

Rates and Predictors of Adherence in Treatment-experienced Women and Men in GRACE (Gender, Race And Clinical Experience)

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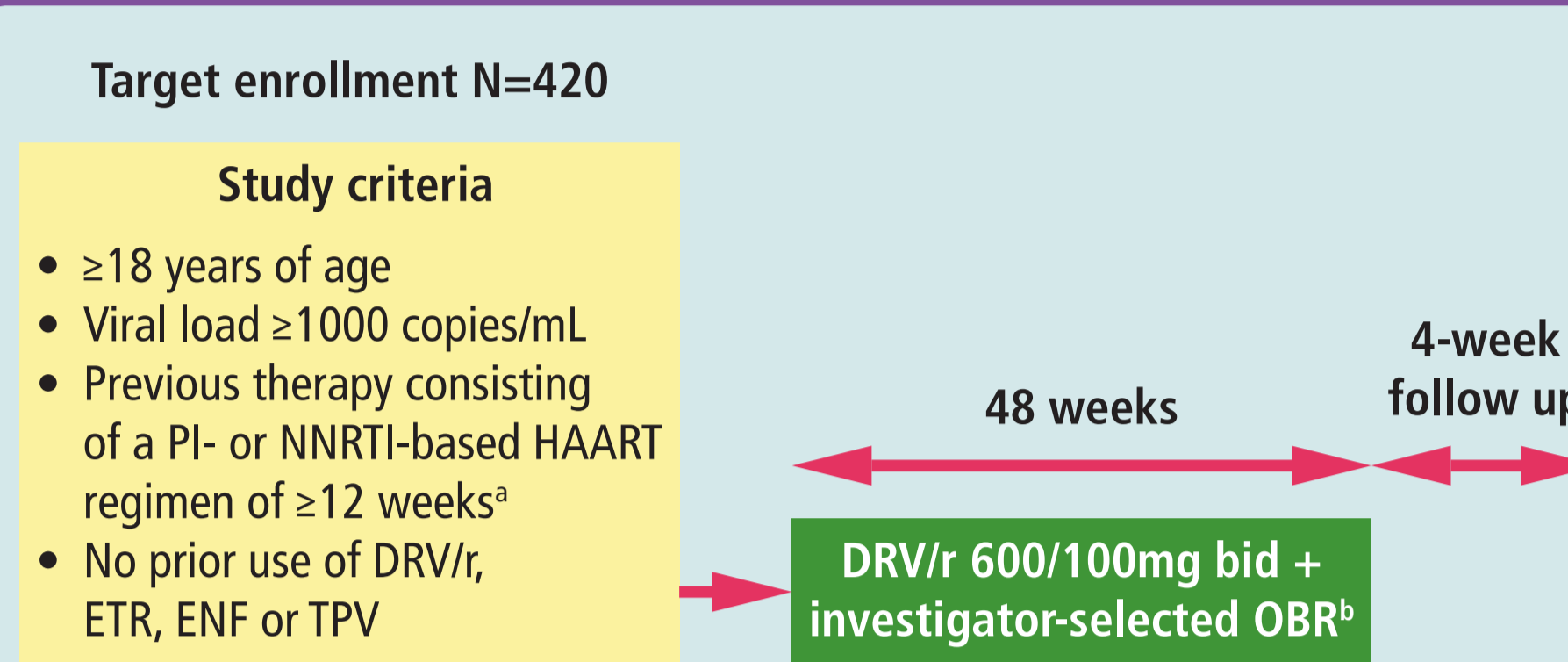
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Background

- GRACE was a multicenter, open-label, Phase IIIb study designed to assess the efficacy and safety of darunavir/ritonavir (DRV/r) plus an investigator-selected optimized background regimen (OBR) (Figure 1)¹
- The study was designed to enroll a high proportion of treatment-experienced women infected with HIV-1 who would reflect the demographics of HIV-infected women in the United States²

Figure 1. Study design



^aPatients were allowed to enter the study on treatment interruption of ≥4 weeks; ^bInvestigator-selected nucleoside reverse transcriptase inhibitors and NNRTIs were allowed; ENF, TPV or agents from novel classes were not allowed; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HAART, highly-active antiretroviral therapy; DRV/r, darunavir/ritonavir; ETR, etravirine; ENF, enfuvirtide; TPV, tipranavir; bid, twice daily; OBR, optimized background regimen

