son, findings such as this, and the finding that prior duration of treatment is not predictive of clinical progression, suggests that individual evaluation of a patient's continuing response to treatment is in order, with there being no hard and fast rules regarding when zidovudine can be expected to have offset of beneficial effect due to resistance.

Resistance to other agents

In discussing resistance to other agents, Dr Crumpacker noted that a recent study has indicated a significant relationship between high-level zidovudine resistance in isolates from long-term zidovudine recipients and decreased susceptibility to didanosine and zalcitabine, with the clinical significance of these findings remaining unknown. Other investigators have not found such a relationship. Dr Crumpacker stated that cross-resistance within classes of agents is likely to be an increasing problem in both the clinical setting and in drug development. He cited the cross resistance among the NNRTIs as a clear example, it having been shown that virus developing resistance to L697,661 is also cross-resistant to nevirapine and the TIBO compound. He also stated that a potential exception in the case of the NNRTIs is the drug delavirdine, which is chemically distinct from and has thus far been found not to exhibit cross-resistance with the other compounds. Dr Crumpacker noted that the agent sensitizes HIV in vitro to the effects of the other agents, with delavirdine-resistant virus remaining susceptible to nevirapine and L697,661, for example. This agent, which exhibits synergistic activity in combination with zidovudine and other NNRTIs, is currently undergoing early clinical evaluation. In discussing potential resistance to protease inhibitors, Dr Crumpacker related recent findings with the Roche compound A77003 indicating that high-level resistance and cross-resistance to other protease inhibitors can be induced in early passages of virus. He also noted, however, that resistant virus exhibited reduced growth kinetics, raising the possibility that resistant strains selected under treatment might be less pathogenic.

Dr Johnson related that it has been difficult to document high-level resistance to didanosine and zalcitabine, with the 2- to 10-fold decreases in susceptibility observed with these agents standing in contrast to the much greater reductions observed with zidovudine, NNRTIs, and such other nucleoside analogues as 3TC and FTC. Specific mutations that have been associated with reduced sensitivity to didanosine include codon 74 mutation, which has been observed to be associated with reversion of zidovudine-resistant virus to susceptibility during didanosine treatment. Both the codon 74 mutation and another didanosine-resistance mutation at codon 184 have been reported to induce cross-resistance to zalcitabine. There has been one report of reduced zalcitabine susceptibility (>5-fold) in association with a codon 69 mutation. Dr Johnson speculated that a factor contributing to the apparently reduced frequency of high-level resistance to these agents may be that the didanosine and zalcitabine molecules may more closely resemble the normal RT substrates; however, in discussing the rapid emergence of drug-resistant populations that has been observed under 3TC treatment, she suggested that rapid selection of resistant mutants may also occur as a result of greater anti-HIV potency against susceptible strains. With regard to resistance to NNRTIs, she stated that the agents have not been abandoned despite rapid emergence of high-level resistance in clinical investigations because of: (1) the possibility of achieving serum drug levels exceeding the IC-50 of resistant virus, which appears to explain prolonged response to high-dose nevirapine therapy in some patients; (2) the synergistic effect exhibited with nucleoside analogue RTIs, suggesting potential benefit in combination treatment; and (3) the possibility of compensatory mutations—eg, the NNRTI resistance mutation at codon 181 that has been found to increase susceptibility to zidovudine of virus with the zidovudine-resistance 215 mutation. Cross resistance to multi-drug regimens may be a possibility and must be considered in patients receiving multi-drug therapy.

In closing her presentation, Dr Johnson presented combined data from a study at her institution in which patients with CD4+ cell counts of 50 to 400/μL had nevirapine added to existing tolerated nucleoside analogue RTI treatment (see 'Continuing Antiretroviral Therapy'). The group data were characterized by a rapid increase in CD4+ cell count and a decrease in viral load according to a number of quantitative measures, followed by a reversal of effect such that cell count and viral load on some measures had returned to near baseline levels by week 24. Dr Johnson noted the initial decrease in viral burden seen in these patients already receiving RT inhibitor treatment and stated that it is hoped that with better antiretroviral agents, greater and more persistent decreases could be achieved with combination treatment. ■

HIV Disease in Women

HIV disease in women was discussed at the Boston meeting by Deborah Cotton, MD, MPH, from Harvard Medical School and Massachusetts General Hospital in Boston.

