

# Women And HIV

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**Background:** Infection with the human immunodeficiency virus (HIV) has emerged as a major health problem for women in the United States. Family physicians can play an important role in the detection and care of HIV-infected women.

**Methods:** The epidemiology and natural history of HIV infection in women were reviewed. Articles were selected by a computer MEDLINE search.

**Results:** HIV infection is now a leading cause of morbidity and mortality among young women in the United States, particularly women of racial and ethnic minorities. Most cases of acquired immunodeficiency syndrome (AIDS) in women occur as a result of injection-drug use or heterosexual transmission. Based on limited information, women and men appear to have similar AIDS-defining conditions. Gynecologic problems are common in HIV-infected women. Pregnancy does not seem to be affected by early HIV infection, but women with advanced disease might be at increased risk for obstetric complications.

**Conclusions:** More women need to be included in natural history studies and clinical drug trials. Early awareness of HIV infection and better access to health care services are required to improve the treatment and survival of HIV-infected women. (J Am Board Fam Pract 1993; 6:367-77.)

Infection with the human immunodeficiency virus (HIV) has emerged as a major health problem for women in the United States. Seroprevalence is alarmingly high in some areas, and many women across the country are unaware they are infected. Women have unique clinical manifestations of HIV infection and often have shorter survival than men. This article reviews current knowledge about the epidemiology and clinical spectrum of HIV disease in women and offers some suggestions to guide family physicians in the detection and care of HIV-infected women.

## Epidemiology of AIDS in Women

More than 27,000 women have been diagnosed with the acquired immunodeficiency syndrome (AIDS) in the United States.<sup>1</sup> Women now account for more than 13 percent of new AIDS cases.<sup>1</sup> From 1990 to 1991, AIDS cases in women

increased 17 percent compared with a 4 percent increase in men.<sup>2</sup>

## Distribution

The incidence of AIDS in women varies geographically. Although most cases have been reported from New York, New Jersey, the District of Columbia, Florida, and Puerto Rico, all states have reported AIDS cases in women.<sup>3</sup> Most women with AIDS (73 percent) live in urban areas with populations greater than 1 million.<sup>4</sup>

That AIDS disproportionately affects racial and ethnic minorities (Table 1) is especially true for women. Compared with white women, African-American women are 13 times more likely to develop AIDS, and Latinas have an eight-fold higher risk.<sup>4</sup> During the last 5 years, the proportion of AIDS cases in women has remained constant for African-Americans, increased for Latinas, and decreased for white women.<sup>4</sup>

## Exposure Categories

Most AIDS cases in women are associated with injection-drug use (Table 2). Women who use cocaine are at particularly high risk for HIV infection,<sup>5,6</sup> including noninjecting crack cocaine users.<sup>7,8</sup> The common practice of exchanging sex for cocaine appears to explain its association with HIV infection.

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**Table 1. Percentage Racial and Ethnic Distribution of the US Population and AIDS Cases in Women and Men, through December 1992.\***

	US Population	AIDS Cases in Women	AIDS Cases in Men
White	80	25.2	56.3
African-American	12	52.9	26.7
Hispanic	6	20.9	16.0
Asian	2	0.5	0.7
Native-American	1	0.2	0.2

\*AIDS = acquired immunodeficiency syndrome. From HIV/AIDS Surveillance Report, February 1993.<sup>1</sup>

Heterosexual activity has emerged as another important HIV risk factor for women in the United States. Between 1982 and 1992 the percentage of women developing AIDS as a result of sexual transmission increased steadily from 12 percent to 36 percent.<sup>1,9</sup> Most cases involved a drug-using partner (Table 3). Because the Centers for Disease Control (CDC) classification allows only one exposure category per person, heterosexual transmission is probably underreported. Women who inject drugs and also have high-risk sexual partners are classified only as injection-drug users.

Two-thirds of heterosexually transmitted AIDS cases in the United States have been diagnosed in women.<sup>1</sup> HIV appears to be more readily transmitted from men to women than from women to men.<sup>10</sup> In addition, because there are more HIV-infected men in the United States, heterosexual women are more likely than heterosexual men to encounter an infected partner. Heterosexual transmission of HIV to women will continue to increase as seroprevalence in men rises.

