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Immune reconstitution disease (IRD) increasing; recognition, management important

Mary J. Murphy, MD

Highly active antiretroviral therapy (HAART) was introduced in 1996. The widespread use of HAART since then has led to a significant decrease in morbidity and mortality among patients infected with the HIV virus. The benefit of HAART is primarily related to a reduction in the incidence of HIV-associated opportunistic infections and malignancies, and results from both control of HIV replication and restoration of immune-competence. At the same time these effects of HAART have been implicated as the cause of a new syndrome known as immune reconstitution or immune restoration disease (IRD). While the exact frequency of this syndrome remains unclear, it is important for clinicians to recognize it, especially since it may have unusual manifestations compared to the classic presentation of HIV-related op-

portunistic infections and malignancies or be confused with toxicities associated with HAART itself.

IRD is characterized by an unexpected or paradoxical clinical worsening in patients who have begun HAART. It typically occurs in the first few weeks after the initiation of HAART but may also present up to several months after starting HIV therapy. The disease process involved may be preexisting or may appear as a new entity if it was subclinical or undiagnosed prior to starting HAART.

The pathophysiology of IRD is thought to be related to an increased inflammatory response brought about by increases in CD4+ and CD8+ T cells, as well as restoration of delayed hypersensitivity. T cell dependent changes in cytokine production may also be involved. The initial rapid decline in viral load secondary to effective HAART is first associ-

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Mental Health

Assessing substance abuse in HIV-positive adolescents

M. Christina Birbaum, Kitty B. Haspel, Casey Hoffman, Deana L. Jefferson, Sandra A. Soenning, Byron A. Hammer, MD, Jill Hayes Hammer, PhD

Adolescence can be a period of significant physical, emotional and social challenges. Teenagers often exhibit an extremely thin line between impulse and action and subsequently put themselves in danger by engaging in high-risk behaviors such as substance abuse and unprotected sex. So it is not surprising that adolescents are at higher risk for contracting and spreading HIV. These high-risk behaviors can also negatively influence their health and can pose an obstacle for clinicians hoping to provide good medical and mental health care. (Kann, et. al., 1993, Morris, Warren & Aral, 1993).

Although few empirical studies investigating the influence of substance abuse in HIV-positive adolescents have been conducted, research on the impact of drugs and alcohol alone suggests that substance abuse significantly impacts the lives of adolescents. Among 15 to 24 year olds, 50 percent of deaths from accidents, homicides, and suicides involved alcohol or drug abuse (American Academy of Child & Adolescent Psychology, 1997). As of 2003, approximately 45 percent of high school students used alcohol, and 28 percent of those engaged in episodic heavy drinking (Center for Disease Control & Prevention^a [CDC], 2003). The 2003 National Survey on Drug Use and Health (CDC^b) revealed

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Medicine

Clinicians should understand the unusual manifestations of IRD

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ated with an increase in T cells due to redistribution of antigen experienced immune effector cells and later due to increased production of naïve CD4+ and CD8+ lymphocytes. Increased inflammatory responses related to this immune recovery are most often seen with organisms that are commonly encountered in the environment such as mycobacteria and some of the herpes viruses.

Many of the reported cases of IRD have been in HIV/TB coinfecting patients starting HAART. Worsening of tuberculosis after initiation of anti-TB therapy has been previously well described in non-HIV patients. This is thought to be due to a restored response to mycobacterial antigens brought about by TB therapy. The incidence and/or severity of clinical deterioration with TB treatment appears to be greatest in HIV-positive patients on HAART compared to HIV patients not on HAART and HIV-negative patients.

