

Pharmacokinetic and Pharmacodynamic Analyses of Darunavir in Treatment-experienced Women and Men in GRACE (Gender, Race And Clinical Experience)

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Introduction

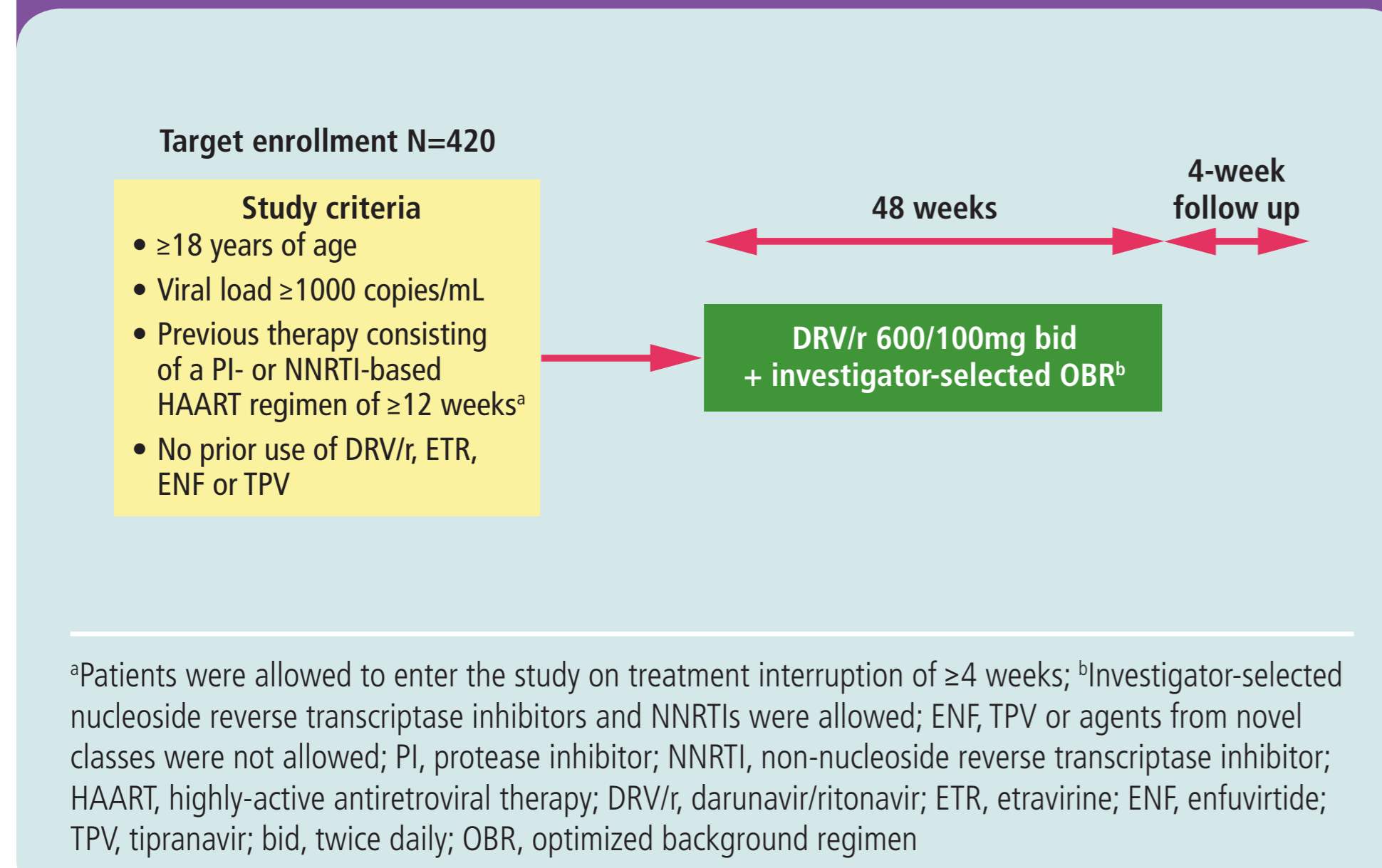
- Darunavir (DRV; PREZISTA®), a protease inhibitor, combined with low-dose ritonavir (DRV/r), has been approved for use in the United States and Europe as a therapeutic option for HIV-1 infected treatment-experienced and treatment-naïve adults and treatment-experienced pediatric patients (aged 6–17 years)^{1,2}
- Previous studies have demonstrated small, non-significant differences in DRV pharmacokinetic (PK) parameters between women and men, and across races^{3,4}
- The GRACE study was specifically designed to enroll a high proportion of women and people of color, in order to assess sex- and race-based differences in the efficacy and safety of DRV/r-based therapy
- In GRACE (N=429), 53.4% and 73.2% of patients achieved HIV-1 RNA <50 copies/mL at Week 48 in the ITT population, which included all patients who took at least one dose of study medication, and the non-virologic failure (VF) censored population, which censored patients that discontinued for reasons other than VF, respectively⁵
 - At Week 48 in the ITT population, the virologic response rate was 50.9% (146/287) in women and 58.5% (83/142) in men⁶; by race, virologic response rates were 48.5% (128/264), 61.5% (59/96) and 60.0% (39/65) in black, Hispanic and Caucasian patients, respectively⁶
 - At Week 48 in the non-VF censored population, the virologic response rate was 73.0% in women, 73.5% in men, 68.8% in black patients, 79.7% in Hispanic patients and 78.0% in Caucasian patients
- The high proportion of women (67%) and people of color (84%) enrolled in GRACE allows for comparisons of DRV PK according to sex and race
- Here we present Week 48 DRV PK data from GRACE according to sex and race, and investigate the relationship of DRV PK with efficacy and safety

