



The Impact of Sex/Gender on Antiretroviral Therapy and Its Complications

Kathleen E. Squires, MD

Following is a modified version of an oral presentation given by Kathleen E. Squires, MD, at the 10th Conference on Retroviruses and Opportunistic Infections (CROI) held February 10–14, 2003, in Boston. It serves as an overview of the range of differences seen between women and men who have taken anti-HIV therapy. Dr. Squires explained in her opening remarks, “I have tried to distill a number of studies that have been reported and to mention some studies that I felt were illustrative, rather than attempt to be exhaustive.”

Effect of Sex/Gender on Response to Antiretroviral Therapy

The first topic is sex or gender and its effect on antiretroviral therapy. There are many ways to think about response to antiretroviral therapy. I want to consider first the now classic parameters, or endpoints, looked at in clinical trials, specifically virologic and immunologic response. In other words, what is the effect of therapy on viral load and CD4 cell counts? I will use as an example the study called Women First. Though it was performed several years ago, Women First was the first trial—at least that I am aware of—that was designed to look specifically at the effect of antiretroviral therapy in a group of women, using what was considered at the time to be a very rigorous type of regimen. By offering the best therapy then available to this group of women, the study researchers tried to answer the question: can women take antiretroviral therapy successfully? As we all know, women traditionally have been underrepresented in clinical trials. There are many reasons for this, one being the assumption that women, because of other issues in their lives, cannot adhere to complicated regimens. This assumption, among others, was examined in Women First.

In terms of virologic and immunologic response, about 65–80% of subjects in this study were able to achieve a viral load of fewer than 400 or 50 copies/mL. They also experienced CD4 cell count increases of anywhere from 175 to 225 cells/mm³, depending on the arm of the study. Nelfinavir [Viracept] and saquinavir [Fortovase or Invirase] were given in combination—not a combination that we give at the present time—with two nucleoside analogs [NRTIs] given either twice or three times daily. Responses in this group of women were therefore similar to those that were reported in concurrent antiretroviral studies enrolling mostly men. But another important conclusion was that women can enroll and participate and be maintained successfully in clinical trials when they see that the treatment under study is interesting to them and likely to be beneficial.

Data from further studies in which gender analyses were performed have shown that, overall, there are no significant differences in outcomes between men and women in terms of classic clinical trial parameters: the percentage of patients who are able to achieve HIV RNA [viral load] levels of fewer than 400, 200, or 50 copies/mL, depending on the particular trial; CD4 cell count increases over baseline; time to virologic failure; and response to therapy. These specific gender analyses have been performed with regimens that are used at the present time, namely triple combination regimens with protease inhibitor [PI] or non-nucleoside reverse transcriptase inhibitor [NNRTI] backbones.

In recent years a number of cohort studies have also compared response rates between women and men after adjusting for factors that might be considered confounding

variables, such as age, race, education, injection drug use, CD4 cell count, and viral load before the initiation of anti-HIV therapy. Results from these studies mirror the gender analyses performed in the antiretroviral trials.

I will mention one such cohort study, an analysis of women and men initiating antiretroviral therapy in a university-based clinic, which was presented at last year's Retrovirus conference [poster 777-W]. Baseline CD4 cell counts among the 80 women and 149 men were similar [a mean of 130 cells/mm³], while viral load was lower in the women. A lower baseline viral load in women is a consistent phenomenon that is seen across cohort studies and clinical trials. Interestingly, the time to initiation of antiretroviral therapy in this study was longer in women than in men [355 vs 184 days], and women were more likely to achieve undetectable viral loads. The CD4 cell response and the durability of response for both CD4 cell count and viral load were very similar.

A few other clinical trials have reported that higher proportions of women achieve virologic success [undetectable viral load] compared with men. The fact that women on average have a lower viral load at the time they start therapy would certainly contribute to such an outcome.

The key message in terms of response to antiretroviral treatment is that there seem to be no substantial differences between women and men among those who are able to take therapy. This has no doubt influenced the substantial benefit seen with the advent of antiretroviral medication, and specifically highly active antiretroviral therapy [HAART]-based regimens, in the parts of the world where there is access to these drugs. Again, one caveat in terms of these response rates is whether patients are able to tolerate and maintain their drug regimens.