Seven percent of women with AIDS have no specific risk factors ("undetermined" risk category), compared with only 4 percent of men.<sup>1</sup> Many of these cases probably result from heterosexual transmission, as only persons with known high-risk partners are counted as heterosexual cases. HIV-infected women who are unaware they are at risk are not likely to have their disease discovered and treated until they develop symptomatic illness.

### **HIV and Mortality in US Women**

HIV has become one of the 10 leading causes of mortality in US women of reproductive age.<sup>11</sup> In

New Jersey and New York, HIV is the third leading cause of death among all women aged 15 to 44 years and the leading cause of death among young African-American women.<sup>11</sup> As the HIV epidemic shifts to include more injection-drug users and heterosexuals, HIV disease is expected to become one of the five leading causes of death in young women nationally.<sup>11</sup>

### **HIV Seroprevalence in Women**

Reported AIDS cases represent only a fraction of women infected with HIV. Information about HIV seroprevalence in women is available from diverse clinical settings. Seroprevalence rates are as high as 65 percent in women enrolled in methadone treatment programs, and infection rates higher than 1 percent have been reported in women attending sexually transmitted disease clinics.<sup>12</sup> The best estimate of overall seroprevalence comes from perinatal testing.

### **Pregnant Women**

The CDC has performed a national survey of more than 1.8 million childbearing women by anonymously testing newborn blood samples for the presence of maternal HIV antibodies.<sup>13</sup> Because 84 percent of women with AIDS are of reproductive age,<sup>1</sup> this population-based study provides the best available estimate of HIV seroprevalence in women. In 1989, 1.5 per 1000 childbearing women were infected with HIV.<sup>13</sup> If seroprevalence is similar in women who do not bear children, approximately 80,000 women of reproductive age are infected with HIV in the United States.<sup>13</sup> Findings from a smaller French seroprevalence study suggested that infection

**Table 2. Percentage Distribution of AIDS Cases in Women by Exposure Category, through December 1992.\***

Exposure Category	Percent
Injection-drug use	50
Hemophilia or coagulation disorder	0
Heterosexual	36
Receipt of blood, blood products, or tissue	7
Other or undetermined	7

\*AIDS = acquired immunodeficiency syndrome. From HIV/AIDS Surveillance Report, February 1993.<sup>1</sup>

**Table 3. Heterosexually Transmitted AIDS Cases in Women Born in the United States by the Exposure Category of Partners.\***

Exposure Category of Partner	Percent
Injecting-drug user	65.9
Bisexual man	9.2
Transfusion recipient	2.4
Hemophiliac	1.3
Person born in country with predominantly heterosexual transmission	1.0
Not specified	20.2

\*AIDS = acquired immunodeficiency syndrome. From HIV/AIDS Surveillance Report, February 1993.<sup>1</sup>

rates might be even higher among women having elective abortions or ectopic pregnancies.<sup>14</sup>

### Adolescents

High HIV seroprevalence rates have been detected in certain groups of adolescent women. HIV prevalence has been 3.2 per 1000 female students entering residential Job Corps programs for disadvantaged youth,<sup>15</sup> and 0.32 per 1000 female adolescent military applicants.<sup>16</sup> Exposure categories were not determined from either site, but young African-American women were most likely to be infected. Only 275 AIDS cases have been diagnosed among teenaged women,<sup>1</sup> because most persons infected with HIV during adolescence probably do not develop AIDS until they are adults.

### Sex Workers (Prostitutes)

The CDC has reported high seroprevalence rates among female sex workers in Newark (57 percent) and Miami (19 percent), areas with comparable infection rates among women injection-drug users. Seroprevalence rates in other cities were much lower, such as San Francisco (6 percent) and Las Vegas (0 percent).<sup>17</sup> The main risk factor for HIV infection in sex workers in the United States appears to be injection-drug use rather than multiple sex partners.<sup>17-19</sup>

Although there has been much concern about the potential role of sex workers in spreading HIV to the heterosexual community,<sup>20</sup> prostitution has not emerged as a major route of transmission in the United States.<sup>18</sup> Prostitutes report that they practice safer sex more often than most women,

with 68 to 78 percent using condoms consistently with clients.<sup>17,21,22</sup> Nevertheless, they remain at risk for acquiring HIV infection from their drug-using private partners with whom they infrequently use condoms.<sup>17,21</sup>

