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GRACE (Gender, Race And Clinical Experience): Outcomes by Race at Week 48

Kimberly Y. Smith[1], Fernando Garcia[2], Robert Ryan[3], Ron Falcon[4], Alan Tennenberg[4], Joseph Mrus[4]

[1]Rush University Medical Center, Chicago, IL; [2]Valley AIDS Council, Harlingen, TX; [3]Tibotec, Inc., Yardley, PA; [4]Tibotec Therapeutics, Bridgewater, NJ

Address correspondence to: Kimberly Y. Smith, MD, MPH, Rush Presbyterian St. Luke's Medical Center, 600 S. Paulina Suite 143, Chicago, IL, 60612, USA; Kimberly_Y_Smith@rush.edu

Introduction

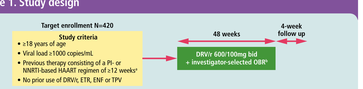
- People of color (black and Hispanic) constitute 25% of the United States (US) population, yet account for nearly 65% of those living with HIV/AIDS in the US[1]
- In 2005, 26% of new HIV/AIDS diagnoses were in women, with women of color constituting over 80% of these cases[1]
  - Despite the disproportionate representation of women and people of color among patients with HIV/AIDS, these populations remain underrepresented in antiretroviral (ARV) clinical trials[1]
- GRACE (Gender, Race And Clinical Experience), a 48-week study, was designed to enroll a high proportion of women and people of color to add to the currently limited pool of clinical data on ARV therapy in diverse patient populations
  - The efficacy and safety of darunavir/ritonavir (DRV/r) plus an investigator-selected optimized background regimen (OBR), which could include etravirine (ETR), was assessed
- Here we report Week 48 data by race from the GRACE study

Methods

Study design and treatment

- GRACE was a multicenter, open-label, Phase IIIb study conducted in 65 study sites across the US, Canada and Puerto Rico for 48 weeks (**Figure 1**)
- The main goal of GRACE was to evaluate sex-based differences in the efficacy and safety of DRV/r-based therapy
  - The analysis by race was a preplanned secondary objective to evaluate race-based differences of DRV/r-based therapy
- To assist in the recruitment and retention of patients in the study, strategies such as media campaigns, site enrollment plans, and provision of childcare and transportation stipends were implemented. Free access to DRV/r, ETR and select nucleoside/nucleotide reverse transcriptase inhibitors in the OBR was available for all patients

Figure 1. Study design



[a]Patients were allowed to enter the study on treatment interruption of ≥4 weeks; [b]Investigator-selected with nucleoside reverse transcriptase inhibitors and NNRTIs included; 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

Efficacy evaluations

- The primary endpoint was virologic response (HIV-1 RNA <50 copies/mL) of DRV/r-based treatment at Week 48
- Secondary efficacy endpoints included:
  - CD4+ count change from baseline to Week 48
  - The proportion of patients with virologic failure (VF; confirmed HIV-1 RNA >50 copies/mL)

Multivariate analyses (all patients [N=429]; intent-to-treat population)

- Factors predictive of virologic response and discontinuation in the total GRACE population were investigated *post hoc*
- Forty-three covariates encompassing patient and disease characteristics, treatment factors, baseline resistance, site characteristics and comorbidities were evaluated in a univariate analysis
- Covariates significant at the $P<.15$ level in univariate analyses were considered for the multivariate analysis, with entry and stay criteria of $P<.15$ and $P<.10$, respectively, for inclusion in the final model
- If two or more covariates were highly correlated ($R^2 > .8$), only the most significant in the univariate analyses was considered for inclusion in the multivariate analysis
- Odds ratios were adjusted for other covariates that were included in the final multivariate analysis

Safety evaluations

- Adverse events (AEs), serious AEs (SAEs) and study discontinuations due to AEs were recorded throughout the study
- Clinical laboratory abnormalities were determined according to the sponsor enhanced Division of AIDS grading severity list

Statistical analysis

- Virologic response was reported using the time-to-loss of virologic response (TLOVR) algorithm for the following populations:
  - Intent-to-treat (ITT): patients who took at least one dose of study medication
  - Non-VF censored: censors patients who discontinued for reasons other than VF
- Changes in CD4+ count were analyzed using observed case and last observation carried forward (LOCF) analyses
- GRACE was not powered for statistical comparisons by race; descriptive statistics are reported

Results

Patient population and baseline characteristics

- Among black patients, 72% were women, compared with 63% and 52% of Hispanic and Caucasian patients, respectively (**Table 1**)
- Black patients had slightly more advanced disease at baseline than Hispanic and Caucasian patients (**Table 1**)
- The mean phenotypic susceptibility score of the OBR was comparable across races; use of ETR in the OBR was similar among black and Caucasian patients, but slightly lower in Hispanic patients (**Table 1**)