Methods

Study design and treatment

- GRACE was a multicenter, 48-week, open-label, Phase IIIb study conducted in 65 study sites across the United States, Canada and Puerto Rico (Figure 1)

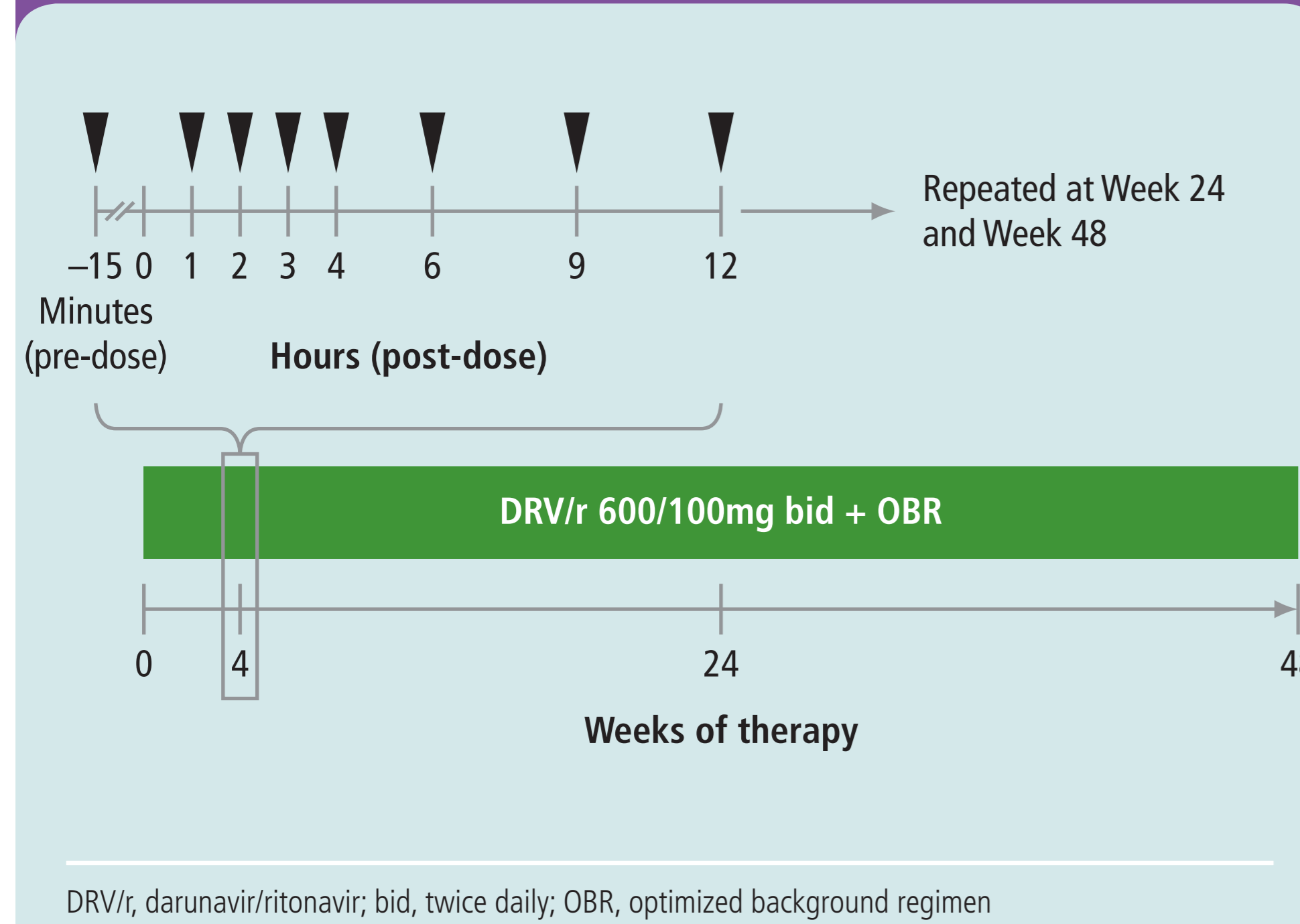
Figure 1. Study design



Pharmacokinetic analysis

- Sparse PK sampling for the determination of DRV plasma concentrations was performed in all patients at Weeks 4, 24 and 48
 - Two samples were taken at Weeks 4 and 24; one immediately before dosing and the second at least 1 hour after the first sample was drawn
 - A population PK model was applied to derive empirical Bayesian estimates of DRV 12-hour area under the curve (AUC_{12h}) and trough concentration (C_{0h})
- Intensive PK sampling was conducted for DRV and ritonavir (RTV) in a subset of patients at Weeks 4, 24 and 48 (Figure 2)