- Virologic response, defined as HIV-1 RNA <50 copies/mL, was calculated using a time-to-loss of virologic response (TLOVR) algorithm in the intent-to-treat (ITT) population, which included patients who took at least one dose of study medication, and in the non-virologic failure (VF) censored population, which adjusted for discontinuations that were not due to VF
- The virologic response rate at Week 48 was 53.4% in the ITT population and 73.2% in the non-VF censored population². The response rates at Week 48 by sex and race are shown in Table 1

Table 1. Virologic response at Week 48 by sex and race^a

HIV-1 RNA <50 copies/mL	Black	Hispanic	Caucasian
ITT-TLOVR, n/N (%)			
Women	89/191 (46.6)	35/60 (58.3)	21/34 (61.8)
Men	39/73 (53.4)	24/36 (66.7)	18/31 (58.1)
TLOVR non-VF censored, n/N (%)			
Women	89/128 ^b (69.5)	35/44 (79.5)	21/27 (77.8)
Men	39/58 ^b (67.2)	24/30 (80.0)	18/23 (78.3)

^aFour patients who self-identified as Asian or Other were not included in the analysis by sex; ^bOne black patient was assessed for response at Week 48 and subsequently discontinued for reasons other than VF; ITT, intent-to-treat; TLOVR, time-to-loss of virologic response; VF, virologic failure

- Results from a *post-hoc* exploratory analysis, conducted to investigate factors predictive of virologic response (ITT-TLOVR) at Week 48, demonstrated that adherence was one of the strongest predictors of virologic response in GRACE³
 - The response rate in patients with ≥95% adherence was 63.1%, while in patients with <95% adherence, the response rate was only 34.7%³
- Based on results from the predictors of response analysis and, specifically, the significance of adherence as a predictor, an additional *post-hoc* analysis investigating factors correlated with adherence was performed

Methods

Adherence

- During the GRACE study, adherence, defined as taking ≥95% of expected doses of DRV/r over the course of treatment, was assessed via 4-day patient recall at Weeks 4, 8, 12, 16, 24 and 48 for patients still on study (total doses expected–total doses missed)/total doses expected; based on the timepoints for which each patient had data)
- Paterson et al. showed that >95% adherence to protease inhibitor (PI) therapy resulted in increased efficacy⁴

Univariate and multivariate analyses

- Forty-two covariates encompassing patient and disease characteristics, treatment factors, baseline resistance, site characteristics and comorbidities were evaluated in a univariate analysis for predictors of adherence
- Covariates significant at the $P < .15$ level in the univariate analyses were considered for the multivariate model
- If two or more covariates were highly correlated ($R^2 > .80$), the most significant covariate in the univariate analysis was selected for the multivariate analysis
- The multivariate analysis was performed using a forward stepwise selection, with entry and stay criteria of $P < .15$ and $P < .10$, respectively
- Odds ratios were adjusted for other covariates that were included in the final multivariate model

