

Topics in **HIV Medicine**TM

A publication of the International AIDS Society–USA

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About This Issue

The International AIDS Society–USA joins the nation in mourning the individuals who perished during the tragic events of September 11. We extend our heartfelt sympathies, and dedicate this issue, to those who are grieving the loss of friends, colleagues, and loved ones.

The 4th Annual HIV Clinical Conference was sponsored by the International AIDS Society–USA and supported through grant number 6 H76 HA00578-02 1 from the HIV/AIDS Bureau of the US Health Resources and Services Administration. The IAS–USA Antiretroviral Guidelines Panel is funded solely by the International AIDS Society–USA.

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Our October issue contains a special contribution: included are questions to and answers from the International AIDS Society–USA Antiretroviral Guidelines Panel on current developments and dilemmas in antiretroviral therapy. The panel was convened at the 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina, in July, 2001, to discuss evolving guidelines with an international audience of scientists and clinicians. The questions were submitted by audience members, and answers are based on what is known about antiretrovirals through clinical trials and HIV patient care.

This issue includes 2 summaries of talks given at the 4th Annual HIV Clinical Conference for Ryan White Title III and IV providers held in San Diego and a summary of a talk given at the International AIDS Society–USA continuing medical education course held in Atlanta in February, 2001. The first article summarizes Dr Patrick G. O'Connor's talk on prescription opioid abuse and office-based opioid maintenance treatment. The second article is a summary of Dr Michael P. Johnson's talk on the role of the provider in HIV infection prevention and elimination of tuberculosis and syphilis. Our third article is based on Dr Harold W. Jaffe's discussion of national and international perspectives on the HIV pandemic.

In addition, we share Dr Douglas T. Dieterich's story, "Epidemic Beginnings," as part of our new *Telling Stories* section.

Topics in HIV Medicine™

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Perspectives

Prescription Opioid Abuse and Potential Role of Office-Based Opioid Maintenance Treatment in Integrating Medical and Substance Abuse Care

Patrick G. O'Connor, MD, MPH, reviewed issues in identifying, managing, and preventing prescription opioid abuse and discussed the potential benefits of office-based opioid maintenance therapy at the 4th Annual HIV Clinical Conference for Ryan White Care Act Title III and IV clinicians, sponsored by the International AIDS Society–USA and funded by the HIV/AIDS Bureau of the US Health Resources and Services Administration. The conference was held in San Diego in June, 2001.

Prescription Opioid Abuse

Case Presentation

Dr O'Connor began his presentation with a case illustrating potential prescription opioid abuse. A 27-year-old woman with HIV infection is added to a physician's schedule as an urgent visit. The patient states that she was in a car accident 5 days ago and has acute back pain. She is traveling by air later today and wants "Percocet" for her pain. Physical examination is unremarkable. The patient has been seen before for chronic and acute back pain and has been receiving oxycodone for both. She does not see her primary care physician regularly. There is a vague reference to "drug abuse" on her chart. While the physician is trying to contact the patient's regular physician, the patient and clinic assistant begin arguing in the hallway; the patient has been going from room to room "looking for the doctor and her prescription." The physician and patient begin arguing, and the patient leaves the clinic untreated.

Dr O'Connor is Professor of Medicine and Director of Primary Care Medicine at Yale University School of Medicine in New Haven, Connecticut.

Considerations in Addressing Potential Abuse

For patients diagnosed with chronic nonmalignant pain, there are a number of clinical criteria for effective treatment. The primary goals of treatment are to relieve pain and to reduce functional impairment that may accompany chronic pain. Development of a feasible treatment plan should include consideration of use of both nonpharmacologic and pharmacologic modalities, with the aim of providing a stable, effective regimen. In general, effective management of pain requiring opioid treatment includes careful consideration of whether short-acting or long-acting opioids are indicated. Long-acting agents are considered to be more suitable in patients with chronic pain, since they provide steady pain relief for a prolonged period. In addition, effective pain control requires a feasible patient-physician interaction, with the relationship remaining stable over time and regular follow-up being conducted.

The course to be adopted in managing a patient who is receiving opioid treatment for chronic nonmalignant pain and who may be a prescription opioid abuser depends on the evaluation of evidence for the presence of pain that requires such treatment and the evidence for prescription drug abuse. Diagnosis of chronic pain depends on consideration of both subjective evidence derived from patient history and objective evidence supporting presence of a chronic pain condition. With regard to subjective evidence, it is important to consider whether the patient history is consistent with a specific diagnosis of chronic pain and whether severity is sufficient to warrant opioid treatment, as well as to evaluate the patient's responses to prior nonpharmacologic treatment, nonopioid medication, and

opioid medication. Objective evidence of a chronic pain condition is derived from physical examination, diagnostic tests, and evaluation by specialists.

The prevalence of prescription drug abuse in patients with chronic nonmalignant pain is rather poorly understood, with most of the little data available coming from studies in pain management centers. One 1992 meta-analysis of

Estimates of prevalence
of prescription drug
abuse in patients
with chronic
nonmalignant pain
range from
3% to 28%

24 studies indicated that 3% to 19% of patients had comorbid substance abuse disorders (Fishbain et al, *Clin J Pain*, 1992). A Seattle Veterans Affairs study indicated that 28% of a relatively small sample of patients (n=76) treated with opioids met the criteria for prescription drug abuse (Chabal et al, *Clin J Pain*, 1997).

However, the prevalence of such abuse among primary care populations of chronic pain patients or HIV disease patients has remained relatively undefined. A recent study by Dr O'Connor and colleagues from Yale University found that history of substance abuse/dependence was high among outpatients in primary care who received opioid treatment for chronic nonmalig-

nant pain (Reid et al, *J Gen Intern Med*, 1999). The most common pain diagnoses were low back pain (35%), degenerative joint disease (15%), injury-related pain (12%), and diabetic neuropathy (9%). The most commonly used opioid was the short-acting agent oxycodone (usually Percocet), which was being taken by 39% of patients. Given the current dictum that long-acting agents are more suitable for treatment of chronic pain, this finding suggests that many patients were being suboptimally managed. The lifetime prevalence of alcohol abuse/dependence was 39% and that of drug abuse/dependence was 28%. Lifetime prevalences of psychiatric diagnoses, including depression (47%) and anxiety (19%) were also high.

Identification/Diagnosis of Prescription Opioid Abuse

Identification of potential opioid abuse in pain patients is difficult, since many "drug-seeking" behaviors are also exhibited by patients who wish only to achieve relief from pain. Nevertheless, such behaviors may prompt suspicion of drug abuse; these include over-reporting of symptoms, reporting of multiple somatic complaints or vague symptom complexes, insistence on specific medication or "brand name only" (which may also occur in cases in which the drug is being sold on the street), arguments about pharmacology, assertion of high tolerance to medication, veiled threats, flattery followed by prescription requests, and demands for polypharmacy. Statements that may indicate abuse include:

- "I spilled the bottle"
- "I lost the prescription"
- "_____ is the only drug that works"
- "I'm allergic to everything but _____"
- "I washed the prescription in the laundry"
- "Someone stole my medication"
- "Only the brand name works for me"
- "I needed to use more this month"

Diagnosis of prescription drug abuse in patients with nonmalignant chronic pain is not straightforward. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for diagnosing substance abuse are difficult to apply to this patient population, since

some of the characteristics figuring in diagnosis—eg, tolerance and dependence—may be expected in patients receiving long-term opioid treatment. Specific diagnostic criteria for prescription drug abuse in this population, proposed by Chabal and colleagues (*Clin J Pain*, 1997), are shown in Table 1.

Several physician actions are in order for patients found to be abusing prescription drugs. The appropriate indications for the drug at issue should be reviewed with the patient, and the patient should be educated about the potential dangers of the drug. It should be clearly stated why the drug is not indicated in the patient's case. Concern over and evidence for drug abuse or dependence should be discussed. Alternative drug treatment or referral should be recommended, with the physician emphasizing that he or she is not refusing to treat the patient but is instead focusing on another form of treatment. Finally, it is imperative that the patient be referred for substance abuse treatment, irrespective of whether it is believed that the patient will act on the referral.

Minimizing Potential for Abuse

Physicians may contribute to prescription drug abuse by relying on outdated drug information, being poorly educated on the effects of mood-altering drugs, remaining unfamiliar with principles of pain management, and by avoiding confrontation of patients for whom there is evidence of abuse. Actions that physicians can take to minimize potential for prescription drug abuse (Table 2) include documenting the rationale for treatment, establishing goals for treat-

ment, identifying how long the drug at issue will be prescribed, and maintaining a flow chart of prescribed controlled substances. Patients should be continually monitored for effectiveness of therapy, evidence of tolerance or dependence, and evidence of abuse. Use of a controlled prescription drug "contract" may be highly advantageous.

**Strategies for
minimizing abuse
include controlled
prescription drug
"contracts" between
physicians and patients**

Dr O'Connor and colleagues currently are conducting a clinical trial of the effect of such contracts on treatment efficacy and frequency of substance abuse in chronic pain patients. Experience in the study thus far suggests that such contracts should acknowledge physician responsibility for good patient care and emphasize patient responsibility for the medication. In addition, they should stipulate that the patient will not request medications from any other provider, only 1 pharmacy will be used for prescription filling, refills will be made on time and at regular appointments, and continuation of medication relies on adherence to the contract. According to Dr

Table 1. Diagnostic Criteria for Prescription Drug Abuse in Patients with Chronic Nonmalignant Pain

Three or more criteria are required for diagnosis:

- Overwhelming focus on opioid issues that persists beyond 3 visits
 - Early refills (3 or more) or escalating drug use in absence of clinical change
 - Numerous phone calls or visits to staff requesting more opioids
 - Pattern of "lost," "spilled," or "stolen" medication
 - Supplemental sources of opioids: multiple providers, emergency departments, illegal sources
-

Adapted with permission from Chabal et al, *Clin J Pain*, 1997.

O'Connor, despite early fears regarding patient acceptance of contracts, most patients receiving opioids have responded well to the contracts in the study and have cited benefits in terms of security and regularity in the provision of medication.

Quality of care and minimization of abuse potential also are enhanced by use of a team approach to management of chronic pain patients. In addition to the patient and primary care physician, the team should include psychiatry personnel to assist in management of long-term treatment with controlled substances. Other important components of the team include qualified pain management specialists and such other professionals as social workers, counselors, and drug treatment program staff, as needed and as available, as well as the patient's family.

Although vigilance regarding drug abuse is warranted in chronic pain patients, physicians prescribing opioids need to be aware of the potential for "auto-lobootomy," whereby suspicion of rampant abuse leads to failure to provide good care. Underprescribing opioids can be as much of a problem as overprescribing them. Patients with substance abuse disorders can have pain-related diagnoses and syndromes just as do patients without such disorders. For physicians managing HIV-infected patients, it should be recognized that such patients may be at increased risk for pain. It also needs to be remembered that due to tolerance, patients on methadone maintenance can require higher doses of opioids that are indicated for pain treatment. The need to remain sensitive to the concerns of individual patients in treatment is also illustrated by frequent expression of fear of readdiction by patients with prior substance abuse problems who require opioids for pain treatment. These patients may require specific support during the course of their pain treatment.

Dr O'Connor noted that after leaving the clinic, the patient described in the case above went to the emergency room and received oxycodone. Eventually, she returned to the clinic and was placed on a controlled drug contract. She failed to comply with the contract on numerous occasions, "losing" prescriptions and running out of medication too soon. The

local pharmacy called the physician regarding the patient's use of altered prescriptions and multiple providers. After much discussion with the patient, she finally accepted referral to methadone maintenance. Although her course has been rocky, the patient currently is doing reasonably well in both medical and substance abuse treatment.

treatment by pharmacologic withdrawal, opioid antagonist treatment (naltrexone), and opioid agonist treatment (methadone), but currently resists drug abuse treatment because of the stigma associated with treatment programs. She has not found a physician to address both her medical problems, including HIV disease, and substance abuse problems.

Office-Based Opioid Maintenance Treatment

Case Presentation

In a second case presentation, Dr O'Connor described a scenario in which office-based opioid maintenance treatment may be an effective therapeutic approach. A 45-year-old woman presents with the complaint "I want my life back." The woman has a medical history of HIV disease, hepatitis C virus infection, hypothyroidism, type 2 diabetes mellitus, opioid dependence, and depression. Of the medications that have been prescribed for her, she is taking only insulin for her diabetes and levothyroxine for hypothyroidism. The patient is married with 2 children, aged 13 and 17 years, and works as a retail clerk. Her substance abuse history includes heroin by injection since age 18 (4 "bags" per day); she has undergone

Rationale for Office-Based Opioid Maintenance Treatment

Recent legislation appears to be clearing the way for office-based opioid maintenance treatment, which could be of considerable utility for patients like the woman in this case. The Narcotic Addict Treatment Act of 1974 established the groundwork for the very strict rules and regulations that govern methadone maintenance programs and serve to isolate such treatment from mainstream medicine. In 2000, the US Food and Drug Administration and the Center for Substance Abuse Treatment released regulations that, when adopted, will allow for exemptions for office-based methadone maintenance care and permit transfer of stable patients to care in physicians' offices.