Epidemiology

As related by Dr Cotton, HIV disease is now the fourth leading cause of death in women of childbearing age in the US. Statistics as of 1992 indicate that AIDS cases in women are clustered in cities on the Eastern seaboard and in such urban centers as Chicago, Houston, Los Angeles, and San Francisco. Although women currently account for approximately 12% of reported AIDS cases, the proportion of women in the total HIV-infected population is projected to be much greater and to be increasing, with steady increases in the proportion of AIDS cases in women thus being expected; as related by Dr Cotton, the proportion of AIDS cases in women in Massachusetts increased from 12% to 18% between 1989 and 1992. Currently, AIDS is disproportionately diagnosed in women of color; as noted by Dr Cotton, of newly diagnosed AIDS cases in children in 1993, almost exclusively reflecting perinatal transmission, 90% were in children born to

Table 3. Transmission category by race/ethnicity among US women with AIDS reported in 1992

	Number (%)		
	White	Black	Hispanic
Injecting drug use	617 (42)	1600 (47)	581 (43)
Heterosexual contact	535 (37)	1328 (39)	549 (41)
Transfusion/hemophilia	143 (10)	78 (2)	49 (4)
Other/risk not reported or identified	163 (11)	388 (11)	158 (12)
Total	1458	3394	1337

*Includes 66 women of unknown or other race/ethnicity.

Data are from CDC, AIDS Public Information Data Set.

women of color. Women newly diagnosed with AIDS are on average several years younger than their male counterparts.

Statistics as of 1992 indicate that 45% of women with AIDS contracted HIV infection through IV drug use, with 39% reporting heterosexual contact as route of transmission (Table 3); an additional 12% reported other/undetermined risk, which Dr Cotton suggested often reflects a past heterosexual contact with a partner whose infection status or risk factors were unknown. The proportion of women infected through heterosexual contact is expected to increase. As stated by Dr Cotton, given the large proportion of women infected through heterosexual contact, women are more likely than men to be unaware of placing themselves at risk for infection; Dr Cotton indicated that failure to acknowledge this has resulted in inadequate or inappropriate targeting of educational efforts for women.

Dr Cotton noted that most transmission of HIV worldwide is associated with vaginal intercourse, with infected males being the primary vectors; since concentrations of virus in semen are higher than those in vaginal and cervical secretions and since the skin of the penis provides relatively greater protection during intercourse, transmission of infection from an infected male is more likely than that from an infected female. According to Dr Cotton, risk of infection through vaginal intercourse for an uninfected female is currently believed to be on the order of 5 to 10 times greater than that for an uninfected male. Genital ulcers increase the risk of transmission for both genders, and passive anal intercourse is associated with greater risk than vaginal intercourse.

Disease characteristics

According to Dr Cotton, relatively little is known about natural history of HIV disease in women. Most funding for cohort studies was dedicated in the mid-1980s to setting up and following cohorts of at-risk gay men. When it became clear that the incidence of HIV disease in women was increasing, there were few available sources for funding. It is only within the past year, after persistent activism, that cohort studies of women have been initiated, with several being performed by the NIH and several by the CDC. Thus, solid epidemiologic data on transmission risk factors, surrogate markers, disease course, and female-specific manifestations of disease are not expected for a number of years. As noted by Dr Cotton, analyses of currently available data for gender-related differences in disease course are potentially confounded by a number of factors, including a different racial/ethnic distribution of cases and a high proportion of cases currently attributable to transmission via IV drug use among women and the possibility that women with infection may not be recognized at the same stage of disease as men.

Dr Cotton stated that concerns that infection characteristics in women were radically different from those in men may have been overstated. Data from the CDC for 1992 indicate that PCP was the most common AIDS-defining illness in women, being observed in 43% of cases, with wasting syndrome and esophageal candidiasis being the next most common defining illnesses (Table 4). It is currently believed that women may be more prone to the latter two illnesses, with the other difference according to gender being the relative absence of Kaposi's sarcoma in women. With regard to the other illnesses shown in Table 4, Dr Cotton stated that they probably occur with similar frequencies and presentations as in males and are amenable to the same diagnostic tests and treatments. Survival in women has been reported both to exceed and to be shorter than that in men. Dr Cotton noted that findings indicating that women have shorter survival than men have been found to reflect less access to and utilization of medical care, including use of antiretroviral therapy and PCP prophylaxis, among women and suggested that potential gender-related differences in survival in the absence of such factors remain undefined.