Table 1. Baseline demographics and disease characteristics

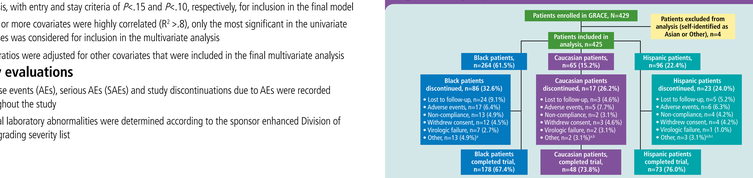
	Black n=264	Hispanic n=96	Caucasian n=65
Sex			
Female, n (%)	191 (72.3)	60 (62.5)	34 (52.3)
Male, n (%)	73 (27.7)	36 (37.5)	31 (47.7)
Mean (SE) age, years	43.0 (0.62)	40.3 (1.05)	45.5 (1.13)
Mean (SE) duration of HIV infection, years	11.0 (0.34)[a]	10.5 (0.58)[b]	13.8 (0.66)[c]
Mean (SE) viral load, $\log_{10}$ copies/mL	4.7 (0.06)	4.7 (0.09)	4.7 (0.10)
Median (range) CD4+ count, cells/mm^3	179 (1, 868)	208 (1, 1125)	249 (6, 826)
CDC Class C, n (%)	111 (42.0)	33 (34.4)	22 (33.8)
Median (range) DRV fold change[d,e]	0.6 (0.30, 148.30)	0.6 (0.40, 20.10)	0.6 (0.50, 39.00)
Prior use of ≥2 PIs, n (%)	156 (59.1)	60 (62.5)	42 (64.6)
>1 major PI mutation, n (%)	79 (29.9)	29 (30.5)	23 (35.9)
Hepatitis B surface antigen (positive), n (%)	15 (5.7)	3 (3.1)	1 (1.5)
Hepatitis C antibody (positive), n (%)	41 (15.5)	12 (12.5)	11 (16.9)
ETR in the OBR, n (%)	131 (49.6)	34 (35.4)	34 (52.3)
Mean (SE) PSS of the OBR[f]	2.0 (0.04)	1.9 (0.07)	2.0 (0.08)

[a]n=262; [b]n=95; [c]n=65; [d]Virco®TYPE HIV-1 resistance analysis; [e]Two patients, one Hispanic and one Caucasian, did not have resistance testing at baseline; [f]Includes ETR, but not DRV; SE, standard error; CDC, Centers for Disease Control and Prevention; DRV, darunavir; PI, protease inhibitor; ETR, etravirine; OBR, optimized background regimen; PSS, phenotypic susceptibility score

Patient disposition

- The primary reasons for study discontinuation were lost to follow-up and AEs (**Figure 2**)
  - No specific AEs were identified as driving discontinuations in any race group
- Higher discontinuation rates were seen in black patients, mostly due to lost to follow up and 'other' reasons (**Figure 2**)
  - 'Other' reasons for discontinuation among black patients included investigator's decision to close the site (n=4), patient moved out of state (n=2), patient missed appointments, patient ineligible to continue, patient taken out of trial due to old age, patient discontinued due to no virologic response by Week 12, patient too busy to come to appointments, patient's primary care physician discontinued study medication and started new regimen, and patient removed from trial due to sponsor's decision

Figure 2. Study disposition

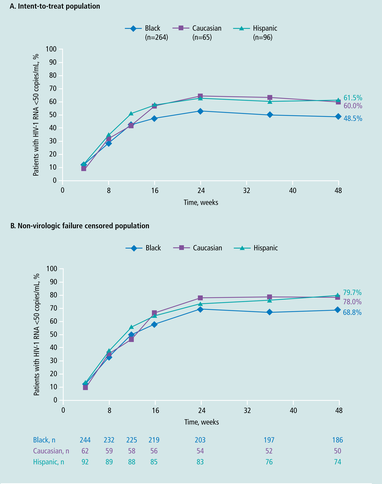


[a]'Other' classification was selected by the investigator as a reason for discontinuation; [b]Includes one patient that became pregnant and one patient that was ineligible to continue; [c]Includes one patient that did not continue with study visits

Efficacy

- At Week 48 in the ITT population, similar response rates were observed in Hispanic and Caucasian patients, with lower response rates seen in black patients (**Figure 3A**); in the non-VF censored population, a similar trend was observed (**Figure 3B**)
  - Differences in response rates were observed between sexes in the black and Hispanic populations in the ITT–TLOVR analysis (**Table 2**)
  - When discontinuations for reasons other than VF were censored, response rates were comparable between women and men within each race/ethnic group (**Table 2**)
- The median change in observed CD4+ count from baseline showed steady improvement over time and was comparable across races (**Figure 4A**)
- The median change from baseline in CD4+ count in the ITT–LOCF analysis was similar in Hispanic and Caucasian patients (**Figure 4B**)
  - The lower median CD4+ change in black patients is most likely due to the higher number of discontinuations in this group
- A lower proportion of black and Hispanic patients were ≥95% adherent (63.3% and 66.7%, respectively) compared with Caucasian patients (73.8%)

