Perspectives

New Developments in HIV Care for Women

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Dr Newman provided a broad review of HIV disease characteristics and treatment considerations in women. Her presentations at the Los Angeles and San Francisco courses examined factors underlying the increased incidence of HIV infection among women.

Epidemiology

Studies initially reported in 1993 provided an indication of the socioeconomic forces driving the HIV epidemic among women. In a study in 600 women in Madras, India, 90% reported feeling powerless to negotiate condom use with their husbands and 95% were financially dependent on their husbands. In a US study in 697 women, 67% of Latino women and 60% of Caucasian women never used condoms, with partner anger at the request often being cited as the reason.

A sampling of more recent reports (culled from a 2-week period in November 1999) indicates that such forces continue to operate: a group of 14 HIV-seropositive women incarcerated for crack cocaine use had a history of childhood and adult sexual and physical abuse that led to unsafe sex; 90% of 57 newly incarcerated women experienced domestic violence from their partners, with most having had high-risk HIV exposures but not perceiving themselves to be at risk; rates of HIV infection in incarcerated women are twice those in men in 9 of 10 US jurisdictions; a gynecologist in Ethiopia has reported that some 30,000 teenage prostitutes working in the capital city are contributing to the spread of HIV; high poverty and unemployment rates are forcing young women in Zambia to trade sex for food, housing, and money.

The changing epidemiology of HIV infection in the United States is illustrated by recent data on AIDS case distribution. Whereas women accounted for 16% of the total 711,244 cases of AIDS reported by June 1999, 23% of cases reported between July 1998 and June 1999 were in women (Figure 1). AIDS is now the third leading cause of death in all women and the leading cause of death in African American women. The incidence of AIDS in African American women was estimated at 49.8 per 100,000 in 1998; in Eastern seaboard cities (New York, Newark, Miami, and Tampa), AIDS rates ranged from 49 to 150 per 100,000.

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Women accounted for 23% of AIDS cases reported in the United States between July 1998 and June 1999

Heterosexual transmission is the leading cause of HIV infection in women. Between July 1998 and June 1999, proportions of female adult and adolescent reported AIDS cases caused by heterosexual transmission of HIV ranged from 23% to 47% by ethnic group (Figure 2). Overall, among the 13- to 19-year-old patients with AIDS reported during this period, 37% of 54 women and 4% of 5 men acquired infection by heterosexual transmission. Among adults aged 20 to 24 years, heterosexual transmission occurred in 51% of women (n=311) and 9% of men (n=77).

HIV exposure categories for women between July 1998 and June 1999 indicate that 40% acquired infection through heterosexual contact, with 66% of these women being unaware of risk in their heterosexual partners (Table 1). In 31% of all cases of infection, risk was not reported or identified. When such cases are reviewed, most of those in women are reclassified as attributable to heterosexual contact. However, current statistics may even underestimate the risk of heterosexual transmission, because risk factors are prioritized so that injection drug use (IDU) is identified as the means of infection before heterosexual transmission. Of a total of 115,364 cases initially classified as "risk not reported or identified" through June 1999, 55,363 cases were reclassified; of the 14,056 reclassified for women, 68% were reclassified as risk through heterosexual contact, 27% through IDU, and 4% through exposure to blood products. In 41,307 cases in men, 54% were reclassified as attributable to homosexual contact, 23% to IDU, and 16% to heterosexual contact.

