

# GRACE (Gender, Race And Clinical Experience): 48-Week Results of Darunavir/r-based Therapy in the Largest Trial in North America to Focus on Treatment-experienced Women

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## Introduction

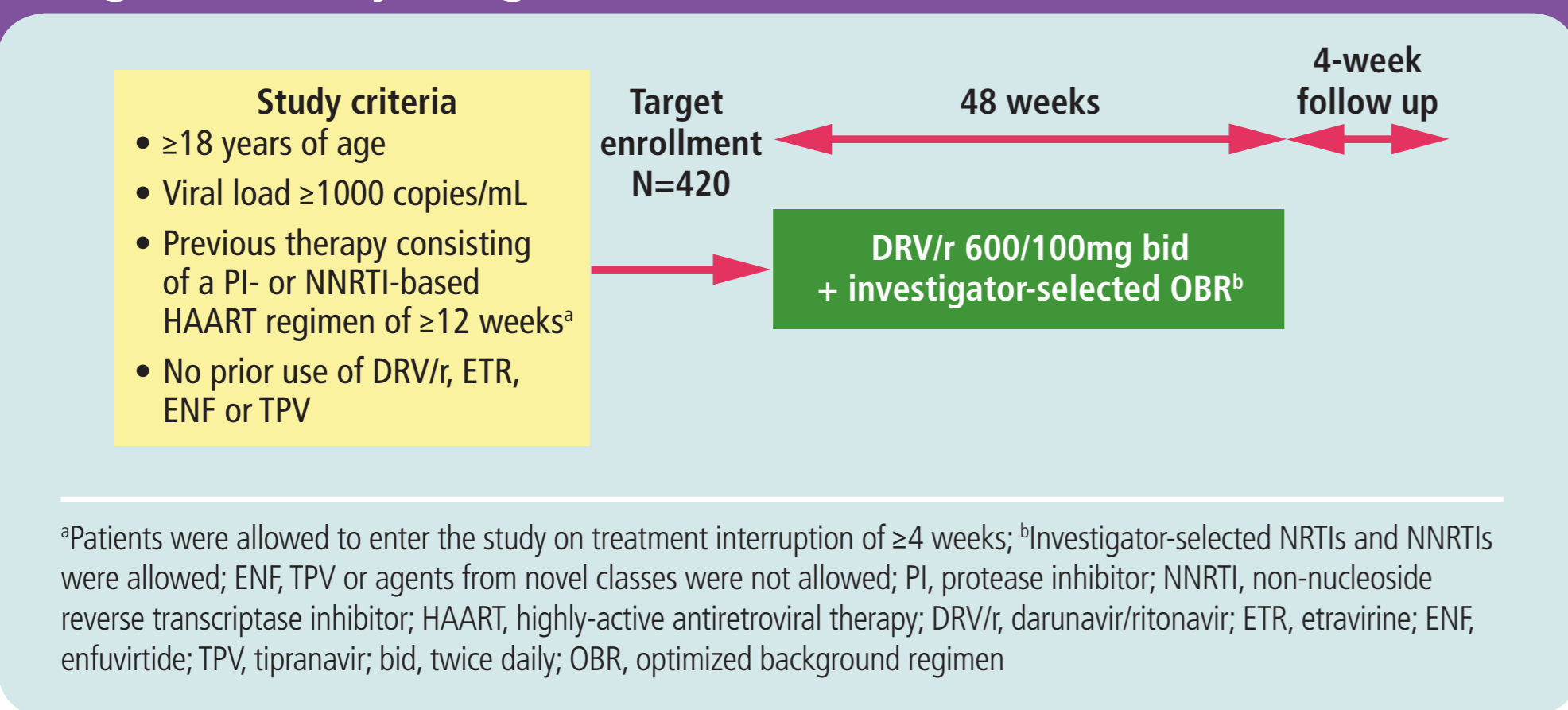
- Women account for an increasing proportion of patients living with HIV/AIDS in the United States (US)<sup>1,2</sup>, yet data on the efficacy and safety of antiretrovirals (ARVs) in women are limited
  - Several challenges, including socioeconomic factors, have led to difficulties in recruiting and retaining women in ARV clinical trials
- Darunavir (DRV; PREZISTA®), a protease inhibitor (PI) combined with a low dose of ritonavir (DRV/r), has been approved for use in the US as a therapeutic option for treatment-experienced, treatment-naïve and pediatric (aged 6 to <18 years) HIV-infected patients<sup>3</sup>
- We report 48-week results from the primary analysis of the GRACE (Gender, Race And Clinical Experience) trial, which was designed to enroll a high proportion of treatment-experienced women, in order to assess sex-based differences in the efficacy and safety of DRV/r-based therapy
  - Analyses by race will be presented elsewhere