Effect of Sex/Gender on Antiretroviral Pharmacokinetics

Next, I would like to consider how women and men differ in terms of a variety of pharmacokinetic factors. [Pharmacokinetics refers to the metabolism, absorption, and elimination of drugs in the body.]

Studies have shown that several of these factors are likely to have an impact on anti-HIV therapy. For example, we know that women on average have lower body weight and higher body fat content than men. There are clear hormonal differences between women and men. In pregnant HIV-infected women the differences in volume and distribution of antiretroviral agents need to be considered. Differences in hepatic [liver] function are related to the cytochrome P450 enzyme system, which metabolizes several anti-HIV drugs. The CP450 enzyme system is made up of an array of specific enzymes [proteins that act as catalysts] called isoenzymes; women and men have a relatively different distribution and percentage of these isoenzymes. And then there is the important issue of drug interactions.

DRUG EXPOSURE AND TOXICITY

A 2001 report by David Burger, PhD [University Hospital Nijmegen], and colleagues included a gender analysis of a therapeutic drug monitoring [TDM] database looking specifically at indinavir [Crixivan] concentrations. [TDM involves measuring drug levels in the blood to ensure the most potent response with a minimum of adverse events.] The researchers found no statistically significant difference between indinavir concentration ratios in women and men.

However, when they considered adverse events attributed to indinavir—hyperbilirubinemia [high bilirubin levels in the blood] and especially renal [kidney] effects, which they called “intoxification”—TDM was indicated for a much higher proportion of women [17.4%] than men [6.6%], a statistically significant difference. The indication for TDM likewise led to a dose reduction due to side effects in a higher proportion of women [9.7%] than men [1.1%]. So there appears to be a relationship between gender, drug exposure, and toxicity.

EFFECT OF SEX AND BODY WEIGHT ON PHARMACOKINETICS

A pharmacological substudy of ACTG 359, which compared salvage regimens for patients whose indinavir-containing regimens had failed, was presented by Richard Brundage, PharmD [University of Minnesota], and colleagues at the 2002 Retrovirus conference. The substudy showed that ritonavir [Norvir] coadministration with saquinavir and nelfinavir led to a three-fold increase in saquinavir exposure compared with nelfinavir across the group as a whole. However, saquinavir clearance in women was reduced by 50%, and it appeared that weight was positively correlated with this outcome. At the least, this study shows that perhaps there are gender issues in terms of a weight differential, and that weight does affect serum drug levels.

DOSE MODIFICATION

Also worth mentioning is the effect of sex or gender and body weight on antiretroviral dose modification. Data from a gender analysis of ACTG 175, which has been presented by Judith Currier, MD [University of California, Los Angeles], and colleagues, demonstrated higher rates of dose modification for women who were randomized to the ddI [didanosine, Videx] arm than men randomized to the same arm. Women in the study were more likely than men to weigh 60–65 kg [132–143 lbs] and hence, on average, to receive the higher dose of ddI on a milligram per kilogram basis; the weight cut-off for dose reduction of this particular drug is 60 kg. In a logistic regression analysis, this result was related in part to a weight difference.

So, while differences in weight between women and men can perhaps lead to toxicity, this study shows that such differences can also result in variances in terms of dose modification.

DRUG INTERACTIONS WITH ORAL CONTRACEPTIVES

Oral contraceptives are commonly used by HIV positive women, and hormone replacement therapy [HRT] by those who are postmenopausal. While we are all aware of changing attitudes as far as using HRT, if we are going to use oral contraceptives in HIV-infected women, we need to understand that there are significant drug interactions between oral contraceptive agents and the PI and NNRTI drug classes. For example, study data have shown that nelfinavir and ritonavir decrease levels of the oral contraception pill [OCP, or “the Pill”] and should not be used in women taking OCP. The same is true of nevirapine [Viramune], which has been shown to cause estrogen AUC levels to drop by 19%. [AUC refers to area under the curve, a measure of total drug concentration over time.]

This is by no means an exhaustive account of drug interactions that have been studied, but it clearly indicates that women who use oral contraceptives need to have their combination regimens carefully selected. Unfortunately, no guidance for dose modification of oral contraceptives when used with HAART is currently available.