### Lesbians

Lesbians have generally been considered to be a group at low risk for HIV infection. Only 79 AIDS cases were reported to the CDC by 1989 in women reporting sexual relations only with women. Almost all cases (95 percent) were attributed to injection-drug use.<sup>23</sup>

Three cases of possible woman-to-woman transmission have been reported.<sup>24-26</sup> Sexual contact during menses and traumatic sexual practices were implicated in one case, and orogenital contact in the others. The risk of HIV transmission from sexual contact between women remains unclear. High-risk sexual practices with men or women, drug use, and artificial insemination can place lesbians at risk for HIV infection.<sup>27</sup>

### HIV and Artificial Insemination

Nine cases of HIV infection have been attributed to artificial insemination with fresh or cryopreserved semen before HIV antibody tests became available in 1985.<sup>28-30</sup> In a more recent case a woman was inseminated by her HIV-infected hemophiliac husband. Infection occurred despite the attempt by special processing to eliminate HIV from his semen.<sup>31</sup> Current recommendations to reduce the risk of artificial insemination include the exclusion of high-risk donors and the quarantine of frozen semen while repeated HIV antibody testing of the donor is performed.<sup>32</sup>

### Natural History of HIV Disease in Women

There are important immunologic differences between healthy men and women that appear to be mediated by sex hormones. Women have more active cell-mediated immunity, higher immunoglobulin levels, and greater resistance to infections.<sup>33-35</sup> In addition, autoimmune disorders, such as systemic lupus erythematosus, are more common in women than men. While a more active immune system might be beneficial, it could also enhance HIV virus replication.<sup>36</sup> Unfortunately, little is known about the effect of the gender on the natural history of HIV disease.

### **Survival of Women with AIDS**

Studies of survival among HIV-infected women have reported contradictory results. In several studies women have had significantly shorter survival than men, living only 3 to 11 months following the diagnosis of AIDS,<sup>37-40</sup> and have been more likely to die during the initial AIDS-defining illness.<sup>38</sup> In most studies, poor survival in women was related to factors other than gender itself, such as age, transmission category, race, AIDS-defining diagnosis, and the lack of zidovudine treatment. In contrast to other studies, CDC data through 1989 indicate comparable survival for women and heterosexual men who have similar demographic characteristics.<sup>4</sup>

Poor survival in women can result from unsuspected HIV infection, late entry into health care, and the lack of access to medical services. In a study of Michigan Medicaid recipients who died of AIDS, women used significantly less medical care than men and had fewer inpatient days.<sup>41</sup> Women with AIDS have been less likely to receive zidovudine than men.<sup>40,42</sup> Life-prolonging therapies and the timely treatment of HIV complications are less available if women do not have regular and timely access to primary health care services.

### **Medical Complications of HIV Infection in Women**

Most complications of HIV infection in women are similar to those of men, although there are some important differences. Women are as likely as men to develop AIDS-defining conditions at similar CD4+ lymphocyte counts.<sup>43</sup> AIDS-defining diagnoses of the first 1819 women reported to the CDC were similar to those of heterosexual men, with *Pneumocystis carinii* pneumonia diagnosed in 66 percent of cases.<sup>9</sup>

The only published natural history study has been a prospective evaluation of 200 Rhode Island women, the majority of whom were white (53 percent).<sup>44</sup> In contrast to CDC data, candidal esophagitis was the most common AIDS-defining event, diagnosed in 15 of 44 women with AIDS (34 percent). *P. carinii* pneumonia occurred in only 9 women (20 percent), and chronic mucocutaneous herpes simplex infections in 8 (18 percent). This study was limited by its small sample size, and findings from this group of predominantly white women might not generalize to other populations.