## Methods

### Study design and treatment

- Open-label, single-arm, Phase IIb study conducted at 65 sites across the US, Puerto Rico and Canada for 48 weeks (Figure 1)
- Samples taken at screening and at virologic failure (VF) were analyzed for resistance by Virco®TYPE HIV-1 genotype and predicted phenotype analysis (Virco BVBA, Mechelen, Belgium)

Figure 1. Study design



### Efficacy evaluations

- The primary endpoint was virologic response (HIV-1 RNA <50 copies/mL) at Week 48
  - The primary objective was to compare sex-based differences in response rates
- Secondary endpoints included:
  - CD4+ count change from baseline to Week 48
  - Virologic failure (confirmed viral load [VL] >50 copies/mL) rates and development of new resistance upon failure

### Safety evaluations

- Adverse events (AEs), serious AEs 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
- A *post-hoc* analysis was conducted to determine if reasons for discontinuation differed by sex

### Patient population and statistical analysis

- To meet the recruitment goal of 420 patients (approximately 70% female, 30% male) and ensure approximately equal race distribution between genders, each site was required to enroll three women before enrolling a man, and the number of Caucasian men enrolled was limited
  - Sample size was determined based on a non-inferiority design with a maximum allowable difference for women versus men of ≤15% with a one-sided significance level of α=0.025 and 80% power; 15% was considered *a priori* to be a clinically relevant difference in response
- Efficacy and safety endpoints were analyzed for the intent-to-treat (ITT) population, defined as all enrolled patients who received at least one dose of study medication
  - Virologic response was also calculated for the non-VF censored population, which censors patients who discontinued the study for reasons other than VF
- Virologic response was reported using the time-to-loss of virologic response (TLOVR) algorithm
- Sex-based differences in response rates were derived from logistic regression models that included sex, as well as covariates for baseline VL and CD4+ count
- Changes in CD4+ count from baseline were evaluated by analysis of covariance, including sex, baseline VL and baseline CD4+ count as factors
- Safety endpoints and resistance determinations were analyzed descriptively according to sex

## Results

### Patient population and baseline characteristics

- A total of 429 patients were enrolled in GRACE and received at least one dose of study drug (287 women; 142 men; Figure 2)
- At baseline, women on average were younger and tended to have less advanced disease, less resistance and be less treatment experienced compared with men (Table 1)
- The optimized background regimen (OBR) for women and men, respectively, included tenofovir (83.3% and 85.9%), emtricitabine (77.0% and 77.5%), etravirine (40.4% and 61.3%), zidovudine (17.4% and 23.9%) and lamivudine (10.5% and 11.3%)
  - The mean (standard deviation) phenotypic sensitivity score of the OBR was 2.0 (0.65) and 2.0 (0.81) in women and men, respectively
- A total of 193 (67.2%) women and 109 (76.8%) men completed the trial with mean (standard error) treatment durations of 38.5 (0.99) and 41.9 (1.20) weeks, respectively
  - The rate of treatment discontinuation was higher in women (n=94 [32.8%]) compared with men (n=33 [23.2%]; P<0.05)
  - The primary reasons for study discontinuation were loss to follow up and AEs (Figure 2); there were no trends toward a specific type of AE driving discontinuations in either group
  - No individual AE led to discontinuation in more than two patients

