## HIV Infection in Women: Implications for Drug Abuse Treatment and Research

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#### INTRODUCTION

This chapter highlights several features of the HIV (human immunodeficiency virus) epidemic in women, particularly women with a history of drug use, emphasizing current trends and research concerning transmission, epidemiology, clinical manifestations, access to care, and pregnancy-related issues.

## THE WORLDWIDE HIV EPIDEMIC AMONG WOMEN

The World Health Organization has proposed that the following three patterns of HIV transmission characterize the epidemic in different populations: pattern 1, primarily male-to-male sex or injection drug use; pattern 2, primarily heterosexual transmission; and pattern 3, other avenues of risk or nonreporting (Chin and Mann 1988).

Worldwide, three-quarters of AIDS (acquired immunodeficiency syndrome) cases occur in heterosexuals. Where heterosexual transmission predominates, as in sub-Saharan Africa, the ratio of new male to new female infections is about 1 to 1 (Chin and Mann 1988). In the United States, injection drug use is the most important risk factor for HIV infection among women (Centers for Disease Control and Prevention 1995a).

These patterns of transmission are far from static. In certain areas of the world, such as Southeast Asia, recent explosive increases in AIDS cases have been linked to injection drug use, heterosexual transmission, and the particular vulnerability of women in the commercial sex industry. Although the United States is viewed primarily as a pattern 1 country, heterosexual transmission of HIV has become of increasing

concern in many areas in the country, including the Northeast and Southeast (Centers for Disease Control and Prevention 1995a).

#### AIDS AS CAUSE OF DEATH

AIDS is currently the leading cause of death among young adults in the United States (Centers for Disease Control and Prevention 1996a). In 1994, for persons 25 to 44 years old, AIDS was the leading cause of death among men, the third leading cause of death among women, and the leading cause of death among African-American women (Centers for Disease Control and Prevention 1996a). In some cities in the northeastern United States, where HIV is concentrated among African-Americans and Hispanics, AIDS has been the leading cause of death among men and women ages 25 to 44 since the early 1990s (Selik et al. 1993).

#### AIDS INCIDENCE AND PREVALENCE

Distribution of incident AIDS cases among males and females in the United States has a clear bicoastal pattern—the Northeast, Southeast, and Southwest and Puerto Rico (Centers for Disease Control and Prevention 1996b). Among women, AIDS incidence is more heavily concentrated in the Northeast and Southeast, Puerto Rico, and to a smaller degree parts of the Southwest and West. It remains uncommon in parts of the nonindustrial Midwest (Centers for Disease Control and Prevention 1996c; Ellerbrock et al. 1991).

AIDS cases associated with injection drug use follow a similar distribution, accounting for a preponderance of local cases in many northeastern States and Puerto Rico (Centers for Disease Control and Prevention 1996c). Thus, among drug users, women, and certain racial/ethnic groups, the AIDS epidemic is generally concentrated in the same geographic areas.

Health practitioners who care for women with HIV are familiar with the sharp peak in the age distribution of those affected (median age 35 years, with women ages 15 to 44 constituting 84 percent of all female cases) (Centers for Disease Control and Prevention 1995a). The secondary implications of this distribution are all too familiar—the impact of a young-adult fatal disease on patients with HIV, their families, and children.

Between 1981 and the end of 1992, more than 250,000 cases of AIDS were reported to CDC (Centers for Disease Control and Prevention 1995b). From 1993 to 1995, this figure doubled: More than 500,000 cases were reported in the United States by the end of 1995 (Centers for Disease Control and Prevention 1995c). Women accounted for 14 percent of this number (Centers for Disease Control and Prevention 1995b), compared with 24 percent during the 12-month period of July 1995 through June 1996 (Centers for Disease Control and Prevention 1996c), further evidence of the sharp rise in the epidemic's toll on women. Seventy-five percent of cases among women, compared with 48 percent of cases among men, were among blacks and Hispanics (Centers for Disease Control and Prevention 1995c).

#### AIDS RISK CATEGORIES

Men who have sex with men still account for the majority (51 percent) of cumulative AIDS cases, although the proportion of such cases has declined steadily over the past decade (Centers for Disease Control and Prevention 1996c, 1995b). Injection drug use accounts for approximately 35 percent of AIDS cases to date (Centers for Disease Control and Prevention 1996c). Among women, nearly one-half (46 percent) of AIDS cases are directly attributable to injection drug use and 38 percent to heterosexual contact (Centers for Disease Control and Prevention 1995c). Whereas approximately one-half of the cases resulting from heterosexual contact involve sex with a male injecting drug user, two-thirds of the AIDS cases among women are linked directly or indirectly to injection drug use.