Clinical manifestations of IRD in HIV patients with TB on HAART include prolonged fever, worsening respiratory symptoms and pulmonary infiltrates, as well as development of lymphadenopathy, pleural and pericardial effusions, cutaneous lesions, intestinal involvement and intracranial tuberculomas. Lymph node enlargement can be both in body cavity and superficial nodes and caseating necrosis with drainage may occur. Histologic examination has frequently revealed granulo-

mas but usually no organisms are seen. Although cultures may sometimes be positive for MTB, they are frequently negative and AFB smears are rarely positive. Time to occurrence of IRD in MTB-infected patients on HAART has ranged from as little as 10 days up to 180 days after initiation of HAART. Interestingly, larger absolute decreases in HIV viral load may be a more significant risk factor for TB-associated IRD than the degree of T cell increase. Preexisting extrapulmonary foci of infection is also a risk factor. Because of

IRD is characterized by an unexpected clinical worsening in patients who have begun HAART.

the frequency of TB-associated IRD in patients on HAART, some clinicians have recommended delaying HAART in HIV/TB infected patients until they have received one to two months of antituberculous therapy.

M. avium was one of the first AIDS-related opportunistic infections to be described in the context of immune reconstitution. In contrast to TB, MAC IRD has occurred frequently in patients without a prior diagnosis of disseminated MAC, reflecting the often subclinical nature of this infection. The hallmark of MAC-associated IRD is that it

infrequently presents as disseminated disease with bacteremia and bone marrow involvement and often presents as focal lymphadenitis involving intraabdominal and superficial nodes. Granulomas are also a frequent histologic finding on biopsy and suppuration may occur. Other unusual manifestations include necrotic skin nodules, osteomyelitis, endobronchial masses, small bowel involvement, bursitis and Addison's disease. AFB smears and cultures may be negative. In most of the reported cases, symptoms developed within a few weeks of starting HAART.

Ocular manifestations of CMV infection following HAART are characterized by an exuberant inflammatory response termed Immune Recovery Vitritis or Uveitis that may involve the vitreous body and also the anterior chamber of the eye. Patients often complain of blurred vision and floaters. Complications include proliferative vitreoretinopathy and posterior subcapsular cataracts that can lead in some cases to permanent visual impairment. Patients with a history of CMV retinitis starting HAART should be followed closely by an ophthalmologist. Serious complications occur more frequently in patients with prior extensive retinal involvement due to CMV. Patients without a history of CMV, but at risk because of low CD4 counts, should be screened for CMV retinitis prior to starting HAART and also closely monitored for visual changes. Despite the potential complications, the outcome in most patients who develop CMV IRD appears to be good. They may also develop significant immunological protection against



CMV allowing discontinuation of anti-CMV therapy. Other manifestations of CMV-associated IRD include colitis, pancreatitis, CMV viremia and pneumonitis.

The incidence of herpes zoster infections has increased in HIV patients taking HAART. Most episodes occur within one to four months after starting HAART, are typical with regard to location, and usually run a mild course. Increased risk for VZV in patients on HAART has been found to correlate with a high baseline CD8+ cell percentage and a significant rise in these cells after four weeks of HAART.

Apparent hepatitis flares may occur in patients with chronic hepatitis B or C after initiation of HAART. Studies have shown increased levels of HCV and HBV DNA in some, but not all, patients with suspected chronic hepatitis flares. Drug toxicity due to antiretroviral medications may also play a role in some patients. The differential diagnosis should also include hepatitis B flare secondary to stopping drugs active against hepatitis B, development of lamivudine resistance, other causes of liver disease such as cholecystitis and new infections such as mycobacterial disease. Liver biopsy may be helpful in differentiating these in some cases. Transient mild to moderate increases in transaminases can usually be managed by observation alone. In severe hepatic decompensation, HAART should be stopped. Of note, there are reports of HAART-associated hepatitis in patients with hepatitis B that led to hepatitis B e antigen antibody seroconversion and clearance of hepatitis B e antigen, hepatitis B surface antigen and HBV DNA. Appearance of extrahepatic manifestations of hepatitis C have been described

in patients starting HAART, including polyarthritis, porphyria and cryoglobulinemia.

