The GRACE Study: A Unique Clinical Trial in Treatment-Experienced Women With HIV

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GRACE Study Team
Introduction

• Despite research suggesting sex-based differences in drug efficacy, toxicity, and tolerability profiles, women have been underrepresented in HIV clinical trials\(^1\)

• Recent data suggest that sex has a small but significant influence on the clinical and laboratory outcomes of HIV infection\(^2\)

• Late initiation and premature discontinuation of antiretroviral therapy has been shown to reduce life-expectancy
  – These losses have been reported with higher frequency in racial and ethnic minorities, especially black and Hispanic women\(^3\)

Total adults, by sex

N = 468,488

Men 73%

Women 27%

Women, by race/ethnicity
n = 126,964

Black 64%

Hispanic 15%

White 19%

American Indian or Alaskan Native <1%

Asian or Pacific Islander 1%

• Women account for over one-quarter of all adults and adolescents in the US living with HIV/AIDS; infection rates are particularly high among women of color

GRACE

- GRACE is the largest treatment trial to focus on women with HIV in North America, and the first to focus on antiretroviral treatment-experienced women in North America.

- GRACE is a multicenter, open-label phase IIIb trial designed to assess sex and race differences in efficacy, safety, and tolerability of darunavir/ritonavir (DRV/r) over 48 weeks in treatment-experienced patients.

Study criteria

- ≥18 years of age
- Viral load ≥1,000 copies/mL
- Previous therapy consisting of a PI- or NNRTI-based HAART regimen of ≥12 weeks\(^a\)
- No prior use of DRV/r, etravirine (TMC125), enfuvirtide, or tipranavir

\(^c\)Target enrollment ratio was approximately 70:30 (women-to-men)

\(^a\)Patients were allowed to enter the study on treatment interruption of ≥4 weeks; NRTIs and NNRTIs included; ENF, TPV, or agents from novel classes were not allowed; OBR = optimized background regimen; DRV/r = darunavir/ritonavir

Target Enrollment

- N = 420

48 Weeks

4-Week follow-up

DRV/r 600/100mg bid + investigator-selected OBR\(^b\)
GRACE Enrollment

• Target enrollment of 420 patients was achieved (November 2006 - November 2007)

• 429 patients have enrolled in the GRACE study
  – 67% (n=287) women, 33% (n=142) men
  – 62% (n=266) black, 22% (n=94) Hispanic

• Women were over-represented to allow for adequate characterization of safety and tolerability in this population
  – Sites were required to recruit 3 women before recruiting their first male subject in order to meet the pre-determined ratio (approximately 70:30)

• The geographical distribution of GRACE study sites reflects current trends in HIV/AIDS cases among women and communities of color in the US
  – The study team solicited novel research sites that treat the targeted patient populations
Number of Active GRACE Study Sites in North America

<table>
<thead>
<tr>
<th>Region</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>58</td>
</tr>
<tr>
<td>Canada</td>
<td>4</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>3</td>
</tr>
</tbody>
</table>

Proportion of HIV/AIDS cases that are female, by state:
- 10.4% - 16.0%
- 16.4% - 19.6%
- 20.1% - 26.2%
- 26.4% - 33.2%

Geographical Distribution of 287 Women Enrolled in GRACE

<table>
<thead>
<tr>
<th>Region</th>
<th>Study sites (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>Southeast</td>
<td>29</td>
</tr>
<tr>
<td>Northeast</td>
<td>16</td>
</tr>
<tr>
<td>West</td>
<td>7</td>
</tr>
<tr>
<td>Midwest</td>
<td>6</td>
</tr>
<tr>
<td>Canada</td>
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## GRACE Demographics

<table>
<thead>
<tr>
<th></th>
<th>Women (n = 287)</th>
<th>Men (n = 142)</th>
<th>All patients (N = 429)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (range), years</strong></td>
<td>42.5 (19–79)</td>
<td>45.8 (22–78)</td>
<td>43.6 (19–79)</td>
</tr>
<tr>
<td><strong>Race/ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>192 (66.9)</td>
<td>73 (51.4)</td>
<td>265 (61.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>60 (20.9)</td>
<td>36 (22.1)</td>
<td>96 (22.4)</td>
</tr>
<tr>
<td>White</td>
<td>34 (11.8)</td>
<td>31 (25.4)</td>
<td>65 (15.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3)</td>
<td>2 (1.4)</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>
Strategies for Site Outreach and Patient Support for the GRACE Study

