Week 4 samples, 9 subjects had values below the limit of quantification (BLQ) for one or more drug(s), but there was no clear association between BLQ values and lack of virologic success. Three successful subjects had switched from DRV to another protease inhibitor prior to the Week 4 sample, accounting for DRV concentrations BLQ. One subject with HIV-1 RNA ≥50 copies/mL at Week 48 had BLQ values for all 3 analytes at Week 4. Five subjects had BLQ concentrations for RTV at Week 4, including 2 who were considered to be successful (see Table S1 below).

Table S1. Subjects with BLQs for one or more analytes on the first occasion at or after Week 4 (N = 9)

Week	Efficacy (Week 48)	MVC (ng/mL)	DRV (ng/mL)	RTV (ng/mL)
4	HIV-1 RNA <50 copies/mL	86.5	0 (SW Day 16)	99.8
4	HIV-1 RNA ≥50 copies/mL	0	0	0
4	No HIV-1 RNA data at Week 48	175	1880	0
4	HIV-1 RNA <50 copies/mL	37.7	0 (SW Day 20)	20.3
4	HIV-1 RNA <50 copies/mL	6.34	764	0
4	HIV-1 RNA <50 copies/mL	0	3020	201
4	HIV-1 RNA <50 copies/mL	474	2050	0
4	HIV-1 RNA <50 copies/mL	534	0 (SW Day 25)	318
4	No HIV-1 RNA data at Week 48	21.2	278	0

DRV, darunavir; MVC, maraviroc; RTV, ritonavir; SW, switch.

Overall the concentrations of all 3 drugs were similar in successful and unsuccessful subjects, but were slightly lower for the subset of subjects with HIV-1 RNA ≥50 copies/mL at Week 48 (see Table S2 below). For subjects with paired samples, repeat PK analysis close to failure did not show evidence of a lowering of concentrations relative to first analysis.

Table S2. Summary of concentrations measured at Week 4

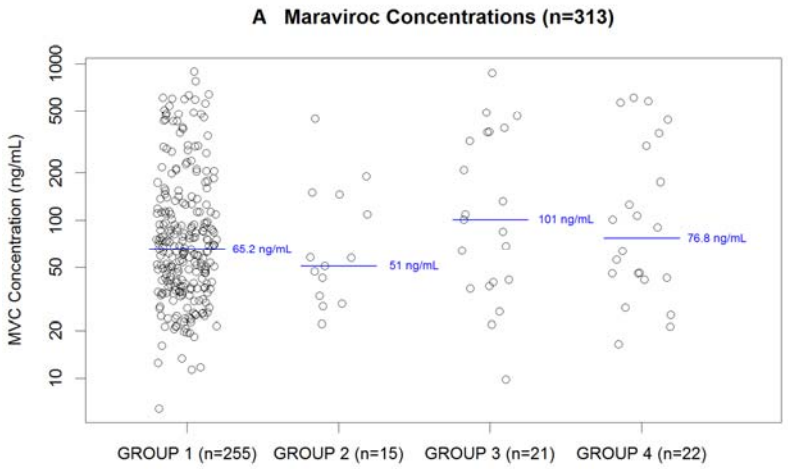
Variable	Min	First quartile	Mean	Median	Third quartile	Max
Successes (N = 255)						
MVC (ng/mL)	0	37.7	121.23	65.2	116.5	891
DRV (ng/mL)	0	1995	3373.73	2900	4370	13,600
RTV (ng/mL)	0	67.6	192.54	126	234.5	1670
Non-successes (N = 58)						
MVC (ng/mL)	0	40.55	163.75	66.2	203.25	871
DRV (ng/mL)	0	2180	4087.22	3465	5600	12,400
RTV (ng/mL)	0	66.77	252.72	136	248.25	1950
HIV-1 RNA ≥50 copies/mL at Week 48 (N = 15)						
MVC (ng/mL)	0	31.15	93.6	51	127.5	441
DRV (ng/mL)	0	1650	3081	2370	4285	7780
RTV (ng/mL)	0	54.55	133.76	85.2	148	486

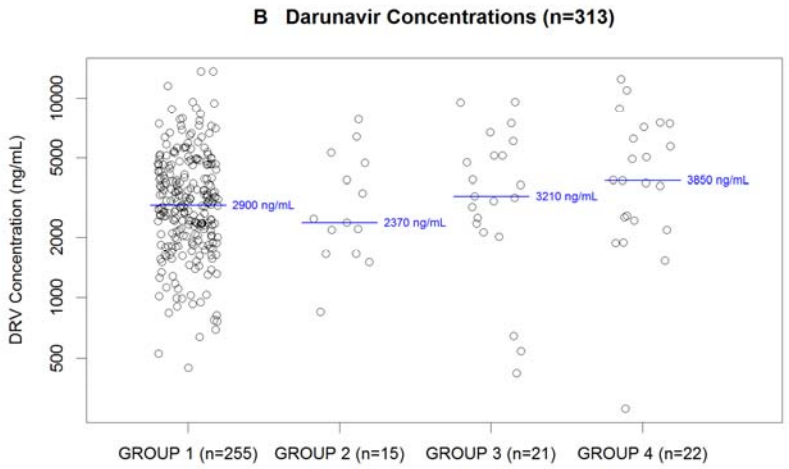
DRV, darunavir; min, minimum; max, maximum; MVC, maraviroc; RTV, ritonavir.

Graphical exploration of the relationships between concentrations of MVC, DRV, and RTV at ~4 weeks and efficacy using scatter plots and the median concentrations for the different categories are shown in Figure S1 for MVC (plot A), DRV (plot B), and RTV (plot C). Overall, it does not appear that success or non-success at Week 48 is strongly related to the concentrations of MVC, DRV, or RTV as the distribution of the various subsets overlaps and the medians are broadly similar.

