Women Underrepresented in Antiretroviral Clinical Trials

By Rodger D. MacArthur, MD [2]

Women tend to be excluded from pharmaceutical company-sponsored trials of antiretroviral medications.

Women accounted for 25% of all HIV-infected persons living in the United States at the end of 2010, and about 21% of all new HIV infections in the United States since 2011 (the last years for which data are available). Nevertheless, HIV-infected women remain underrepresented in clinical trials of promising new antiretroviral therapies, especially in those trials sponsored by the pharmaceutical industry. Two recent examples illustrate the point: 1) in a Gilead Sciences-sponsored trial comparing tenofovir alafenamide (new formulation of tenofovir) with tenofovir disoproxil fumarate, 170 HIV-infected participants were enrolled from more than 30 participating sites. Of the 170, only 5 (3%) were women; 2) in a Tobira Therapeutics-sponsored trial of cenicriviroc (investigational drug) versus efavirenz, 143 HIV-infected participants were enrolled from close to 40 participating sites, of whom only 8 (6%) were women.

For comparison, the soon-to-be-completed National Institutes of Health (NIH)/National Institute of Allergy and Infectious Disease/Division of AIDS/AIDS Clinical Trials Group (ACTG)-sponsored trial, ACTG 5257, comparing raltegravir with atazanavir/ritonavir with darunavir/ritonavir enrolled 1813 HIV-infected persons, of whom 25% were women.

Why are women underrepresented in many industry-sponsored trials? Answers may be gleaned from the recently-published article, “Insights on GRACE (Gender, Race, And Clinical Experience) from the Patient’s Perspective: GRACE Participant Survey.” The authors point out that between 2000 and 2008, “only 15% of treatment-experienced patients enrolled in the 18 randomized controlled trials of HIV drugs submitted for approval to the Food and Drug Administration (FDA) were women.” The original GRACE trial, designed to evaluate sex- and race-based differences in response to darunavir/ritonavir-based therapy, enrolled 67% women across North America. That trial was sponsored and funded by Jannsen, manufacturer of darunavir. In the follow-up GRACE Participant Survey, study discontinuation and medication non-adherence were found to be related to being the primary caregiver for children, unemployment, and transportation difficulties.

Nevertheless, 77% of those surveyed reported that they did not have any difficulty arranging transportation to the study site; 93% reported that the site was very flexible with scheduling visits; and 99% reported being comfortable or very comfortable with the study site. In other words, while there are some factors unique to women that potentially limit their enrolment into studies, attention to these factors can result in a high and representative percentage of female participants. However, too often it seems that companies funding the trials assign rapid accrual a higher priority than enrolling a diverse study population. There is an easy path to rapid accrual—enroll from sites serving primarily a higher socioeconomic group of individuals, which typically have a very high percentage of majority-white males. On the other hand, Protocol Co-Chair of ACTG 5257 Dr. Jeffrey Lenox told me that 2 mid-study modifications to the enrolment procedures of that study—requiring that sites enroll at least 1 woman for every 2 men enrolled and eventually closing accrual to men altogether—delayed study accrual by only 1 to 2 weeks from the original estimate. Had the
modifications not been made, the study might have fully accrued earlier than originally projected, but with only about 17% to 18% female participants.

**Do we need women?**

But does it really matter, in assessing a drug’s efficacy and safety/tolerability, that women, most often, are underrepresented in clinical trials? The answer appears to be “sometimes” or “maybe.”

For instance, Dr. Kimberly Smith and her colleagues in the ACTG found that women on an atazanavir/ritonavir-based regimen did worse than men who were assigned to take that regimen, but women in the same study assigned to take efavirenz did at least as well as men in the study on efavirenz. On the other hand, a recently-completed meta-analysis of gender differences in efficacy outcomes in randomized controlled clinical trials of antiretroviral therapy submitted to the FDA between 2000 and 2008 did not find any statistically or clinically significant efficacy differences between men and women. Certain subgroup analyses, however, did suggest potentially important differences: antiretroviral-naive white males were more likely to achieve HIV RNA levels less than 50 copies/mL compared with antiretroviral-naive white females. And treatment-experienced North American males were more likely than treatment-experienced North American females to achieve HIV RNA levels less than 50 copies/mL. It also is worth noting that the FDA requires that analyses based on sex and race/ethnicity be performed on all drugs submitted for approval. When there is not enough diversity to perform such analyses, the package insert typically indicates that no conclusions can be drawn in certain populations.

Pharmaceutical companies have as much of an obligation to ensure diversity in clinical trials as does the NIH. The time for making excuses has long-since passed. It is time for companies to take the steps necessary to achieve a diverse population in clinical trials, and it is perfectly reasonable for consumers to demand that they do so. Physicians should refuse to prescribe products to their patients if efficacy and safety/tolerability has not been demonstrated in a diverse population.

**References**


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