- Reducing barriers to care
  - Provision of some commonly used NRTIs for use in OBR
  - Provision of an experimental antiretroviral (etravirine)
  - Per diem for child care and travel

- Awareness and outreach
  - Unique study branding, including logo and colors
  - Targeted awareness campaigns in minority media

- Recruitment
  - Inclusion of sites with a focus on the care of women
  - Regular site visits, site support meetings, and site-specific enrollment plans

- Study retention
  - Supplemental site grants for patient support activities
  - Site and patient toolkits
  - Increased flexibility and availability of healthcare practitioners at study sites

- Continuous involvement with patient advocates, study sites and investigators throughout all phases of the study
GRACE Toolkit Contents

**Site Outreach**

- CD
  - Templates for public service announcements
  - “Dear Colleague” letter
  - Templates for flyers and ads
  - Grant applications
- Balloons and buttons
- Inclusion/exclusion cards
- Novel activity reporting form
- GRACE pens
- Site pamphlet on women in research

**Patient Support**

- Black tote bag with GRACE embroidery
- Day planner with calendar
- GRACE pen
- Water bottle
- Single-dose pill box
- Site contact card
- Insulated cooler bag
GRACE Summary

• GRACE is the largest treatment trial to date in North America to focus on women with HIV

• GRACE target enrollment figures were met according to schedule, including sex-specific targets

• The racial/ethnic composition of women enrolled in GRACE is reflective of “real-world” HIV demographics in the US and distribution of US study sites reflects current epidemiologic trends among women and communities of color

• Novel approaches to site selection, outreach, and recruitment have increased awareness and overcome hurdles for participation in this understudied population
  – The effectiveness of these strategies may have additional implications for improving access to HIV care and enhancing treatment outcomes for women and communities of color outside of a clinical trial setting

• Preliminary PK data from a sub-study of GRACE were recently presented at the 9th International Workshop on Clinical Pharmacology of HIV Therapy
  – Median exposure to DRV (AUC$_{12h}$) at Week 4 was approximately 20% higher in women compared with men
Acknowledgments

• The patients and their families for their participation and support during the study

• The GRACE study team and the investigators and coinvestigators:
  
  – Aberg, Judith A., MD • Albrecht, Helmut, MD • Albrecht, Mary A., MD • Barker, David E., MD • Brar, Indira, MD • Bullock, Delia, MD • Burdge, David, FRCP, MD • Cadden, Joseph, MD • Casey, Kathleen K., MD • Catalla, Robert, MD • Clark, Rebecca, MD • Clough, Lisa, MD • Condoluci, David V., MD • Currier, Judith, MD • Davis, Charles, MD • Diaz, Leslie, MD • Elion, Richard A., MD • Feinberg, Judith, MD • Garcia, Fernando, MD; Gathe, Jr., Joseph C., MD; Goulston, Claudia, MD • Haas, David W., MD • Hagins, Debbie, MD • Hanna, Barbara, MD • Hicks, Charles B., MD • Hodder, Sally, MD • Jayaweera, Dushyantha T., MD • Kadlecik, Peter, MD • Kanter, Tim, MD • Kumar, Pricyn, MD • Lennox, Jeffrey L., MD • Martorell, Claudia T., MD • Morales Ramirez, Javier, MD • Myers, Jr., Robert A., MD • Ortiz, Roberto, MD • Osiyemi, Olayemi O., MD • Patterson, Kristine B., MD • Pearce, Daniel D., DO • Pegram, P. Samuel, MD • Pollard, Richard B., MD • Presti, Rachel, MD • Puga, Ana, MD • Race, Elizabeth, MD • Rachlis, Anita, MD • Ramgopal, Moti, MD • Rawlings, M. Keith., MD • Saag, Michael S., MD • Santiago, Steven, FAAFP, MD • Scribner, Anita R., MD • Sepulveda, Gladys E., MD • Skolnik, Paul, MD • Smaill, Fiona, MD • Smith, Kimberly, MD • Smith, Stephen M., MD • Squires, Kathleen, MD • Tedaldi, Ellen, MD • Thompson, Melanie A., MD • Townsend, Gregory, MD • Tsoukas, Christos M., MD • Wade, Barbara H., MD • Witt, Mallory D., MD • Workowski, Kimberly, FACP, MD • Wright, David P., MD • Yin, Michael, MD • Zorrilla, Carmen D., MD