Figure 2. Pharmacokinetic substudy design



- Plasma concentrations of DRV and RTV were determined by a validated liquid chromatography-mass spectrometry method. The lower limit of quantification was 10.0ng/mL for DRV and 5.0ng/mL for RTV
- Relationships between DRV AUC_{12h}, C_{0h} and virologic efficacy at Week 48 were assessed using analysis of covariance models
 - The efficacy measurement tested in the model was change in log₁₀ viral load (VL) from baseline and the proportion of patients achieving a VL <50 copies/mL
- Relationships between DRV PK and safety were investigated descriptively
 - Rash-, cardiac-, gastrointestinal (GI)-, liver-, lipid-, glucose-, psychiatric- and nervous system-associated adverse events (AEs) were investigated

Results

Baseline population and baseline characteristics

- In GRACE (N=429), at baseline, on average women were younger and tended to have less advanced disease and be less treatment experienced compared with men; at baseline, patients had more advanced disease than Hispanic or Caucasian patients (Table 1)
 - Of the patients in GRACE, 376 had sparse sampling data and were included in the DRV PK analysis
 - Among the 376 patients with sparse samples, 66% (n=248) were women, 61% (n=228) black and 22% (n=84) Hispanic
 - 37 patients (25 women, 12 men) underwent intensive PK sampling; of these, 25 were black, 10 Hispanic and two Caucasian

Table 1. Baseline demographics and disease characteristics

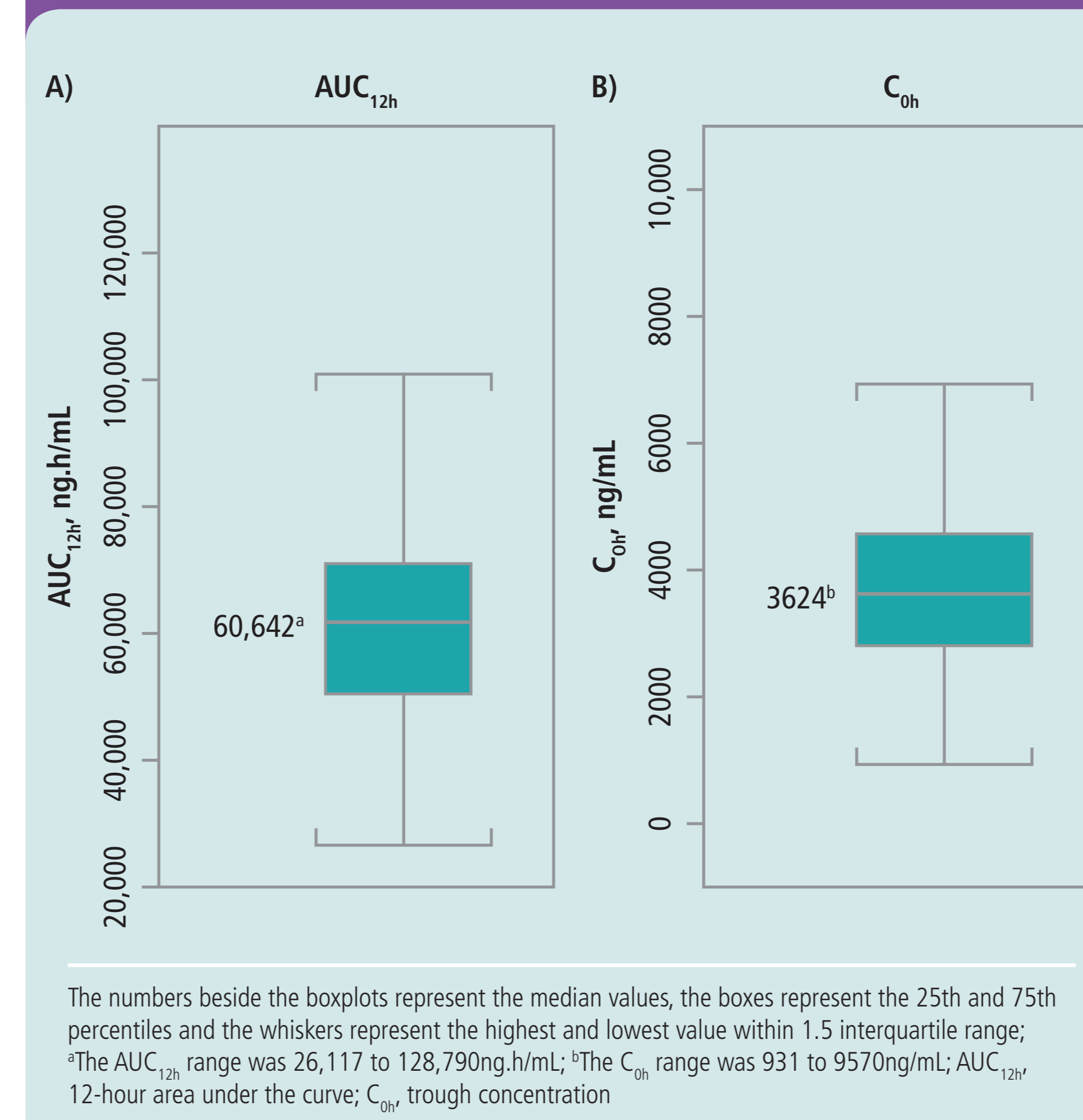
Parameter	Sex-based comparisons		Race-based comparisons ^a		
	Women n=287 (67%)	Men n=142 (33%)	Black n=264 (62%)	Hispanic n=96 (22%)	Caucasian n=65 (15%)
Mean (SE) age, years	41.7 (0.63)	45.2 (0.75)	43.0 (0.62)	40.3 (1.05)	45.5 (1.13)
Mean (SE) weight, kg	75.5 (1.27)	77.6 (1.32)	77.4 (1.31)	72.8 (1.56)	77.4 (2.32)
Mean (SE) BMI, kg/m ²	28.2 (0.44)	25.4 (0.42)	27.6 (0.44)	26.8 (0.58)	26.7 (0.88)
Mean (SE) duration of infection, years	10.9 (0.32)	12.2 (0.49)	11.0 (0.34)	10.5 (0.58)	13.8 (0.66)
Mean (SE) viral load, log ₁₀ copies/mL	4.65 (0.05)	4.73 (0.07)	4.66 (0.06)	4.68 (0.10)	4.73 (0.10)
Median (range) CD4+ count, cells/mm ³	210 (1, 868)	175 (2, 1125)	179 (1, 868)	208 (1, 1125)	249 (6, 826)
CDC Class C, n (%)	102 (35.5)	67 (47.2)	111 (42.0)	33 (34.4)	22 (33.8)
Median (range) DRV fold change ^{b,c}	0.6 (0.3, 128.7)	0.6 (0.4, 148.3)	0.6 (0.3, 148.3)	0.6 (0.4, 20.1)	0.6 (0.5, 39.0)
Prior use of ≥2 PIs, n (%)	168 (58.5)	92 (64.8)	156 (59.1)	60 (62.5)	42 (64.6)
Hepatitis B surface antigen (positive), n (%)	12 (4.2)	7 (4.9)	15 (5.7)	3 (3.1)	1 (1.5)
Hepatitis C antibody (positive), n (%)	39 (13.6)	25 (17.6)	41 (15.5)	12 (12.5)	11 (16.9)