Kaposi sarcoma is uncommon in women, diagnosed in only 3 percent of cases reported to the CDC. Nevertheless, clinically aggressive Kaposi sarcoma has been reported in women.<sup>45,46</sup> Other conditions that have been associated with HIV-related mortality in women include non-*P. carinii* pneumonia, pulmonary tuberculosis, and sepsis.<sup>11</sup> In states with a high rate of AIDS in women, death rates from these conditions have increased among women not known to be HIV-infected, suggesting additional HIV-related cases that were never diagnosed.<sup>11</sup>

### **Gynecologic Complications of HIV**

Gynecologic problems are common among HIV-infected women. Infections with herpes simplex virus, human papillomavirus, and *Candida albicans* can be especially troublesome. These infections tend to be severe, recurrent, and difficult to treat.<sup>44,47,48</sup>

Chronic vaginal candidiasis is often the initial clinical manifestation of HIV disease in women, developing much earlier than oral candidiasis (thrush).<sup>44,48</sup> In one cohort of women, candidal vaginitis was associated with asymptomatic HIV infection and mean CD4+ lymphocyte counts of 506/ $\mu$ L. Oral thrush developed almost exclusively in women with previous candidal vaginitis and mean CD4+ lymphocyte counts of 230/ $\mu$ L.<sup>49</sup> Vaginal candidiasis is common because of immunosuppression and the frequent use of antibiotics. It usually responds well to conventional treatment in women with early HIV infection,<sup>49</sup> but systemic therapy can be required for persons with advanced disease.

Several studies have found a high rate of HIV infection among women with pelvic inflammatory disease.<sup>50-52</sup> Whether HIV is a cofactor for pelvic inflammatory disease or simply a marker for an increased risk of sexually transmitted diseases is unclear. In one study HIV-infected women with pelvic inflammatory disease were less likely to have a white-cell count greater than 10,000/ $\mu$ L and there was a trend toward more tuboovarian abscesses and surgical intervention.<sup>51</sup> It is recommended that HIV-infected women with pelvic inflammatory disease be hospitalized and treated with intravenous antibiotics.<sup>53,54</sup>

Cytomegalovirus infection of the cervix in a woman with AIDS has been reported,<sup>55</sup> but it is not clear that other infections were excluded. An unusual vulvar ulcer was reported in another



HIV-infected woman.<sup>56</sup> After negative findings from an evaluation for sexually transmitted diseases, the ulcer resolved with concurrent zidovudine treatment.

### ***Cervical Dysplasia and Cancer***

HIV-infected women are at high risk for cervical dysplasia, with rates of 17 to 100 percent reported in uncontrolled studies.<sup>44,57-62</sup> HIV-infected women have higher rates of cervical dysplasia than HIV-negative controls,<sup>63,64</sup> although only a few studies have controlled for known cervical dysplasia risk factors.<sup>65-67</sup> Coinfection with human papillomavirus is common in HIV-infected women<sup>68</sup> and is strongly associated with the presence of cervical dysplasia.<sup>65-67</sup> The incidence and severity of cervical dysplasia also correlates with low CD4+ lymphocyte counts and advanced HIV disease.<sup>59,69</sup> The mean CD4+ lymphocyte count in one study of women with invasive cervical cancer, however, was 362/ $\mu$ L, suggesting that cervical cancer can develop before profound immunodeficiency occurs.<sup>70</sup>

HIV infection appears to alter the natural history of cervical dysplasia, increasing the risk of high-grade, extensive, and multifocal lesions.<sup>70</sup> Women with invasive cervical cancer are more likely to have advanced disease diagnosed, to have unusual sites of involvement, and to respond poorly to therapy.<sup>70,71</sup> At least 10 deaths from cervical cancer have been reported in HIV-infected women, underscoring the importance of regular Papanicolaou smears for these patients.<sup>70-72</sup>

It has been suggested that Papanicolaou smears are less sensitive for detecting cervical dysplasia in HIV-positive women. In a study of 32 women, 13 cases of cervical dysplasia were diagnosed by colposcopy; only one was detected by Papanicolaou smear.<sup>59</sup> Based on these findings, the investigators recommended routine colposcopy for all HIV-infected women. The detection of cervical dysplasia by Papanicolaou smear was unusually low, however, compared with other studies of HIV-positive women. In addition, colposcopy is more sensitive than the Papanicolaou smear in diagnosing cervical dysplasia in healthy HIV-negative women.<sup>73</sup> Routine colposcopy has not been shown to improve clinical outcome in any group of women. Although the CDC recommends only yearly Papanicolaou smears for HIV-infected women,<sup>74</sup> many experts suggest that they be per-

formed every 6 months. Women with abnormal results, including inflammation and koilocytosis, should be referred for colposcopy.<sup>72</sup>