Figure 2. Study disposition

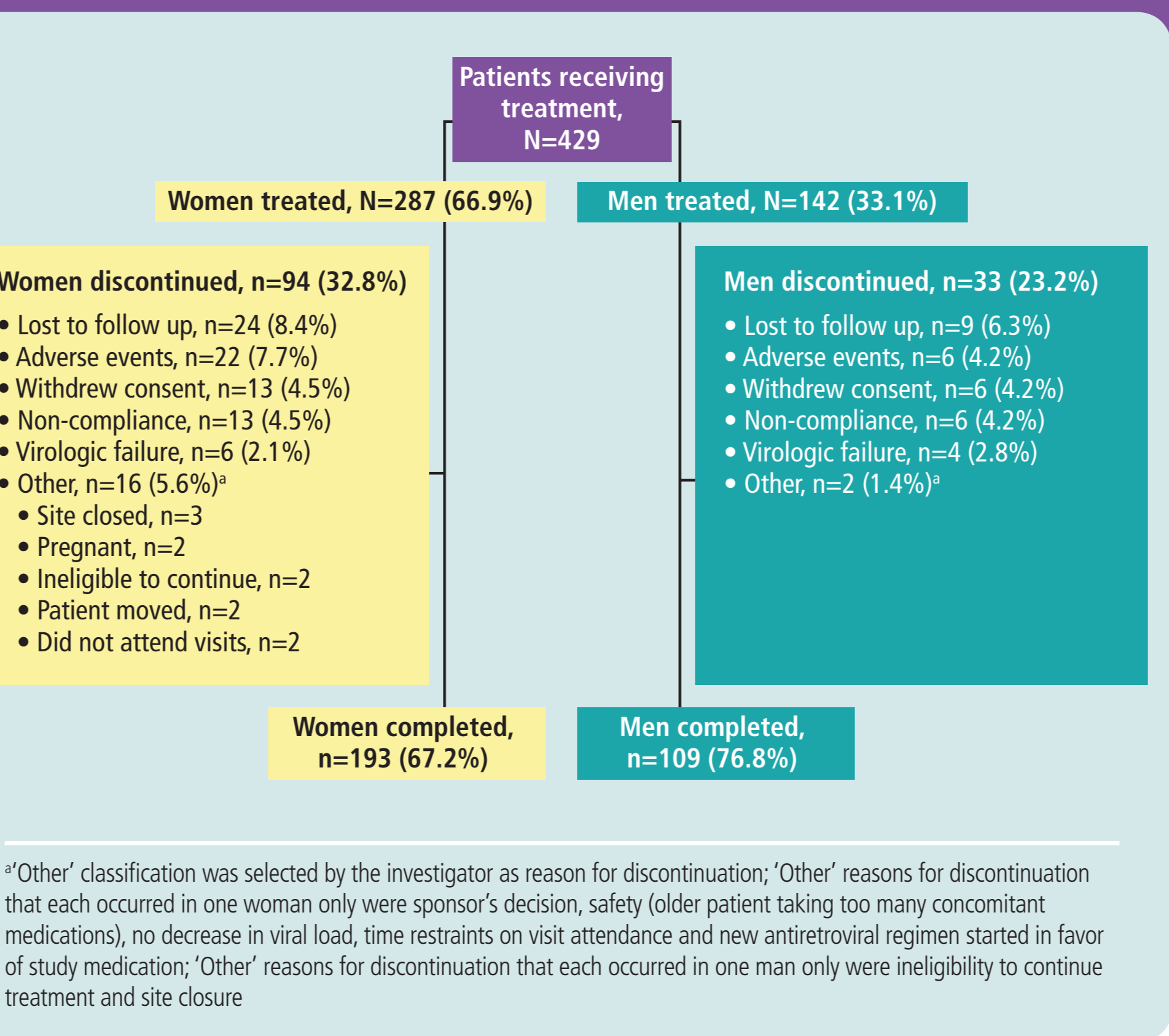


Table 1. Baseline characteristics and demographics

Parameter	Women N=287	Men N=142
Mean (SD) age, years	42 (10.6)	45 (9.0)
Race/ethnicity, n (%) <sup>a</sup>		
Black	191 (66.6)	73 (51.4)
Hispanic/Latino	60 (20.9)	36 (25.4)
Caucasian	34 (11.8)	31 (21.8)
Other	2 (0.7)	2 (1.4)
Mean (SD) BMI, kg/m <sup>2</sup>	28.2 (7.41)	25.4 (5.06)
Mean (SD) duration of infection, years	10.9 (5.36)	12.2 (5.84)
Mean (SD) viral load, log <sub>10</sub> , copies/mL	4.7 (0.88)	4.7 (0.86)
Median (range) CD4+ count, cells/mm <sup>3</sup>	210 (1, 868)	175 (2, 1125)
CDC Class C, n (%) <sup>b</sup>	102 (35.5)	67 (47.2)
Entry on treatment interruption, n (%)	100 (34.8)	51 (35.9)
Prior use of ≥2 PIs, n (%)	168 (58.5)	92 (64.8)
>1 IAS-USA major PI mutations, n (%) <sup>b</sup>	77 (27.0)	57 (40.1)
Hepatitis B surface antigen (positive), n (%)	12 (4.2)	7 (4.9)
Hepatitis C antibody (positive), n (%)	39 (13.6)	25 (17.6)

<sup>a</sup>Significantly different for women and men (P<0.05); <sup>b</sup>By Virco®TYPE; SD, standard deviation; BMI, body mass index; CDC, Centers for Disease Control and Prevention; PI, protease inhibitor; IAS, International AIDS Society