In conclusion, although the lack of information regarding time of dose relative to the time of blood sampling limits the utility of this analysis, there does not appear to be

a strong association between study drug concentrations and likelihood of virologic success in MODERN.


A Maraviroc Concentrations (n=313)
MVC Concentration (ng/mL)
10
20
50
100
200
500
1000
65.2 ng/mL
51 ng/mL
101 ng/mL
76.8 ng/mL
GROUP 1 (n=255)
GROUP 2 (n=15)
GROUP 3 (n=21)
GROUP 4 (n=22)


B Darunavir Concentrations (n=313)
DRV Concentration (ng/mL)
500
1000
2000
5000
10000
2900 ng/mL
2370 ng/mL
3210 ng/mL
3850 ng/mL
GROUP 1 (n=255)
GROUP 2 (n=15)
GROUP 3 (n=21)
GROUP 4 (n=22)

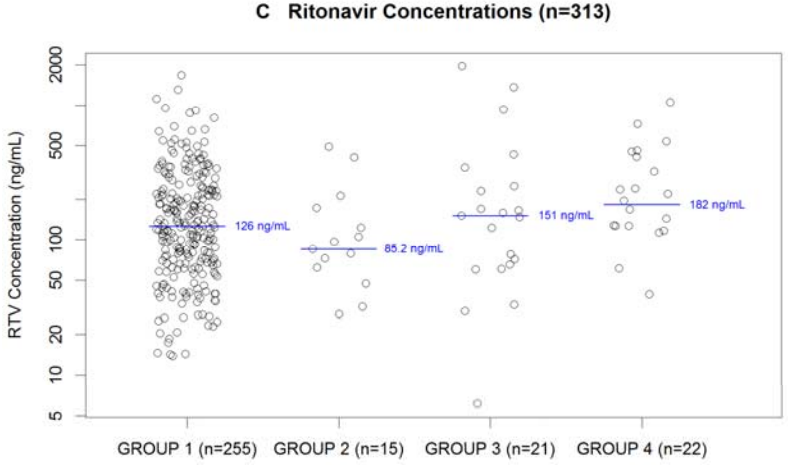

C Ritonavir Concentrations (n=313)
RTV Concentration (ng/mL)
5
10
20
50
100
200
500
2000
126 ng/mL
85.2 ng/mL
151 ng/mL
182 ng/mL
GROUP 1 (n=255)
GROUP 2 (n=15)
GROUP 3 (n=21)
GROUP 4 (n=22)

Figure S1. Week 4 concentrations of (A) maraviroc (MVC), (B) darunavir (DRV), and (C) ritonavir (RTV) vs efficacy categories with median values shown in blue with horizontal lines. Group 1–virologic success: HIV-1 RNA <50 copies/mL at Week 48; Group 2–virologic failure: HIV-1 RNA ≥50 copies/mL at Week 48; Group 3–no HIV-1 RNA data at Week 48 and discontinued prior to Week 48 with HIV-1 RNA ≥50 copies/mL; Group 4–no HIV-1 RNA data at Week 48 and not discontinued or discontinued prior to Week 48 with HIV-1 RNA <50 copies/mL, or for adverse events.

Evaluation of bone mineral density, bone turnover, and body fat distribution

The dual-energy x-ray absorptiometry (DEXA) sub-study included 143 subjects (MVC: n = 66; TDF/FTC: n = 77). The median age was 34.0 years, 10.5% were female, 23.8% were non-white, and the mean body mass index was 25.4 kg/m^2. Week 48 changes from Baseline after adjusting for baseline covariates such as age, race, gender, and screening body mass index are summarized in Table S3.

Tenofovir/emtricitabine was associated with greater decreases in hip bone mineral density (BMD) and higher concentrations of C-terminal telopeptide of type 1 collagen (CTx) than was MVC over 48 weeks (Table S3). No significant correlations between changes in BMD and osteocalcin or CTx levels were observed. Lower baseline CD4+ count (<200 cells/mm^3) was the only observed predictor for a larger decrease in hip BMD after adjusting for the covariates (estimate: -2.14%, P = 0.0055).

Table S3. Changes from baseline in BMD (DEXA), bone turnover (osteocalcin and CTx), and body fat distribution

DEXA/Bone parameter	MVC + DRV/r mean (± SD)	TDF/FTC + DRV/r mean (± SD)	*P* value
Hip (%)	-1.4 ± 2.2	-2.6 ± 2.3	0.0052
Femoral neck (%)	-2.2 ± 3.8	-3.2 ± 3.1	0.1640
Lumbar spine (%)	-2.5 ± 3.9	-3.0 ± 3.2	0.5441
Peripheral fat mass (g)	402 ± 1693	349 ± 1910	0.8379
Trunk to limb fat ratio (%)	3.2 ± 19.6	1.1 ± 12.6	0.3376
Osteocalcin (ng/mL)	5.6 ± 8.0	6.7 ± 8.3	0.1769
CTx (pg/mL)	121 ± 243	222 ± 288	0.0075

BMD, bone mineral density; CTx, C-terminal telopeptide of type 1 collagen; DEXA, dual-energy x-ray absorptiometry; DRV/r, darunavir/ritonavir; MVC, maraviroc; SD, standard deviation; TDF/FTC, tenofovir/emtricitabine.

Health outcomes measures

Approximately 80% of the subjects in each group had a mean adherence score of ≥95% during Weeks 12 to 48 according to responses on the Modified Medication Adherence Self-Report Inventory. Virologic response rate was higher in these subjects during Weeks 12 to 48 compared with subjects with <95% adherence in both groups. There were no discernible differences between the groups for changes in health-related quality of life, and no apparent differences in the numbers of nights spent in the hospital, clinic/office visits, or emergency room visits.