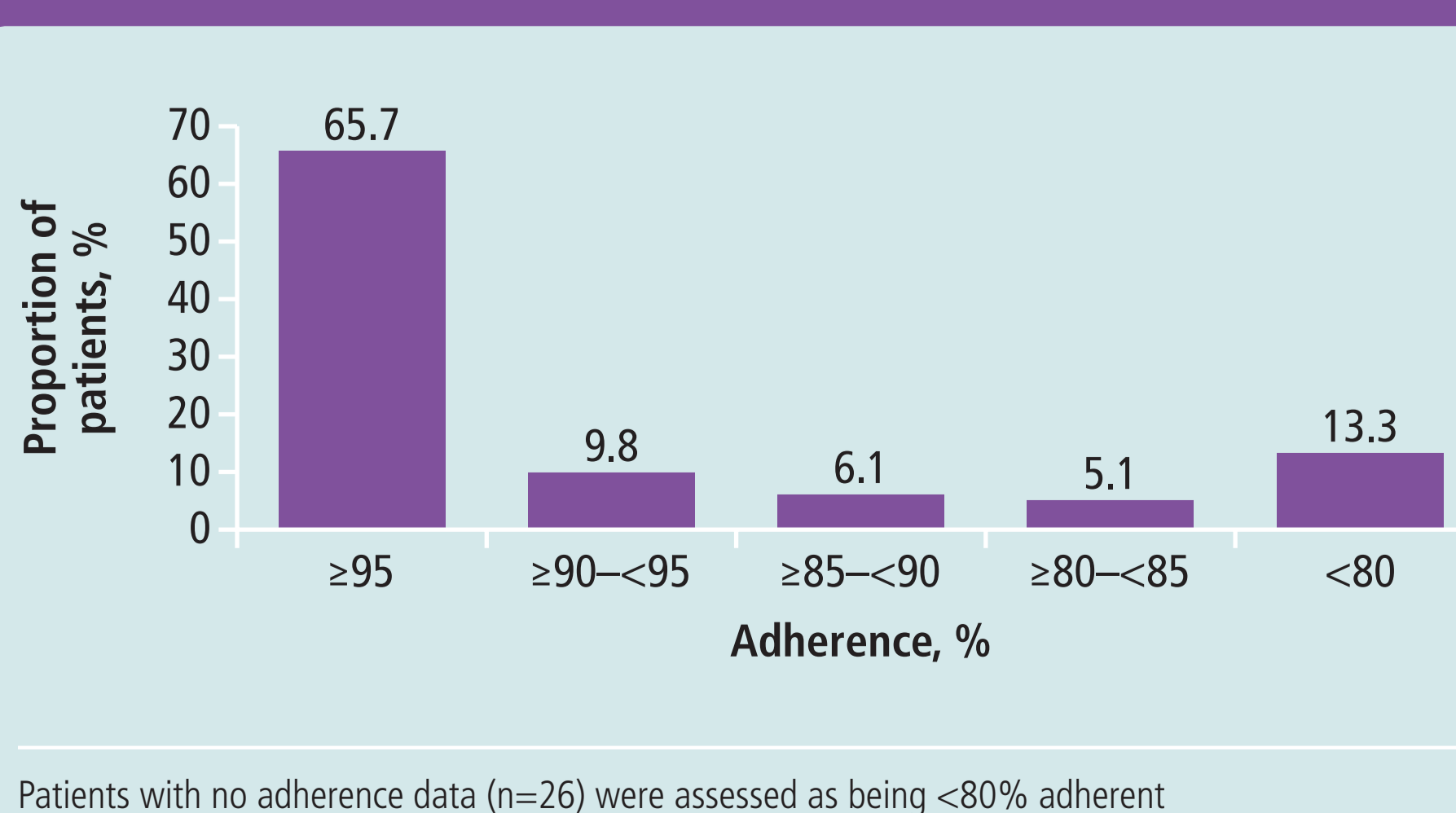
Results

- The mean age of patients enrolled in GRACE was 42.9 years, 66.9% of patients were female, and 61.5% and 22.4% of the total population were black or Hispanic, respectively
- At baseline, the median CD4+ count was 200 cells/mm³ and mean viral load was 4.67 log₁₀ copies/mL
- At baseline, women were younger on average and tended to have less advanced disease, less resistance and be less treatment-experienced compared with men²

Adherence

- Overall, 65.7% of patients in the ITT population were ≥95% adherent during GRACE (Figure 2)

Figure 2. Mean adherence on study



Univariate analyses

- Overall, 14 covariates were identified as significantly related to adherence at the $P < .15$ level in the univariate analyses (Table 2; green text)
 - Of these, three covariates were excluded from the multivariate analysis due to strong correlation with other covariates: the number of International AIDS Society (IAS-USA) PI resistance-associated mutations (RAMs; highly correlated with the number of IAS major PI mutations), the number of DRV mutations (highly correlated with the number of IAS major PI mutations) and the inclusion of a non-nucleoside reverse transcriptase inhibitor in the OBR (highly correlated with etravirine in the OBR)
 - The covariate most strongly associated with adherence in the univariate analysis ($P < .010$) was a higher number of IAS-USA PI RAMs
- Sex was not identified as significantly associated with adherence in the univariate analyses
- When assessing race, only white (versus non-white) race was associated with improved adherence in the univariate analysis ($P = .1371$)