The currently proposed female-specific markers of HIV-disease include cervical dysplasia and neoplasia, vulvovaginal candidiasis, and pelvic inflammatory disease (PID). As related by Dr Cotton, HIV-infected women have been found to have a higher incidence of cervical abnormalities on routine screening and appear to be more likely to progress to cervical dysplasia and frank cervical carcinoma. Human papilloma virus (HPV), which has been implicated as a cause of cervical cancer, is found with increased frequency in women with HIV disease, with similarities in the acquisition risk profiles including multiple sexual partners and sexual activity beginning at an early age. Recent studies have indicated that women who are positive for both HIV and HPV have a greater risk of cervical dysplasia than do those who are HPV-negative and HIV-positive or those who are HPV-negative and HIV-negative, with one study in New York City showing respective rates of 52%, 18%, and 9%. Additional evidence indicates that cervical dysplasia is more rapidly progressive and, perhaps, multifocal in HIV-infected women, apparently in association with declining CD4+ cell count. Invasive cervical carcinoma became an AIDS-defining condition in 1993. With regard to the other female-specific markers, Dr Cotton noted that HIV-infected women have a high incidence of vaginal candidiasis, which tends to be recurrent and refractory to treatment and appears to precede oral candidiasis in onset; it may constitute the first presentation of symptomatic disease. Although vaginal candidiasis is very common in the HIV-uninfected population, Dr Cotton suggested that the threshold for recommendation for HIV screening be lowered for women presenting with chronic candidiasis in the absence of such explanatory factors as diabetes, pregnancy, or antibiotic use. PID also occurs with high incidence in HIV-infected women; as noted by Dr Cotton, this may also be influenced by convergence of risk factors. However, she stressed that HIV-infected women tend to have more severe and treatment-refractory disease.

Dr Cotton noted that results of one study have indicated that Pap smear is a relatively

Table 4. Most common AIDS-indicator diseases in US women in 1992

Rank	Diagnosis	Percentage of patients*
1	PCP	43
2	HIV wasting syndrome	21
3	Candidiasis, esophageal	21
4	HIV encephalopathy	6
5	Herpes simplex	6
6	Toxoplasmosis of the brain	6
7	MAC	6
8	Cryptococcosis, extrapulmonary	4
9	CMV disease	3
10	CMV retinitis	3

*Some women had multiple diagnoses.

Data are from CDC, AIDS Public Information Data Set.

insensitive method of diagnosis of cervical dysplasia in HIV-infected women when compared with colposcopy. She suggested that although a minority of gynecologists are recommending routine colposcopy instead of Pap smear in HIV-infected women, most believe that the latter should remain the routine screening procedure in the absence of further definitive data, with colposcopy being employed in cases in which any Pap smear abnormality is observed.

Pregnancy

Early findings in pregnant women indicated that those with CD4+ cell counts of <300/μL were more likely to experience HIV-associated illness during pregnancy. Pregnant HIV-infected women exhibit a greater CD4+ cell count decline during pregnancy than do women without HIV infection, with counts in the former not returning to prepregnancy levels as they do in uninfected women; Dr Cotton suggested that the overall declines in HIV-infected women likely represent declines that would have occurred in the absence of pregnancy and maintained that there currently is no evidence that pregnancy accelerates disease progression. Currently, she informs pregnant patients who intend to give birth who have CD4+ cell counts >200/μL that pregnancy is unlikely to have a deleterious impact on their health; the likelihood of the mother being severely ill while still caring for a young child is raised in discussion with patients with lower cell counts.

Early studies of risk of vertical transmission of HIV infection to infants indicated a risk of 50%. More recent US studies suggest a risk of 20% to 30%, with the recent ACTG 076 study of zidovudine treatment in pregnant women and their newborns finding a transmission rate of 25% in the placebo group. As stated by Dr Cotton, transmission may occur at various times: virus has been isolated from fetuses as early as 8 weeks of gestation; however, many infected infants exhibit a pattern of being first PCR-positive and then culture-positive, suggesting relatively later transmission; breast-feeding poses additional risk for transmission postpartum. Dr Cotton noted that the importance of intrapartum transmission has been underscored by twin studies showing that first borns had a much greater risk of acquiring infection than did second borns; in addition, there is some evidence that delivery via cesarean section may be associated with reduced risk of transmission compared with vaginal delivery. Other findings suggest that lower CD4+ cell count in the mother is a risk factor for transmission.