The Congressional Drug Addiction Treatment Act of 2000 now permits qual-

Table 2. Actions to Minimize Prescription Opioid Abuse

Document treatment rationale and plan and period of time drug will be prescribed in patient chart

- Maintain a flow chart of prescribed controlled substances, recording number of pills and number of refills
- Evaluate patient for continued use of the drug:
 - Is there a documented cause for patient's symptom(s)?
 - Is there evidence of tolerance (eg, escalating dose) or dependence?
 - Is the therapy effective—eg, does it allow patient to function at higher level?

Establish policies for prescribing controlled substances

- Use controlled substance contracts
- Do not leave prescriptions in unsecured areas
- Do not refill prescriptions for patients you do not know unless you have access to their medical records
- Do not write controlled prescriptions initiated by another physician; establish with the patient and other provider that there will be just 1 physician responsible for renewing the prescriptions
- Practice good prescription "hygiene": write prescriptions clearly and spell out all numbers

ifying office-based physicians to use approved schedule III, IV, and V controlled substances for treatment of opioid dependence. The US Department of Health and Human Services has proposed additional exemptions for office-based care, but has emphasized that more data on this issue need to be collected.

There is considerable rationale for office-based opioid maintenance treatment. It would increase access to treatment, an important issue since approximately 80% of opioid-dependent individuals are not in treatment, and it would improve coordination of medical, psychiatric, and substance abuse care. Movement of such treatment into the medical mainstream would weaken the distinction between opioid dependence and other chronic diseases and allow for recognition and reinforcement of patients' treatment successes within their medical care setting. It has also been suggested that treatment in the office setting would permit a beneficial limiting of contact between the patient and other patients who are still using drugs. Data supporting the feasibility of office-based opioid treatment come from uncontrolled studies (Novick et al, JAMA, 1988; Novick et al, *J Gen Intern Med*, 1994; Schwartz et al, *Am J Addict*, 1999) and a small number of randomized clinical trials showing that properly conducted office-based treatment is effective in stabilized patients transferred from methadone maintenance clinics (Senay et al, *J Addict Dis*, 1993), or in those who are entering maintenance treatment (O'Connor et al, *Am J Med*, 1998).

There is at least preliminary evidence that physicians will accept a role in office-based opioid maintenance treatment. Dr O'Connor and colleagues in the Connecticut Medical Maintenance Project (JAMA, in press) recently completed a study of patients who had received treatment at a narcotic treatment program for more than 1 year and had no evidence of illicit substance use for 1 year, no medical or psychiatric contraindication to leaving the program, and no dependence on cocaine or alcohol. The patients were randomized to continued care in the program or to office-based methadone maintenance. Treatment retention rates were approxi-

mately 80% in both the office setting and narcotic treatment program setting and rates of illicit drug use were equivalent at the 2 treatment sites. The measure of patient satisfaction with office-based treatment was higher than that for the maintenance program. Assessment of provider satisfaction indicated that physicians in the office-based maintenance arm were just as satisfied with providing treatment as were program treatment providers, with satisfaction

for injection of the opioid). Buprenorphine has been shown to be as effective as methadone and LAAM (levomethadyl) in treatment of opioid dependence in randomized trials (eg, Johnson et al, *N Engl J Med*, 2000).

Dr O'Connor noted that the patient in the second case has succeeded in "getting her life back." She entered office-based methadone maintenance treatment, was abstinent after 1 month, and has had excellent long-term success in treatment. She has been reengaged in primary care for her other conditions. She initiated antiretroviral therapy for HIV disease and has shown excellent compliance with treatment. She underwent evaluation for hepatitis C virus infection at a liver clinic and currently is being closely monitored for infection status. Her blood glucose control has improved with institution of twice-daily insulin treatment. She is doing well on levothyroxine treatment for hypothyroidism and has initiated selective serotonin reuptake inhibitor therapy and counseling for treatment of depression.

Pharmacologic treatment is very successful in decreasing illicit opioid use and associated medical and social complications. There is accumulating evidence that office-based opioid maintenance treatment is feasible and associated with high patient and physician satisfaction. Office-based care may improve access to and coordination of care of patients who require medical and substance abuse treatment and management, a factor that may be particularly beneficial for many patients with HIV disease.

Presented in June, 2001; reviewed and updated by Dr O'Connor in September, 2001.

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Suggested Reading

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Coming in December: Update on Drug Resistance Mutations in HIV-1

Members of the International AIDS Society–USA Resistance Mutations Project, a subgroup of the Resistance Testing Guidelines Panel, are currently updating their listing of antiretroviral

drug resistance mutations to reflect new data from recent scientific conferences. Updated mutations figures will be published in the December, 2001, issue of *Topics in HIV Medicine* and posted on

the International AIDS Society–USA Web site (www.iasusa.org). More information about the Resistance Mutations Project and the current version of the mutations figures are available at www.iasusa.org.

Perspectives

Role of the Provider in Prevention of HIV Infection and Elimination of Tuberculosis and Syphilis

The role of the primary care provider in improving HIV disease prevention and contributing to elimination of tuberculosis and syphilis was discussed by Michael P. Johnson, MD, MPH, at the 4th Annual HIV Clinical Conference for Ryan White Title III and IV providers in San Diego in June, 2001. The conference was sponsored by the International AIDS Society–USA and supported by the HIV/AIDS Bureau of the US Health Resources and Services Administration.

Primary care providers to persons with HIV disease play a pivotal role in prevention and treatment of HIV infection and related diseases and conditions. National efforts are underway to emphasize and support HIV primary care providers in preventing transmission of HIV, as well as to promote goals in the elimination of tuberculosis and syphilis. Recent disease-specific recommendations have been formulated by the Institute of Medicine in 2 studies—*No Time to Lose: Getting More From HIV Prevention and Ending Neglect: The Elimination of Tuberculosis in the United States*—and by the Centers for Disease Control and Prevention (CDC) in *The National Plan to Eliminate Syphilis from the United States*. It is likely that few of the specific recommendations in these studies and plans are unknown to clinicians. However, many of the recommendations are not always followed in busy clinical practice settings and need to be more rigorously implemented if dramatic reductions in these infections are to be achieved.

Dr Johnson is Director of the Division of Training and Technical Assistance, and Chief Medical Officer, HIV/AIDS Bureau, Health Resources and Services Administration, Rockville, Maryland.

HIV Prevention

Our Patients Are Having Sex and Using Drugs

For much of the HIV epidemic in the United States, prevention interventions have been focused on uninfected individuals. As prevention efforts have evolved, there has been increasing emphasis on prevention in high-risk individuals and, more recently, increasing attention to interventions targeting HIV-infected individuals in clinical care. The high and increasing levels of risk behavior in high-risk and HIV-infected patients documented in many recent studies point out the need to redouble prevention efforts in these populations.

A 4-city study of men who have sex with men (MSM) showed a generally steady increase in numbers of cases of gonorrhea between 1995 and 1999 (Figure 1; Fox et al, *Am J Public Health*, 2001). A study of risk behavior among 293 MSM in 5 cities reported this year showed that 93% had sex within the past 6 months, 43% had unprotected sex

within the past 6 months, 29% were known to be HIV-seropositive, 23% were in regular medical care, and 18% were taking antiretroviral therapy (Valleroy et al, 8th CROI, 2001). A study conducted in 317 women and 361 men with HIV infection at a Baltimore sexually transmitted disease (STD) clinic in 1997 and 1998 found that 56% of women and 60%

A related article, "Approaches to HIV Prevention Among Seropositive Patients in the Clinical Care Setting," was published in the July, 2001, issue of *Topics in HIV Medicine*.

of men had had sex within the past 90 days; 7% and 14%, respectively, had had sex with a new partner in the past 90 days; and 64% and 67%, respectively, reported condom use in the last sexual encounter (Erbelding et al, *AIDS*, 2000).

Data for 1993 through 1998 from 354 women and 796 men at the Baltimore clinic show that 12% of women and 14% of men had a new STD after receiving

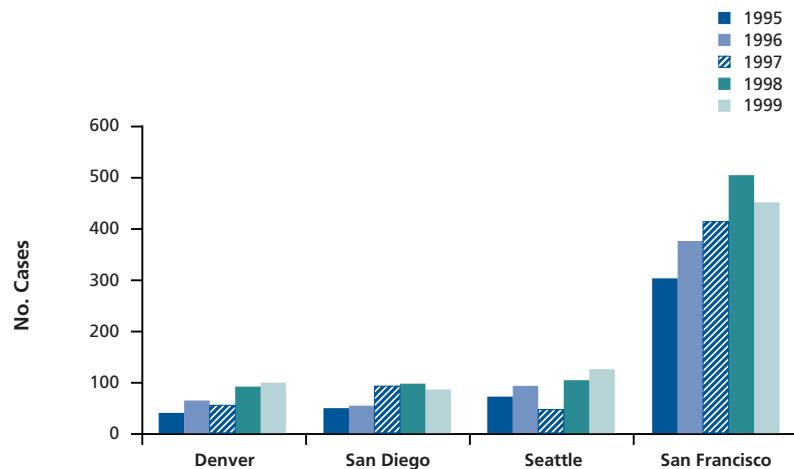


Figure 1. Cases of gonorrhea from 1995 to 1999 among men who have sex with men. Adapted with permission from Fox et al, *Am J Public Health*, 2001.

diagnosis of HIV infection, including gonorrhea (3% and 5%), syphilis (3% and 1%), and trichomonas and/or nongonococcal urethritis (8% and 8%; Erbelding et al, *Int J STD AIDS*, 2001). A 1999 study of HIV-infected individuals in Atlanta found that among 112 women and 228 men, 16% and 11%, respectively, had an STD within the past 3 months, including gonorrhea (6% and 4%), chlamydia (4% and 3%), and syphilis (4% and 3%). Thirty-one percent and 13%, respectively, had STD symptoms without diagnosis in the past 3 months, and 36% and 18%, respectively, had an STD or STD symptoms over that period (Kalichman et al, *Sex Transm Infect*, 2001). Among this group of HIV-infected persons, the occurrence of STDs (diagnosed by laboratory diagnosis and/or symptoms suggestive of an STD) was positively correlated with sexual risk behaviors (numerous partners, no condom use) and use of drugs.

Another study assessing changes in behavior among individuals recently diagnosed with HIV infection showed that at 1 year after diagnosis, 58% used recreational drugs compared with 84% at time of diagnosis (baseline), 50% of MSM reported more than 5 sex partners in the past 6 months versus 74% at baseline, and 44% of MSM reported having public sex versus 63% at baseline (Sey et al, 8th CROI, 2001). A 1998 report of drug use among HIV-infected injection drug users in a 12 state and city health department study from 1990 to 1995 showed that 786 of 1527 study participants had injected drugs within the past year, with 391 sharing syringes during that time (Diaz et al, *J Acquir Immune Defic Synd Hum Retrovir*, 1998).

We Are Not Talking Enough To Our Patients About Sex and Drugs

The high prevalence of risk behaviors among HIV-infected persons despite ongoing involvement of many in medical care raises the question of whether more can be made of the opportunity to influence behavior during ongoing medical care contacts. A variety of data indicate, however, that risk screening and education are not routine elements of care in the clinical setting. In a 2000 study of 74 HIV care providers in Seattle, all clients were asked about sexual

behaviors, STD history, and current drug use by only 32%, 18%, and 47% of providers, respectively. Sexual risk reduction, STD risk reduction, and drug use risk reduction were discussed with

**In a study of 44
HIV care providers in
San Francisco in
1996-1997, only
12% reported
routinely conducting
risk behavior discussions**

all clients by only 26%, 19%, and 28% of providers, respectively (Jeff Natter, personal communication). In a 2000 study of 63 providers of HIV clinical care in 4 major cities, 56% reported discussing prevention at every visit or most visits, 72% provided prevention counseling to new patients, and only 19% provided prevention counseling to established patients.

A 1996 to 1997 study of 44 physicians in San Francisco with extensive experience in treating HIV-infected patients found that the issue of HIV prevention was revisited in response to a medical cue (eg, STD) by 44% of physicians, patient report of change in relationship by 36%, and doubt about patient report of behavior by 12%. Twelve percent of physicians indicated that they routinely conducted risk behavior discussions (Gerbert et al, *AIDS Education Prev*, 1999). In a study of 49 HIV-seropositive patients from 2 Ryan White CARE Act-funded clinics who were interviewed as they were leaving a clinic visit, 61% reported being sexually active, 23% reported being concerned about transmitting HIV in the past year, 57% had been counseled about safer sex in the past year, and 4% had been counseled about HIV transmission during the current clinic visit (Steve Morin, personal communication).

Can We Do More to Assess Risk and Intervene?

Definitive data on the effectiveness of risk screening and prevention interventions are lacking. However, data indicating the benefit of counseling are accumulating. For example, a randomized controlled study conducted at 5 clinical sites serving persons at high risk for HIV from 1993 to 1996 showed that both extended behavioral client-centered counseling and brief client-centered counseling were associated with a reduction in incidence of STDs of approximately 20% to 30% compared with provision of didactic prevention information over 12 months (Figure 2; Kamb et al, *JAMA*, 1998). These findings suggest that brief counseling in the clinic setting may be a feasible approach to prevention.