^aFour patients self-identified as Asian or Other and were not included in the analysis by race; ^bemtricitabine (FTC) resistance analysis; ^cTwo patients, one Hispanic and one Caucasian (both women), did not have resistance testing at baseline; SE, standard error; BMI, body mass index; CDC, US Centers for Disease Control and Prevention; DRV, darunavir; PI, protease inhibitor

Pharmacokinetics

- For all patients evaluated, DRV C_{0h} was above the protein binding corrected half maximal effective concentration (EC₅₀) value for resistant virus (550ng/mL); the overall median DRV C_{0h} was 6.5-fold higher than the EC₅₀ value for resistant virus (Figure 3)

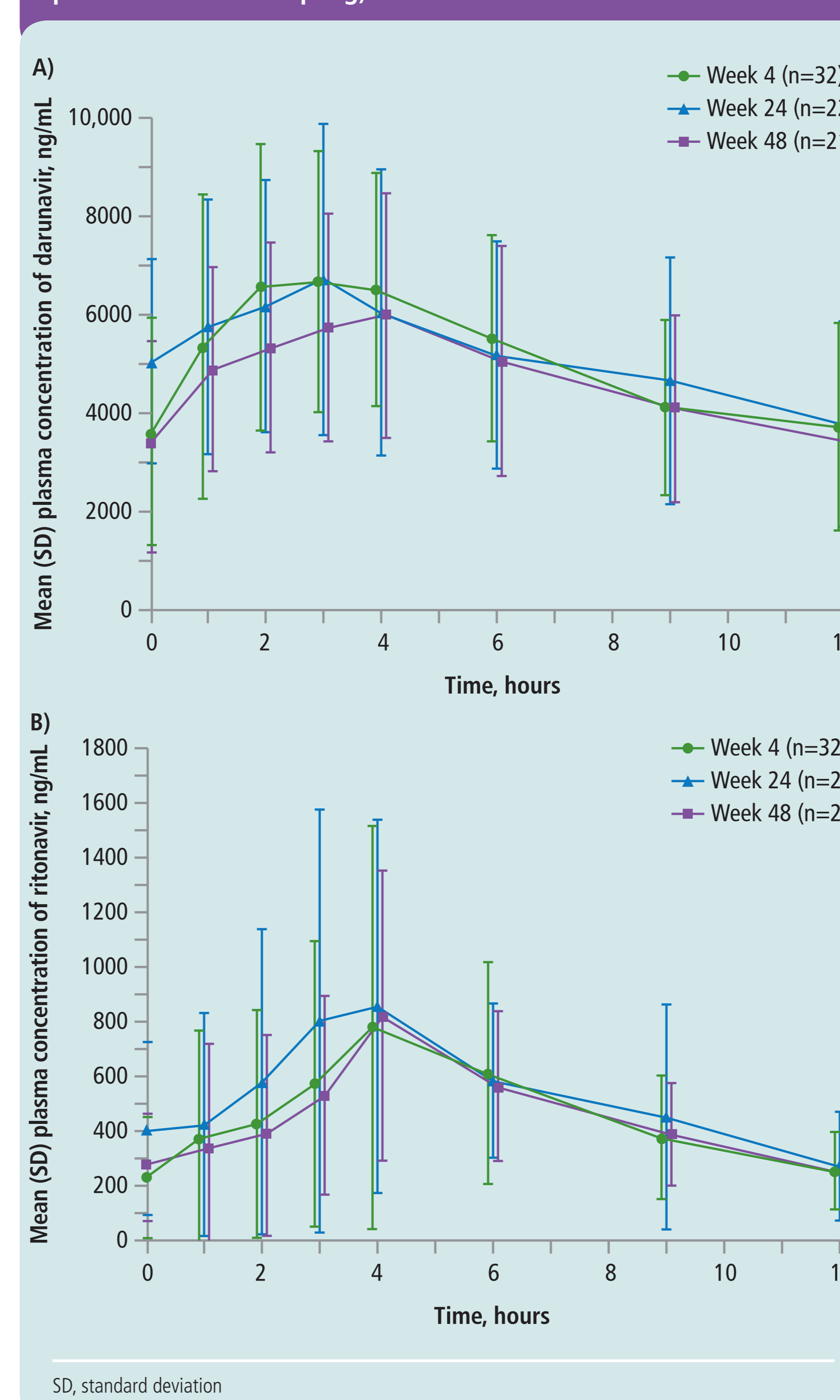
Figure 3. Darunavir (A) AUC_{12h} and (B) C_{0h} (sparse pharmacokinetic sampling; n=376)



