Gender Matters

Until AIDS drugs are tested in enough women, one in five PWAs won't know if she's taking the right drug or the right dose

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Donna Godbold was straining to understand a medical lecture at the National Conference on Women and HIV in Pasadena, California last May, when a voice cried out: "How many women are in that study?" The audience bristled. "Yeah, tell us the truth!" yelled another woman. Godbold was aghast. "How rude. I wish they would just be quiet," she whispered to her mother. But by the time the conference closed, Godbold, a PWA from Huntington Beach, California, ended up joining women from ACT UP in protesting the failure of government, medical institutions and the pharmaceutical industry to endure the inclusion of women in research and health care.

Given a year to live more than 18 months ago, Godbold's nascent activism was born of fright and frustration with the antiretroviral guessing game. Indinavir (Crixivan) gave her high fevers, and ritonavir (Norvir) landed her in bed for two weeks with nausea, neuropathy and a burning sensation in and around her mouth. She managed on saquinavir (Invirase) for seven months until suddenly her viral load shot up and her CD4 cells sank. A spreading rash and nausea forced her off nevirapine (Viramune). Now she's tolerating a combination of nelfinavir (Viracept), d4T and ddC-so far. "By the day of the demostration, I was angry-not at the person who had infected me, but at the medical profession for not knowing more after all these years," Godbold says. "Here we are pressuring the FDA for more drugs, but they don't even known how these drugs operate in women's bodies."

Proliferating reports from doctors and PWAs, plus the first few tentative studies, suggest that women with HIV experience drugs and their side effects differently from, or more severely than, men. Take kidney function: Pat Rolands of Santa Monica followed the Crixivan regime, including drinking more than the recommended amounts of water, but suffered extremely painful kidney failure-not the more widely seen kidney stones-caused by a "heavy sludge of thousands of Crixivan crystals." Rolands notes that dosages of some drugs are based on weight. "Why isn't [this adjustment] done for these incredibly strong, toxic drugs we are all taking? Should a 115-pound woman really take the same as a 180-pound man?" Marlene Diaz of New York City says she "doubled over" with kidney stones from Crixivan, an experience "worse than labor pains." Was this due to their special biologies as women? No one knows, and that's the problem.

For these and other women with HIV, determining dosage, side effects and effectiveness of FDA-approved drugs winds up being a crapshoot. That's because the government does not require

researchers to include enough women, who make up 20 percent of all U.S. AIDS cases, in clinical trials to smoke out possible gender differences. In fact, until repealed four years ago, FDA regulations required that most trials exclude women of “child-bearing potential.”

The systematic failure to study drugs in women, activists say, is a clear indictment of a pervasive medical attitude that women are unworthy of the same considerations automatically granted men. And it may be causing women to die unnecessarily. “Even if you are a woman with all the money in the world and David Ho was your doctor, you still wouldn’t know how HIV medicine would work in your body because that medicine still wouldn’t have been tested in women’s bodies,” says Mary Lucey, a woman with HIV who is an AIDS policy analyst for the City of Los Angeles.

These concerns are also voiced by people with greater political influence. “Clinical research has traditionally been focused on men,” Rep. Maxine Waters (D-CA) told the Pasadena conference. “As a result, [information on] the unique effect of the female hormonal system on drugs is not being gathered, and drug therapies cannot be designed for the female biology.” Most AIDS-drug research in women has focused on pregnancy and preventing HIV transmission to newborns, she noted. “While this work is critical, we must also recognize the value of women’s lives apart from their children. Effective treatment strategies for women have also lagged behind men. This must change.”

The issue resonates for Waters, chair of the Congressional Black Caucus. AIDS is now the leading cause of death for African-American women between the ages of 25 and 44. AIDS is also the third leading cause of death among all women in this age range. Experts predict a continuing surge in new infections among women. And women have not fully shared in the recent decline in AIDS death rates. The Pasadena conference was abuzz with news from the Centers for Disease Control and Prevention (CDC): In the first six months of 1996, men’s deaths had declined by 15 percent since 1995, while women’s deaths had increased by 3 percent. In July, the CDC released updated figures for the first nine months of 1996, reporting the decline to be 22 percent among men but only 7 percent among women.

What might account for this gender disparity? One factor, supported by several studies, is that women are often diagnosed or seek treatment later in their disease, resulting in faster AIDS deaths. Another is that women with HIV-overwhelmingly African-American, Latina and poor-may have less access to comprehensive medical services and state-of-the-art drugs. And when they do seek treatment, they often face bias from ill-informed doctors. Sandra Thurman, the White House AIDS policy coordinator, says that medical professionals “continue to overlook women because they don’t fit into some stereotype identified 15 years ago. It’s not only irresponsible, it’s nearly insane.”