Other studies have examined approaches to risk screening. One study showed that use of a computer-assisted self-interview technique was more likely than personal interview to elicit "yes" answers to questions about engaging in socially undesirable behaviors, particularly among women and youths (Kissinger et al, *Am J Epidemiol*, 1999). A similar, but nonsignificant, trend was observed using a similar approach in another recent study (Gerbert et al, *Med Care*, 1999). The latter study showed no effect of reporting of risk behaviors according to whether patients were told that their provider would or would not be informed of their report, suggesting that the provider's knowledge of risk behavior may not be a disincentive to reporting.

Small studies have indicated a benefit of training of providers using simulated patients to improve the frequency of risk screening and risk reduction counseling. In one study, use of a simulated HIV-infected patient for training had a beneficial effect on HIV risk screening practices among 65% of the providers studied (Epstein et al, *J Gen Intern Med*, 2001). In another study, this technique increased the frequency of STD risk reduction counseling to 73% of client encounters, as compared with 42% of encounters in a control arm and 53% among providers who received educational materials alone (Rabin et al, *Ann Intern Med*, 1994).

There are a number of ongoing studies examining approaches to HIV prevention that may contribute substantially to optimizing prevention efforts. These include the CDC/Health Resources and Services Administration (HRSA) Prevention for HIV-Infected Persons Project, multisite intervention studies of the National Institute for Mental Health (eg, the Partnership for Health Project), and the HRSA Center for AIDS Prevention multisite study of prevention practices among Ryan White CARE Act-funded clinics. It is hoped that results will guide the development and refinement of evidence-based prevention interventions for HIV-infected persons.

In the meantime, guidelines for screening and prevention based on expert opinion exist. A 1996 document from the American Medical Association and Kaiser Family Foundation suggests approaches to sexual risk screening, injection drug use risk screening, and prevention planning (available at <http://www.ama-assn.org/special/hiv/treatmnt/guide/hivguide.htm>). New guidelines currently are being developed jointly by the CDC, HRSA, and Infectious Diseases Society of America, and are expected to be available in late 2001. These guidelines will include recommendations for risk screening, behavioral intervention, and partner notification.

Partner notification is often performed in collaboration with health departments. Evidence for the effectiveness of this approach comes from a 1992 study in which partner notification was more effective when performed by a health department (78 partners of 39 HIV-infected patients notified) compared with notification by HIV-infected patients (10 partners of 35 HIV-infected patients notified; Landis et al, *N Engl J Med*, 1992). However, the recent experience of Jordan and colleagues (Wilbert Jordan, personal communication) indicates that patients can be effective in partner notification as well. The use of patient incentives, such as movie passes, led to HIV testing in 192 partners and contacts of 76 HIV-infected patients, 103 (53%) of whom were found to be HIV-seropositive. This remarkably high rate of HIV infection suggests that motivated patients might be best able to select

partners and other individuals at high risk for HIV infection for referral to HIV testing and care.

One important aspect of HIV prevention that is just beginning to be investigated and understood is the effect of antiretroviral therapy on risk behavior.

**Two recent studies
reported an
association between
use of antiretroviral
therapy and increased
risk behavior**

Available data indicate that risk of transmission is greatly reduced with effective viral suppression on antiretroviral therapy, with an approximately 2.5% increase in risk of transmission with each log-increase in viral load (Quinn et al, *N Engl J Med*, 2000). However, that risk is reduced but likely not eliminated even at plasma viral loads of less than 400

HIV-1 RNA copies/mL because of the occurrence of discordance between serum viral load and that in genital secretions. There is considerable concern that the belief that antiretroviral therapy will prevent transmission leads to increased risk behavior. Two recent articles have reported such an effect, with one group in San Francisco finding a 4-fold increase in risk of STD in association with use of potent antiretroviral therapy (Scheer et al, *Lancet*, 2001) and a group in Amsterdam finding an association between achievement of viral load below the limit of detection on potent therapy and a 3-fold increased risk of unprotected sex with casual partners (Dukers et al, *AIDS*, 2001).

Moreover, other data suggest that increased risk behavior may be associated with reduced adherence to antiretroviral medication (Flaks et al, 8th CROI, 2001). In one study, 38 patients with no reported risk behavior exhibited 92% adherence, and 35% of this group had a viral load level below 50 copies/mL. Among 36 patients with a low level of risk behavior, 80% were adherent and 26% had a viral load below 50 copies/mL. Finally, among 21 patients with a high level of risk behavior, 74% were adherent, with 9% having viral load below 50 copies/mL. Such findings

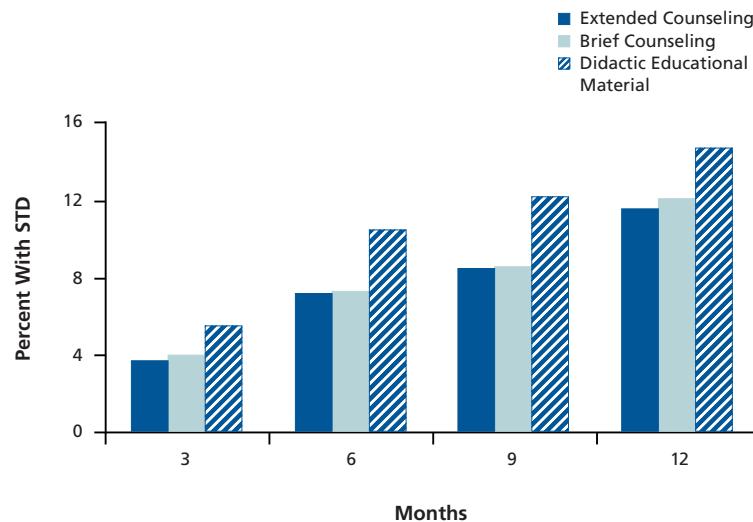


Figure 2. Proportions of individuals with a new sexually transmitted disease (STD) from 1993 to 1996 at clinics in Baltimore, Md; Denver, Colo; Long Beach, Calif; Newark, NJ; and San Francisco, Calif, according to whether they had received extended counseling, brief counseling, or didactic educational material alone. Adapted from Kamb et al, *JAMA*, 1998.

emphasize that good treatment practices include not only providing antiretroviral therapy according to guidelines, but ensuring that patients are counseled with regard to the potential for developing a false security about risk behaviors during treatment.

Tuberculosis Elimination

The Institute of Medicine target case rate for tuberculosis elimination (to be distinguished from eradication, which represents complete absence of disease) is less than 0.1 case per 100,000 population. The current case rate in the United States is 6.4 cases per 100,000 population. Tuberculosis rates declined by approximately 39% between 1992 and 1999 (Figure 3), after the increase in the late 1980s and early 1990s that was associated with both HIV disease and the reduced resources available to tuberculosis management infrastructure. Preliminary data indicate a further 7% decrease between 1999 and 2000. During this decline, cases in foreign-born persons have accounted for an increasing proportion of total cases, including 46% of new cases in 2000. Clinicians treating patients with HIV disease confront a case rate among their patients that is 50-fold greater than the national rate, with cases among patients with HIV disease accounting for approximately 5% of cases in this country.

Key elements of the elimination strategy proposed by the Institute of Medicine include (1) maintaining control of tuberculosis by improving treatment of active disease while adapting to declining disease incidence and changes in systems of health care financing and management, (2) speeding the decline in case rate through increased efforts related to targeted tuberculin skin testing and treatment of latent infection, (3) developing new tools for the diagnosis and treatment of and vaccination against tuberculosis, (4) increasing US involvement in global tuberculosis control, and (5) mobilizing support for and measuring progress toward tuberculosis elimination.

Care providers can contribute to the elimination of tuberculosis by maintaining practice patterns that are consistent with current recommendations for treatment of active disease, by targeted

screening of persons at high risk for tuberculosis, including those with HIV infection, and by treatment of latent tuberculosis infection. Recommendations for these clinical interventions exist and are regularly updated. It is important to note that several of these recommendations, such as those concerning drug choices based on drug interactions, interpretation of skin testing results, and monitoring of adverse drug effects differ between HIV-infected and uninfected persons. They can be accessed in print versions (CDC, MMWR, 1998; CDC, MMWR, 2000; American Thoracic Society/CDC, MMWR, 2000) and on the CDC Division of Tuberculosis Elimination Web site (<http://www.cdc.gov/nchstp/tb>). They can also be accessed on the Web sites of the 3 model centers for tuberculosis research and education: the National Tuberculosis Center at the University of Medicine and Dentistry of New Jersey (<http://www.umdnj.edu/ntbcweb>), the Charles P. Felton National Tuberculosis Center at Harlem Hospital (<http://www.harlemtbcenter.org>), and the Francis J. Curry National Tuberculosis Center at the University of California San Francisco (<http://www.nationaltbcenter.edu>). Both the CDC and the model centers also have free educational and teaching materials that are easily accessed by telephone, mail, or Internet. Finally, HIV care providers should maintain close working relationships with

tuberculosis control experts in local health departments who can assist with clinical recommendations and client referral.

Elimination of Syphilis

The target specified in *The National Plan to Eliminate Syphilis from the United States* is a reduction of the number of annual cases to 1000 or fewer (or less than 4 cases per 1 million population) and an increase in the proportion of syphilis-free counties to 90% or greater by 2005. The local definition is absence of transmission of new cases within the jurisdiction except within 90 days of report of an imported case. For 1999, a total of 6657 primary or secondary cases were reported, with 79% of counties (2473 of 3115) reporting no cases. Less than 1% of counties accounted for more than 50% of cases, with most of these counties being in the southeastern United States. Since the early 1990s, there has been a consistent decline in the huge epidemic of syphilis among African Americans. Despite declines in all age groups, rates of disease in 15- to 19-year-old men and women are still more than 30 times higher than in the corresponding white populations (Figure 4).

The National Syphilis Elimination Plan has 5 key elements: (1) enhanced surveillance, (2) strengthened community involvement and partnership, (3) rapid outbreak response, (4) expanded

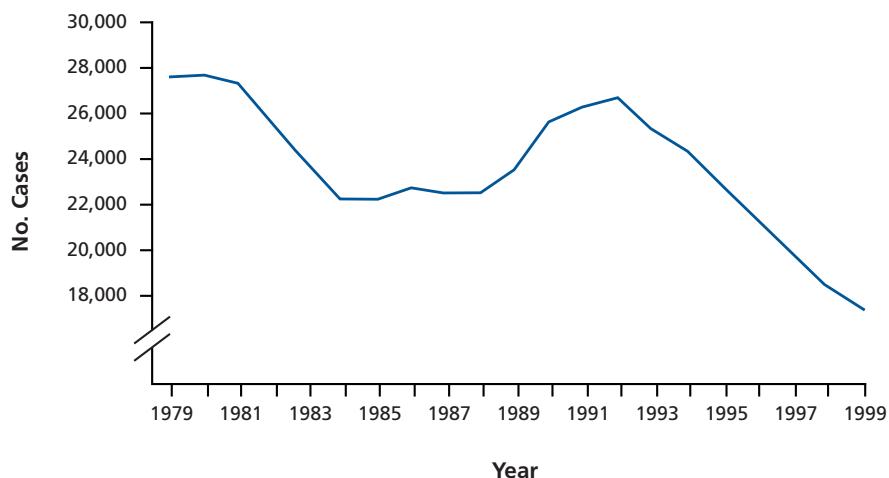


Figure 3. Reported tuberculosis cases in the United States, 1979 to 1999. Adapted from the Centers for Disease Control and Prevention; available at: <http://www.cdc.gov/nchstp/tb>.

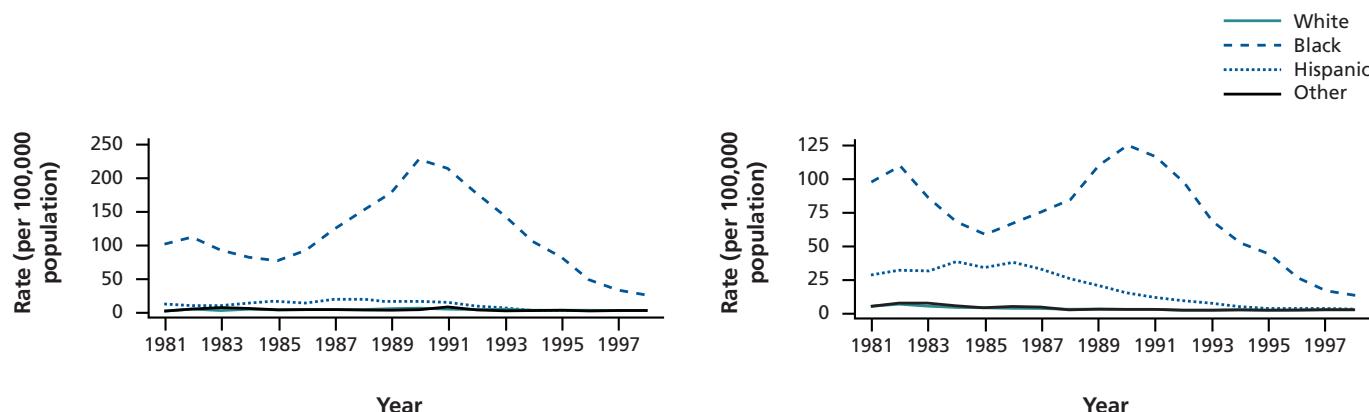


Figure 4. Reported rates of primary and secondary syphilis among 15- to 19-year-old women (left) and men (right) in the United States, 1981 to 1998. Persons included in "black," "white," and "other" categories were non-Hispanic. Adapted from the Centers for Disease Control and Prevention; available at: <http://www.cdc.gov/nchstp/dstd/dstdp.html>.

clinical and laboratory services, and (5) enhanced health promotion. Providers can play pivotal roles in all of these strategies, but have most obvious roles in providing clinical services and enhancing health promotion. Providers should assess high-risk sexual behavior, deliver client-centered prevention messages, link with local health departments for follow-up and contact tracing, and maintain current clinical practices regarding the diagnosis and treatment of syphilis.