As recounted by Dr Cotton, ACTG 076 demonstrated that treatment with zidovudine in pregnancy, during delivery, and in the newborn was associated with a reduction in the rate of transmission from 25% to 8%, with the trial being stopped after interim analysis revealed this highly significant difference. In the trial, pregnant women between 14 and 34 weeks of gestation received placebo or zidovudine 600 mg/d orally in six divided doses and high-dose IV zidovudine during labor and delivery and for 24 hours postdelivery; newborns received oral zidovudine or placebo according to maternal treatment group for 6 weeks after birth. According to Dr Cotton, time to PCR- and culture-positive findings in infected treatment group infants parallels that in infected placebo group infants, suggesting that the effect of zidovudine was not merely that of delaying time to positive culture. In addition, in the subgroup of infants thus far followed to the time at which HIV antibody testing could be expected to be diagnostic, antibody testing findings have supported the dramatic reduction in transmission associated with zidovudine. Dr Cotton suggested that these results should prompt a concerted public health campaign targeting pregnant women.

As stated by Dr Cotton, overall experience with zidovudine in pregnancy suggests that the agent is not associated with a major risk of teratogenicity. At least three cases of intrauterine growth retardation have been reported; of two for which details were available, one occurred in the infant of a cocaine user and one in the infant of a woman with symptomatic HIV disease who was receiving multiple medications. One case of oligohydroamnios has been reported. As related by Dr Cotton, no significant problem with neonatal anemia was observed in ACTG 076, with a clinically nonsignificant decrease in hemoglobin levels being observed in treatment group infants.

With regard to women who have had prolonged exposure to zidovudine, have failed treatment, or are known to harbor resistant virus, Dr Cotton stated that there currently is very little information on the use of other nucleoside analogue RTIs in pregnancy. Didanosine appears to be metabolized by both placenta and fetus, and there is evidence that fetal and amniotic fluid drug levels are reduced; no data on potential fetal toxicities of didanosine or zalcitabine are available. Dr Cotton stated that in the absence of relevant data, the selection of an alternative agent is a highly individual decision. She suggested that given current skepticism on the part of some about the benefit of treating patients with asymptomatic infection, a reasonable strategy for HIV-infected women with CD4+ cell counts >200/μL who are considering pregnancy would be to delay zidovudine treatment until time of pregnancy in order to minimize chances of development of resistance. She also maintained, however, that decisions regarding timing of initiation of antiretroviral therapy and what course to take in terms of a possible future pregnancy are highly individual ones, to be made by the patient after appropriate consultation with the physician.

Dr Cotton stated that trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred agent for PCP prophylaxis, with the most commonly used dosages being one double strength tablet qd or three times per week. Dr Cotton indicated that although TMP-SMX has been associated with theoretical risks of teratogenicity and neonatal kericterus, most obstetricians believe that actual risk is minimal and prefer use of TMP-SMX to aerosolized pentamidine. Concerns with the latter include decreased preventive efficacy compared with TMP-SMX, occasional systemic absorption, and questions about absorption of the agent into the lungs in pregnancy, particularly after elevation of the diaphragm in the second trimester. Although no animal pregnancy data on dapsone are available, the agent has been used in leprosy for many years without obvious teratogenic effects and, thus, constitutes an alternative. Dr Cotton maintained that use of steroids in treatment of PCP is indicated in pregnancy, using standard criteria.

With regard to other agents used in prophylaxis, Dr Cotton stated that fluconazole generally is avoided in pregnant women due to an antiestrogen effect; she also noted that the findings in ACTG 981—ie, significant effects of fluconazole in preventing fungal disease without an associated mortality benefit (see above)—do not provide clear guidance regarding clinical practice of fluconazole prophylaxis, with analysis of the benefits of prevention versus cost of treatment and potential for promoting resistance needing to be performed before specific recommendations can be made. Dr Cotton related that it is her practice to use amphotericin B in treatment of cryptococcal disease, both because of the antiestrogen effect of fluconazole and because there are data that suggest the latter may provide inferior results. She also stated that although there are no strong animal data suggesting a teratogenic effect of rifabutin, many practitioners are avoiding use of the agent in pregnant women in the absence of definitive evidence of a survival benefit or more compelling evidence of a marked delay in onset of disease with use of the agent in MAC infection prophylaxis. ■