Sex/Gender and Complications Associated with HAART

Research data suggest that differences exist between women and men in terms of complications associated with antiretroviral agents. On a positive note, it appears that women have a lower risk for triglyceride increases with the use of some anti-HIV agents. However, an increased incidence of pancreatitis [inflammation of the pancreas] has been seen in women, and they have an increased risk for hepatic steatosis [fat buildup and subsequent tissue degeneration in the liver] and lactic acidosis [a life-threatening buildup of lactic acid in cells]. In the realm of body shape changes, women across a number of studies have shown a greater risk for fat accumulation and breast enlargement. I have a question about decreased bone mineral density, and fortunately we are now beginning to see some bone-related studies in HIV-infected women. Finally, it appears that women are at increased risk for rash, specifically NNRTI-associated rash.

RASH AND HEPATOTOXICITY

Starting with the issue of nevirapine hepatotoxicity [liver toxicity] as well as nevirapine-associated rash, I will refer to the results of the FTC-302 trial reported in 2001, in which nevirapine and efavirenz [Sustiva] were compared with each other together with a backbone of NRTIs, including FTC [emtricitabine, Emtriva]. Ten percent of subjects in this trial experienced grade 4 [life-threatening] liver enzyme elevations, and the incidence of these grade 4 elevations was two times greater in women than in men. Two fatalities were reported in the study, both of which occurred in women who experienced liver enzyme elevations, although other clinical factors may have been responsible.

In other studies looking at the issue of nevirapine toxicity, women have not been shown to have an increased risk of hepatotoxicity. In addition, I was fortunate to see the data set that Boehringer Ingelheim [the manufacturer of nevirapine] has put together looking across all of their nevirapine trials, as well as cohorts and other clinical trials that have used this drug. The overall conclusion from their rather large data set is that female sex is not an independent risk factor. So there is some controversy around this issue. Nevertheless, the FTC-302 study was compelling, and the results should be kept in mind as nevirapine is commonly used in HIV-infected women.

As for nevirapine-associated rash, I will mention a study reported by Judith Aberg, MD [Washington University], looking at two clinic populations and showing that rash was significantly more common in women. A number of other studies in the literature also show that rash is more commonly reported in women taking nevirapine than in men. In fact, in the Boehringer Ingelheim data set female sex does fall out as an independent risk factor for nevirapine-associated rash. Such data need to be considered when using this particular agent in women.

PANCREATITIS

What about pancreatitis? At least one report in the literature features an analysis of adverse events related to NRTI use in a large urban HIV clinic at Johns Hopkins University, in patients who were receiving NRTIs with or without hydroxyurea [Hydrea]. In a multivariate analysis, female sex was an independent risk factor for pancreatitis. There are other isolated reports in the literature also suggesting a difference in risk between women and men.

ADVERSE EVENTS RELATED TO PARTICULAR DRUGS

Looking at adverse events related to particular drugs, I have tried to summarize data gathered several years ago focusing on the PIs ritonavir and nelfinavir. In the case of ritonavir, the definition of intolerance was abdominal pain, nausea, vomiting, and circumoral [around the mouth] numbness. It appeared that women experienced these side effects more commonly than men.

In the case of nelfinavir, an analysis of the combined data from three registrational trials indicated that women were less likely to experience grade 2 [moderate, persistent] diarrhea than men; this result also has been shown in more recent studies. Yet in these same trials abdominal pain, pruritis [itching], and rash were more commonly seen in women. Data in the literature therefore suggest differences in the incidence, frequency, and types of adverse events seen in women compared with men with the use of these agents.

SERUM LIPID ABNORMALITIES

As I have mentioned, women may have an advantage in the case of serum lipid [blood fat] abnormalities. START I and START II, two trials in which specific sex or gender analyses were done, compared different NRTI backbones—

d4T [stavudine, Zerit]/ddI, d4T/3TC [lamivudine, Epivir], and AZT [zidovudine, Retrovir]/3TC—given in combination with indinavir. Both START studies showed that across all of the NRTI arms, women were less likely to experience grade 1 to 4 [mild to life-threatening] elevations of serum triglycerides than men.

There is also a gender analysis that we have done of the Glaxo Wellcome-sponsored trial ESS4001, presented at last year's Retrovirus conference. This was a comparison of a triple NRTI regimen vs a PI-based regimen using nelfinavir, and a comparison of AZT/3TC vs d4T/3TC as an NRTI backbone. Again, women were less likely to experience triglyceride elevations than men across the three arms of the study. Data from other studies substantiate these results.