Specific recommendations for diagnosis and treatment of syphilis are available (CDC, MMWR, 1998; <http://www.cdc.gov/nchstp/dstd/dstdp.html>). These include information on the clinical presentation of syphilis in HIV-infected persons, interpretation of serologic tests (for diagnosis and for evaluation of the effectiveness of treatment), evaluation for neurosyphilis, treatment (including that for penicillin-allergic patients), and recommendations for follow-up after treatment. Certain issues are specific to HIV-infected persons, particularly the range and rapidity of the development of clinical signs and symptoms following syphilis infection, index of suspicion and evaluation for neurosyphilis, and more intensive follow-up with serologic testing after treatment.

Summary

Providers of care for HIV-infected persons can and must play prominent roles

in the prevention of HIV infection and elimination of tuberculosis and syphilis by (1) being aware of and practicing according to updates in prevention, screening, and treatment guidelines; (2) sharing knowledge regarding effective prevention and screening with others; (3) establishing referral and reporting linkages with experts in local health departments; (4) documenting activities for the prevention, screening, and treatment of these illnesses; and (5) including the evaluation of these prevention and elimination activities as part of quality improvement activities.

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Perspectives

The HIV Pandemic: Worldwide Perspective and Focus on the United States

At the International AIDS Society-USA course in Atlanta in February, 2001, Harold W. Jaffe, MD, discussed current worldwide HIV disease epidemiology, several aspects of disease trends in the United States, and prevention goals of the Centers for Disease Control and Prevention for 2000 to 2005.

Global Burden of Disease

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that approximately 36.1 million persons worldwide were living with HIV/AIDS as of the end of 2000. Disease in Sub-Saharan Africa and South and Southeast Asia accounts for approximately 85% of the total global burden; disease in North America is estimated to account for less than 2.5% of the worldwide total. There were approximately 15,000 new HIV infections per day in 2000. More than 95% of these infections occurred in developing countries. Approximately 1700 per day occurred in children under age 15 and approximately 13,000 per day occurred in persons in the 15 to 49 year age group, with 47% of these infections being in women and more than half occurring in individuals aged 15 to 24 years.

According to 1999 World Health Organization data, HIV/AIDS was tied with chronic obstructive pulmonary disease as the fourth leading cause of mortality for 1998 (4.2%), after ischemic heart disease (13.7%), cerebrovascular disease (9.5%), and acute lower respiratory infection (6.4%). In Africa, HIV/AIDS accounted for 19% of deaths in 1998, making it the leading cause of mortality on the continent. It is estimated that 13.2 million HIV-seronegative children had lost their mother or both parents to

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AIDS before the age of 15 years as of the end of 1999 (UNAIDS, 2000), with AIDS orphans in Sub-Saharan Africa accounting for the vast majority of this number. Life expectancy at birth has decreased markedly in many African nations; experts project that life expectancy in Botswana, which has one of the highest infection rates worldwide, will be approximately 29 years by 2010.

Heterogeneity of Infection Rates in Africa and International Disease Trends

Areas of Sub-Saharan Africa exhibit a wide variation in estimated HIV infection rates, ranging from less than 0.5% to greater than 36% in young adults. Factors that contribute to this heterogeneity likely include (1) between-region differences in sexual behavior (eg, age at first intercourse, number of partners, frequency of contact with commercial sex workers); (2) frequency of other sexually transmitted diseases (eg, ulcerative genital diseases such as chancroid, syphilis, and herpesvirus infection); (3) frequency of other infections that may increase susceptibility to HIV infection by acting as immune activators (eg, tuberculosis, schistosomiasis); and (4) circumcision practices. With regard to circumcision, recent data from a study in Uganda indicate that lack of circumcision is associated with increased risk of genital ulcer disease and may constitute an independent risk factor for HIV infection. In addition, there is some evidence to indicate that biologic differences among HIV-1 subtypes may be associated with differences in transmissibility. Although definitive evidence is lacking, there is some speculation that subtype C, the predominant subtype in southern Africa, is more readily transmissible than other subtypes.

Although the highest HIV/AIDS prevalence rates are in the countries in

Sub-Saharan Africa, the most rapid increase in infection rates currently is observed in the former Soviet Union. Data on cumulative HIV infections in Russia through 1999 indicate an increase from approximately 1000 in 1995 to approximately 15,000 in 1999, with most infections being attributed to injection drug use.

One example of prevention program success comes from experience documented by Centers for Disease Control and Prevention (CDC) and Thai investigators in Chiang Rai, a province of northern Thailand with a population of 1.2 million (Kilmarx et al, AIDS, 2000). Although the first cases of HIV disease were not reported in Thailand until 1988, an explosive spread of infection, particularly in northern Thailand, resulted in rates that were the highest in Asia within a short time. Epidemiologic investigation indicated a central role of commercial sex in transmission in Chiang Rai. Data from 1992 showed that there were 1177 female sex workers in 169 brothels in the province, with these women having high rates of sexually transmitted diseases. Data from 1991 indicate that 75% to 81% of male Thai army conscripts in the region had had sexual contact with female sex workers.

In response to the rapid spread of infection, the Thai government undertook an educational campaign through the mass media and in schools in the late 1980s. In 1991, it implemented the "100% condom" program, which included enlisting the cooperation of sex workers and brothel owners to enforce condom use in all sex acts, using police sanctions against establishments in which sexually transmitted diseases were detected (prostitution is technically illegal in Thailand), and distributing of 1.2 million free condoms per year. As a result of this initiative, rates of reported sexually transmitted diseases decreased by 59-fold between 1989 and 1999, from a high of 725.5 to 12.2 per

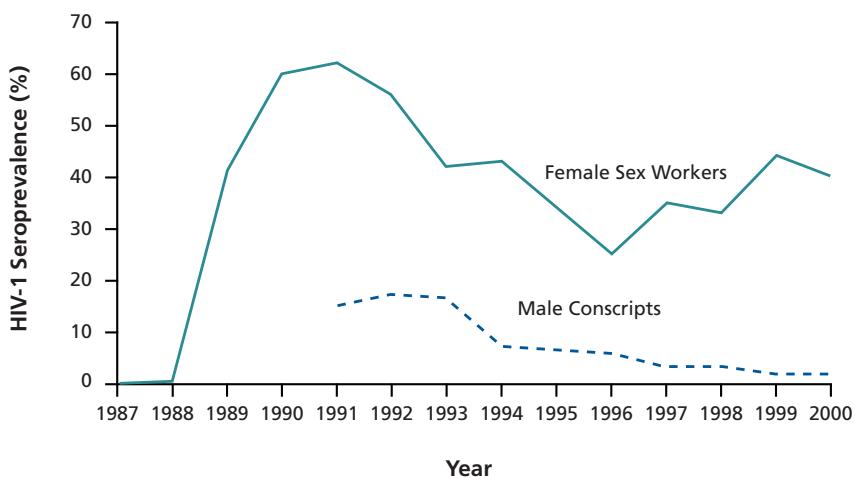


Figure 1. HIV-1 seroprevalence among female sex workers based in brothels (solid line) and among male army conscripts (dashed line) in Chiang Rai, Thailand, 1987 to 2000. (In 2000, prevalence was measured among conscripts in May only.) In 1991 the Thai government implemented its “100% condom” program. Adapted from Kilmarx et al, *AIDS*, 2000.

100,000 population. HIV-1 seroprevalence decreased from a high of 62% among female sex workers in 1991 to a low of 25% in 1996; the rate has subsequently increased to approximately 40% in 2000 (Figure 1). At the same time, HIV-1 seroprevalence among male army conscripts decreased from a high of 17.3% in 1992 to less than 2% in 2000. These findings should provide hope that it is possible to positively affect infection spread through the combination of science-based prevention and political initiative.

HIV-1 subtype B is the predominant virus in infection in North America. The potential for encountering HIV-1 infection with viral subtypes other than type B or HIV-2 infection raises some diagnostic and therapeutic issues for US physicians. Although HIV-1 antibody tests reliably detect antibody to all known subtypes of HIV-1, at least some of the commercially available tests do not reliably detect HIV-2 infection. Individuals with signs or symptoms suggestive of HIV infection who come from West Africa or who report sexual contact with someone from West Africa, the region to which HIV-2 infection appears largely confined, should undergo testing with a “Combi-test”; these tests, used in US blood banks, reliably detects antibodies to both HIV-1 and HIV-2. Commercial viral load assays do not reliably quantify HIV-2, although a pro-

totype assay is available on a “research test only” basis (Roche Diagnostics, Indianapolis, Ind). For measurement of viral load of non-subtype B HIV-1, the Quantiplex version 3.0 (Bayer Diagnostics, Tarrytown, NY) is commercially available, although not approved by the US Food and Drug Administration. Also available on a “research test only” basis is Amplicor version 1.5 (Roche Diagnostics, Indianapolis, Ind).

With regard to therapeutic implications, limited available data indicate that response to potent antiretroviral therapy is similar in infections due to subtype B and those due to non-B subtypes; antiretroviral resistance mutations are generally similar among viral subtypes. Very few data are available on treatment of HIV-2 infection, in part because it is often untreated due to the low rate of disease progression. However, it is known that HIV-2 is intrinsically resistant to currently available nonnucleoside reverse transcriptase inhibitors, and these agents should thus not be used in attempts to treat HIV-2-infected patients.

US Disease Trends

Data from the CDC on reported AIDS cases and deaths in the United States through June 2000 indicate totals of 745,103 cases and 433,709 deaths in adults and adolescents and 8804 cases and 5086 deaths in children. Among 46,137 adult and adolescent AIDS cases reported in 1999, 66% occurred in black or Hispanic persons and 23% occurred in women; 44% of men with AIDS reported sex with men as their only risk factor. Figure 2 shows numbers of AIDS cases and deaths by quarter-year and preva-

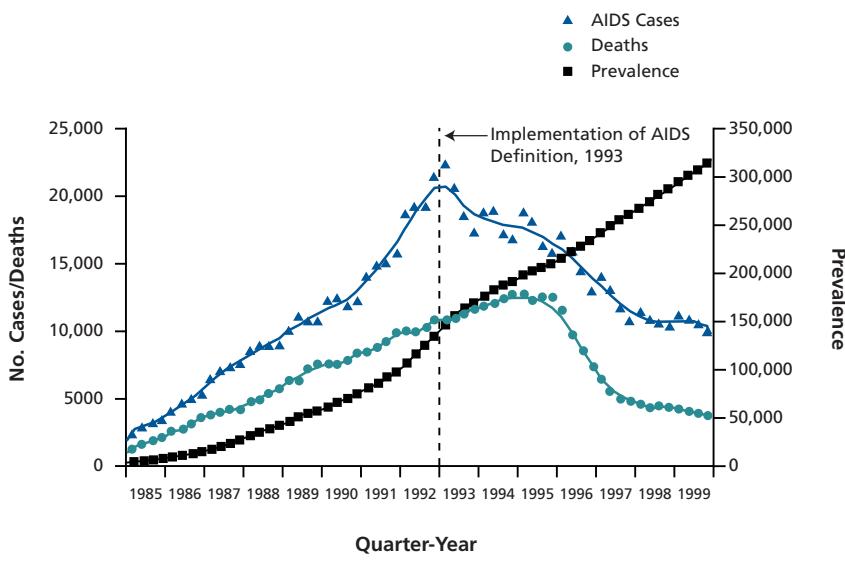


Figure 2. Estimated incidence of AIDS and AIDS deaths and number of persons living with AIDS (prevalence) by quarter year from 1985 to 1999 (adjusted for reporting delays). Adapted from Centers for Disease Control and Prevention, AIDS surveillance-trends L207 slide series, available at <http://www.cdc.gov/hiv/graphics/trends.htm>.

lence of AIDS (number of individuals living with AIDS) between 1985 and 1999. The trends in reported AIDS cases may be distorted because of an expansion in the AIDS case definition in 1993. Nonetheless, the number of cases per quarter has declined since 1993 and the number of deaths per quarter began declining around 1996, when potent antiretroviral therapy became broadly available. Rates have appeared to plateau at about 10,000 cases and 4000 deaths per quarter; with the reduction in mortality and continued accumulation of new infections, the number of persons living with AIDS continues to increase, reaching approximately one third of a million in 1999.