HAART has been shown to lead to improved survival in AIDS patients with PML. It also decreases levels of JC virus in the CSF and increases anti-JC antibody. Still, HAART initiation has been associated with a PML IRD characterized by the development of new or worsening neurologic findings. Most cases have been mild and show neurologic improvement with HAART continuation. MRI may show contrast enhancing lesions that are atypical in HIV patients with PML who are not taking HAART and reflect the intensity of the inflammatory response.

Cryptococcal meningitis presenting after initiation of HAART has been associated with significant CSF pleocytosis and unusually high CSF cryptococcal antigen titers, both of which are not characteristic of cryptococcal meningitis in HIV patients not taking HAART. Other manifestations of cryptococcal IRD are new onset pneumonitis, lymphadenitis and cutaneous abscesses.

Noninfectious processes associated with IRD include malignancies and autoimmune diseases. Development or recurrence of both Kaposi sarcoma and lymphoma have occurred temporally related to HAART initiation. Graves disease with symptoms and signs of hyperthyroidism, systemic lupus erythematosus and sarcoidosis have also emerged following HAART.

No controlled trials have been done to evaluate treatments for IRD. Treatment recommendations are currently based only on case and case series reports. Because the pathophysiology of this syndrome involves a brisk inflamma-

tory response, management has relied on attempting to control this response using anti-inflammatory drugs. In mild cases, frequently no additional treatment is needed other than continuing or starting treatment for the underlying disease when effective treatment exists and also continuing HAART. NSAIDs may also be useful but data are lacking. In more severe cases, and especially when vital organs such as the brain or eye are involved, tapering courses of steroids have been used successfully. In the case of CMV IRD, topical steroids have sometimes been used in conjunction with systemic steroids. Short courses of steroids appear to be well tolerated in patients with AIDS. Again, treating the underlying disease is important and HAART should be continued whenever possible.

Identification of syndromes consistent with IRD in patients on HAART is increasing. The diagnosis of IRD is one of exclusion and careful assessment to exclude other new infections, drug toxicity and treatment failure should be undertaken. Clinicians should be familiar with the unusual manifestations of IRD in patients taking HAART so that the diagnosis is considered and appropriate treatment instituted when IRD is suspected or confirmed. ♦

Mary Murphy is Assistant Professor of Clinical Medicine at LSU School of Medicine, and Medical Director, MCL-NO HIV Outpatient Program (HOP)

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Mental Health

How should clinicians ask adolescents about substance use?

Substance abuse, from page 1

that four percent of young adolescents (age 12-13 years) engaged in illicit drug use and that almost half of all drug users nationwide were between the ages of 12 and 25 years.

Alcohol and drug use not only increases the risk of contracting HIV (Howard & Wang, 2004; Petry, 1999), but also impedes effective treatment. Researchers indicate that chronic drinking within the HIV-positive population is associated with increased medical and psychiatric complications, delays in seeking treatment (Samet, Freedberg, & Stein, 1998), problems with HIV medication compliance (Cook, Sereika, & Hunt, 2001), and poorer HIV treatment outcomes (Lucas et al., 2002). Decreasing substance abuse among adolescents who have HIV or who are at risk for becoming infected is likely to reduce the spread of HIV. In addition, reducing substance abuse is likely to improve medical compliance and longevity among those already infected.

Substance-using HIV-positive adolescents present a clinically complex picture. Professionals who work with this population need to understand the unique aspects of adolescent assessment and treatment. Assessing drug use is often difficult with adolescents because many do not feel comfortable revealing the extent of their drug abuse or dependence. Even visiting and consulting with helping professionals may be difficult for adolescents who wish to be unique and fear being labeled (Erikson, 1968). Conversely, other adolescents may inflate the amount of substances they use, possibly in an attempt to appear "cool." Many clinicians feel like they do not know how to ask adolescents questions about substance use; some fear what the answers could be (i.e., what do I do with the information I get?), and others report that they feel like they are not asking the right questions. Given this discomfort, the **HOW** guidelines presented below are good to keep in mind when working with substance-using HIV-positive adolescents (Howard Wetsman, personal communication). The **HOW** guidelines refer to 1) **Honest** communication about what the clinician knows and does not know about drug use, 2) **Openly** talking to the adolescent about his/her experiences with substances, and 3) **Willingness to listen to the adolescent and empathize**.