Prognosis and Antiretroviral Therapy

Although studies in the mid- and late 1980s suggested that prognosis in HIV disease was worse for women than men, subsequent analysis indicated that the poorer outcome was explained by inferior access to medical care. In a study performed prior to the era of potent antiretroviral therapy, Carpenter and colleagues found that CD4+ cell counts in women declined to below 500/µL in 4 to 5.1 years and to below 200/µL in 9.6 years, values consistent with the respective durations of 4.1 years and 8 years in men. Similarly, a recent Center for Disease Control and Prevention (CDC) study showed that 24-month probabilities of survival in AIDS cases, diagnosed by a CD4+ cell count of less than 200/µL between 1993 and 1997, were 0.79 for women (n=37,687) and 0.77 for men (n=150,634). Sixty-month probabilities of survival in AIDS cases diagnosed on the basis of opportunistic disease were 0.63 in women (n=19,409) and 0.60 for men (n=83,922). These and other studies in the 1990s have confirmed that the most important predictors of disease progression and survival are AIDS-specific diagnosis, CD4+ cell count, viral load, and age, with gender not appearing to be associated with a significant predictive value.

Among the issues to be considered in whether the effects of antiretroviral thera-

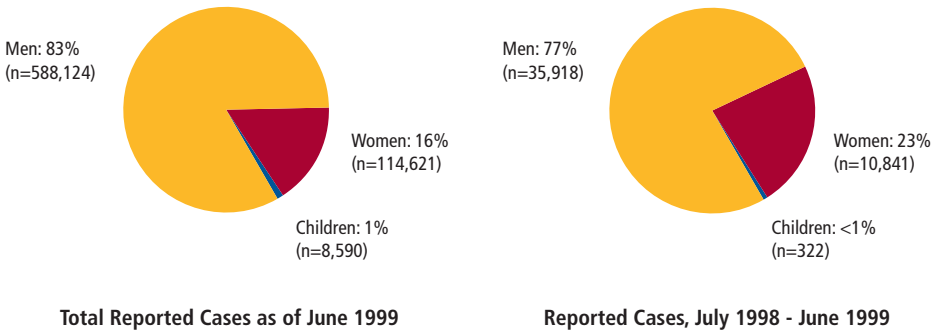

Figure **1.** Gender and age distribution in 711,344 total reported AIDS cases as of June 1999 (left), and in 47,083 cases reported between July 1998 and June 1999. Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report.* 1999.

py are different in women and men is that women tend to weigh less and thus to receive a higher dose per kilogram with standard drug doses. Further, women may exhibit changes in drug metabolism and clearance during phases of the menstrual cycle, and hormonal changes may play a role in viral replication. In one study assessing the safety and efficacy of nelfinavir in 78 women and 616 men, women experienced more abdominal pain, itching, and rash, had similar decreases in viral load, and had greater increases in CD4+ cell count (116/µL v 84/µL). In an Italian study examining the effects of a number of factors in predicting ritonavir intolerance in 56 male and 37 female patients, female sex was associated with a greater risk for gastrointestinal or neurologic intolerance (66% v 34%), a finding that may reflect higher peak drug concentrations in women. In a Federal Drug Administration evaluation of 60 cases of lactic acidosis associated with nucleoside reverse transcriptase inhibitor (nRTI) use, 20 cases were fatal, with 17 of the 20 fatalities occurring in women and 11 of these occurring in obese women. These data are limited, and further information on these potential gender differences is needed.

A number of studies have suggested that viral load levels are different in women and men with similar CD4+ cell counts. In one study in injection drug users, initial plasma HIV RNA and CD4+ cell counts were 3000 copies/mL and 518/µL, respectively, in women, and 9000 copies/mL and 518/µL, respectively, in men. Three-year follow-up values were 45,000 copies/mL and 417/µL, respectively, in women, and 93,000 copies/mL and 390/µL, respectively, in men. Another study found that viral load levels in women were 24% lower than those in men when CD4+ cell counts were between 200/µL and 500/µL, but that viral load levels were similar at CD4+ cell counts of less than 200/µL. The CDC reviewed data from 3776 participants (2467 men and 1309 women) in 4 CDC-supported studies to further investigate potential differences in this regard. Viral load in women was 57% lower for patients with CD4+ cell counts above 500/µL, 48% lower for those with counts between 200/µL and 499/µL, and 40% lower in those with counts below 200/µL, although none of these differences were statistically significant. Gender was not significantly associated with either time to an AIDS-defining opportunistic illness or time to death. On the basis of these data and the other studies indicating absence of a significant effect of gender on disease progression, the CDC, the Department of Health and Human Services, and the International AIDS Society–USA do not currently recommend changing antiretroviral prescribing guidelines in women.