### ***Pregnancy and HIV***

Because most HIV-infected women are of child-bearing age, considerable research has been conducted on pregnancy-related issues. Fertility does not seem to be affected by asymptomatic HIV disease.<sup>75</sup> Although counseling women about the 25 to 35 percent risk of perinatal transmission is important,<sup>76</sup> it has not increased the likelihood that HIV-infected women will choose pregnancy termination.<sup>77,78</sup>

### ***Impact of HIV Infection on Pregnancy Outcome***

In uncontrolled studies of pregnant HIV-infected women, high rates of obstetric complications, such as low birth weight, preterm labor, and premature rupture of membranes, have been observed.<sup>79,80</sup> Controlled studies report inconsistent findings. Researchers reporting on three prospective studies in Italy and the United States that controlled for drug use found no increase in obstetric complications.<sup>75,81,82</sup> These studies included mostly women with asymptomatic HIV infection. An additional retrospective study reported similar findings.<sup>83</sup>

In contrast, several African studies have found an association between maternal HIV infection and pregnancy complications, including low birth weight,<sup>84-87</sup> prematurity,<sup>85,86</sup> chorioamnionitis,<sup>86</sup> fetal demise,<sup>85</sup> and third-trimester bleeding.<sup>84</sup> The inclusion in these studies of more women with advanced HIV disease might explain the increased pregnancy complications observed. In one of the studies, women with AIDS were more likely to have premature and low-birth-weight infants than were HIV-positive women without AIDS.<sup>86</sup> In addition, a review of 26 women with AIDS who died during or within 1 year of pregnancy found that 4 women had stillbirths and 15 had preterm labor.<sup>88</sup>

HIV-related infections can also complicate pregnancy, especially among women with low CD4+ lymphocyte counts. These infections include bacterial pneumonias, *P. carinii* pneumonia, and other opportunistic infections.<sup>75,88-93</sup> Careful monitoring for both medical and obstetric complications is indicated for all HIV-infected pregnant women.

### **Impact of Pregnancy on HIV Disease**

Cell-mediated immunity decreases during normal pregnancy, presumably to protect the fetus.<sup>94</sup> CD4+ lymphocyte counts gradually decline and can fall below 600/ $\mu$ L during the third trimester, returning to normal levels by 3 to 5 months postpartum.<sup>95-98</sup> Certain bacterial, viral, and fungal infections can be more common and virulent during normal pregnancy,<sup>94,99,100</sup> although some authors have argued that clinically important immunologic impairment does not occur.<sup>101,102</sup>

In one study of HIV-infected pregnant women, CD4+ lymphocyte counts declined more rapidly than in pregnant HIV-negative controls and failed to return to baseline postpartum levels.<sup>103</sup> In another study HIV infection did not influence pregnancy-related CD4+ lymphocyte changes.<sup>104</sup> Prospective studies comparing HIV-infected pregnant women with HIV-infected nonpregnant controls will be necessary to determine whether pregnancy accelerates HIV disease progression.

### **Treatment of HIV Infection during Pregnancy**

Zidovudine (AZT) and prophylaxis against *Pneumocystis carinii* pneumonia are recommended for pregnant women whose CD4+ lymphocyte counts are fewer than 200/ $\mu$ L.<sup>72,105</sup> Experience with the use of zidovudine during pregnancy is limited, and safety to the fetus has not been established. It is known that zidovudine crosses the placenta readily<sup>106</sup> and can be detected in fetal tissues and amniotic fluid.<sup>107</sup> When zidovudine is given shortly before therapeutic abortion or delivery, serum concentrations in the newborn are similar to or higher than those of the mother.<sup>108-111</sup>

In a survey of 43 pregnant women, zidovudine was well tolerated, and no adverse effects were observed in the infants.<sup>112</sup> The sample size was not large enough, however, to exclude the possibility of serious teratogenicity. Zidovudine can increase fetal loss in mice,<sup>113</sup> but teratogenicity has not been reported.<sup>114</sup>

Other antiretroviral drugs, such as didanosine (ddI) and zalcitabine (ddC), have not been studied in pregnant women. Safety to the fetus has not been established for most drugs used to treat HIV-related opportunistic infections. Dosages at the high end of the dosing range might be required because of altered pharmacokinetics during pregnancy.<sup>115</sup>