Table 2. Baseline demographics and disease characteristics

Parameter	Adherence <95% on study (n=147)	Adherence ≥95% on study (n=282)	Univariate P value
Patient characteristics			
Mean age ^a (SD), years	42.0 (10.44)	43.3 (10.13)	NS
Sex, n (%)			NS
Male	44 (29.9)	98 (34.8)	
Female	103 (70.1)	184 (65.2)	
Race/ethnicity, n (%)			NS
Black	97 (66.0)	167 (59.2)	
Hispanic/Latino	32 (21.8)	64 (22.7)	
Caucasian ^b	17 (11.6)	48 (17.0)	
Other	1 (0.7)	3 (1.1)	
Mode of HIV transmission			
MSM/sexual contact, n (%)	18 (12.2)	49 (17.4)	NS
Mean (SD) BMI ^c , kg/m ²	26.9 (6.36)	27.4 (7.09)	NS
HIV disease characteristics			
Mean (SD) duration of infection ^d , years	11.32 (5.28)	11.34 (5.69)	NS
Mean (SD) viral load ^e , log ₁₀ copies/mL	4.74 (0.91)	4.64 (0.86)	NS
Median (range) CD4+ count ^f , cells/mm ³	185 (1, 814)	209 (1, 1125)	NS
Median (range) CD8+ count ^g , cells/mm ³	703 (46, 3760)	801 (65, 4189)	.0742
CDC Class, n (%)			NS
A	47 (32.0)	75 (26.6)	
B	40 (27.2)	98 (34.8)	
C	60 (40.8)	109 (38.7)	
Entry on treatment interruption, n (%)	58 (39.5)	93 (33.0)	NS
Mean (SD) number of prior PIs ^h	1.96 (1.24)	2.09 (1.49)	NS
Baseline resistance			
Mean (SD) number of IAS-USA major PI mutations ^{i,j,k}	0.53 (1.25)	1.03 (1.69)	.0025
Mean (SD) number of IAS-USA PI RAMs ^k	4.03 (3.34)	5.10 (3.87)	.0051
Mean (SD) number of all PI mutations ^k	8.48 (4.35)	9.62 (4.83)	.0179
Mean (SD) number of IAS-USA NRTI RAMs ^k	1.14 (1.29)	1.21 (1.37)	NS
≥2 DRV RAMs ^k , n (%)	9 (6.1)	33 (11.7)	.0348 ^d
Mean (SD) PSS of the OBR ^k	2.04 (0.65)	1.96 (0.74)	NS
Mean (SD) DRV fold change ^k	2.51 (13.11)	2.28 (8.91)	NS
Comorbidities			
Hepatitis C (positive), n (%)	27 (18.4)	37 (13.1)	.1494
CV medical history ^l , n (%)	47 (32.0)	119 (42.2)	.0397
GI medical history ^l , n (%)	64 (43.5)	111 (39.4)	NS
Endocrine medical history ^l , n (%)	27 (18.4)	64 (22.7)	NS
Psychiatric medical history ^l , n (%)	61 (41.5)	98 (34.8)	NS
Neurological medical history ^l , n (%)	59 (40.1)	105 (37.2)	NS
Respiratory medical history ^l , n (%)	34 (23.1)	79 (28.0)	NS
Smoker, n (%)	64 (43.5)	93 (33.0)	.0317
Drug use, n (%)	23 (15.6)	38 (13.5)	NS
Alcohol use, n (%)	55 (37.4)	96 (34.0)	NS
Treatment factors			
NNRTI in OBR, n (%)	66 (44.9)	149 (52.8)	.1191
ETR in OBR, n (%)	59 (40.1)	144 (51.1)	.0319
≥2 NRTIs in OBR ^l , n (%)	139 (94.6)	256 (90.8)	.0187 ^d
Site characteristics			
Attended site with limited trial experience, n (%)	20 (13.6)	47 (16.7)	NS
Region			NS
Midwest + Canada	19 (12.9)	28 (9.9)	
Northeast	31 (21.1)	62 (22.0)	
Puerto Rico	15 (10.2)	13 (4.6)	
Southwest	75 (51.0)	159 (56.4)	
West	7 (4.8)	20 (7.1)	
Male principal investigator, n (%)	64 (43.5)	158 (56.0)	.0143
Attended academic site, n (%)	87 (59.2)	132 (46.8)	.0153
Attended ACTG site, n (%)	62 (42.2)	108 (38.3)	NS
Specific site attended	NA	NA	NS