Figure 3. Virologic response (TLOVR) in (A) the intent-to-treat population and (B) the non-virologic failure censored population



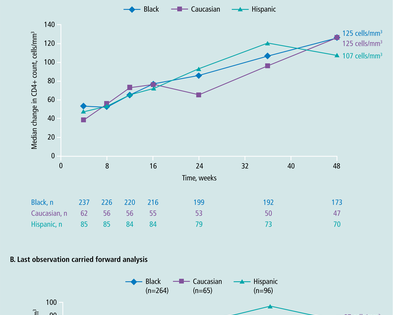
TLOVR, time-to-loss of virologic response

Table 2. Virologic response at Week 48

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[a] (69.5)	35/44 (79.5)	21/27 (77.8)
Men	39/58[a] (67.2)	24/30 (80.0)	18/23 (78.3)

[a]One 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

Figure 4. Median change from baseline over time in CD4+ count in (A) observed case and (B) last observation carried forward analyses



Multivariate analysis (all patients; intent-to-treat population)

- A *post-hoc* multivariate analysis of all 429 patients enrolled in GRACE showed that being of a non-black race was significantly associated with improved response and a lower likelihood of discontinuation for reasons other than VF or AEs (**Table 3**)

Table 3. Factors predictive of virologic response and discontinuation from a multivariate analysis of the total GRACE population (intent-to-treat)

Covariate	Adjusted OR	*P* value	95% CI
Improved response			
Adherence ≥95%	2.98	<.0001	1.92, 4.65
Lower baseline viral load[a]	1.81	<.0001	1.39, 2.34
Race/ethnicity other than black	1.79	.0093	1.15, 2.76
Older age[a]	1.03	.0184	1.00, 1.05
No GI medical history	1.65	.0252	1.06, 2.55
Participation at study site with limited clinical trial experience	1.89	.0358	1.04, 3.44
ETR in OBR	1.56	.0424	1.02, 2.38
Lower likelihood of discontinuation			
Adherence ≥95%	0.34	<.0001	0.21, 0.56
NNRTI in OBR	0.49	.0054	0.29, 0.81
Lower baseline viral load[a]	0.74	.0391	0.55, 0.98
No previous/current illegal drug use	0.56	.0750	0.29, 1.06
Race/ethnicity other than black	0.63	.0855	0.37, 1.07

[a]Continuous; OR, odds ratio; CI, confidence interval; GI, gastrointestinal; ETR, etravirine; OBR, optimized background regimen; NNRTI, non-nucleoside reverse transcriptase inhibitor

Resistance

- The rate of confirmed VF was 32.2% (n=85) in black patients, 24.0% (n=23) in Hispanic patients and 21.5% (n=14) in Caucasian patients
  - Not all patients that experienced VF discontinued the trial; rates of discontinuations due to VF (**Figure 2**) were lower than overall rates of VF
- Patients with treatment-emergent International AIDS Society-USA major PI resistance-associated mutations (RAMs) or DRV RAMs (**Table 4**) had substantial resistance at baseline, with 1–6 major PI RAMs present[4]

Table 4. Number of patients with new treatment-emergent resistance-associated mutations

Emerging mutations	Black[a,b]	Hispanic[a,b]	Caucasian[a,b]
IAS-USA major PI RAMs, n (V32I, M46I[2], M46I/L, L33F, I50V[2])	2	1	1
IAS-USA NRTI RAMs, n	2	1	1
DRV RAMs, n (V32I, L33F, I50V[2], L89V)	1	1	1
ETR RAMs, n	5	0	1

[a]Out of 85 black, 23 Hispanic and 14 Caucasian patients with confirmed virologic failure (HIV-1 RNA >50 copies/mL), 35, 7 and 5, respectively, had genotypes available at baseline and virologic failure; [b]Genotype determined only for patients with HIV-1 RNA >1000 copies/mL; IAS, International AIDS Society; PI, protease inhibitor; RAM, resistance-associated mutation; NRTI, nucleoside reverse transcriptase inhibitor; DRV, darunavir; ETR, etravirine

Safety

- The most frequent SAEs were pneumonia and *Pneumocystis jirovci* pneumonia, which were observed in black (2.7% and 1.5%, respectively) and Caucasian (6.2% and 1.5%, respectively) patients
  - Neither of these SAEs were reported in Hispanic patients
- Four deaths were reported; all were considered unrelated to study treatment by the investigator (**Table 5**)