### **Clinical Trials for HIV-infected Women**

Because of their reproductive potential, young women have been excluded often from drug trials, especially Phase I studies.<sup>116,117</sup> Drug therapy for women is frequently based on extrapolations from studies of men,<sup>118</sup> despite known gender differences in drug metabolism, toxicity, and efficacy.<sup>119,120</sup> As of June 1990, 7.9 percent of the AIDS Clinical Trials Group (ACTG) subjects were women,<sup>121</sup> even though women accounted for nearly 10 percent of AIDS cases at that time.<sup>4</sup> Similarly, only 3 percent of persons who received zidovudine during its initial availability for compassionate use were women.<sup>122</sup>

Women of childbearing age are now eligible for most clinical AIDS trials, but they often are not included because of pregnancy, lack of access to health care, or intravenous drug use.<sup>121</sup> Community-based trials, where research is conducted in primary care settings, are more accessible to women. Studies that include social and outreach services, transportation, and child care are likely to be more successful at recruiting women.<sup>123</sup>

### **Conclusions and Recommendations**

HIV infection is a major health problem and a leading cause of death among young women in the United States. At this time HIV predominantly affects women of racial and ethnic minorities. Although injection-drug use is involved in most cases, at least one-third of women with AIDS have been infected heterosexually. The increasing rate of heterosexually transmitted infection makes HIV a concern for most sexually active women.

As seroprevalence continues to rise, most family physicians can expect to become involved in the care of HIV-infected women. Educating about HIV, screening for risk factors, and appropriate counseling and antibody testing must become part of routine health care for women. Physicians must also counsel HIV-infected men about the need to inform at-risk female partners.

The poor survival of many women with AIDS highlights an urgent need for earlier diagnosis, followed by prompt and comprehensive medical care. HIV infection should always be considered when treating women with drug addiction, sexually transmitted diseases, chronic vaginal candidiasis, cervical dysplasia, tuberculosis, and other serious infections.

Information about the natural history of HIV disease in women is limited, despite known gender differences in normal immune function. Gynecologic infections and cervical dysplasia are common clinical problems that can be difficult to manage. Because cervical dysplasia is more aggressive in HIV-infected women, and fatal cervical cancer has been reported, many physicians are performing Papanicolaou smears every 6 months. Prompt colposcopy for even minimal cytologic abnormalities is indicated. Although AIDS-defining diagnoses reported to the CDC have been similar for heterosexual women and men, candidal esophagitis might be more prevalent in women.

Our understanding of HIV disease in women remains years behind our understanding of other aspects of this disease. Most research involving HIV-infected women has related to pregnancy. Although the effect of asymptomatic HIV infection upon pregnancy remains uncertain, women with advanced HIV disease are at increased risk for obstetric problems. Little information is available about the effect of pregnancy on HIV disease progression.

While research efforts have focused on the role of women as potential vectors of HIV, the impact of HIV on the health of women themselves has received little attention. The care of HIV-infected women continues to be based on extrapolations from studies of men. Natural history studies are needed to understand and treat HIV disease manifestations unique to women. Women must also be represented adequately in clinical drug trials so that toxicity and pharmacokinetic differences can be defined early. In addition, women should have access to new drugs that are initially available only through research studies. Study protocols might need to include transportation, child care, and social services to ensure that women are able to participate in clinical trials.

Finally, the HIV epidemic affects some of the most socially and medically vulnerable persons in the United States. The survival of many HIV-infected women is already jeopardized because of minority status, drug addiction, poverty, and the lack of access to health care services. Their frequent responsibilities as single mothers or caregivers for HIV-infected partners and children further limits the ability of many women to obtain care for themselves. HIV disease not only has

devastating personal consequences for infected women, but it also poses a serious threat to the communities in which they live. For poor women, the HIV epidemic occurs in the context of a social system that fails to provide adequate health care. Neglected problems that affect mostly poor minority communities, such as tuberculosis, drug dependency, and the lack of primary health care and prenatal services, are magnified in the setting of HIV and can no longer be ignored. Services that address the special needs of HIV-infected women are essential to improve access to care, acceptability of treatment, and ultimately survival.

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