The numbers beside the boxplots represent the median values, the boxes represent the 25th and 75th percentiles and the whiskers represent the highest and lowest value within 1.5 interquartile range; ^aThe AUC_{12h} range was 26,117 to 128,790ng·h/mL; ^bThe C_{0h} range was 931 to 9570ng/mL; AUC_{12h}, 12-hour area under the curve; C_{0h}, trough concentration

- Results from intensive PK sampling showed no time-dependent relationship for DRV or RTV over 48 weeks and were similar to the population PK results (Figure 4)

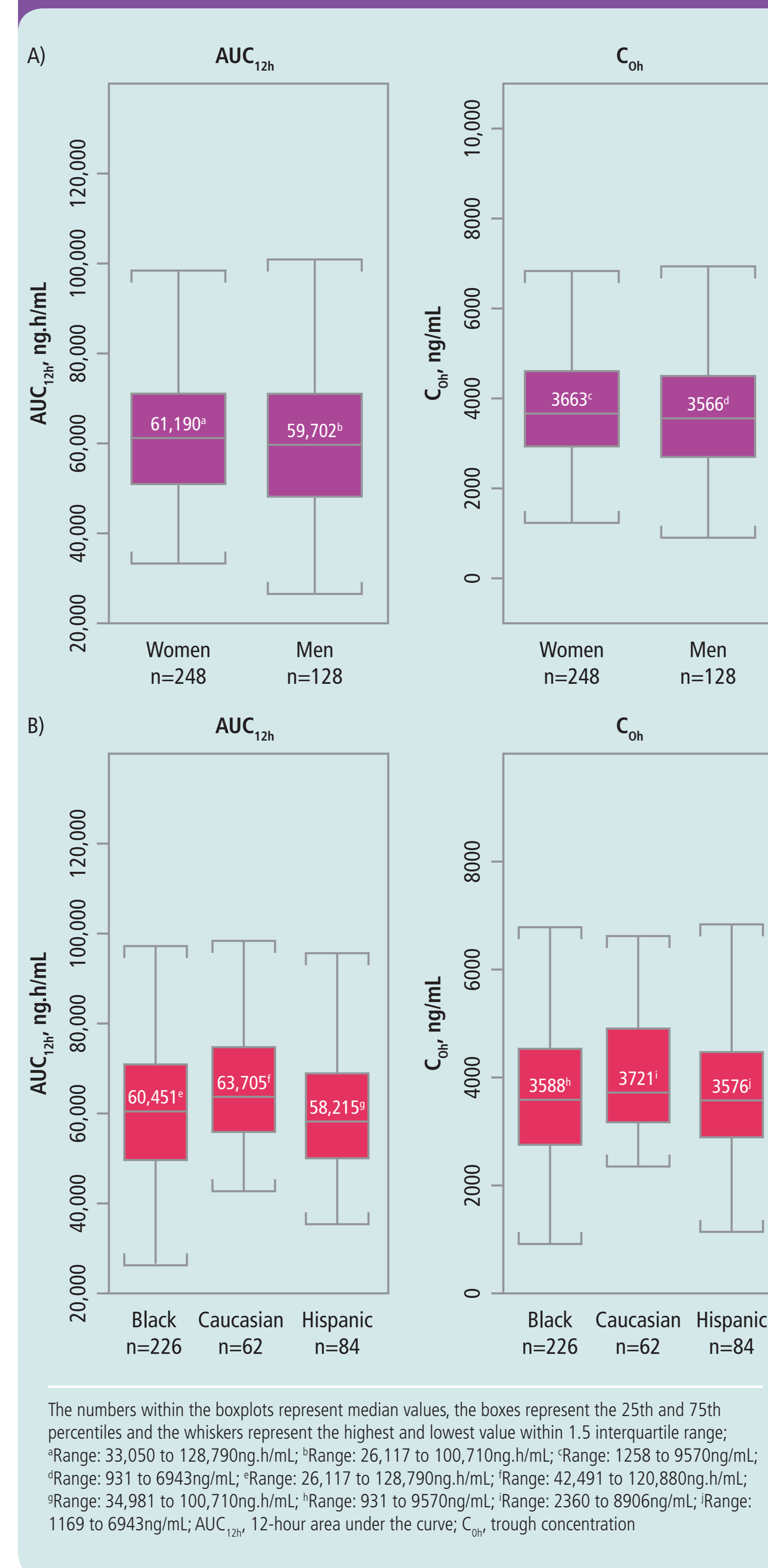
Figure 4. Plasma concentration–time curves of (A) darunavir and (B) ritonavir at Weeks 4, 24 and 48 (intense pharmacokinetic sampling)