LACTIC ACIDOSIS

Lactic acidosis is a severe complication of antiretroviral therapy associated with a rather high mortality rate. In a Food and Drug Administration [FDA] review of 107 reported cases presented in 1999, lactic acidosis was associated with dual NRTI use. Thirty [83%] of the cases occurred in women, 50% of whom weighed 175 lbs or more, and in that whole series the mortality rate was 55%.

Single case reports as well as small case series of lactic acidosis have been reported over the past decade. I now have a fellow working with me doing a retrospective analysis of all reported cases of the condition, and although I have not looked at every one of them, we have a pretty complete data set. Our calculations indicate that over 80% of all cases in which sex was reported occurred in women. Women thus appear to be much more commonly affected by this complication.

LIPODYSTROPHY

I have tried to distill data from lipodystrophy studies looking at women only, as well as comparing women and men in terms of lipoatrophy [fat loss], central adiposity [fat gain in the abdomen], and mixed syndrome [fat loss and gain in different body areas of the same person]. From the data gathered so far, fat accumulation is more common in women, while fat depletion is more commonly seen in men. The prevalence of mixed syndrome appears to be equivalent in women and men. Since the definition of lipodystrophy is still changing, future studies might help us more clearly identify differences that exist between women and men in terms of body fat irregularities.

OSTEOPENIA AND OSTEOPOROSIS

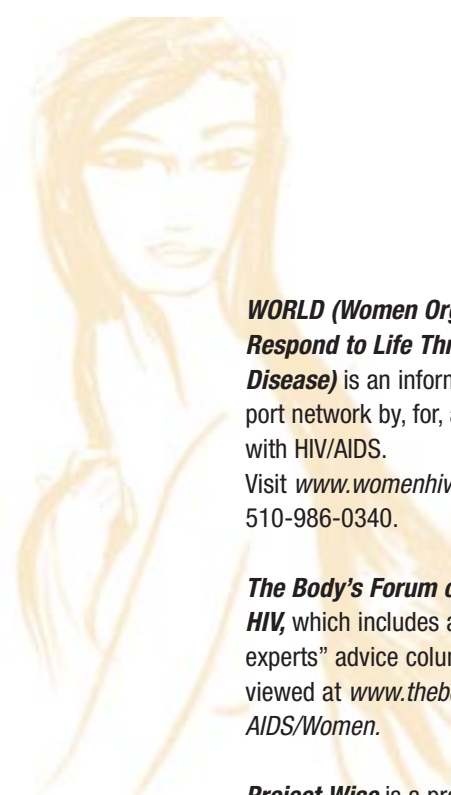
The earliest studies looking at the effect of antiretroviral therapy and/or HIV infection on rates of osteopenia and osteoporosis [reduced bone mineral density] were pursued exclusively in men. We now have data, including some presented at this conference, looking at bone mineral density specifically in women. Yet results to date are conflicting as to whether osteopenia and osteoporosis are more commonly seen in HIV positive women as opposed to HIV negative women, and whether antiretroviral therapy such as PI use

increases the risk. We need to look at more studies coming out on this issue for definitive answers.

Summary

In summary, response to antiretroviral therapy is similar in women and men; an equal virologic and immunologic benefit is seen in patients of both sexes who can tolerate these drugs. There are differences in pharmacokinetic parameters, however, that lead to disparities in drug levels and toxicities between women and men. There are also sex- and gender-based differences in adverse events and drug and HIV-associated complications. The overall efficacy and success of anti-HIV regimens may be impaired as a result of these various differences. I would like to suggest that we carry out prospective studies designed to define optimal antiretroviral regimens for HIV-infected women.

Kathleen E. Squires, MD, is associate professor of medicine at the Keck School of Medicine at the University of Southern California (USC) in Los Angeles, and medical director of the Los Angeles County and USC Medical Center HIV/AIDS clinic.



RESOURCES

WORLD (Women Organized to Respond to Life Threatening Disease) is an information and support network by, for, and about women with HIV/AIDS. Visit www.womenhiv.org or call 510-986-0340.

The Body's Forum on Women and HIV, which includes an "ask the experts" advice column, can be viewed at www.thebody.com/Forums/AIDS/Women.

Project Wise is a program of Project Inform focusing on HIV/AIDS treatment information and advocacy for women. For information about Project Wise and to subscribe to its publication, *Wise Words*, visit www.projectinform.org.