But even women who use the latest therapies may not be getting the right drugs at the right dosage. ACT UP/New York veteran Maxine Wolfe, PhD, who has carefully monitored AIDS research for a decade, says drugs are prescribed-based on studies almost entirely made up of men-as if “one size fits all.” Yet evidence of gender differences in side effects and rates of metabolizing, absorbing and eliminating drugs has been accruing for years. In 1990 The Journal of the American

Medical Association reported evidence that the female hormonal cycle affects the way a drug is absorbed and the length of time it remains in the body. A 1995 Dutch study found that women metabolized AZT 42 percent slower than men.

“If something works well for men, it often works well for women and vice versa. But the side effects, partially because of hormonal differences that affect metabolism, can mean that some things are different,” says Dr. Kenneth Mayer, director of the AIDS research program at Brown University. “Only through careful dosing studies can these differences be uncovered.”

Yet such studies have never been performed for any AIDS-related drug. At last year’s International AIDS Conference in Vancouver, Dr. Judith Currier, medical director of the AIDS clinic at the University of Southern California, presented results from a federal trial that was kept open until an “adequate number” of women--“an unprecedented” 18 percent-enrolled, to determine whether drug responses differed by gender. The study (ACTG 175) compared single drug therapy with AZT or ddI to double-drug therapy with either AZT and ddI or AZT and ddC. Currier says that while “overall there were no dramatic differences,” the study found that “women were more likely to develop severe symptoms”-the type they could notice themselves-“while men were more likely to develop severe laboratory toxicities”-the type that showed up through blood tests. And among antiretroviral rookies, women were significantly more likely than men to discontinue their medication due to side effects. “We don’t know why,” Currier says. “There needs to be more investigation into how well antiretrovirals are tolerated and how effective they are in women.”

Perhaps most significant were the findings on dosage. Dose reduction, allowed for anyone having serious side effects, occurred more frequently among women than men. But despite the dose decrease, there was no difference in efficacy. “The possibility that women may do as well on lower doses of some medications merits further study,” she concludes.

At the conference on women and HIV, two more studies were added to the evidence of gender differences in drug effects:

- Women had a 1.8-times higher blood level of the antiretroviral delavirdine (Rescriptor) in a trial by manufacturer Pharmacia & Upjohn, which enrolled 19 percent women. (No gender differences in effectiveness or side effects were found.) P&U researcher Lynne Wathen, PhD, offers several possible explanations: “Women tend to have smaller body size, so they have a higher dose-per-kilogram ratio than men; women may also have altered metabolism at various phases of the menstrual cycle; or there may be gender differences in drug clearance.” The study shows, Wathen says, that “pharmaceutical companies should make a commitment to have significant numbers of women in clinical trials.”
- Women on Agouron’s nelfanavir experienced higher CD4-cell increases and more side effects

such as stomach pain, itching and skin rash, according to pooled data from three studies, which collectively included 11 percent women.

Meanwhile, a recent U.S. Department of Health and Human Services report states flatly that drugs approved to treat HIV and opportunistic infections “appear to be similarly effective in men and women.” But USC’s Currier cautions, “If you don’t have enough women involved, you can conclude that there’s no difference when a difference really exists, but you didn’t study enough women to find it.” Wolfe of ACT UP adds that this creates a circular logic: If you doubt there are gender differences, you don’t enroll many women in your study. Thus, she says, “you never find differences, and then you have no reason to believe you will and the circle continues.”

So how many women are enough to do a meaningful by-gender analysis? In 1992, Currier presented a paper (written with several colleagues) on this very question. “We ended up concluding that for most large trials, if you had over 15 percent, it’s a good start,” she says. “And depending on various statistical factors, the figure should sometimes be considerably higher.”

After years of activist pressure, the overall percentage of women in AIDS drug trials has steadily increased, although the track record is still quite uneven. In most drug company trials, there are now more women enrolled, but rarely sufficient numbers for meaningful by-gender analysis. Brown’s Mayer says, "The onus of responsibility has to be on the company to demonstrate why additional information wasn’t obtained-as opposed to saying, ’Well, we think it should work the same way, so why make a big deal about it?’ That’s not acceptable.

The National Institutes of Health (NIH), which funds far fewer AIDS drug studies than does the industry, reports that it has also improved the total proportion of women enrolled in studies by its AIDS Clinical Trial Group (ACTG)-a national consortium of researchers mainly at elite teaching hospitals-from 7 percent in 1987 to 15 percent cumulatively by this year. (However, activists say the new number misleadingly includes pregnant women in drug trials to prevent transmission of HIV to their children, rather than for their own benefit; after subtracting them, the figure is only 12 percent.) Meanwhile, the current figure for NIH’s Community Program for Clinical Research on AIDS (CPCRA), a network of smaller neighborhood-based research projects mandated by Congress in the late 1980s to remedy the underenrollment of women and people of color, is 19 percent cumulatively (though some trials still have much lower percentages).