Table 5. Summary of adverse events and laboratory abnormalities

Parameter	Black n=264	Hispanic n=96	Caucasian n=65
Adverse events, n (%)			
Patients with ≥1 AE	231 (87.5)	85 (88.5)	59 (90.8)
Patients with ≥1 SAE	54 (20.5)	12 (12.5)	14 (21.5)
Deaths[a]	1 (0.4)	1 (1.0)	2 (3.1)
Patients with ≥1 AE at least possibly related to DRV/r (all grades)	117 (44.3)	44 (45.8)	33 (50.8)
Grade 2–4 AEs at least possibly related to DRV/r (≥2% incidence in any subgroup)[a], n (%)			
All	71 (26.9)	28 (29.2)	18 (27.7)
Diarrhea	13 (4.9)	6 (6.3)	1 (1.5)
Nausea	15 (5.7)	2 (2.1)	1 (1.5)
Rash (preferred term)	7 (2.7)	1 (1.0)	2 (3.1)
Weight gain	4 (1.5)	3 (3.1)	1 (1.5)
Vomiting	5 (1.9)	2 (2.1)	0
Dyspepsia	0	4 (4.2)	1 (1.5)
Dizziness	0	2 (2.1)	2 (3.1)
Abdominal pain, upper	1 (0.4)	2 (2.1)	1 (1.5)
Abdominal discomfort	0	3 (3.1)	0
Abdominal distension	1 (0.4)	2 (2.1)	0
Abdominal pain	1 (0.4)	2 (2.1)	0
Hypertension	1 (0.4)	0	2 (3.1)
Asthenia	0	2 (2.1)	0
Grade 3–4 laboratory abnormalities (≥2% incidence in any subgroup), n (%)			
Liver enzymes			
AST	10 (4.1)	4 (4.3)	1 (1.6)
ALT	5 (2.0)	4 (4.3)	1 (1.6)
Lipids			
Total cholesterol	7 (3.4)	2 (2.6)	4 (7.8)
Triglycerides	2 (1.0)	4 (5.1)	5 (9.8)
Hyperglycemia	9 (3.7)	1 (1.1)	0
Lipase	5 (2.0)	2 (2.2)	3 (4.8)
Pancreatic amylase	5 (2.0)	3 (3.3)	2 (3.2)
Plasma prothrombin time	1 (0.7)	3 (4.4)	0

[a]All deaths unrelated to DRV/r or etravirine; [b]Excludes lab abnormalities reported as AEs; AE, adverse event; SAE, severe adverse event; DRV/r, darunavir/ritonavir; AST, aspartate aminotransferase; ALT, alanine transaminase

Discussion

- GRACE successfully enrolled a population of black, Hispanic and Caucasian patients that was representative of the HIV epidemic across the US. Regardless of race, all patients responded well to DRV/r-based therapy
- Overall, black patients had a higher discontinuation rate (mainly due to loss to follow up and 'other' reasons) and a lower response rate (ITT and non-VF censored) than Hispanic or Caucasian patients
  - Black patients had more advanced disease at baseline than the other groups, which, among other potential reasons, could reflect differences in care and may have led to increased treatment complexity[3,5]
  - Black patients also had lower adherence rates than Hispanics or Caucasians, which may have contributed to their lower response rate and higher VF rate
  - Being of a race/ethnicity other than black was found to be a significant predictor of virologic response in the *post-hoc* analysis of GRACE; the HEAT study, another North-American based trial, also observed this correlation between race and virologic response[6]
  - Race-based differences in discontinuation rates have not previously been observed in large, global DRV/r studies[7,8]
  - We believe higher discontinuation rates among black patients in GRACE may have been due to socioeconomic and other factors unique to North America that were not measured in the trial. These factors may include lower health literacy and higher levels of depression and injection drug use[3]
  - Differences in virologic response did not appear to be driven by differences in response by sex
- DRV/r safety and tolerability was similar across races; no clinically relevant race-associated differences in AEs or lab abnormalities were noted, and no specific AEs were identified as driving discontinuations in any race group
  - The lower rates of SAEs observed in Hispanic patients compared with black and Caucasian patients may be due to their less severe HIV disease at baseline
  - Overall, the incidence of AEs and lab abnormalities was similar to other DRV/r studies in treatment-experienced patients[7-9]

Conclusions

- This analysis of the Week 48 results from GRACE, stratified by race, demonstrates that DRV/r treatment is safe and effective in treatment-experienced patients regardless of race
- Despite the trial design, which sought to equalize a multitude of variables, including access to care and study drugs, we were not able to account for socioeconomic and other differences that we believe led to more black patients discontinuing than Hispanic or Caucasian patients and the resulting lower response rate in black patients
- Further investigation of factors, such as differences in care, socioeconomic disparities, health literacy and adherence, which may impact race-based differences in response and discontinuation rates, is warranted

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