Green text represents covariates significant at the $P < .15$ level in the univariate analyses; ^aP value calculated using the Wald test; ^bContinuous variable; ^cWhite (versus non-white) race was associated with improved adherence ($P = .1371$); ^dBy vircoTYPE; ^eThis P value refers to the continuous, rather than discrete, covariate; ^fBased on currently active medical histories; ^gSD, standard deviation; ^hNS, not significant at the $P < .15$ level; ⁱMSM, men who have sex with men; ^jBMI, body mass index; ^kCDC, US Centers for Disease Control and Prevention; ^lPI, protease inhibitor; IAS, International AIDS Society; RAM, resistance-associated mutation; NRTI, nucleoside reverse transcriptase inhibitor; DRV, darunavir; PSS, phenotypic susceptibility score; OBR, optimized background regimen; CV, cardiovascular; GI, gastrointestinal; NNRTI, non-nucleoside reverse transcriptase inhibitor; ETR, etravirine; ACTG, AIDS Clinical Trials Group; NA, not applicable

Multivariate model

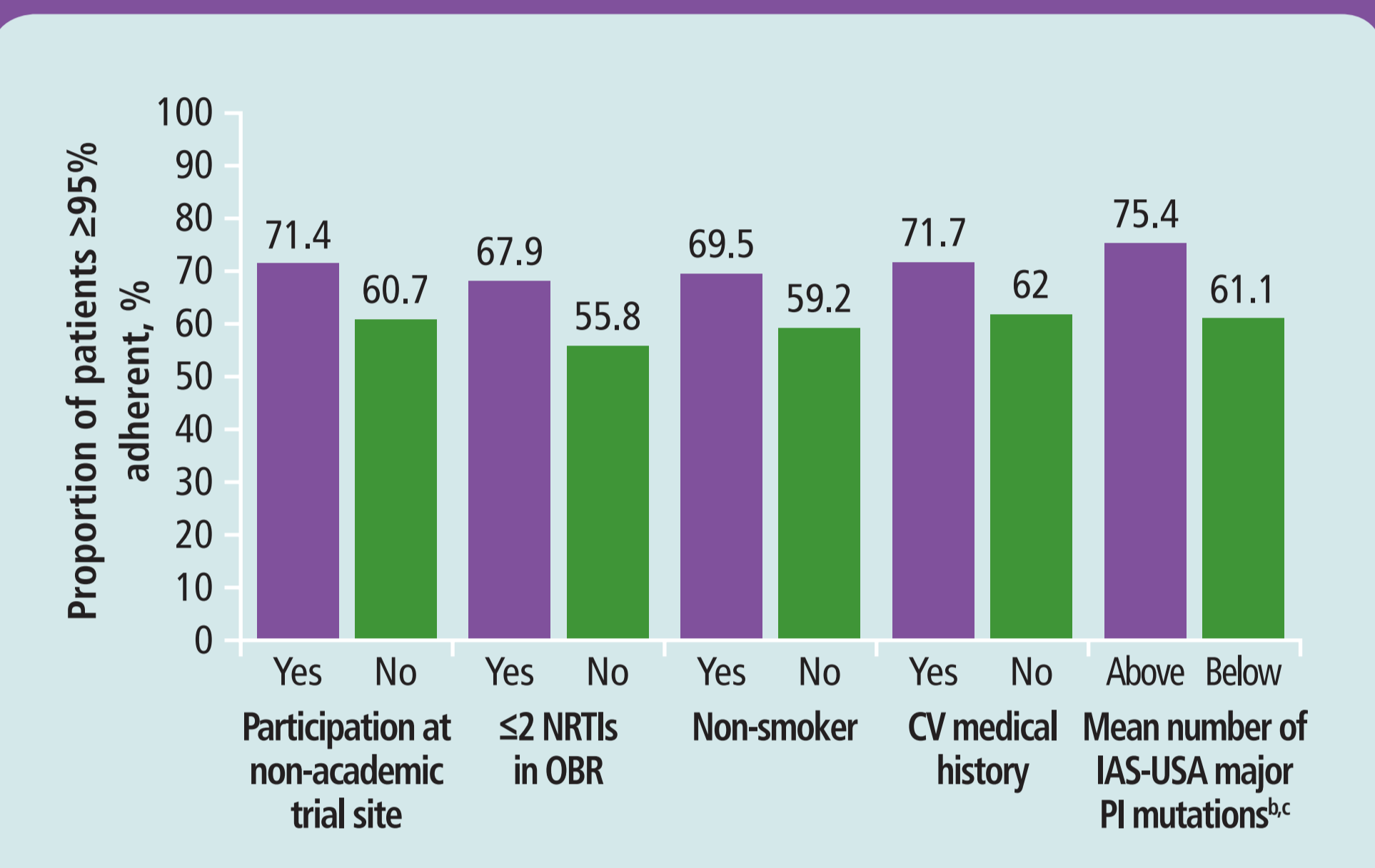
- Five covariates were selected for the final multivariate model of adherence (Table 3)
- Adherence rates for the covariates included in the final multivariate model are shown in Figure 3

