Current Report — HIV
AIDS at the Crossroads: A Report from the 1990 International Conference on AIDS — San Francisco

Ronald H. Goldschmidt, M.D., Betty J. Dong, Pharm.D., George W. Saba, Ph.D., Priscilla A. DeRemer, N.P., M.S., and Jill J. Legg, M.D.

The Sixth International Conference on AIDS in San Francisco presented a picture of AIDS at a scientific, clinical, political, and epidemiologic crossroad. The incredible growth in our understanding of HIV over the past few years was clearly evident. Nevertheless, a cure for HIV disease remains elusive. Well-established diagnostic and treatment modalities, including effective antiviral therapy and treatment of opportunistic infections, are reminders of the intense efforts that have been directed at AIDS. Ahead lie more refinements in clinical care as well as the hope and expectation of major therapeutic breakthroughs.

The demographics of AIDS in the United States has changed from a predominantly male homosexual and intravenous drug user disease to one affecting much larger segments of the population, including women, children, and adolescents, especially in poor minority communities. The next few years seem critical in determining whether the AIDS epidemic is contained or continues to expand, depending on our educational, medical, political, and community responses. For many countries in the developing world, there is no crossroad, only a road that leads deeper into the epidemic.

Many clinicians, scientists, and other conference participants expressed strong dissent, both in public political protests and during the scientific sessions, with existing policies. Some of these negative comments were directed at the United States’s restrictive immigration policy against people infected with AIDS. In addition, the bureaucratic process of clinical trials was vehemently attacked by AIDS activists voicing the collective frustration of those who are HIV-infected. Recognition by authorities within the government and the scientific community that the clinical trials process is, indeed, imperfect has led to an acknowledgement that multiple treatment options are appropriate independent of formal clinical trials.

Conference planning attempted to provide a forum for voices not usually heard at other conferences. For example, plenary speakers were selected with attention to minorities, women, various academic disciplines, and AIDS experts who had not spoken at previous conferences. The attendance and participation by hundreds of HIV-infected persons served as a constant reminder of the human aspects of HIV. Although the 3050 abstracts, posters, and oral presentations emphasized primarily the work of providers who specialize in the care of HIV-infected patients, the application to primary care could be inferred from many of the presentations. This “Current Report” highlights some of the important developments that have direct relevance to family physicians and other primary care providers.

Epidemiology: More Bad News than Good News

The expected increase in the number of newly infected intravenous drug users has already occurred. Despite increased use of bleach to disinfect intravenous drug equipment “works” and decreased sharing of “works,” unsafe practices among intravenous drug users continue to predominate. In addition to using potentially contaminated “works,” intravenous drug users do not consistently use condoms. One speaker credited the American approach to drug use with successful components, such as community outreach and methadone programs, but criticized it for falling short in other ways, such as the lack of adequate numbers of treatment programs, the absence of needle exchange programs, and not allowing primary care providers to prescribe meth-
Advances in Clinical Care

Despite the advances in AIDS therapeutics of the past 5 years, only a few new and important developments were presented. Nevertheless, some significant improvements in care were emphasized. The most important of these include the use of zidovudine in asymptomatic persons, additional refinements in the treatment of Pneumocystis carinii pneumonia, and the use of fluconazole for cryptococcal meningitis.

Antiviral Therapy

No one therapy has emerged as being superior to zidovudine (AZT, Retrovir®) in the treatment of asymptomatic or symptomatic HIV disease. The apparent efficacy of zidovudine in asymptomatic persons was discussed in countless presentations, but questions remain about the optimal time to initiate zidovudine. Strong support for as-early-as-possible intervention with zidovudine was voiced by Dr. Margaret Fischl of the University of Miami School of Medicine (Coral Gables, FL). She argued that zidovudine would exert its greatest benefit when the viral burden is low and the immune system most intact. Arguments against very early use include the possibility of drug resistance because of viral mutations and the potential for limited long-term efficacy of the drug. Four mutations of the virus have been reported thus far. The clinical significance of these in-vitro mutations is unclear. Zidovudine is approved for asymptomatic patients with fewer than 500 CD4+ (T-helper) lymphocytes/mm³. The usual dosage is 500 mg orally daily.

Patients with AIDS or symptomatic HIV disease can be treated with 600 mg of zidovudine orally daily. This dosage was stressed throughout the conference as being therapeutically equal to higher dosages (1200 mg daily) but considerably less toxic. Whether low-dose zidovudine is effective in AIDS dementia remains uncertain.