Cases of perinatally acquired AIDS have decreased from a peak of more than 200 per quarter in 1992 and 1993 to less than 200 per year in 1999. This decrease is associated with the dramatic increase in use of antiretroviral therapy in HIV-infected pregnant women or their infants. Data on rates of such use from 34 states indicate an increase from approximately 10% in 1993 to 80% or more in 1997 to 1999. Many of the cases of lack of treatment of the mother or infant are associated with not knowing the infection status of the mother. To aid in achievement of the goal of eliminating perinatal transmission in the United States, increased efforts at determining infection status of pregnant women are

needed. Although early identification of infection is optimal, such efforts may include use of new technology for rapid testing during labor.

Table 1 shows distribution of AIDS cases reported in 1999 in metropolitan and nonmetropolitan areas by geo-

Alabama between 1995 and 1997 indicates that the high-risk behaviors exhibited in rural settings are the same as those in urban settings. Slightly more than half of those with HIV infection were homosexual or bisexual men, with the remainder of the population consisting of equal proportions of heterosexual men and heterosexual women. During the period in which infection was presumed to occur (between last seronegative HIV test or 1981 and first seropositive HIV test), 45% of these persons resided only in nonurban Alabama; 19% used crack cocaine, 18% exchanged sex for money or drugs, and 13% injected drugs. The proportion of infected individuals who practiced such high-risk behaviors and who lived usually or exclusively in nonurban settings increased over time.

Findings in such studies suggest that individuals may have acquired infection in urban settings earlier in the epidemic and then returned to their more rural places of residence, establishing networks of HIV transmission in their communities with sex and needle-sharing partners. Figure 3 shows a sex network identified in a CDC investigation in a small community in Mississippi (MMWR, 2000). The investigation began in early 1999 with the diagnosis of HIV infection in 2 individuals as part of a routine sexually transmitted diseases evaluation, and eventually identified 44 involved individuals, all of whom were African American, including 7 with HIV infection. The infected men had an average age of 25 years and the median age among the 5 women in the cluster was 16 years. Only 2 of the infected individuals knew that treatment exists for HIV infection.

There is also reason for concern regarding increased risk behavior among homosexual men, given a number of reports of increases in sexually transmitted diseases in this population in several locales. A marked increase of syphilis cases predominantly involving homosexual men in Seattle and King County, Washington, was observed in 1998 and 1999 (CDC, MMWR, 1999), at a time of a record low national incidence of syphilis; many of the affected individuals in this outbreak also have HIV infection. A similar outbreak of syphilis has been observed among homosexual men

The considerable number of AIDS cases in US rural populations indicates the need for special emphasis on HIV prevention in such settings

graphic region of the United States. HIV disease predominantly affects urban populations. However, the reporting of a considerable number of cases in rural populations indicates the need for special emphasis on prevention in such settings. One study by Beltrami and colleagues (*South Med J*, 1999) among 417 persons receiving HIV services in rural

Table 1. AIDS Cases Reported in 1999 by Size of Place of Residence and by Geographic Area

	Metropolitan Area >500,000 Population (%)	Metropolitan Area 50,000- 500,000 Population (%)	Nonmetropolitan Area (%)
Northeast: n=14,006*	91.1	5.8	3.0
North Central: n=433*	79.3	11.8	8.7
South: n=18,770*	71.6	15.0	11.7
West: n=7887*	90.0	6.2	3.8

*Includes AIDS cases with unknown metropolitan area of residence. Unpublished data from Centers for Disease Control and Prevention.

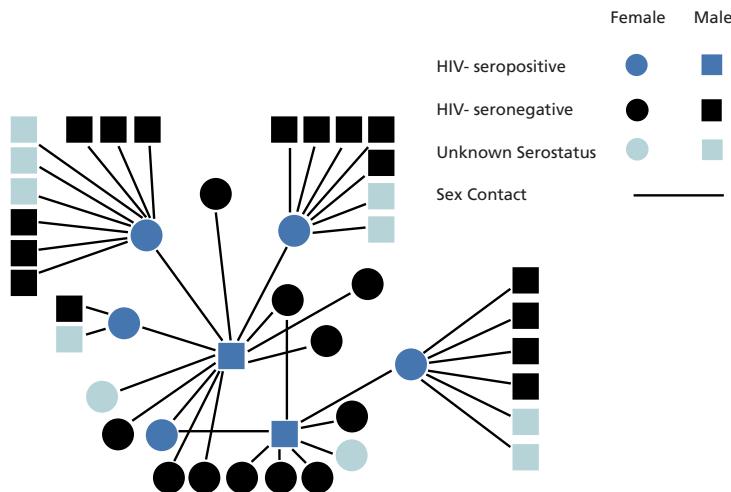


Figure 3. Sex networks of HIV-infected adolescents and young adults in a nonurban community in Mississippi. Shown are sex contacts among 44 individuals who were HIV-seropositive, HIV-seronegative, or had unknown HIV-serologic status. Adapted from Centers for Disease Control and Prevention, MMWR, 2000.

in Southern California. Cases of rectal gonorrhea and rectal chlamydia infection in homosexual men in Seattle and King County also increased by 2-fold or more between 1997 and 1999; a similar increase in cases of rectal gonorrhea in homosexual men in San Francisco occurred between 1994 and 1998 (CDC, MMWR, 1999). Increases in such sexually transmitted diseases have also been observed in such cities as Chicago and Washington, DC.

Although certainly worrisome, these trends in sexually transmitted diseases may not necessarily indicate increasing rates of HIV transmission. For example, the use of antiretroviral therapy may be reducing the infectiousness of persons engaging in high-risk behaviors. However, preliminary data from a study of almost 3000 young homosexual men from 6 American cities indicated an overall HIV prevalence of 13% and incidence of 4.4%. Infection rates in black and Hispanic participants were even higher (CDC, MMWR, 2001).

The factors underlying these trends are unclear, but may include the beliefs that HIV disease is now curable and that infected persons receiving treatment are not infectious, as well as fatigue with safer sex messages and practices. Whatever the reasons for these outbreaks, the possibility of a resurgence of the HIV epidemic in the male homosexual popu-

lation should be met with renewed prevention efforts.

CDC HIV Prevention Goals for 2000 to 2005

The CDC has established 3 domestic HIV prevention goals to be met by 2005. The first is to reduce the annual incidence of new HIV infection by 50% from the current level of approximately 40,000 per year. The second is to increase the proportion of infected persons who know of their HIV serologic status to 95% from the current estimated level of 70%; such new technology as rapid HIV tests may help in this regard. Finally, it is hoped that by 2005 the proportion of infected persons who are linked to appropriate health care can be increased to 80% from the current level of 50%. Although these goals may appear modest, their achievement will require a substantial increase in commitment to prevention on the parts of affected communities and their health care providers and both government and nongovernment agen-

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Questions to and Answers from the International AIDS Society–USA Antiretroviral Guidelines Panel

From the 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina

The International AIDS Society–USA Antiretroviral Guidelines Panel was initially convened in 1995 when several advances in knowledge regarding HIV biology, monitoring, and treatment were emerging. The Panel continues to update its recommendations for antiretroviral therapy for adult HIV-1 infection based on new information and drugs that are available.

It is presently known that the most effective care requires individualized management and ongoing attention to relevant scientific and clinical information in the field. At the 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina, the Panel was convened to discuss evolving guidelines with an international audience of scientists and clinicians. As has been done in past issues of Topics in HIV Medicine, the Panel collected questions from the audience. Individual Panel members have provided

their answers and opinions on the issues raised by the conference attendees. Many questions were addressed based on what is known about antiretroviral drugs through clinical trials, HIV patient care, and basic science. The importance of adherence, emerging long-term complications of therapy, recognition and management of antiretroviral failure, new monitoring tools, and continued evolution of the thresholds for starting antiretroviral therapy are among the most current topics of discussion in the field. In addition to the Antiretroviral Guidelines Panel members who were in Buenos Aires, we were honored to have Dr Pedro Cahn, Chair of the conference, participate in the Panel discussions.

The Panel is preparing an update of its guidelines, which will be submitted for publication in the peer-reviewed literature shortly.

Question 1: Is it still recommended that primary infection be treated, and if so, for how long, and then what?

Dr Hirsch: The rationale for treating primary HIV-1 clinical syndromes is to optimize the chances of maintaining HIV-1-specific CD4+ helper T cells, which are the major targets for HIV infection as well as the principal cells involved in orchestrating host responses against the virus. Once these cells are lost because of infection, the likelihood of developing and maintaining effective anti-HIV cytotoxic T cell responses is greatly diminished. Aggressive therapy during primary HIV-1 infection has been shown by Rosenberg and colleagues to result in maintenance of HIV-1-specific CD4+ T cells (Rosenberg et al, *Science*, 1997). Whether this translates to longer disease-free survival

is not known. The theoretical benefit of early therapy in this situation must be weighed against the known toxicities and costs of the drugs to be used.

If it is chosen to begin therapy during the acute HIV syndrome, the goal is to inhibit virus replication as completely as possible (ie, plasma HIV-1 RNA levels below the limits of detection of the assay). How long treatment must be continued is unknown, and studies of supervised treatment interruptions in such patients are underway (Rosenberg et al, *Nature*, 2000).

Dr Cooper: The data on preservation of HIV-specific immunity by treating primary HIV infection are very compelling. In order to verify these outcomes we urgently need data from controlled clinical trials. Therefore, where possible, care providers should encourage their

patients to enroll in clinical studies. Unfortunately, because of lack of patient and provider awareness, this phase of the illness is often missed. If this concept is proven, then the major public health issue becomes the identification of persons with primary infection by increasing surveillance and awareness by use of the detuned HIV antibody assay, for example. More recently there has been concern about transmission of drug-resistant virus, so resistance testing may have to be considered in order to optimize the initially selected antiretroviral therapy.

Question 2: Under what clinical conditions would you use a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen for initial therapy?

Dr Schooley: At this point I do not think there are any well worked out

clinical situations in which I would not plan to use nRTIs as part of an initial regimen. Several studies are underway or have been completed in which nRTIs have been avoided. In general, these studies have used a nonnucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor. Virologic results have been reasonable in these limited studies, with roughly 60% of patients with levels of HIV-1 RNA below detection at 24 weeks. Whether this approach will be more widely used in the future will depend on the extent to which the nRTI studies currently underway prove to provide durable suppression of viral replication and what we learn about longer-term effects of nRTIs. Until these data are available, nRTI-sparing initial regimens should probably be reserved for research settings.

Dr Yeni: A very uncommon situation could be the case of a patient with acute infection, contaminated with a virus with broad nRTI cross-resistance. In such a case, however, an NNRTI/protease inhibitor combination is not meant to “spare” nRTIs, but only to provide the patient with active drugs. There is no general recommendation for nRTI-sparing regimens for initial therapy.

Question 3: Is the rate of rise in HIV RNA level an important factor in choosing when to start therapy? This has not been mentioned in the discussions so far; the emphasis seems to have switched back to absolute CD4+ cell levels.

Dr Carpenter: Many clinicians feel that the rate of rise of HIV RNA is an indication for more frequent monitoring of the CD4+ cell count level, as a rapid rise in HIV RNA level does predict the likely rate of fall of the CD4+ cell count. However, a rapid rise of HIV RNA level is not, in itself, an indication to recommend treatment of HIV infection, as long as the CD4+ count remains above 350 cells/ μ L. If the CD4+ count is less

than 350 cells/ μ L, in the face of a rapid rise in HIV RNA to a level above 60,000 copies/mL, many physicians would initiate antiretroviral therapy. You are correct in stating that the absolute CD4+ cell count level is now considered the most important laboratory guide to initiation of antiretroviral therapy, whereas the HIV RNA level alone is no longer considered to be an independent indicator for initiation of therapy.

Dr Hirsch: HIV replication, as measured by plasma viral load, and immunologic deterioration, as measured by CD4+ cell count, are closely linked. Although absolute CD4+ cell counts are the best immediate predictors of progression risk, the rate of HIV RNA level rises should also be monitored closely. In an individual with CD4+ cell counts between 200 and 350/ μ L, a rising viral load, particularly in the range above 60,000 copies/mL, would encourage me to initiate therapy before further declines in CD4+ cell counts occur.

Question 4: What would be the ideal dose of indinavir? Would the Panel advise indinavir 400 mg plus ritonavir 100 mg twice a day in order to decrease toxicity? Would the indinavir dose work considering the pharmacokinetic profile?

Dr Saag: The original FDA-approved dose of indinavir was 800 mg by mouth every 8 hours. This dose was best absorbed if given 1 hour before or 2 hours after meals but, even under these optimal conditions, there was substantial interpatient variability. Several pharmacokinetic studies have now demonstrated markedly improved pharmacokinetic parameters of indinavir when given with low-dose ritonavir (100-200 mg). This “boosted” dosing strategy allows twice-daily dosing, without food restrictions, and is associated with much less interpatient variability. Although the optimal dosing is yet to be fully worked

out, most clinicians use a 100 mg (ritonavir)/800 mg (indinavir) dose given every 12 hours. When absorption is thought to be suboptimal, 200 mg of ritonavir might be used, but this dose is associated with more gastrointestinal adverse effects. Boosted indinavir doses of 800 mg twice daily are associated with higher peak (C_{max}) concentrations, which may result in a higher incidence of nephrolithiasis. Indinavir doses less than 800 mg (such as the 400 mg dose mentioned in the question) are associated with lower trough levels at the end of the dosing interval that are subtherapeutic and cannot be recommended.