### Efficacy

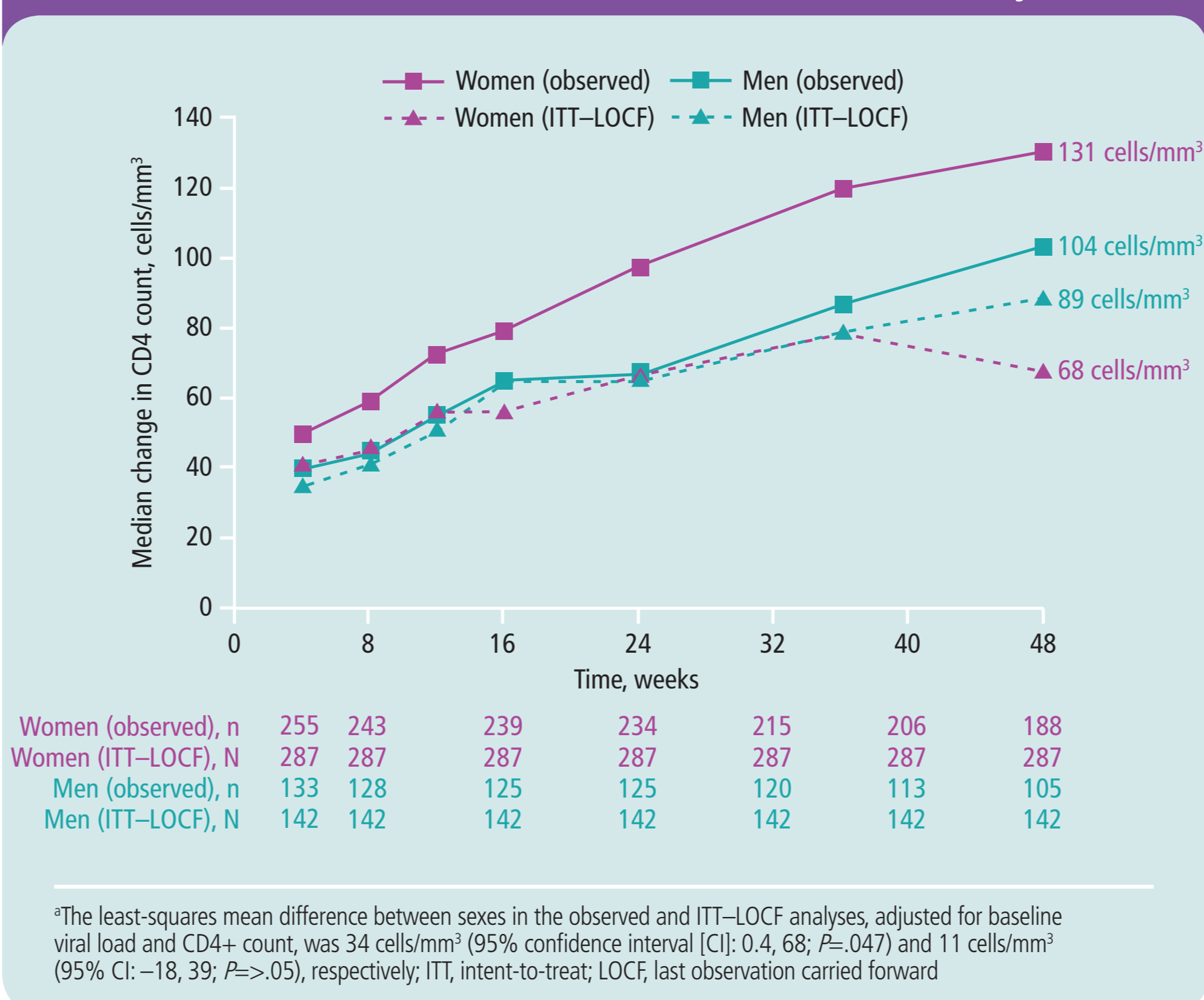
- At Week 48 in the ITT–TLOVR analysis, virologic response rate was higher in men than women; in the non-VF censored population, response rates were similar between men and women (Figure 3)
  - When adjusted for baseline VL and CD4+ count, the difference in response rates between women and men was –9.6% (95% confidence interval [CI]: –19.9%, 0.7%) in the ITT–TLOVR analysis and –3.9% (95% CI: –13.9%, 6.0%) in the TLOVR–non-VF analysis
- The rate of VF was 28.6% (n=82) in women and 28.2% (n=40) in men

Figure 3. Confirmed virologic response in intent-to-treat and non-virologic failure censored populations<sup>a</sup>



- The median change from baseline in the observed CD4+ count was higher in women than men (Figure 4)
- The median change from baseline in CD4+ count for the ITT–last observation carried forward analysis was similar in women and men (Figure 4)

Figure 4. Median change from baseline over time in CD4+ cell count in observed case and last observation carried forward analyses<sup>a</sup>



### Resistance

- Patients developing new International AIDS Society–USA major PI resistance-associated mutations (RAMs) or new DRV RAMs (Table 2) had substantial resistance at baseline, with 1–6 major PI RAMs present<sup>4</sup>

Table 2. Number of patients with new treatment-emergent resistance-associated mutations

Mutations	Women <sup>a,b</sup>	Men <sup>a,b</sup>
IAS-USA major PI RAMs, n (%)	2 (7.4)	2 (11.8)
(V32I, M46I(2), M46I/L, L33F and I50V(2))		
IAS-USA NRTI RAMs, n (%)	2 (7.4)	2 (11.8)
DRV RAMs, n (%)	1 (3.7)	2 (11.8)
(V32I, L33F, I50V(2) and L89V)		

<sup>a</sup>Out of 82 women and 40 men with confirmed virologic failure (HIV-1 RNA >50 copies/mL), 27 and 17, respectively, had genotypes available at baseline and virologic failure; <sup>b</sup>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