#### **REVISED AIDS CASE DEFINITION**

In 1993 CDC revised its AIDS case definition. Three clinical conditions (invasive cervical cancer, pulmonary tuberculosis, and recurrent bacterial pneumonia) now qualify as AIDS diagnoses when present in people with HIV infection (Centers for Disease Control 1992). The new definition was the result of empirical, scientific, and epidemiologic evidence as well as advocacy and support from those affected by HIV and AIDS, who argued that women, certain racial/ethnic groups (particularly African-Americans and Hispanics), and injecting drug users were

underreported and undercounted by earlier AIDS definitions and case reporting.

#### **CLINICAL MANIFESTATIONS**

One of the most striking findings regarding women and the AIDS epidemic is that the clinical features of HIV among women are similar to those among men—after controlling for access to care, other sociodemographic variables, and gynecologic manifestations. CDC reviewed AIDS-defining conditions from approximately 7,000 female and 22,000 male injecting drug users with AIDS from 1988 through 1991 (Fleming et al. 1993). On multivariate analysis, after controlling for race, age, and geographic region, there were only four differences in AIDS-defining conditions by gender (out of a total of 22 specific infectious disease conditions and cancers included in the AIDS case definition at that time). Women were somewhat more likely to be diagnosed with esophageal candidiasis (19.8 percent of women v. 13.7 percent of men), cytomegalovirus disease (2.2 percent v. 1.5 percent), and herpes simplex virus disease (4.4 percent v. 2.6 percent), and they were less likely to be diagnosed with Kaposi's sarcoma (1.6 percent v. 2.7 percent). Women with HIV infection may be at greater risk for candidal infections than men, perhaps because vaginal candidiasis may serve as a reservoir for such infections. Other studies, however, found no significant differences between the sexes in clinical manifestations of HIV disease, apart from the well-known association between male gender and Kaposi's sarcoma (Vlahov et al. 1994; Morlat et al. 1992; Beral et al. 1990).

### STUDIES OF AIDS, WOMEN, AND DRUG ABUSE

#### Studies of Gynecologic Conditions and HIV

Investigators in Rhode Island studying women with HIV infection developed a model depicting the progression of mucosal candidiasis (Imam et al. 1990). Women presenting initially with vaginal candidiasis had CD4 counts close to the normal range. Women with oral, and not vaginal, candidiasis typically presented with substantially lower CD4 counts, whereas those with esophageal candidiasis had the lowest counts (below 100/mm³).

A CDC-associated study of patients with HIV infection from several geographically diverse American cities investigated gynecologic manifestations among the approximately 500 women in their sample. CD4 counts in women with candidal vaginitis (approximately 15 percent of women) were lower than in those without candidiasis. Chronic or recurrent candidal vaginitis was less common (approximately 5 percent of women), bearing no clear relationship to immune status (Farizo et al. 1992).

Thus, the exact relationship between vulvovaginal candidiasis and level of immune function remains to be fully defined. Similarly, the actual incidence, severity, and relationship of pelvic inflammatory disease (PID) to immune function in women with HIV infection has not yet been clearly established. Further study is needed to define the impact of HIV infection and associated immunosuppression on these and other gynecologic diseases.

A 1987 to 1991 study of Louisiana women with HIV compared those who injected drugs with those who did not (Clark et al. 1993). Thirty-eight percent of women in the drug-using group had a history of syphilis compared with 14 percent in the noninjection group. PID occurred in about 5 percent of women in each group.

In a 1992 comprehensive review of the literature on cervical disease and HIV, Mandelblatt and coworkers (1992) examined the association between HIV and cervical neoplasia and found odds ratios (ORs) ranging from 3 to 10 (summary OR=4.9) for increased risk of cervical dysplasia in women with HIV infection. Since then, additional studies have shown a strong relationship between cervical dysplasia and HIV infection (Adachi et al. 1993). Cervical dysplasia worsens with the degree of immune suppression (Klein et al. 1994). It appears to be mediated through human papilloma virus (HPV) and especially through the more oncogenic HPV subtypes. More research is needed to determine the most effective strategy for cervical cytologic screening and long-term followup and on the impact of newer antiretroviral therapies and other HIV care interventions on cervical disease and other gynecologic conditions in women with HIV. Several prospective cohort studies of women with HIV now under way should help answer many of these questions.