Table 3. Factors predictive of 95% adherence or greater over the course of treatment^a from the multivariate analysis

Covariate	Adjusted odds ratio (95% CI)	P value
More IAS-USA major PI RAMs	1.29 (1.100, 1.515)	.0017
Participation at a non-academic trial site	1.87 (1.225, 2.843)	.0037
Fewer NRTIs in OBR	1.55 (1.099, 2.188)	.0124
Non-smoker	1.66 (1.080, 2.538)	.0208
CV medical history	1.57 (1.009, 2.431)	.0455

^aPercent adherence for all visits captured for an individual patient's treatment duration; CI, confidence interval; IAS, International AIDS Society; PI, protease inhibitor; RAM, resistance-associated mutation; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; CV, cardiovascular

Figure 3. Adherence rates for covariates included in the final multivariate model for predictors of adherence over the course^a of GRACE



^aPercent adherence for all visits captured for an individual patient's treatment duration; ^bMean=0.85; ^cNumber of IAS-USA major PI resistance-associated mutations was modeled as a continuous, rather than bivariate, covariate; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; CV, cardiovascular; IAS, International AIDS Society; PI, protease inhibitor

Discussion

- Based upon results from this multivariate analysis, neither sex nor race were identified as significant predictors of adherence in GRACE in the multivariate model
 - White race alone (versus non-white race/ethnicity) did meet the criteria for inclusion in the multivariate analysis, but was not identified as a significant predictor of adherence in the final model
- Of those factors identified as predictors of adherence in GRACE, none appear to lead to obvious interventions that could improve adherence, with the exception of the number of nucleoside reverse transcriptase inhibitors (NRTIs) in the OBR
- We can, however, hypothesize the factors that may underlie these results. Further, these findings indicate a need to consider and assess additional variables associated with adherence in future studies
 - Patients with more advanced disease (i.e. more IAS-USA major PI mutations) may be more adherent due to greater experience in the management of their disease or an increased perception of their disease as an immediate concern compared with people with less advanced HIV disease
 - Smoking status may be a surrogate indicator for patients' lifestyles, with non-smoking being considered a health-promoting behavior and this patient population, therefore, being more concerned with treatment adherence
 - Identification of cardiovascular (CV) medical history as a predictor of adherence may relate to patients' experiences with managing chronic illnesses; those patients with a CV medical history may be more used to conforming with a regular treatment regimen
 - It could be speculated that the identification of participation at a non-academic site being associated with adherence may relate to the types of patients participating at these sites, and other site factors not collected in GRACE

Conclusions

- There were no significant differences in adherence between sexes or across races in GRACE
 - Neither sex nor race were associated with adherence in the final multivariate model
- In the final multivariate model, more IAS-USA major PI RAMs, participation at a non-academic trial site, fewer NRTIs in the OBR, being a non-smoker and having a CV medical history, were all identified as factors predictive of ≥95% adherence

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