The optimal dosage of zidovudine for both symptomatic and asymptomatic HIV disease remains unknown; however, preliminary observations indicate that dosages as low as 300 mg daily may still be effective in AIDS. Also noted were elevated plasma levels of zidovudine in methadone users. These elevated levels may reflect a decrease in zidovudine metabolism.

A major emphasis in the clinical sessions was on combination drug therapy. Although more clinical experience is needed, some predicted that multidrug regimens that can reduce drug toxicity, increase efficacy, and combat the emergence of resistance will be the standard of care in the future. Preliminary reports of trials that use alternating and intermittent regimens of zidovudine and dideoxycytidine (ddC) suggested enhanced efficacy and significant reduction of both zidovudine-induced bone marrow toxicity and ddC-induced peripheral neuropathy. Studies of combination therapy with interferon and zidovudine...
Pneumocystis Carinii Pneumonia

Enthusiasm was expressed for the promising potentials of both dideoxycytidine and dideoxynosine (ddI). Primary toxicities of ddC and ddI include pancreatitis and dose-dependent peripheral neuropathy but minimal hematologic toxicity. Ongoing studies with peptide T, CD4 analogs, alpha and beta interferon, ampligen, thiosanthin (Compound Q), diethylthiocarbamate (ditiocarb), and selective inhibitors of HIV replication hold some promise.

**Pneumocystis carinii Pneumonia**

Strong evidence was presented for routine and early use of high-dose corticosteroids in acute severe *Pneumocystis carinii* pneumonia (PCP)\(^{18,19}\). When begun within 3 days of initiating therapy in patients with moderate-to-severe PCP, regimens using high-dose prednisone (e.g., 40 mg orally twice daily for 5 days, 40 mg orally daily for 5 days, then 20 mg orally daily to the end of PCP therapy) tended to decrease acute respiratory failure and short-term mortality. A group of AIDS experts recently reviewed these and other studies and will be issuing a consensus statement supporting the use of routine adjunctive corticosteroids in the treatment of patients with moderate-to-severe PCP. Questions remain about the influence of corticosteroids on long-term prognosis and survival.

The therapy of choice for treatment of acute *Pneumocystis carinii* pneumonia is either intravenous or oral trimethoprim-sulfamethoxazole (TMP-SMX) or intravenous pentamidine. A multicenter double-blind study comparing aerosolized pentamidine with TMP-SMX in the treatment of moderate-to-severe PCP confirmed the superiority of TMP-SMX.\(^{20}\) Although more patients treated with TMP-SMX had the drug discontinued because of side effects, only 18 percent failed to respond to 21 days of treatment compared with 39 percent who failed to respond to aerosolized pentamidine. In other studies, the efficacy of clindamycin plus primaquine as second-line therapy for acute PCP was confirmed.\(^{21}\)

Further clinical experience with use of inhaled pentamidine for PCP prophylaxis confirms earlier accounts of suboptimal results in some patients.\(^{22,23}\) Atypical PCP (with upper lobe disease and bullous changes) and disseminated *Pneumocystis carinii* infection continue to be observed. Therapy failure (especially in patients with low CD4 counts) was described.

Trimethoprim-sulfamethoxazole and dapsone plus pyrimethamine also have activity against *Toxoplasma gondii*. Therefore, when these combinations are given for PCP prophylaxis, they can provide possible primary prophylaxis against toxoplasmosis.\(^{24}\) Inhaled pentamidine is not effective against toxoplasmosis.

**Cryptococcal Meningitis**

Data were presented supporting the use of oral fluconazole in the treatment and suppression of cryptococcal meningitis.\(^{25}\) When fluconazole was compared with amphotericin B in the treatment of acute cryptococcal meningitis, response and survival rates were similar. A trend toward early deaths in the fluconazole-treated group was viewed with concern. Therefore, some physicians are reluctant to initiate treatment with fluconazole and are using amphotericin B for at least the initial 2 weeks. The usual recommended dosage of fluconazole for acute therapy of serious cryptococcal disease is 400 mg orally daily. For chronic suppression of cryptococcal meningitis, 200 mg of fluconazole daily appears to be more effective than daily intravenous amphotericin B. Oral fluconazole is much easier to use and, therefore, may become the drug of choice for chronic suppression of cryptococcal meningitis. Because fluconazole is considerably more expensive ($10 or more per 200-mg capsule) than ketoconazole, there is a reluctance among many experts to recommend it as a first-line drug for other fungal infections such as oropharyngeal and esophageal candidiasis. The lack of data on primary prophylaxis of cryptococcal disease precludes strong recommendations at this time.