## SEROPREVALENCE AND SEROINCIDENCE STUDIES

Chiasson and colleagues (1990) conducted a study of HIV sero-prevalence in a sexually transmitted disease clinic in New York. The study included a multivariate analysis of risk factors for HIV infection by sex in relation to different predictor variables. Among women, crack use, prostitution, and sex-for-drug relationships were important risk factors. Independent risk factors that predicted HIV infection in women and men included syphilis, crack use, and contact with prostitutes using crack. More recently, a strong association has been shown between having early syphilis and undergoing HIV seroconversion among female drug users in the Bronx (Gourevitch et al. 1996). Such findings highlight the urgent need for research and intervention trials aimed at enabling women to avoid some of these well-defined pathways of acquiring HIV.

#### **Survival Studies**

Early in the HIV epidemic, women who developed AIDS did very poorly. Data from a 1981 to 1985 San Francisco study showed that the median survival time after AIDS diagnosis for women was a scant 1.1 months compared with approximately 10 months in men. Survival for both groups increased over time, but in 1990 the survival timeframe remained lower for women (11.1 months v. 14.6 months) (Lemp et al. 1992).

Differences in survival by gender often diminish or disappear, however, when stage at presentation and access to and utilization of care are taken into account. In the same San Francisco study, treatment with antiretroviral therapy—either AZT (zidovudine) or ddI (didanosine)—had a major effect on survival rates (Lemp et al. 1992). Women who received therapy survived longer than those who did not, and the percentages of women and men receiving therapy who survived for 1 year were indistinguishable. In more recent analyses, in which access to care and socioeconomic status were assessed, no difference in rates of disease progression or of survival between men and women with HIV infection was found (Chaisson et al. 1995). When differential rates of disease progression are observed in women and men, such differences should not be ascribed to biologic factors.

#### Access to and Utilization of Care Studies

Additional data support the notion that women with HIV infection may have poorer access to or less use of medical care than men. Data published by Schoenbaum and Webber (1993) demonstrated that HIV is often underrecognized among women during an emergency room visit. In their seroprevalence study, the investigators determined whether any evidence existed for screening for HIV infection or drug abuse in patients who received care in the emergency room. Of persons who had undiagnosed HIV infection, males with infectious disease were screened for HIV more often by the emergency room staff. Women at high risk for HIV were underevaluated and underscreened for HIV infection compared with men who presented with similar conditions.

Differences in access to care for women and men have been demonstrated in other settings as well. Moore and colleagues (1991) used medicaid records from the State of Maryland to determine whether people diagnosed with AIDS during the period following the initial release of AZT (mid-1987 through 1989) had indeed received the medication during that period. Only one-third of the women studied were offered or received AZT compared with more than one-half of the men. People of color and injecting drug users were less likely to receive AZT than men who had sex with men. In keeping with these data, Stein and coworkers (1991) studied persons with HIV infection in several cities to determine the likelihood of AZT being offered in different clinical settings. This study found that injecting drug users, women, and African-Americans were less likely to be offered AZT. Differences in access to and effective use of health care resources must be considered in interpretation of data suggesting gender differences in the observed course of progression of HIV infection.

Another study looked at characteristics predicting which HIV-infected women with newborns would seek care for HIV (Butz et al. 1993). Women whose babies were HIV-infected were more likely to seek care than women whose babies were not infected. Of those women seeking care, however, injecting drug users and those who had been incarcerated were less likely to receive care. Combinations of demographic and behavioral variables may distinguish those not trying to access care and those trying to do so without success.

In a correlational analysis, Piette and coworkers (1993) analyzed persons who needed a specific service—mental health, housing, home

care, transportation, or entitlements (e.g., medicaid, Aid to Families with Dependent Children)—to learn whether they were in need of other services. One-half identified as needing drug treatment services also needed, but were not receiving, mental health services; one-half needed housing; one-third needed transportation and entitlements; and one-fifth needed home care. Women who are HIV-infected and use drugs thus face multiple risks and are subject to a broad array of influences and adverse conditions that affect health outcomes. Innovative approaches are needed to improve such outcomes.

#### **Drug Use and Methadone Studies**

At Montefiore Medical Center, several studies of women and men who were drug users in a methadone treatment program were conducted (Gourevitch et al. 1996; Schoenbaum et al. 1989; Selwyn et al. 1989a, 1989b, 1989c). A prospective cohort study also was conducted to assess disease manifestations and use of care over time (Selwyn et al. 1989d, 1992, 1993). These studies linked AIDS research projects and comprehensive onsite medical care to patient-scheduled visits at a methadone maintenance treatment program. High levels of compliance were achieved both with the clinical care provided and with the associated research effort (Selwyn et al. 1993).