Subgroup analyses by sex and race

- Analysis of DRV PK parameters by sex and race showed no substantial difference in AUC_{12h} or C_{0h} between women and men, or by race (Figure 5)

Figure 5. Darunavir AUC_{12h} and C_{0h} by (A) sex and (B) race (sparse pharmacokinetic sampling; n=376)

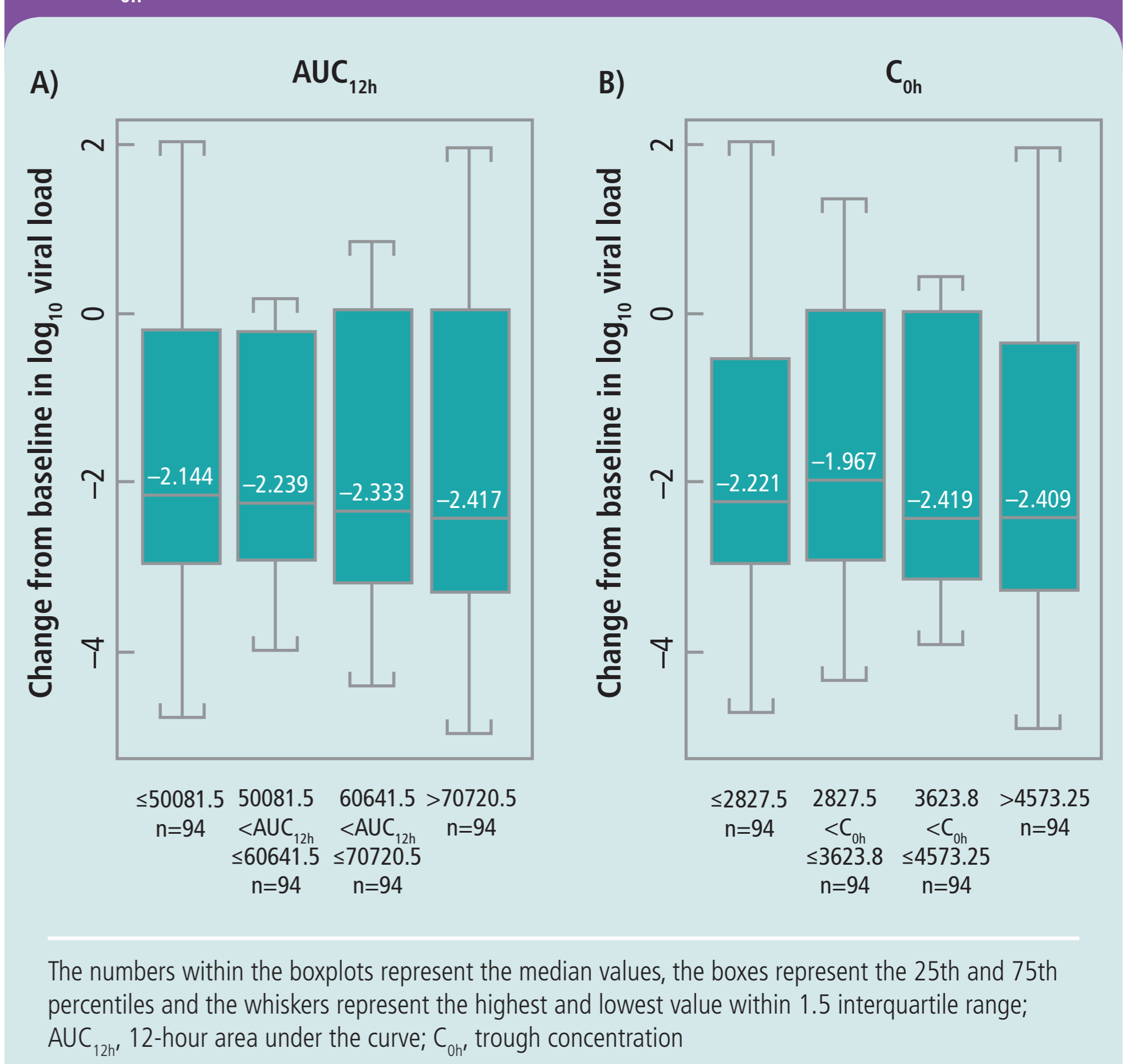


The numbers within the boxplots represent median values, the boxes represent the 25th and 75th percentiles and the whiskers represent the highest and lowest value within 1.5 interquartile range; ^aRange: 33,050 to 128,790ng·h/mL; ^bRange: 26,117 to 128,790ng·h/mL; ^cRange: 1258 to 9570ng/mL; ^dRange: 931 to 6943ng/mL; ^eRange: 26,117 to 128,790ng·h/mL; ^fRange: 42,491 to 120,880ng·h/mL; ^gRange: 34,981 to 100,710ng·h/mL; ^hRange: 931 to 9570ng/mL; ⁱRange: 2360 to 8906ng/mL; ^jRange: 1169 to 6943ng/mL; AUC_{12h}, 12-hour area under the curve; C_{0h}, trough concentration