Question 5: Would you recommend stavudine before zidovudine or vice versa? Why?

Dr Volberding: Stavudine and zidovudine are each extremely useful nRTIs and find their way into the care of essentially every HIV-infected patient. The drugs have comparable potency, and more cross-resistance than previously appreciated. The toxicity problems are relatively distinct, but each may cause adverse effects through mitochondrial damage. Zidovudine commonly causes anemia or neutropenia. Both drugs cause a benign macrocytosis. Although zidovudine has been associated with myositis, stavudine can cause peripheral neuropathy. Lipodystrophy and lactic acidemia may be caused by either drug, but stavudine is implicated in more reports.

The choice of which to use first arises in each patient beginning initial therapy, as one of these is employed in almost all common antiretroviral regimens. Zidovudine and stavudine have antagonistic effects and should never be used simultaneously. The choice of one or the other is based primarily on expected tolerance, toxicity, and underlying medical problems that may increase the probability of spe-

cific adverse effects. Both are good drugs and it is not possible in most cases to express a strong preference of one over the other.

Webcasts of selected presentations given at the 1st IAS Conference on HIV Pathogenesis and Treatment are available at:

http://www.aids2001ias.org/aids2001asp/webcast_FrameBusqueda.asp.

Dr Yeni: It is now demonstrated that zidovudine and stavudine share common virus resistance patterns, leading to cross-resistance. Therefore, from a virologic point of view, there is no clear reason to prefer a zidovudine-then-stavudine sequence to a stavudine-then-zidovudine sequence. The choice of one or the other to start with will be dictated by underlying medical problems (eg, peripheral neuropathy) that could be predictive of a risk of toxicity higher with one drug than with the other.

Question 6: What are the nRTI combinations that should be used with protease inhibitors or NNRTIs in naive patients?

Dr Gazzard: As initial treatment often fails it is likely that a sequence of nRTIs will be given during the life span of an HIV-infected patient. The best nRTI backbone to be used first to give the optimum chance of the second regimen being successful is currently unknown and requires strategic trials. It was initially thought that mutations in the reverse transcriptase part of the viral genome following exposure to one member of the nRTI class did not reduce sensitivity to other members of this class. However, it is now clear that the accumulation of successive mutations in reverse

transcriptase, as a result of continuing drug therapy despite virologic failure, does reduce the likely effectiveness of the second nRTI backbone with subsequent therapy.

Dr. Montaner: It is easier to decide the right nRTI combination for a given patient than to give a broad recommendation regarding this issue. In general we rarely use zalcitabine because of its significant potential for neurotoxicity and the need for 3-times-a-day administration. There are in vitro data which suggest that stavudine and zidovudine should not be given in combination. In a recent clinical trial this concern was at least partially substantiated. There is recent evidence of increased toxicity when stavudine and didanosine were used together and therefore we are less enthusiastic about this combination at the present time. We tend not to recommend abacavir and nevirapine together as initial therapy because there is evidence that the nevirapine rash may complicate the management of suspected abacavir hypersensitivity. Most of the experience for initial therapy has been accumulated regarding zidovudine plus lamivudine, or stavudine plus lamivudine. Both of these combinations are very popular in our clinic. Zidovudine plus didanosine has been extensively studied in the past but issues of palatability related to the didanosine formulation had precluded widespread use of this combination. More recently, with the availability of an enteric-coated formulation of didanosine, this has been circumvented and in fact the newer formulation allows for once-daily dosing, which is particularly attractive for certain patients. Despite the limited data available for abacavir in the initial regimen, this agent has worked well, particularly with lamivudine or as part of a zidovudine and lamivudine triple combination. Finally, the likelihood of potential toxicities will ultimately help us to decide what is the best

backbone nRTI combination for a given patient.

Question 7: What do you think about stavudine/didanosine/efavirenz compared with zidovudine/lamivudine/efavirenz?

Dr Cahn: I am not aware of large randomized controlled trials comparing these combinations. Some clinicians may prefer the zidovudine/lamivudine option, based on simplicity of the twice-a-day schedule with the fixed-dose formulation, and tolerability issues regarding didanosine. With the new formulation of didanosine (enteric coated), the stavudine/didanosine option has improved greatly. In the future, with more information regarding mitochondrial toxicity available, these options may or may not be influenced by safety issues.

Dr Hirsch: Studies comparing these 2 regimens are currently underway (eg, AIDS Clinical Trials Group [ACTG] study 384), and results will be available in 2002.

Question 8: What are the preferred protease inhibitor combinations?

Dr Cooper: Combination protease inhibitor therapy has been used in 2 main ways. In the first situation small doses of ritonavir (usually 100 mg bid) are used to boost the plasma concentrations of the active protease inhibitor by inhibiting cytochrome P450 3A4, the major isoenzyme responsible for protease inhibitor metabolism. Protease inhibitors that can be boosted in this way are saquinavir (generally dosed at 1000 mg bid), indinavir (800 mg bid), amprenavir (600 mg bid), and lopinavir (400 mg bid coformulated with ritonavir). Usually the plasma trough levels of the protease inhibitor are greatly enhanced above the IC₉₀ level for the virus through all of the dosing inter-

val. This is much more reliable than single protease inhibitor use. Nonetheless, pharmacokinetic monitoring is recommended especially if additional drugs that affect cytochrome P450 metabolism are used.

The second way of using double protease inhibitors is as a combination in which both drugs are given at doses that have anti-HIV activity. Given the ability of some protease inhibitors to salvage a failing protease inhibitor regimen, this is a biologically plausible approach. It has been well studied for ritonavir/saquinavir and to a lesser extent for ritonavir/indinavir but there is no good evidence to prove that double protease inhibitor-based regimens are superior to single protease inhibitor-based regimens.

Question 9: Given the recent data presented at this meeting, what is the role of hydroxyurea in the management of HIV-infected individuals?

Dr Montaner: As pointed out by Murphy and colleagues (Abstract 450) from Northwestern University, the results of the 3D study seem to offer some hope that we may be able to define the role of hydroxyurea as an adjuvant in selected groups of patients, particularly in the context of drug-resistant viruses. In the 3D study, treatment-experienced patients randomized to hydroxyurea had better virologic outcomes despite higher toxicity rates. Hydroxyurea blunted the absolute CD4+ cell count responses but not the CD4+ percentage increases. Lower doses of hydroxyurea should be considered for further study in treatment-experienced patients with virologic failure in order to determine if we can retain the virologic effect but avoid the excess toxicity seen in the 3D study. Until these issues are resolved, the use of hydroxyurea should be limited to the experimental setting.

Dr Richman: It is important to emphasize no proven role for

hydroxyurea has been identified. Although it does appear to show virologic benefit in some studies, it does blunt CD4+ responses and it does have significant toxicity.

Question 10: When would the Panel recommend treatment interruption for a patient who is not experiencing adverse events, has good tolerance, and has a viral load below 50 copies/mL? All trials about this issue show increased viral load (though not significant increases). But a viral load of below 50 copies/mL is not the same as a viral load above 1000 copies/mL.

Dr Saag: The situation where treatment might be interrupted in a patient with good tolerance, no adverse events, and a viral load less than 50 copies/mL is when the patient had originally been started on treatment (years ago) with a viral load and CD4+ cell status that would clearly not warrant initiation of treatment today. In 1996, the mantra for the initiation of therapy was to “treat early, treat hard.” This was based in large part on the concept that complete blocking of viral replication could lead to eradication of HIV within 3 to 4 years. More recent evidence suggests that even a complete block, sustained for up to 60 years, will not lead to eradication of all latently infected cells from the body.

With the increasing recognition of long-term complications of therapy, including the potentially fatal (though rare) cases of lactic acidosis, many clinicians are now suggesting that patients whose original baseline CD4+ counts were over 500 cells/ μ L (and especially if their original viral load value was low, eg, <20,000 copies/mL) consider stopping therapy and going on a “supervised” treatment interruption.

Strong emphasis should be placed on the supervised nature of this interruption. Once patients stop therapy, checks of CD4+ counts and viral load values should be

made monthly for 2 to 3 months and then every other month for 6 months in order to assure there is no precipitous decline or increase in CD4+ counts or viral load, respectively.

Dr Gatell: Treatment interruptions should be considered clinical research, not routine clinical practice, and only performed in the setting of well controlled clinical trials. In responding patients (viral load <50 copies/mL), interruption may be considered when the actual CD4+ cell count is above the current recommendation for initiation of antiretroviral therapy, and the situation is even better if the lowest CD4+ cell count has never been below the current recommendation for initiation of antiretroviral therapy.

If antiretroviral therapy is interrupted, viral load most likely will rebound and this may represent an increased likelihood of HIV transmission in cases of unprotected risk practices. This public health concern should be balanced with the potential individual benefit associated with less drug exposure.

Question 11: In my 13 years of experience in the Johannesburg Hospital HIV Clinic, I have noticed that a significant number of patients (approximately 7%-10%) have a steady decline in CD4+ cell numbers for 4 to 6 years from about 200 to 300/ μ L or so and then stabilize after a few years at a lower level. Why does this happen?

Dr Schooley: It is difficult to answer this question without knowing whether you are referring to patients who are on or off antiretroviral therapy and, if on therapy, the extent to which viral replication has been controlled. If you are speaking of a situation with patients on optimal viral suppression (ie, with HIV-1 RNA levels <20-50 copies/mL) over the period in question, I would have to say that most patients I have encountered have either had stable

or gradually rising CD4+ cell counts and a noticeable decline over the long term has been an unusual experience.

Dr Cooper: This observation that you have made is inconsistent with the known natural history of HIV disease. Untreated persons with HIV infection lose approximately 50 to 60 CD4+ cells/ μ L per year. The rate of decline is steady until in some patients there is a change from non-syncytium-inducing to syncytium-inducing viral phenotype when the rate of decline often accelerates. In some patients the biological noise generated by frequent measurement of CD4+ cell counts may give the false impression of stabilization. I am unaware that HIV-infected populations in the developing world have different CD4+ count trajectories but clearly your observation should be followed up with more prospective data.

Question 12: Is it justified to put a patient with CD4+ cell count of 284/ μ L and plasma viral load of 72,000 copies/mL on highly active antiretroviral therapy (HAART)? In India, we would wait and watch without HAART and I think the patient would do better in the long run. We would initiate HAART when his CD4+ cell count declines to below 200/ μ L and his HIV RNA is 100,000 copies/mL.

Dr Richman: Not only is it justified, it is recommended. Data from the Multicenter AIDS Cohort Study (MACS) would predict that patients with more than 30,000 copies/mL of HIV RNA plasma lose on average 76 CD4+ cells/ μ L per year. This patient is entering the range of CD4+ cell count values in which the risk of AIDS-related diseases begins to increase. Thrush, infections with herpesviruses, and other symptomatic complications also develop in such patients. The risk of delaying therapy also includes a diminished probability that the treatment will produce a viral load response to

below detection limits of the assay. The ability of treatment to produce an HIV RNA level below detection limits progressively diminishes with lower CD4+ cell counts and higher HIV RNA values. It should also be pointed out that the patient's HIV RNA value may not significantly increase in the absence of treatment. Many patients die whose HIV RNA values have never exceeded 100,000 copies/mL. The value of HIV RNA determines the rate of CD4+ cell decline, but a low CD4+ count (eg, 100 cells/ μ L) confers the same risk whether it was achieved quickly or slowly.

Dr Hirsch: Patients who have CD4+ cell counts below 200/ μ L and HIV RNA levels above 100,000 copies/mL are at substantial risk for rapid progression. A CD4+ cell count of 284/ μ L with a plasma viral load of 72,000 copies/mL is getting dangerously close to those thresholds, and large cohort studies suggest that therapy is indicated at those levels. Other factors, such as patient preferences and rate of change in CD4+ cell counts or viral loads, should also be considered.

Question 13: How would you manage a patient who has been HIV-seropositive for 15 years, and has taken almost all medications, including zidovudine, lamivudine, stavudine, indinavir, nelfinavir, amprenavir, efavirenz, and adefovir? Now the patient is on lamivudine/stavudine/efavirenz/amprenavir/ritonavir. Genotype results show resistance to all drugs except lopinavir and adefovir. Viral RNA is rising from below 50 to about 10,000 copies/mL and CD4+ cell count is stable at 400/ μ L. What do you recommend?

Dr Saag: In order to best answer this question, it is important to know what was the patient's original baseline (pretreatment) HIV RNA value. If the current viral load is more than 0.5-log (3-fold) below the pretreatment value, there is strong

evidence that the patient is not likely to progress clinically over the next 3 to 6 months. In this instance, it is very reasonable to continue the patient's current regimen. The principal risk to this approach is the likelihood that further resistance-conferring mutations will accumulate; however, since this patient has already developed a virus with multiple resistance mutations, the prevention of resistance development is no longer the primary goal of therapy and prevention of clinical progression is now the sole objective. In many clinical situations such as this, the pretreatment viral load value is not known. In that setting, the patient could either stop therapy for 2 to 4 weeks to roughly establish the viral load "set point" (natural baseline) for that patient or the patient could continue with the current regimen until there is some decay in the CD4+ cell count.