#### **HIV Progression to AIDS**

The cohort study at the center followed 318 HIV-infected drug users, about one-half of them women, and found no difference by gender (or by race or ethnicity) in the rate of progression from HIV infection to AIDS over a median of 3 years of followup (Selwyn et al. 1992). Thus, in a seroprevalent population with ready and equal access to drug treatment and medical services, sex and race had no influence on clinical outcome. Greater age was associated with increased risk for progression, as has been found in other studies, because of either the increased time since infection or biologic phenomena associated with aging.

More than 80 percent of male and female patients (stratified by CD4 cell counts) participating in methadone treatment in the authors' program voluntarily used the onsite primary care services (Selwyn et al. 1993). In the group considered most eligible for HIV-related therapies

(fewer than 200 CD4 cells/mm³), approximately 80 percent were receiving ongoing antiretroviral therapy with AZT or prophylaxis for *Pneumocystis carinii* pneumonia. Persons in this more immunosuppressed group used primary care services at an average rate of once per month, without differences in use between men and women. The incidence of AIDS among HIV-infected study participants with a CD4 count below 500/mm³ who received AZT was 62 percent lower than those not receiving AZT (Selwyn et al. 1992). Thus, in a structured setting in which medical care is linked to drug abuse treatment, gratifying outcomes can be achieved in terms of ongoing care. Men and women showed no significant differences in use of services or in the course of their disease. Active drug use was not associated with a decline in immune status or more rapid progression of HIV disease.

Although it is important not to ignore possible effects of drug use on viral replication, disease expression, and immune function, any such biologic effects on HIV progression are probably eclipsed by the impact of HIV-related therapies, when they are used. Active drug users may be less likely to seek and receive therapy and ongoing care than drug users in recovery or nonusers. Thus, not seeking therapy and ongoing care is likely to be the principal manner in which drug use affects the progression of HIV-related disease.

#### **Pregnancy Outcomes**

Several studies have suggested that HIV infection, at least in its earlier stages, does not have a deleterious effect on the course of pregnancy or on the frequency of adverse birth outcomes (Selwyn et al. 1989c; Minkoff et al. 1990). The effect of late-stage HIV infection on pregnancy outcome is less defined. Moreover, pregnancy, which has been hypothesized to be an immunosuppressive state, does not appear to adversely affect the clinical course of HIV infection (Deschamps et al. 1993). For HIV-infected women who use drugs during pregnancy, the effects of the drug use on pregnancy and birth outcomes may be more deleterious than the effects of HIV itself.

#### **ACTG 076**

ACTG 076, the international clinical trial of the effect of AZT on perinatal HIV transmission, included women with CD4 counts

greater than 200/mm³ who received AZT during the second and third trimesters of pregnancy (Connor et al. 1994). The results showed that 25.5 percent of the infants whose mothers received placebos during pregnancy acquired HIV infection compared with 8.3 percent of infants whose mothers received AZT—less than one-third the risk of transmission in the AZT group. This was the first study to demonstrate the efficacy of any intervention in preventing HIV transmission between mother and infant. In the United States, drug-using women constitute the majority of women with HIV infection. Intensive efforts are needed to make interventions available to HIV-infected drug users before and during pregnancy to maximize the effectiveness of treatment for this high-risk population.

#### **SOCIAL ISSUES**

The issues of abuse, victimization, and other violence against drug-dependent women are particularly important, not only as they relate to drug dependence in general, but also because of their connection to HIV infection. The prevalence of sexual and other types of abuse—both prior and current—among drug users is believed to be high and must be addressed in the context of drug treatment programs and medical treatment settings (Dansky et al. 1995).

A medical anthropologist recently wrote of the importance of understanding not only the epidemiology and biology of AIDS, but also the social context in which the disease and the epidemic take place for women, particularly for poor women of color. An HIV-positive woman in New Orleans was quoted as saying, "You think AIDS is a problem? No way, I got real problems" (Ward 1993). This statement highlights the perception among some populations affected by AIDS that they are also vulnerable to violence, homelessness, poverty, and drug abuse.

Ironically, AIDS is now the leading cause of death in many of these populations. An agenda must be developed for more cross-disciplinary research, not only in epidemiology and biology, but also in the behavioral and social sciences, to address the social context of AIDS, with the ultimate goal of improving the integration of women with HIV into the system of medical care and other services.

#### **CONCLUSION**

For women with HIV, one aspect of continuing clinical research should be gynecologic manifestations of the disease, including research on the most effective strategies for treating these complications in women with HIV infection and the impact of new HIV therapies on these conditions. In addition, health service research is important to reach across disciplines and focus on the important questions of improving access to and utilizing needed medical and social services for HIV-infected women. Finally, without attention to the basic issues of gender inequality, empowerment, and self-sufficiency for women, efforts to prevent the further spread of HIV and treat its complications in women will continue to be compromised.

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