**Other Opportunistic Infections**

Several reports confirmed the efficacy of foscarnet for acute treatment of sight-threatening cytomegalovirus (CMV) retinitis.\(^{26,27}\) Particularly when ganciclovir-resistant CMV was present.\(^{28}\) Toxicities that may require discontinuation of foscarnet therapy include penile ulcerations,\(^{29}\) electrolyte disturbances, neutropenia, and renal impairment.
No compelling data were presented to guide proper therapy of *Mycobacterium avium*-intracellulare infection. Hyperimmune bovine colostrum proved an effective treatment against cryptosporidial diarrhea in some AIDS patients. \(^{40}\)

**Immunotherapies and Vaccines**

Immunotherapies and HIV vaccines were topics of considerable interest.\(^{33-35}\) Human monoclonal antibodies to the HIV glycoprotein 120 (gp 120) and other cell surface antigens appear to hold therapeutic promise. Plasmapheresis was effective in 8 of 11 patients with HIV-related immune complex syndromes.\(^{46}\) Progress toward an HIV vaccine was evident, and some scientists predict an AIDS vaccine by 2000 A.D. HIV vaccines being investigated target the viral envelope (gp 160 and gp 120), the p24 protein, the inactivated virus with depleted envelope, anti-CD4 complex, and combinations of these. Some vaccine studies have been completed successfully in rhesus monkeys and chimpanzees. Limited human vaccine trials are encouraging. All human trials currently underway are Phase I and II trials in seronegative healthy patients. These trials will move into Phase III efficacy trials next year.

**Cigarette Smoking**

Smokers were found to have slightly higher CD4+ (T-helper) lymphocyte counts than nonsmokers.\(^{41}\) In another study, smoking appeared to correlate with more HIV disease progression.\(^{42}\) The significance of these findings remains uncertain.

**Controversy over Clinical Trials: Much Ado about Something**

Clinical drug trials were the subject of heated discussions. Frustrated patients, families, clinicians, scientists, and government officials have found a convenient target in the methods in which AIDS clinical research is conducted. Criticisms of delayed and poorly executed government-sponsored drug trials\(^{47}\) were counterbalanced by concerns about suboptimally controlled community trials.\(^{38}\)

Examples of bureaucratic delays, inaction, and a lack of coordination of clinical drug trials abound. An excessively cautious approach, it was argued, has resulted in the failure to evaluate the potential effectiveness of numerous agents. The paucity of research on women, children, and minorities was cited as a major deficiency in AIDS research. The under-representation of blacks and Hispanics will only be corrected when clinical trials are offered in conjunction with more comprehensive programs to meet patients' overall medical, social, and family needs.\(^{45}\)

For the patient with a poor prognosis, the distinction between research and treatment blurs. The experience of awaiting enrollment in clinical trials can be infuriating. Failing to meet strict criteria because one is too sick, not sick enough, or experiencing other problems (such as opportunistic infections that will complicate the analysis of data) drives patients to alternate sources of experimental therapy. Unfortunately, when patients receive experimental drugs outside of a formal clinical trial, it is difficult to establish scientific significance to any observed findings. The availability of experimental drugs by prescription also has the potential to retard research. One study reported that when an experimental drug was made generally available, many more patients received the drug outside the clinical trial than in it.\(^{49}\) Nevertheless, this alternative process of "expanded access" to experimental drugs was viewed as a step in the right direction.\(^{40}\) One speaker implored physicians to enroll patients in clinical trials—stating that we desperately need scientific data, not anecdotes.\(^{41}\)

Thus, patients' need for rapid access to any new possibly effective intervention conflicts with the need for data from well-controlled, large-scale studies. There was general agreement that both positions are simultaneously valid and important.

**Prevention**

**Nonoxynol-9**

One controversial presentation concluded that the spermicide nonoxynol-9 should not be used in combination with latex condoms.\(^{42}\) In a sample of 24 women who are sex trade workers in Vancouver, British Columbia, 38 percent reported they had experienced symptoms of vaginal irritation when condoms were lubricated with nonoxynol-9. The theoretical possibility of irritation promoting HIV transmission was entertained; however, HIV seroconversion was not monitored in this study. Until more conclusive studies are available, it will remain uncertain whether possi-
Adolescents

Perinatal Transmission
A 30% transmission rate from infected mother to infant was reported at Harlem Hospital. Cesarean section does not prevent HIV transmission. Breast-feeding may also infect the child. It is essential that primary care providers share this information when counseling an HIV-infected woman about pregnancy. Another factor to consider is that social and cultural factors, such as a woman's strong desire to have children and the fulfillment of the social role of motherhood, can be more important to a woman than knowledge of transmission rates.