Relationship between pharmacokinetics and efficacy

- No relationship was identified between DRV AUC_{12h} or C_{0h} values and the change in log₁₀ VL from baseline to Week 48 (Figure 6)

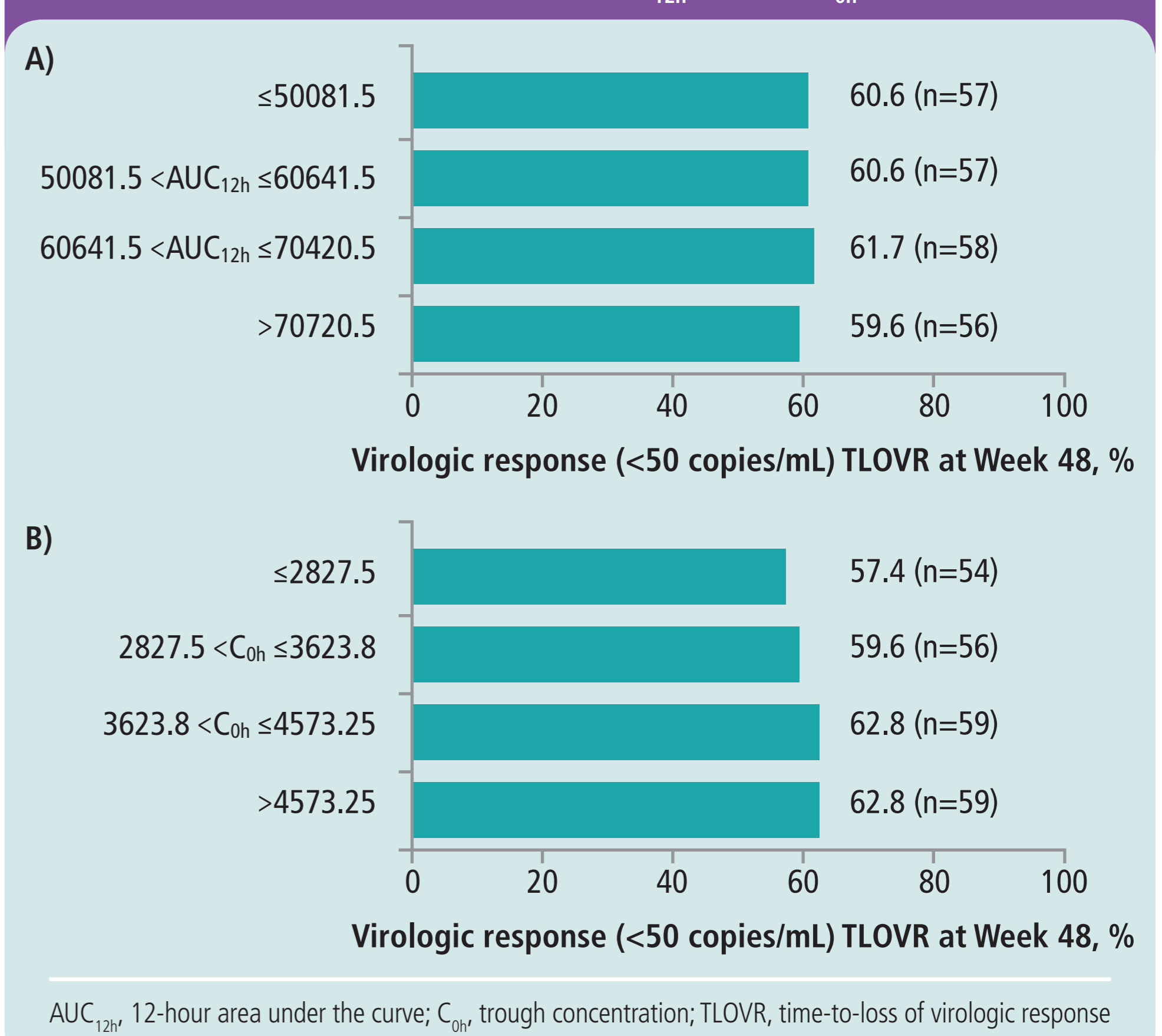
Figure 6. Change in log₁₀ viral load from baseline at Week 48 (ITT NC=F) by quartile ranges of darunavir (A) AUC_{12h} and (B) C_{0h} (sparse pharmacokinetic sampling; n=376)



The numbers within the boxplots represent the median values, the boxes represent the 25th and 75th percentiles and the whiskers represent the highest and lowest value within 1.5 interquartile range; AUC_{12h}, 12-hour area under the curve; C_{0h}, trough concentration

- There was no relevant relationship between DRV AUC_{12h} and C_{0h} and the proportion of patients that achieved HIV-1 RNA <50 copies/mL at Week 48 (Figure 7)

Figure 7. Virologic response (HIV-1 RNA <50 copies/mL) at Week 48 by quartile ranges of darunavir (A) AUC_{12h} and (B) C_{0h}