> Although there are data suggesting that women have lower viral load levels than men at comparable CD4+ cell counts, gender does not appear to be predictive of disease progression

The CDC has also collected data on causes and rates of mortality of 871 known HIV-infected women and 14 who seroconverted to HIV-positive during the period of April 1993 to December 1998. Of 196 deaths, 176 had verifiable causes; of these, 16% of patients died with AIDS-defining illnesses and 40% died of HIV-related disease. A total of 44% of deaths were not attributable to HIV disease or AIDS, with one third of these deaths being associated with drug use (eg, endocarditis, sepsis, or hepatitis). Potent antiretroviral therapy use was reported by only 24% of patients with CD4+ cell counts below 200/µL. Overall, no use of potent antiretroviral therapy, viral load above 10,000 HIV RNA copies/mL, and CD4+ cell count below 200/µL were strong predictors of mortality ($P<0.001$). That there is a large group of women at high risk of poorer outcome indicates that more attention needs to be focused on services for such women, including appropriate provision of drug treatment and counseling.

Pregnancy and Mother-to-Child Transmission

Transmission of HIV from mother to infant primarily occurs in the intrapartum period via the conjunctival or oral mucosa. Duration of rupture of the membrane is correlated with increased transmission for both vaginal and cesarean deliveries, with transmission rates of 8% at 2 hours and 31% at 24 hours having been documented. This increased risk of HIV transmission with increased duration of membrane rupture was not observed in women without AIDS; however, this finding should not reduce attention to the standard of care of bringing HIV-infected women to delivery as soon as possible.

The benefits of cesarean delivery in reducing mother-to-child transmission have been called into question by recent findings. In the French Perinatal Cohort Study, the benefits of cesarean delivery were lost if zidovudine therapy was not used. The group undergoing cesarean delivery, which was found to be highly selected in the cohort, exhibited

decreased transmission rates compared with vaginal delivery only if cesarean delivery occurred prior to labor and membrane rupture. In the randomized European Mode of Delivery Collaboration involving 370 infants, 70% of whom received zidovudine, elective cesarean delivery was associated with a transmission rate of 1.8%, compared with 10.5% for vaginal delivery. By intent-to-treat analysis, transmission rates were 4.3% for vaginal delivery with zidovudine and 0.8% for cesarean delivery with zidovudine. The difference between groups became smaller when outcome was assessed by the actual mode of delivery used among those receiving zidovudine.

A number of recent studies have underlined the lack of attention given to the adverse effects of cesarean delivery in HIV-infected women. Two series suggest that cesarean delivery may be associated with a 2-fold increase in perioperative complications in HIV-infected women and another study has indicated an increase in major complications (odds ratio, 6.0) and minor complications (odds ratio, 3.0) with cesarean delivery in these women. Viral load data were not reported in most of the studies that have indicated that cesarean delivery is more effective than vaginal delivery in preventing transmission, a factor that can confound the reported outcome rates. Further, no combination therapy was used in any of the studies; this is particularly important given that case series including approximately 200 women treated with combination therapy and no cesarean delivery have shown no cases of vertical transmission of HIV to date.

Table **1.** Exposure Categories for Women, July 1998 to June 1999

	Number	Percent
Injection Drug Use	3043	28
Hemophilia	21	<1
Heterosexual Contact	4296	40
Injection Drug User	1208	29
Bisexual Man	200	4.6
Person with Hemophilia	27	<1
Transfusion Recipient	18	<1
HIV-Infected Person, Risk Not Identified	2843	66
Blood Products	120	1
Risk Not Reported or Identified	3361	31

Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report.* 1999.