Adolescents
A powerful presentation by Dr. Mindy Fullilove (HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute, Columbia University) linked a discussion of adolescent HIV infection with broader societal values. She pointed out that AIDS prevention must address a comprehensive range of issues. These include sexuality, school performance, and the role of the family.

Dr. Fullilove observed that our culture publicly endorses sexuality through advertising, entertainment, and the media. However, the formal message given to teens is that it is never safe to have sex and that contraception is not appropriate. She also said some studies have reported that condoms are used by teenagers less than 25% of the time and that the average sexually active female adolescent does not begin using contraception until more than 1 year after initial sexual relations. Fullilove challenged adult society to prepare teens better for this difficult period of time.

School life was highlighted as a key influence upon teenagers' growth and development. Schools provide a cultural nexus where success breeds success and failure breeds failure. School performance correlates strongly with social behavior. Risk factors for teenage drug use include low grade point average, low self-esteem, poor relationship with parents, early alcohol use, and perceived drug use by peers and adults. She declared that we must ensure that all children are allowed the opportunity to succeed in school.

Current trends in family structure were cited as most pervasive in their effects. Children now have much less contact with their families than in the past. Frequently, family units are fragmented. In other instances, both parents work outside of the home, making them less accessible to their children. The children's world then becomes one of commercial entertainment and the creation of an independent "teen culture." The lack of family availability and guidance places adolescents at an increased risk for experimenting with dangerous behaviors. Fullilove also challenged parents and families to become guides for children in the passage from childhood to adolescence. "Adults," she said, "must reinvent loving guidance for kids."

Family Aspects of HIV
The International Conference has traditionally focused on the basic sciences, diagnostic and treatment approaches, and community aspects of care. Investigations into the psychological aspects of HIV primarily have examined how HIV affects the individual. A few presentations this year shed some light on HIV in the family setting.

One study from New Jersey showed that 72% of persons with AIDS lived with someone, most commonly family members. Mothers were most frequently involved in providing support (41%). Women provided the bulk of unpaid daily care regardless of transmission type and racial or ethnic background. The special needs of caregivers for AIDS patients were addressed. Health care providers should relate to caregivers as caring family members rather than as outsiders providing care. Caregivers should be acknowledged for their expertise gained from living with a person with AIDS and be involved in and informed about decisions. Homophobia and a focus on the patient alone have blocked health care providers from including these caregivers in treatment planning.

When more than one family member is HIV infected, care tends to be more fragmented, duplicated, episodic, and unstructured. Specific issues arise when multiple family members are infected. These include difficulties encountered when caregivers become ill, problems occurring...
when infected parents compromise their own care to maximize their children's care, and resent-ment and anxiety arising among family members when some members participate in clinical trials and others do not. An increased emphasis on an examination of a family's special needs, family treatment, and family-focused clinical trials was recommended.

Important behavioral and academic problems (e.g., running away from home, academic failure, truancy, aggressiveness, and severe depression) occur among noninfected siblings. These children display an unusual need to overprotect; they have difficulty in establishing long-term heterosexual relationships and in dealing with the impending death of their sibling.

Adult children of persons with AIDS experience social isolation, stigmatization, a sense of betrayal, a reassessment of values and lifestyle choices, and a reemergence of family concerns. Perhaps the most eloquent presentations about the personal and familial aspects of AIDS came from speakers who are HIV-infected. They provided painful details of how far-reaching HIV is. This disease affects relationships, careers, finances, and interactions with health care providers. Stories of creativity and courage mixed with tragedy provided a hopefulness that was less evident in the biomedical presentations.

Summary

Major scientific and clinical breakthroughs in HIV disease are rarely saved for the International Conference on AIDS. Nevertheless, this conference provides an opportunity for experts, providers, and patients to gain new information, exchange ideas, and assess progress. The Conference is also a public forum for political and social discussion and serves as a barometer of scientific and social trends as well. This year's conference featured refinements in clinical care, a deeper understanding of the epidemiologic trends, and a public awareness of the many political aspects of the AIDS epidemic. Contributions from family physicians and other primary care providers about problems they face and the family aspects of HIV need still greater prominence and exposure. Hopefully family physicians will use their expertise and report at future international conferences.

We wish to thank Mary A. Hanville, Barbara Brodie, F.N.P., and Claire A. Rappoport, M.A., for their valuable help in the conceptualization and preparation of this article.

References


44. Fullilove M. Epidemiology and primary prevention of HIV infection in adolescents. Presented at the Sixth International Conference on AIDS, San Francisco, June 20-24, 1990.