But is gender analysis being done? “NIH guidelines [adopted in 1994 by congressional directive] state that if there’s a hint of difference when the drug is being developed, we must look at it,” says Dr. William Duncan, associate director for therapeutic research at the AIDS Division of the National Institute for Allergies and Infectious Diseases (NIAID). “When [gender differences] come up, we look at them closely to determine if we should do additional studies” of possible problems with the drug. “I’ve seen no proof of this,” ACT UP’s Wolfe responds. “Study teams aren’t even required to include a women’s health specialist or to look for possible drug effects on women-specific symptoms.”

But even if federal policy encourages women's inclusion in clinical trials, Wolfe notes that ACTG grantees are rarely held accountable for low enrollments of women. She and other activists charge that many ACTG researchers at elite hospitals prefer their existing white, middle-class, gay male clientele, who they believe will adhere to strict drug regimens. "White male researchers do not take into account women's 'real lives,' juggling children, home and work," says Michelle Lopez, a Bronx PWA who identifies herself as a black Hispanic immigrant lesbian mother. And word of mouth spreads like neon-light skywriting: If a woman is allotted only five minutes by a trial doctor, if there's no gynecological exam, if there's no one on staff to talk to-don't go there.

There are other barriers to enrollment of women (and often, men) from poor neighborhoods, such as failure to offer funds for child care or transportation, inadequate outreach, and printed material and staff assistance in English only. Anne DeGroot, an associate professor of medicine at Brown University, observes: "It's hard to collect the numbers of women needed for a study, but it's not impossible. The problem is really devoting the attention to getting those women into clinical trials."

Indeed, until 1993 more attention was devoted to keeping women out of trials-specifically women with "child-bearing potential." FDA regulations limited enrollment in most studies to sterilized or postmenopausal women. The rationale usually offered was to avoid damage to a "potential fetus," which Europe's thalidomide disaster of the 1960s had shown was possible, and prevent lawsuits that might result. Yet there is no evidence of any such suits about experimental drugs, as opposed to approved therapies like DES or the Pill. And men with "childbearing potential" have never been excluded from trials, despite evidence that drug-damaged sperm might adversely affect fetal development. The bottom line, activists say, is that many male researchers simply don't trust women-no matter how carefully they are warned about the risks-to avoid getting pregnant during a trial.

Even now, trials routinely require women (even exclusive lesbians and celibate heterosexuals)-but not men-to provide proof of birth control other than barrier methods. Wolfe notes that the effects of the IUD and such chemical contraceptives as the Pill, Norplant (an arm implant) and Depo-Provera (an injectable) have not been adequately researched in women with HIV. What is already known is cause for serious concern: IUDs work by setting up a low-grade infection in the cervix-a potentially high risk for a PWA. Oral contraceptives can cause blood abnormalities and can increase vaginal infections. And at least one HIV drug, nelfinavir, is known to decrease blood levels of oral contraceptives-which could require increasing the dose to dangerous levels to maintain birth-control effectiveness.

In fighting the push to enroll sufficient women and analyze results by gender, opponents argue that these steps would cost time and money that might deny all PWAs quick access to new drugs. "The detection of significant differences among relevant subgroups generally requires clinical trials that are prohibitively large, time-consuming and expensive," Dr. J. Claude Bennet and colleagues from the federal Institute of Medicine wrote in a 1993 article in The New England Journal of Medicine. Theresa Toigo, director of the FDA's Office of Special Health Issues, adds: "We're never going to know all the possible side effects before a drug is approved. Doing all the possible studies

that one might think are good would increase the drug development time." But women activists say that's precisely why the FDA must require meaningful by-gender analyses before approving new drugs. "The industry must comply with every FDA regulation; they do it all the time," says Linda Meredith, a New York City immunologist and longtime advocate for women with HIV. "If the FDA said companies had to have 10 purple-eyed, orange-haired people, they would find them. When there's a race to the finish line, the industry figures out a way to get it done."

Another objection comes from a leading community advocacy organization, the Treatment Action Group (TAG). While TAG's Spencer Cox supports inclusion of "an array of people living with HIV" in clinical trials, he is concerns that by-gender analysis could yield "spurious results" that might "frighten women with the idea that their response to treatments is likely to be radically different than men's" and lead to "real treatment fear." Donna Godbold, the PWA newly inspired into activism, responds: "Has providing that information engendered fear in men? I don't see the difference. I think it would give women more of a real choice."