Intrauterine transmission may occur early or late in pregnancy. Infections acquired early in utero may be more frequently associated with fetal death, and babies surviving in utero infection may have more rapidly progressive disease than those acquiring infection in delivery or through breast-feeding.

It is now the standard of care to offer potent antiretroviral therapy to all pregnant women with HIV. Optimal regimens are determined by the mother's CD4+ cell count, viral load level, and comorbidities. Risks and benefits of beginning therapy before the 14th week should be discussed and the paucity of data regarding safety of treatment in the first trimester should be acknowledged. Currently, initiation is recommended after the 14th week unless the mother prefers earlier initiation. Viral load should be followed monthly and therapy changed if viral breakthrough occurs.

With regard to specific regimens, standard of care for pregnant women should be the same as that for nonpregnant adults, with one caveat. Efavirenz is contraindicated for pregnant women due to data showing alarming rates of anencephaly in primates receiving the drug. It is not known if a similar teratogenic effect could also occur in humans. Zidovudine is generally thought to be safe. If prior zidovudine use has been associated with detectable viral load or if genotypic analysis indicates presence of resistance mutations, an alternative regimen should probably be used.

A single dose of nevirapine can reduce plasma viral load by 1.3 log. The drug crosses the placental barrier and has a half-life of 61 to 66 hours in the mother during labor and 45 to 54 hours in the newborn. A single dose maintains blood concentrations of 10 times the 50% inhibitory concentration for HIV for a week in the newborn. In the HIVNET 012 Study, 626 women were allocated at onset of labor to receive nevirapine 200 mg or zidovudine 600 mg followed by 300 mg

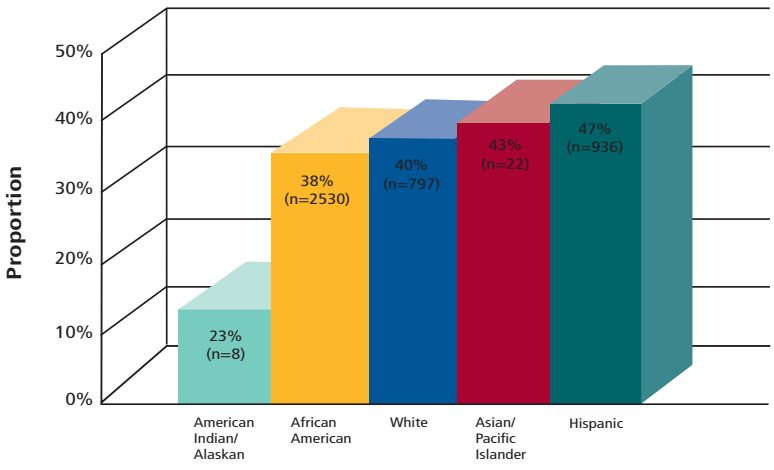

Figure **2.** Proportion of female adult and adolescent AIDS cases reported between July 1998 and June 1999 attributed to heterosexual transmission by ethnic group. Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report.* 1999.

each hour until delivery. The babies received nevirapine 2 mg/kg within 72 hours of birth or zidovudine 4 mg/kg orally twice a day for 1 week. A total of 98.8% of infants were initially breast-fed, with 95.6% being breast-fed at 16 to 18 weeks. Estimated risks of transmission at birth were 8.2% in the nevirapine group and 10.4% in the zidovudine group. Risks at 6 to 8 weeks were 11.9% in the nevirapine group and 21.3% in the zidovudine group; and risks at 14 to 16 weeks were 13.1% and 25.1%, respectively. These findings are encouraging with regard to the use of single-dose nevirapine to prevent mother-to-child transmission.