Either approach is acceptable, though with the latter it is important to check CD4+ cell counts more often, eg, every 6 to 8 weeks. If it is decided to change the regimen, my approach would be to anchor the regimen with the 2 agents with the highest degree of susceptibility (in this case, lopinavir and tenofovir, if available, which may have a resistance profile similar to the no-longer-available drug adefovir) and fill out the regimen with other agents that the patient has tolerated well in the past. In either scenario, it is critical to discuss options with the patient and chart the course together.

Dr Montaner: It should be noted that prior exposure to most or all medications and even cumulative evidence of viral load rebound with all available medications will not preclude achieving a sustained plasma viral load level below detection with the use of multidrug therapy. This approach has been applied in our clinic with considerable success. We generally think that in the absence of a clear therapeutic option, in a patient who is at high

risk for short-term disease progression with evidence of 3-class resistance and objective evidence of viral load rebound with most if not all available drugs, a therapeutic trial with multidrug rescue therapy may be considered. Obviously, the patient's preference as well as comorbidities and history of toxicity should be considered carefully before undertaking such a course of action.

Question 14: When would you consider initiating an STI? At what viral load and CD4+ cell count? When would you reinitiate therapy and at what viral load or CD4+ cell count? When you reinitiate, would you go back to the initial regimen?

Dr Volberding: Structured or strategic treatment interruption (STI) has raised many practical and theoretical questions. As a way of re-exposing the immune system to HIV antigens after periods of prolonged suppression on successful antiretroviral therapy, STI becomes a form of auto-vaccination. This strategy has worked well in a preliminary study in patients with acute or extremely recent HIV infections. The results in established infection have been less promising. I would not recommend STI in these patients outside of carefully controlled clinical trials.

Another form of STI is to temporarily stop antiretroviral drugs in patients with advanced virologic failure in whom HIV has become resistant to all drugs. Here, STI is used to allow an overgrowth of drug-selective, wild-type HIV. Although this strategy may allow a brief period of resuppression of virus, failure occurs rapidly unless new drugs that do not have cross-resistance can be used.

A final type of STI, named structured intermittent therapy (SIT), has recently been suggested by National Institutes of Health investigators. Here, therapy is used intermittently, for example on alternate weeks, simply to decrease or delay cumulative

drug doses and hence toxicity. Again, this must be seen as a research strategy and cannot be recommended apart from controlled trials.

Dr Montaner: I fully agree with Dr. Volberding's overview of this very difficult topic. We think that the recent enthusiasm with regard to the use of STI should be tempered by the lack of efficacy data and more importantly safety data in support of it, particularly as it pertains to the long-term implications of this therapeutic maneuver. We do not routinely use STI in our clinical practice, but we have been fairly liberal in considering a patient's wishes in terms of indeterminant treatment interruptions, if a patient had started effective antiretroviral therapy with what today we would consider a relatively benign laboratory profile. Data from our group and others have suggested that the 2- to 3-year AIDS-related morbidity and mortality rates are quite low as long as effective antiretroviral therapy is initiated at CD4+ cell counts over 200/ μ L, regardless of plasma viral load. In contrast, there is a definitive risk for toxicity and evolution of resistance, which has led us to reassess the risk-benefit ratio of aggressive early intervention with currently available therapies.

Question 15: The patient is a 44-year-old man in his fifth year of taking zidovudine/didanosine/nevirapine. Since introduction of viral load tests that detect to levels of 40 to 50 HIV RNA copies/mL of plasma, he has had detectable viremia of a few hundred copies/mL. He experimented with efavirenz but could not tolerate the drug, so he returned to nevirapine and intensified his regimen with abacavir. Detectable viremia persisted at similar levels but for the past 9 months has bounced between 400 and 8600 copies/mL with no clear trend. The CD4+ cell count is consistently stable around 300/ μ L. Two genotype test

results indicate resistance to zidovudine, didanosine, and nevirapine.

Would you recommend now changing to lopinavir/ritonavir/lamivudine/tenofovir or something else? Would you recommend changing only when viral load is clearly on a rising trend above 10,000 copies/mL or on evidence of further evolution of resistance? Or change the regimen according to some other criteria?

Dr Richman: The risks of continuing a failing regimen are the progressive increase of resistance to the nRTIs that the patient is taking and increase in cross-resistance to the whole class of drugs. Sticking with a failing regimen makes little sense unless there are limited alternatives. This patient has alternatives and if his CD4+ cell count drops significantly, he is at risk for HIV disease progression. I think your proposed regimen is as good as any, and to wait would only limit future options.

Dr Gazzard: Optimal therapy in this case is bound to remain a matter of opinion as there is no evidence base on which to guide us. The danger of continuing the present therapy is that, almost inevitably, further mutations in the viral genome will emerge that will increase the "fitness" of the virus under the selective pressure of the same drugs. This is likely to be associated with a rising viral load and a falling CD4+ count. There is no evidence that this would impede the future response to protease inhibitors.

The main issue would therefore be whether or not further mutations would reduce the sensitivity to lamivudine, to which he has not been exposed previously, or to tenofovir. Available data indicate that virus with mutations producing reduced sensitivity to nRTIs remains sensitive to tenofovir unless a codon 210 or 41 mutation emerges (associated with reduced sensitivity to zidovudine) or a codon 69 muta-

tion emerges (coding for multiple serine insertions that reduce sensitivity to all presently available nRTIs).

My view would be that in this particular individual, the CD4+ count indicates that his short-term risk of opportunistic infections is small and the risk of development of resistant mutations to lamivudine and tenofovir is also small; therefore I would continue present therapy with frequent monitoring of his CD4+ count until this showed a clearly downward trend.

Question 16: In Bolivia we only have zidovudine and zalcitabine. Can you initiate either or both of these drugs in patients with clinical symptoms? The CD4+ cell count is not accessible to everyone.

Dr Cahn: In this difficult scenario, I would defer therapy until the latest moment, which without CD4+ cell counts is to be identified by clinical symptoms (AIDS-defining diseases or oral thrush, hairy leukoplakia, unexplained fever, diarrhea, weight loss, etc).

In no case would I use either zidovudine or zalcitabine in monotherapy.

Dr Katzenstein: The best data we have in this setting is from the Delta and ACTG 175 trials where the combined use of zidovudine/zalcitabine was better than zidovudine alone. I agree with Dr Cahn that treatment with dual nRTIs in this setting should be delayed until there are clinical symptoms, to optimize the use of the drugs. If it is possible to obtain didanosine and stavudine through the sponsor's access program (publicly announced at a cost of US \$1.00/day) this combination may be a less expensive dual nRTI combination with fewer adverse effects than zidovudine and zalcitabine.

Question 17: A 50-year-old patient diagnosed HIV-seropositive has a CD4+ cell count of

100/ μ L and viral load 400,000 copies/mL. After 3 months of lamivudine/zidovudine plus indinavir, the patient's CD4+ cell count is 150/ μ L and viral load is 500 copies/mL. How should treatment proceed?

Dr Gatell: This is a patient with a fairly advanced HIV-1 disease who started triple therapy including a protease inhibitor (indinavir) with a reasonably good response at 3 months. My advice would be to continue with the same therapy and to check the situation at 6 months. If by then viral load is below detectable levels and CD4+ cell count continues to rise, one may consider the possibility of simplifying therapy depending on the tolerance and the preferences of the patient. Reasonable options to simplify might be replacing indinavir with efavirenz or with abacavir (fixed-dose lamivudine/zidovudine/abacavir).

Dr Gazzard: I think it is clear that 12 weeks on initial antiretroviral therapy is too soon to decide whether such therapy is working when the viral load was 400,000 copies/mL prior to treatment. Indeed, a viral load of 500 copies/mL would imply that the plasma virus will almost certainly fall below detectable limits within the next 4 to 8 weeks. A more difficult question is whether or not indinavir, combined with zidovudine and lamivudine, is the optimum initial regimen. Randomized controlled trials with clinical endpoints indicate an improvement in outcome using this therapy, and a subgroup of such patients had advanced HIV infection. Comparable experience using other therapies initially in this group of patients is limited. Although many would use indinavir combined with ritonavir for pharmacokinetic enhancement to simplify the regimen, there is an increased risk of side effects. I would personally still use a double nRTI/NNRTI combination as

I am impressed by the relative freedom from adverse effects, the "forgiveness" of such a regimen, and the ease of adherence. This, in my mind, more than compensates for the relative lack of clinical controlled trial evidence for efficacy in this particular group of individuals.

Question 18: In resource-poor settings, when CD4+ cell counts and clinical response are adequate and patients on adefovir are doing well in spite of a not-too-good decrease in viral load count, why not avoid frequent measurements of rise so that expensive tests are avoided?

Dr. Katzenstein: The issue of "how much monitoring is enough" where there has been a good clinical, but a minimal virologic, response to antiretroviral drugs is difficult. In resource-constrained settings there is little reason to monitor virus load, particularly when further options for new treatments are limited and the cost of virus load testing is significant. However, the same is not true for toxicity monitoring. If, for example, adefovir were being used as treatment and there is a "good clinical response," I would suggest frequent, inexpensive assessments of electrolytes and renal function. The single test and strategy that may help decide whether to continue treatment is observing clinical and CD4+ changes with the discontinuation of antiretrovirals.

Question 19: Is there rationale to use lamivudine in patients carrying an M184V mutation, especially in patients in whom numerous drugs have caused multiple failures? Are other options available?

Dr Katzenstein: Although there have been no prospective randomized trials completed that have directly addressed this important salvage question, many physicians continue to use lamivudine, generally in combination with either zidovudine or stavudine in salvage

regimens. The rationale for the continued use of lamivudine in patients with the M184V mutation and multidrug failure comes from randomized trials of nRTI therapies including lamivudine (ACTG 302 and 303). These studies have shown that on average, patients who continued on a "failing regimen" including lamivudine sustained more than a 0.5-log (70%) reduction in HIV RNA from baseline after 48 weeks, even though the M184V (or I) mutation had emerged in the virus of most. One explanation for this may be found in phenotypic studies of viruses from highly nRTI-experienced subjects that show that the M184V mutation "re-sensitizes" viruses to thymidine nRTIs, reducing high-level zidovudine resistance by nearly 10-fold and stavudine resistance by 50%.

In contrast, there is clear evidence that the M184V mutation increases resistance to didanosine and abacavir in the presence of multiple thymidine nRTI mutations. These data provide a rationale for the continued use of lamivudine, although with the caveat that the continuation as well of either zidovudine or stavudine is important to this activity. Triple-nRTI regimens, whether zidovudine/didanosine/lamivudine, stavudine/didanosine/lamivudine, or fixed-dose lamivudine/zidovudine/abacavir appear to exert continuing virologic activity, despite the presence of resistance to each of the drugs in the regimen, including the M184V mutant.

An upcoming option for reverse transcriptase inhibition as part of a regimen in patients in whom multiple drugs and classes have failed is the addition of the nucleotide reverse transcriptase inhibitor (nRTI) tenofovir. Like adefovir, this compound demonstrates activity against M184V-containing viruses and may be useful in continued treatment of patients in whom multiple nRTIs have failed.

The inclusion of multiple nRTIs

in a salvage regimen depends on the tolerance, toxicities, and cost of the drugs, as well as evidence of benefit.

Question 20: When would you recommend postexposure prophylaxis? Which regimen would you select? When would you stop postexposure prophylaxis?

Dr Yeni: Postexposure prophylaxis (PEP) is recommended when the risk of transmission from an occupational or non-occupational exposure is significant. A high risk of transmission following occupational exposure results from blood or fluids containing blood, or potentially infectious fluids or tissue from a patient with HIV infection documented or likely, coming into contact with a mucous membrane or not-intact skin, or through percutaneous injury or bites resulting in blood exposure. A significant risk of transmission following non-occupational exposure results from unprotected sexual intercourse or sharing drug injection equipment with a patient with HIV infection documented or likely. In case of non-occupational exposure, prophylaxis is recommended in the absence of predicted, recurrent HIV exposure, or if a decision to engage into risk-reduction practices is taken.

PEP should be started as soon as possible after the exposure, and in all cases within 48 hours. Once initiated, PEP should be continued for 4 weeks if tolerated, unless the source patient with an unknown HIV serostatus when PEP was started, is determined to be HIV-seronegative.

The regimen of choice, in the absence of HIV drug resistance, remains debated but a systematic triple-drug combination may be warranted in order to simplify recommendations (rather than selecting a double- or triple-combination according to the level of exposure risk), and to achieve the highest antiretroviral activity. The use of drugs that may be responsible for severe adverse events (such as nevi-

rapine or abacavir) should be discouraged. Efavirenz should not be used in women of childbearing age, because of the potential of teratogenic effects.