Honest communication about what the clinician knows and does not know about drug use, including drug terminology: In the assessment of substance abusing adolescents, knowing their drug language (e.g., the street names of drugs) can be invaluable to the professional who is attempting to foster greater honesty in disclosure. Even if the clinician thinks he or she knows what the adolescent is talking about, clarity should be sought to determine the specific substances the youth is using, and how the adolescent is using them. Illicit drug names are often culturally and geographically dependent, and they also tend to change over time. Fortunately, professionals can now consult the Internet for the most current terms (see Table 1). The clinician would also benefit from recognizing that some terms can have more than one meaning. For example, the term "clickum" may refer to marijuana laced with PCP, or, conversely, marijuana dipped in embalming fluid. In addition, many drugs can be taken in different ways. For instance, an adolescent can snort, smoke, or inject cocaine. Therefore, health care providers need to understand the contemporary vernacular and the current patterns of use and abuse within the adolescent subculture.

Open to talking about the adolescent's experiences with substances: Given the high rates of drug use in adolescents with HIV, affirmative or assumptive questioning may increase the likelihood that adolescents will provide accurate information about their current substance use. For example, instead of asking, "Have you ever smoked marijuana?" the clinician might ask, "How many blunts (joints, etc.) do you smoke per week?" However, depending on the population, this technique may not be the best way to begin talking with an adolescent about drugs. Asking affirmative and assumptive questions may increase the likelihood that an adolescent will provide false positive reports or will inflate the amount of substances he or she is using. Additionally, if an adolescent is not a drug user, then this line of questioning may make him feel defensive, angry, or possibly like he is different from his peer group. Therefore, knowing the adolescent's history is the best way to determine whether to ask assumptive questions or questions such as, "Have you ever used any ____?" If the adolescent responds negatively,

then you may want to follow up with: "Come on, are you sure you've never even tried it, not even once?" If the adolescent responds positively, you would follow up with questions asking about quantity, duration, age at first use, situations in which the adolescent uses, etc. Since you are seeing the adolescent in connection with HIV care, it is often advisable when an adolescent is using substances to ask her if she feels that substance use is affecting her HIV care or health. Asking HIV positive adolescents about the impact of substances on their health provides them with the opportunity to begin thinking about the deleterious effects of drugs.

Willingness to listen to the adolescent and empathize: Treatment with substance abusing patients is a complex process (see Table 2). Some research (Prochaska, Diclemente, and Norcross, 1992) suggests that individuals in the process of modifying addictive behaviors move through a series of five stages:

- 1) *Precontemplation* represents the stage during which the individual is unaware of his or her problem with drugs (i.e., "I don't have a problem at all").
- 2) *Contemplation* refers to a period in which the individual is aware that a problem exists and begins to weigh the pros and cons of substance use (i.e., "I don't want to think about it").
- 3) *Preparation* is a stage characterized by small behavioral changes such as reducing the use of preferred drugs (i.e., "I think I have a problem, but I'm not sure what to do about it").
- 4) *Action* refers to a period in which the individual effectively alters his or her addictive behavior for at least a small period of time.
- 5) *Maintenance* is a stage marked by a commitment to relapse prevention.

If an adolescent is in the precontemplation stage and is using needles, attempts to get him or her to abstain immediately may fail. A more realistic goal may be to encourage the use of clean needles. In the contemplation stage, the provider may want to pick one adverse health effect of using the drug of choice (i.e., if the adolescent combines cocaine/crack with alcohol, this combination increases the likelihood of sudden death or heart attack; crack can cause aggressive, paranoid behavior). While the adolescent is unlikely to immediately use the information provided, he or she will retain that knowledge for use in the preparation



and action stages. In contrast, when an adolescent is in the preparation stage, he or she may be willing to discuss his or her concerns and ask questions regarding chronic or addictive substance abuse, and he or she may be open to treatment options.