A recent meta-analysis found no association between deaths in children who were HIV-exposed but uninfected and evidence of mitochondrial toxicity

Potential downsides of nevirapine use include the rapid development of the K103N resistance mutation. This mutation was present in 3 of 15 women in this study at 6 weeks after the single dose; assessment of isolates at 1 week after dosing is being performed to determine if more of the women initially developed the mutation. A related issue is the efficacy of nevirapine in second and third pregnancies, especially for mothers who breast-feed.

A recent concern regarding treatment to prevent mother-to-child transmission is the potential for mitochondrial toxicity in the infant. Blanche and colleagues reported on the neurologic deaths of 2 HIV-exposed but uninfected infants who had been exposed to zidovudine or zidovudine/lamivudine. Six cases of nonfatal mitochondrial toxicity in infants who had been exposed to nRTIs were subsequently reported. These cases prompted reassessment of data from approximately 20,000 children from the National Institutes of Health, Women and Infants Transmission Study, Pediatric AIDS Clinical Trials Group, and CDC cohorts to determine presence of findings such as failure to thrive, cardiomyopathy, metabolic acidosis, liver failure, bone marrow failure, seizure, developmental delay, ataxia, brain stem alteration, blindness, retinitis pigmentosa, and sudden infant death syndrome. None of the deaths in children who were HIV-exposed but uninfected were associated with limited or definitive evidence of mitochondrial toxicity. These findings have allayed some of the fears regarding the potential for such toxicity with in utero exposure to antiretroviral therapy.

Any known pregnancy in which antiretroviral drugs have been used may be reported to the Antiretroviral Pregnancy Registry at:

1-800-722-9292 or 919-483-9437

Gynecologic Care

Women with HIV infection should undergo a full pelvic exam with a Pap smear, and the exam should include careful inspection of the vulvar, vaginal, and perianal areas. If findings are normal, Pap smear and inspection should be repeated every 6 months; in some cases, women who have had significant and maintained immune reconstitution on antiretroviral therapy can be seen on an annual basis. Colposcopy should be performed in women with low-grade or high-grade squamous interstitial lesions, atypical squamous cells of undetermined origin, atypical glandular cells of undetermined origin, or persistent inflammation. The pelvic exam should include wet mounts and serum rapid plasma reagin and testing for chlamydia and gonococci. Patients should also receive routine counseling on sexually transmitted disease, including human papilloma virus (HPV) infection and cervical intraepithelial neoplasia, as well as on pregnancy, contraception, and safer sex.

A recent analysis of oncogenic HPV findings in 507 women with measurements at 3 visits in the Women's Interagency HIV Study cohort indicates that the overall rate of progression on Pap smear was associated with number of HPV infections detected at the 3 visits. Progression occurred in 16% of women with an infection detected at 1 visit (37% of the women had 1 infection), 24% of those with infection at 2 visits (29%), and 25% of those with infection at all 3 visits (34%). Analysis by CD4+ cell count and Pap smear status showed that women who were receiving potent antiretroviral therapy were 1.4 times more likely to show regression on follow up Pap smear. This finding is particularly important for women with HIV infection, since it is estimated that 20% to 36% have abnormal Pap smear results.

Recent data from a study of the effect of the menstrual cycle on the presence of HIV in the genital tract showed that among 55 women with CD4+ cell counts below 350/μL and median plasma HIV RNA of 3.73 $\log_{10}$, there were significant increases in levels of viral nucleic acids in the genital tract just prior to menses (assessed by endocervical wicking) and during menses (assessed by cytobrush and lavage), with no change in peripheral blood viral load being observed during menses. These findings suggest the potential for increased risk of transmission prior to and during menses. Finally, another small study has suggested that antiretroviral therapy is not associated with alteration in hormone levels. In this report, progesterone and estradiol levels in 55 women with HIV infection with self-reported normal menstrual cycles were similar to those in 9 uninfected women with normal cycles. Only 5 of the HIV-infected women were not receiving antiretroviral therapy, with 41 receiving a regimen including a protease inhibitor and 9 receiving a regimen without a protease inhibitor.

Suggested Reading

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