Dr Cahn: This is quite a difficult issue, since any current or future recommendation is to be based on our best guess, and since controlled clinical trials are not feasible, neither in the occupational nor in the sexual exposure setting. In our practice, we follow the Centers for Disease Control and Prevention (CDC) guidelines for health care worker injuries, trying to provide counseling and support to the injured health care worker. Regarding sexual exposure, we encourage rape victims to take a triple-drug prophylaxis regimen for 1 month. The rationale is that in the vast majority of attacks, the serostatus of the offender is unknown, and frequently violence is involved, increasing the risk of mucosal damage. Regarding the drugs to be selected, again, no controlled clinical trials are or will be available. The CDC has released recommendations against nevirapine use in the occupational setting. Abacavir hypersensitivity reaction is diagnosed in around 4% to 6% of cases, and has not been linked with high CD4+ cell levels, as some studies showed in the case of nevirapine. Simplicity of 1 pill taken once daily, allowing potentially better tolerance and adherence, has to be weighed against the potential of a hypersensitivity reaction. Potency is a matter of debate in patients with plasma viral loads higher than 100,000 copies/mL, but this may not be relevant in the setting of prophylaxis, as we learned from zidovudine efficacy in prophylaxis of mother-to-child transmission. So, a strong recommendation against should only be applied to nevirapine and to ritonavir (full dosage 600 mg bid), due to toxicity and tolerance respectively.

Question 21: Should efavirenz be used in women of child-bearing age who plan to become

pregnant in the near future but are using only condoms for contraception?

Dr Carpenter: Primate data indicate that serious central nervous system abnormalities occur with the administration of efavirenz during the first trimester of pregnancy. Since condoms are far from "100%" effective in preventing pregnancy, I advise women not to utilize efavirenz in this situation.

Question 22: An HIV-seropositive woman had been on zidovudine/lamivudine/indinavir, but stopped the drugs for 2 years. She is now 2 months pregnant. What drugs would you recommend now?

Dr Schooley: Prevention of perinatal transmission of HIV-1 infection is best accomplished by crafting a regimen for the mother to which the virus is likely to be susceptible and providing the infant with effective postexposure prophylaxis. In this case, it would be important to know the full details of the mother's prior antiretroviral chemotherapeutic experience. Was zidovudine/lamivudine/indinavir the only regimen she had previously received? How successful was it in suppressing virus during the time she received it?

If the data strongly suggest that her virus was "fully" suppressed while she received this regimen, one could expect that her virus would be susceptible to these drugs at this point in time. On the other hand, if she had previously received zidovudine monotherapy to which lamivudine and indinavir were sequentially added, one would be concerned that she might harbor virus that is resistant to 1 or more of these drugs.

Because of competition between wild-type and drug-resistant virus, it could be possible that drug-resistant virus would not be detectable in the plasma or in the lymphoid reservoirs with currently available techniques. Because of these fac-

tors, the selection of a specific regimen cannot be made on the basis of currently available data. If she, indeed, had not been on other drugs prior to her zidovudine/lamivudine/indinavir experience and if the virus was fully suppressed by these drugs while she was on therapy, it would be reasonable for these drugs to be reinstated in the context of her pregnancy. If there are concerns that prior drug exposure might have selected for resistance, alternative drugs should be selected.

Resistance testing should be employed in the selection but it should be noted that this testing might miss minority species or archived virus that was replaced in the plasma by competition with wild-type virus.

Question 23: A patient is taking stavudine/didanosine/efavirenz plus antituberculosis treatment. She presents with hepatotoxic encephalopathy and drugs are suspended. How should treatment continue? Should antiretroviral therapy be reinstated? Hepatic enzymes are now normal, the patient is asymptomatic, and does not have hepatitis B or C virus infections.

Dr Carpenter: The presentation strongly suggests that the patient's encephalopathy was directly related to hepatitis caused by administration of drugs. Since the hepatotoxicity was more likely caused by the antituberculosis medications than by the antiretroviral medications, it would be appropriate first to reinstate the antiretroviral therapy that the patient was originally receiving, with close monitoring of the liver enzymes and bilirubin levels.

If the patient had active tuberculosis, it would also be appropriate at this time to reinstate treatment with streptomycin and ethambutol, the 2 antituberculosis agents least likely to cause hepatic damage, as a holding regimen. Then if no hepatic

abnormalities developed over a period of 4 weeks, it would be appropriate to add rifampin with continued close monitoring of the hepatic enzymes. If no hepatic abnormalities developed over an additional 4-week period, it would be reasonable to add isoniazid, with continued close monitoring of hepatic enzymes. (Pyrazinamide is the most hepatotoxic of the frequently-used antituberculosis drugs, and it should probably not be reinstated at any time in the management of this patient).

Antiretroviral Guidelines Session Participants

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Note: The IAS (based in Sweden) is not affiliated with the IAS-USA.

Telling Stories

Epidemic Beginnings

Douglas T. Dieterich, MD, FACP

He was uncharacteristically cheerful as he lay in the intensive care unit in Bellevue Hospital. It was December, 1980, and his name was Harvey. He had a mysterious illness with voluminous intractable diarrhea and a strange purple nose. We were called in to perform a small bowel biopsy on him to try and determine the cause of his diarrhea. It was a difficult procedure, but he was very cooperative. The biopsy was successful, but not revealing of the cause of his diarrhea or his purple nose. It was only after his autopsy several weeks later that we had some hints. The pathology report said he had Kaposi's sarcoma, an illness formerly confined to elderly Jewish men and Africans. The diagnosis was as much of a puzzle as the symptoms.

Twenty years ago this past June physicians throughout the United States were alerted to the first clinical symptoms of an elusive new disease that would forever transform the world landscape: AIDS. Harvey, as it turned out, was my first AIDS patient some 6 months before the report in *Morbidity and Mortality Weekly Report*, the Centers for Disease Control and Prevention publication that appeared in June, 1981. At Bellevue Hospital in New York, where the challenge of mysterious diseases was commonplace, we had just been through another new disease, Legionnaires disease, and had conquered it. At the time, with the optimism typical of young physicians, we thought the medical profession would determine the cause of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in these young men within about 6 months, as we had done with Legionnaires disease. We could not have been more wrong. Twenty years later, the medical profession is still battling the same virus, but the disease is completely different.

One by one, more young men appeared with Kaposi's sarcoma, cytomegalovirus, cryptosporidiosis, or other mysterious opportunistic infections with long names. As a gastroenterologist in those early days of the epidemic, I spent a large part of my time seeing HIV patients with severe diarrhea and with liver failure, typical gastroenterological diseases. By 1983 I was one of only a handful of physicians willing to see patients with this strange disease. Many physicians were afraid of this still-mysterious illness. One "expert" told me at the time, "I can't see those patients, I have a family and we don't know how it is transmitted." I am sure my thinking was colored by my personal experience of contracting hepatitis C virus from a needlestick

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in 1977, while I was still a medical student. I, too, had been treated like a leper once when hospitalized for my hepatitis infection and I identified strongly with my AIDS patients' plight. I knew how it felt to be considered infectious. Most of us who were caring for these patients thought it was not just unethical for any physician to avoid patients out of fear of contagion, but dead wrong.

In those days, a patient would often be admitted to the hospital late at night, short of breath. *Pneumocystis carinii* pneumonia was the diagnosis. The patient's family—often in some place in the Midwest, like Kansas—would be notified. A day later they were in New York, faced not only with their son's mysterious illness but also with the fact that he was gay and that he was likely to be dead within weeks, if he survived the weekend. These were scenes of unimaginable heartbreak. Fortunately for the patients, surprisingly few parents turned away from their sick sons despite all their shock, grief, and fear at hearing the news. At the peak of the epidemic, many of us would lose 2 or 3 patients per week. This was a devastating situation, for which most of us, whom by circumstance became HIV "specialists," could never have been prepared. Most gastroenterologists and infectious diseases specialists were used to treating serious but treatable diseases. Suddenly we felt like we were in a war and losing. The best we could do was to provide comfort care for the dying.

The situation today in New York and other places in the United States is a far cry from those early days. Thanks to advances in antiretroviral therapy, instead of 2 or 3 patients dying each week, the number is maybe 2 or 3 each year. Instead of affecting mostly gay white men, the epidemic has moved to women and minorities. Interestingly enough, more than half of our HIV-infected patients are dying of liver failure caused by hepatitis C, the disease that drew me into the epidemic and made me more sensitive to my patients' illness. Hepatitis and liver disease are just two of many obstacles in the way of caring for those in the world fortunate enough to receive treatment for HIV. Side effects of the very medications that are extending the lives of our patients are the largest issue in HIV care today, not opportunistic infections as it was 20 years ago.

A vaccine remains one of our greatest hopes for conquering HIV/AIDS, but it is unlikely that a successful one will be developed for another 5 to 10 years. A successful vaccine will likely be one that produces cell-mediated immunity, not just antibodies as is standard in existing vaccines. So far, development of this type of vaccine eludes our grasp.

We can only hope that 20 years from now we can eradicate HIV from the body by using a combination of vaccines and pharmaceuticals. Until then, the hopeful message of our progress in battling AIDS is that physicians will get better and better at fighting the disease, one patient at a time.

Defining HIV Expertise: Summary of a Recent Study of Physicians in HIV Medicine

In the fall of 1999, the International AIDS Society–USA collaborated with investigators at the University of California San Francisco to conduct a study among physicians actively involved in HIV medicine about their degree of experience in HIV medicine, their self-perceived expertise, and their confidence in providing HIV medical care. A comprehensive survey was administered to physician attendees at IAS–USA continuing medical education (CME) courses in New York, Chicago, San Francisco, and Los Angeles, all part of the IAS–USA annual fall CME series, *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management*. Data from 359 physicians were analyzed for the study.

With more than 15 currently available antiretroviral drugs, drug resistance, and emerging complications of HIV disease and its therapies, many physicians in HIV

medicine have wondered what it means to be an HIV "specialist," how to define HIV expertise, and what formal standards, if any, should be required of those who practice HIV medicine. This study is a first step toward answers to these questions. Several physician professional organizations, including the HIV Medical Association of the Infectious Diseases Society of America, have proposed criteria for defining HIV expertise. More information is now needed on how physician experience, confidence, and expertise relate to patient outcomes. Clearly, however, the IAS–USA believes that the high quality education we provide will remain critically important.

The abstract and full citation of the published study are reprinted below. The authors and the International AIDS Society–USA are grateful to the course attendees who participated in the study. —**Paul A. Volberding, MD**

Abstract

Medical care for human immunodeficiency virus (HIV)-infected persons has grown increasingly complex, yet few studies have examined experienced HIV physicians' views about current HIV medical care. The objective of this study was to examine the relationship between physicians' HIV experience, self-perceived expertise, and confidence with providing 18 aspects of HIV medical care and between confidence in aspects of care and medical specialty. At geographically diverse, HIV continuing medical education programs conducted in the fall of 1999, 359 currently practicing HIV physicians completed a written survey measuring partici-

pants' demographic characteristics, experience, HIV expertise, and level of confidence providing essential aspects of HIV care. Participants currently managed a median of 50 HIV-infected patients with a career total of 300. Significant correlations were found between experience and expertise items and experience and 15 of 18 confidence items. Confidence levels varied from 11% to 85% highly confident across 18 aspects of HIV care. Physicians' confidence with providing aspects of HIV care varied by the three predominant specialty groups (infectious diseases, internal medicine, and family practice/general medicine). Physicians who have informally specialized in HIV care reported a range of self-perceived

expertise and confidence, indicating the complexity of HIV medical care today. Our results suggest that even the most experienced HIV physicians in the United States continue to benefit from more experience and that each medical specialty examined in this study brings its own set of skills needed to provide optimal HIV care. This study constitutes a first step toward defining and formalizing HIV medical care.

Gerbert B, Moe JC, Saag MS, Benson CA, Jacobsen DM, Feraios A, Hill ME, Bronstone A, Caspers N, Volberding PA. Toward a definition of HIV expertise: a survey of experienced HIV physicians. *AIDS Patient Care STDs*. 2001;15:321-330.

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¹International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med*. 1997;336:309-315.

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Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for physicians who are actively involved in HIV and AIDS care. The organization's educational activities are particularly intended to bridge clinical research and patient care.

Cosponsored Sessions at Scientific Meetings

IAS–USA Interactive Session at the 39th Annual IDSA Meeting

For registered attendees of the IDSA Meeting

Clinical Management of HIV Infections

Sunday, October 28, 2001, 10:30 am–12:30 pm

Moscone Center, San Francisco, California

Chairs: Robert L. Murphy, MD, and Robert T. Schooley, MD

IAS–USA Interactive Symposium at the 41st Annual ICAAC

For registered attendees of ICAAC

Current Issues in the Management of HIV

New Date: Wednesday, December 19, 2001, 8:30 am–11:00 am*

McCormick Place Lakeside Center, Chicago, Illinois

Chairs: Martin S. Hirsch, MD, and Diane V. Havlir, MD

*Due to the terrorist attacks on September 11, ICAAC has been rescheduled for December 16–19, 2001.

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Atlanta, Georgia

Monday, March 18, 2002

Chairs: Michael S. Saag, MD, and Jeffrey L. Lennox, MD

New York, New York

Monday, March 25, 2002 (**Please Note New Date**)

Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

Chicago, Illinois

Tuesday, April 16, 2002

Chairs: John P. Phair, MD, and Harold A. Kessler, MD

San Francisco, California

April, 2002

Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD

Washington, DC

May, 2002

Chairs: Henry Masur, MD, and Michael S. Saag, MD

Cases on the Web - <http://hivinsite.ucsf.edu/cme/index.html>

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Initiation of Antiretroviral Therapy

Constance A. Benson, MD

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Gerald H. Friedland, MD

Withdrawal of Prophylaxis for Opportunistic Infections in Persons with HIV Infection

Michael A. Polis, MD, MPH

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