Most adolescent substance abusers will spend a significant amount of time fluctuating back and forth through the stages of precontemplation and preparation. This waffling pattern is often frustrating for professionals who work with them, but allowing substance-using adolescents to progress through the stages at their own pace while providing support will hopefully improve their success rates. Providing precontemplative adolescents with too much concrete information and negative feedback about their substance use can destroy rapport and drastically reduce treatment effectiveness. Referring these adolescents to trained substance abuse counselors can often assist in reducing substance use. "Motivational Interviewing," a technique developed by Miller (1983) and later by Miller and Rollnick (1991), assumes that ambivalence or lack of resolve is the primary obstacle in overcoming or changing harmful behaviors. Therapists skilled in this technique do not directly persuade the adolescent, but rather motivate and guide him in changing his behavior. Exploring ambivalence by weighing the pros and cons of substance use is extremely important in moving a teenager towards a decision to stop using drugs and/or alcohol. Illustrative of this ambivalence is that teenagers know there may be a price to substance use (i.e., health effects, social problems), but they also enjoy using. For example, consider the following contradictory statement: "If I stop smoking, I will feel better about myself, but I may also put on weight, which will make me feel unhappy and unattractive" (Miller, 1983; Rollnick & Miller, 1991; Rollnick & Miller, 1995).

In conclusion, health care providers of HIV-positive adolescents who engage in risky or dangerous substance abuse would benefit from employing the techniques reviewed in this article, in particular the importance of the **HOW** technique, to successfully talk with an adolescent:

(H) Today's health providers need to be aware of the popular drug vernacular in order to facilitate honest communication and effective assessment. The clinician does not need to use these terms; rather, understanding and clarifying what the adolescent is saying is the goal.

(O) Framing questions about adolescents' substance use in an assumptive manner will increase open communication between them and the health provider.

(W) A willingness to consider the adolescent's stage of drug use and meet him where he is at provides the health provider with a guide for the most effective education and intervention strategies

With genuine concern and openness towards HIV-positive adolescents, and using techniques and advice from mental health professionals, treatment providers can help stem the combined deleterious effects of drug use, impulsivity, and health problems. ♦

M. C. Birbaum, K. B. Haspel, C. Hoffman, D. L. Jefferson and S. A. Soenning are doctoral candidates completing clinical psychology internships at the LSUHSC Department of Psychiatry. B. Hammer is Adjunct Assistant Professor with LSUHSC Department of Psychiatry and child psychiatrist for the drug court in Jefferson Parish. J. Hayes Hammer is Assistant Professor at LSUHSC Department of Psychiatry and clinical psychologist/neuropsychologist at the HIV Outpatient Program of MCLNO.

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Table 1

Examples of Drug Slang Terms

Cocaine = Coke, Nose candy, Blow, Snow, Aspirin, Bernie, Double bubble, Roxanne
Crack = Rocks, Apple jacks, Beamers, Casper, Golf ball, Kangeroo, Real tops, Yayoo,
Ecstasy = X, Disco Biscuite, 69s, Care Bears, Hug drug, Morning shot, Playboys, Wafers
Heroin = Smack, Big H, Crop, Thunder, Helldust, Al Capone, China cat, Flea powder, Mr. Brownstone, Little boy, Tootsie roll
Inhalants = Whippets, Air blast, Bullet bolt, Heart-on, Highball, Moon gas, Oz
LSD = Acid, Dots, Mellow Yellow, Window Pane, Blue chairs, Goofy's, Watercolors
Marijuana = Blunts, Chronic, Aunt Mary, Boo boo bama, Panama red, Weed, Meggie
Methamphetamines = Ice, Speed, Tweek, Crystal, Black beauty, Getgo, Spackle, Work
PCP = Angel dust, Tic Tac, Boat, Zoom, Cliffhanger, Elephant tranquilizer, Shermans
Ketamine = Special K, Cat Valium, Bump
Rohypnol = Roofies, Circles, Mexican Valium, Date rape drug
Psilocybin = Shrooms, Magic mushrooms, musk, Silly putty, Simple simon
* Other terms for substances and combinations of substances may be found at the following websites:
• www.whitehousedrugpolice.gov/streetterms
• www.drugs.indiana.edu/slang/home.html
• www.drugs-info.co.uk/streetnames/slangnamesenglish.htm