### Safety

- Overall, 259 (90.2%) women and 118 (83.1%) men experienced at least one AE (Table 3)
  - The majority of AEs were mild-to-moderate in severity
  - In total, 134 (46.7%) women and 61 (43.0%) men experienced at least one AE considered by the investigator to be at least possibly related to DRV/r
- The most common AEs were nausea (women, 24.4%; men, 14.1%), diarrhea (women, 16.4%; men, 22.5%), upper respiratory tract infection (women, 11.1%; men, 7.7%) and vomiting (women, 11.5%; men, 6.3%)
- Serious AEs were reported in 47 (16.4%) women and 33 (23.2%) men; the most commonly reported were pneumonia (2.6% overall) and *Pneumocystis jiroveci* pneumonia (1.2% overall)
  - Four deaths were reported; all were considered unrelated to DRV/r by the investigator

Table 3. Summary of adverse events

Adverse events, n (%)	Women N=287	Men N=142
Patients with ≥1 AE	259 (90.2)	118 (83.1)
Patients with ≥1 SAE	47 (16.4)	33 (23.2)
Patients with ≥1 AE at least possibly related to DRV/r	134 (46.7)	61 (43.0)
Patients with ≥1 grade 2–4 AE at least possibly related to DRV/r <sup>a,b</sup>		
Diarrhea	13 (4.5)	7 (4.9)
Nausea	15 (5.2)	4 (2.8)
Rash	6 (2.1)	4 (2.8)
Weight increase	5 (1.7)	3 (2.1)
Vomiting	4 (1.4)	3 (2.1)
Grade 3–4 laboratory abnormalities		
Total cholesterol (grade 3 only)	10 (4.6)	5 (4.2)
Triglycerides	1 (0.5)	11 (9.2)
Aspartate aminotransferase	8 (3.0)	7 (5.1)
Alanine aminotransferase	6 (2.2)	4 (2.9)
Hyperglycemia	6 (2.2)	4 (2.9)
Lipase	5 (1.9)	5 (3.7)
Pancreatic amylase	4 (1.5)	6 (4.4)
Hyperuricemia	0	4 (2.9)
Plasma prothrombin time	0	4 (4.4)

<sup>a</sup>Occurring in ≥2% of patients in either group; <sup>b</sup>Excluding laboratory abnormalities reported as AEs; No grade 3 or 4 creatinine elevations were reported; AE, adverse event; SAE, serious adverse event; DRV/r, darunavir/ritonavir

## Discussion

- In the ITT–TLOVR analysis, which treats all study discontinuations as failures, the difference in virologic response rates between men and women was 9.6% (CI: –19.9%, 0.7%) at Week 48
  - After accounting for differential rates of discontinuation for men and women due to reasons other than VF, the response rates for men and women were similar
- Women had significantly higher increases in CD4+ count compared with men in the observed analyses, as noted in previous ARV trials
- Treatment with DRV/r was similarly tolerated between women and men, with no unexpected AEs, based on results from previous trials<sup>5–8</sup>
  - No specific AE was identified as driving discontinuations in either group
- Discontinuations due to loss to follow up, relocation and withdrawal of consent reflect challenges that may be unique to women with respect to clinical trials

## Conclusions

- The GRACE study successfully enrolled a high proportion of women and is, to date, the largest study in North America to assess sex-based differences in the efficacy and safety of an ARV regimen
- Overall, the data from GRACE suggest that DRV/r can be used in women and men with similar safety and efficacy outcomes
- Higher rates of discontinuation among women highlight the need for investigation into the retention of women in clinical trials
  - Addressing the unique needs and challenges of women during the screening process and throughout the study may improve study retention
- GRACE provides insight for the development and design of future clinical trials
  - Setting a requirement of enrolling three women to one man appears to be an effective method of increasing the enrollment of women

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