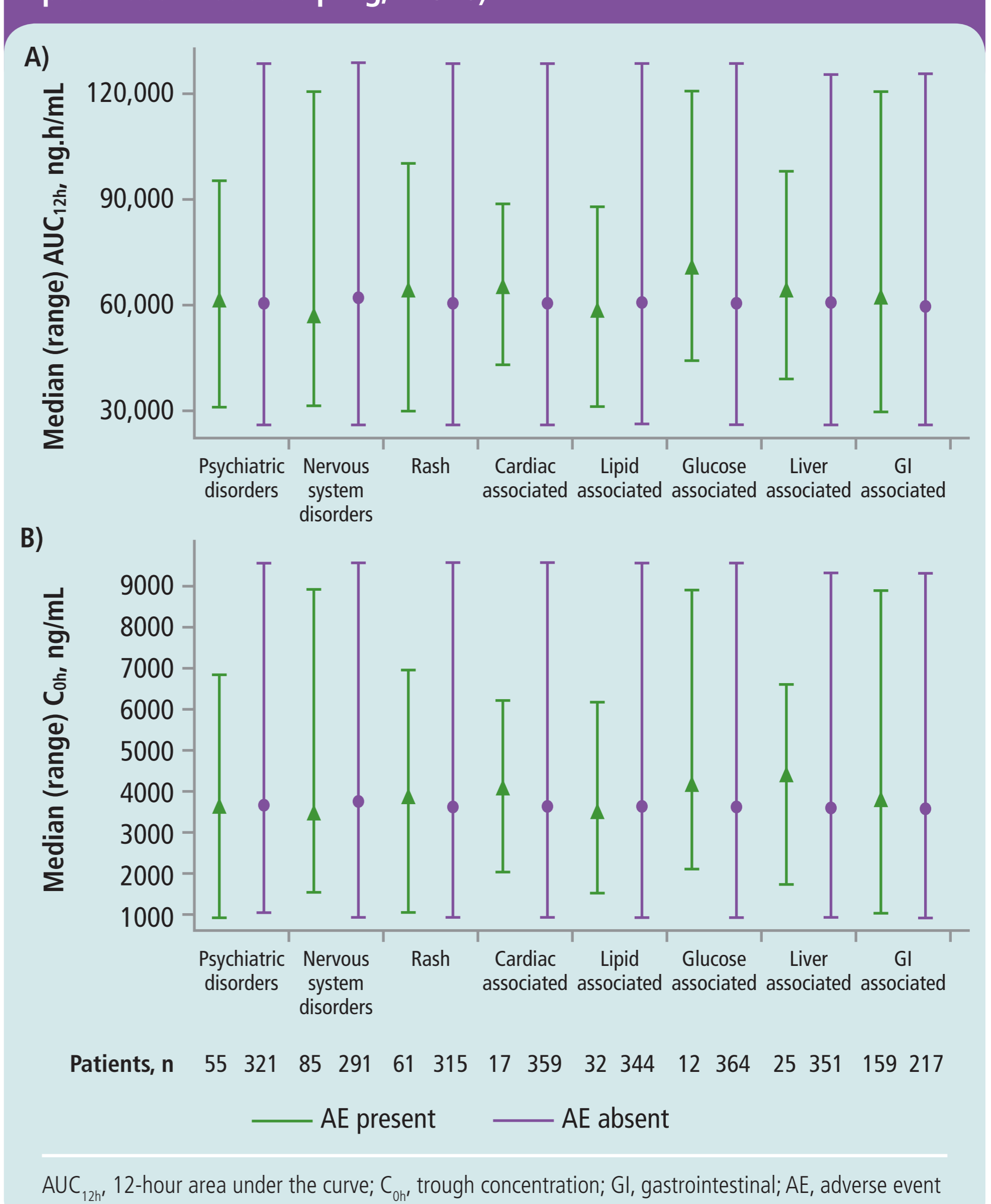


AUC_{12h}, 12-hour area under the curve; C_{0h}, trough concentration; TLOVR, time-to-loss of virologic response

Relationship between darunavir pharmacokinetics and safety

- No apparent relationships were observed between the DRV PK parameters and the incidence of rash-, cardiac-, GI-, liver-, lipid-, glucose-, nervous system disorder- or psychiatric disorder-associated AEs (Figure 8)

Figure 8. Presence or absence of adverse events of interest (regardless of severity or causality) by darunavir (A) AUC_{12h} and (B) C_{0h} (sparse pharmacokinetic sampling; n=376)



AUC_{12h}, 12-hour area under the curve; C_{0h}, trough concentration; GI, gastrointestinal; AE, adverse event

Discussion

- The GRACE trial demonstrated that DRV/r-based therapy is effective, generally safe and well tolerated across sexes and race/ethnic groups^{5,6}
- DRV C_{0h} was above the protein binding corrected EC₅₀ value for resistant virus (550ng/mL) for all patients, regardless of sex or race
- Similar median DRV exposures were observed in the POWER 3 and TITAN trials^{4,7}
- No differences in DRV PK parameters were observed between sexes or race/ethnic subgroups

Conclusions

- Pharmacokinetic results from GRACE demonstrated that sex and race did not appear to substantially affect DRV exposure
- No relevant relationship was observed between DRV PK parameters and the efficacy/safety of DRV/r-based therapy, which is consistent with previous findings^{4,8}

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Acknowledgements

The authors would like to thank the patients and their families, the study sites and the principal investigators for their participation in the trial. The authors would like to acknowledge Gilead for supplying tenofovir, emtricitabine and emtricitabine/tenofovir. The authors would additionally like to thank internal study support staff, as well as Cali Howitt, PhD, Medicus International, for her editorial assistance. Funding for the GRACE study and editorial support was provided by Tibotec Therapeutics.