One possible tool to provide that information would be drug labeling. The FDA currently requires specialized labeling information on the effectiveness and safety of drugs in children, the elderly and pregnant women-but not nonpregnant women. "If they wanted to, the FDA could require manufacturers to show efficacy in women to get labeling for women," says Peggy Johnston, a former NIAID researcher and current scientific director of the International AIDS Vaccine Initiative. Activists have proposed that labels on already-approved drugs include the statement that effectiveness and safety in women have not yet been determined. The FDA's Toigo replies that under current policy, labeling is changed if a drug is found, after approval, to induce a specific reaction in women. "After AZT was approved, we started getting reports about liver toxicity in obese women," she says. "We updated the label to reflect that."

Although there were already five known cases of women with AIDS in 1981, women have, throughout the epidemic's history, often been the forgotten and invisible PWAs. Finally, with the formation of ACT UP in 1987, activists started loudly protesting on behalf of HIV positive women. A turning point was the 1990 storming of NIH headquarters in Bethesda, Maryland by 1,200 protesters. Among the demands that day for broader AIDS research was a targeted plan to incorporate women in AIDS studies. This was the first of many demonstration on this issue.

In December 1992, Terry McGovern, director of New York City's HIV Law Project, filed a citizen's petition with the FDA on behalf of Mary Lucey (who had been denied admission to numerous trials), ACT UP and other AIDS and feminist groups, seeking to repeal the agency's 1977 guidelines that excluded women "of childbearing potential" from trials, and to institute regulations requiring women's inclusion in adequate numbers. In July 1993, the FDA announced new guidelines essentially lifting the ban and adoption language that merely "encouraged" drug companies to include more women and do by-gender evaluation.

The following year, McGovern was appointed to the National Task Force on AIDS Drug Development, an advisory body that included top Clinton administration health officials. For many months, she pressed for a resolution calling on the FDA to "put some teeth" into the regulations.

Finally, in January 1995, after three ACT UP protests, the Task Force unanimously adopted a much-compromised version of McGovern's proposal. Joining the vote was then-FDA commissioner David Kessler.

The FDA's Toigo says "considerable attention has been paid" to the Task Force's proposals, which she says are on the "fast track." But almost three years later, none is in place. In September 1995, the FDA published a draft rule that companies must perform gender analysis if women are enrolled in a study, and must report annually on women's trial participation. Toigo says its language is still "being worked on." But even if adopted, the rule itself says "it does not require the inclusion of particular numbers of [women] in any study"-and thus would not guarantee meaningful gender analyses. "David Kessler has blood on his hands because he refused to change the regulations," Lucey says. "A lot of women probably died because of incorrect doses and more severe side effects that proper drug testing might have avoided."

So the grass-roots activity continues. "At the women's conference, we collected 700 signed postcards demanding that the FDA require drug companies to test drugs in women," Lucey says. "Women AIDS activists have won many battles before, and we can do it again." (As POZ went to press, the FDA announced a draft rule to block clinical trials that exclude women "for inappropriate reasons.")

Meanwhile, Donna Godbold is forming a women's support and advocacy group in Orange County and plans to begin public speaking. "All I keep reading is how well men are doing on protease," she says. "I'm hopeful about the prospects for new treatments, but most clinical trials don't apply to me. So, depending on how I'm feeling, I fully intend to be involved in this fight."

HOPEFUL SIGNS

At last, some institutions are moving to involve more women in trials

While the FDA may be dragging its feet on requiring more inclusion of women in drug research, other institutions are moving ahead on their own:

"After yaers of screaming and badgering, there's finally a shift in some of the companies toward recruiting more women," says HIV positive Dawn Averitt, who recently merged her Project WISE (Women's Information Service and Exchange) with Project Inform, the HIV treatment advocacy group. Pharmacia & Upjohn likes to cite its 19-percent-women delavirdine study. And Agouron is trumpeting an all-women's trial of nelfinavir/saquinavir/d4T/3TC it is conducting jointly with Hoffmann-La Roche. (But activists call the new study too little-it excludes anyone with prior antiretroviral experience-and too late, coming after the drugs' approval.)

Bristol-Myers Squibb recently allocated $220,000 for the Women's Initiative, a one-year pilot program coordinated by the American Foundation for AIDS Research (AmFAR). This will offer researchers at various centers grants to develop better methods for recruiting and retaining women in clinical trials.

Mary Fisher, a PWA and founder of the Family AIDS Network who spoke at the 1992 Republican Convention, is helping launch small trials conducted by renowned University of Alabama AIDS researcher Dr. Michael Saaf on how approved antiretrovirals work in women, looking at the role of hormonal surges in viral replication and what Saag calls “the age factor”-the impact of menopause on drug effects.

“I think it should be mandatory that clinical trials are designed to look like the epidemic,” says Dr. Scott Hitt, chair of the President’s Advisory Council on HIV/AIDS. “And it shouldn’t be difficult. The patients are there. They need health care. It’s just a matter of reaching out to them.” He plans to ask the council to recommend that the FDA adopt a stronger policy on this issue.