Table 2

Links to Useful Websites and Resources

- A.** Websites that address typical adolescent developmental considerations:
 - <http://health.yahoo.com/health/centers/parenting>
 - <http://inside.bard.edu/academic/specialproj/darling/adolesce.htm>
- B.** General information on substances and sexual behavior in adolescents:
 - http://parentingteens.about.com/cs/drugsofabuse/adrugs_sex.htm
 - <http://www.athealth.com/Consumer/adolescents/facts.htm>
 - <http://hab.hrsa.gov/programs/factsheets/substancefact.htm>
 - <http://teens.drugabuse.gov/>
 - <http://ncadi.samhsa.gov/govpubs/phd725/>
- C.** National substance abuse resources:
 - <http://www.drugfreeinfo.org/natres.html>
- D.** Information on assessing/screening for and treating substance abuse in adolescents:
 - <http://ncadi.samhsa.gov/govpubs/BKD306>
 - <http://ncadi.samhsa.gov/govpubs/BKD307>
 - <http://www.health.org/govpubs/bkd342>
 - http://www.guideline.gov/summary/summary.aspx?doc_id=1816&nr=1042&string=substance+AND+abuse
 - http://www.guideline.gov/summary/summary.aspx?doc_id=1818&nr=1044&string=substance+AND+abuse
 - http://www.athealth.com/practitioner/ceduc/health_tip31n.html
 - <http://www.fpnotebook.com/PSY28.htm>
- E.** Information on substance abuse treatment for individuals with HIV/AIDS:
 - <http://ncadi.samhsa.gov/govpubs/bkd359/37b.aspx>



Legal

New dilemmas as patients live longer and side effects take hold

Linton Carney, JD
Aimee A. Dugas, JD

In the two decades since the isolation of the HIV virus, medical practice for infected patients has undergone tremendous change. With the advent of new drug therapies, care has shifted from purely palliative and emergency measures to quell opportunistic infections to a more comprehensive, long-term care that stresses adherence to drug regimes. The result has been a decrease in overall deaths, and lengthened and improved lives for patients.

But as more patients live longer, they are more likely to encounter other serious ailments that require extensive and expensive treatments. At the end of June 2004, 4% of infected people in Louisiana were 60 years of age or older, and an additional 5% were between 55 and 59.¹ On the other hand, with a large percentage of the HIV-infected population taking some sort of HIV drug therapy, more and more patients experience serious side-effects which may exacerbate HIV/AIDS symptoms, or even cause new problems. These side-effects can range from the life-threatening to less dire ones that nevertheless change the patient's life.

In this article, we examine two issues: access to treatment for serious conditions which have been customarily excluded as experimental or investigative; and access to treatments for side-effects that are not life-threatening but that affect the patient's life detrimentally.

Access in General

Under federal law, state Medicaid plans are required to fund certain enumerated medical services whenever they are found to be "medically necessary."² Included among these mandatory services are inpatient hospital services, various outpatient services, and laboratory and X-ray services.³ On the other hand, the United States Supreme Court has held that "it is hardly inconsistent with the objectives of the [Medicaid] Act for a State to refuse to fund unnecessary—though perhaps desirable—medical services."⁴ The Veterans Administration (VA) and Medicare programs also provide for medically necessary services and applicable regulations also refer to these services as those usually provided in the course of treatment.⁵ Private medical insurance policies, whether group or indi-

vidual, generally employ the similar terms, and patients will face the same argument based on the language of the particular insurance policy.

Therefore, whether patients get the treatment they and the practitioner deem necessary can depend on the treatment being classified as necessary, and thus covered, or experimental and therefore excluded from coverage.⁶ If the procedure is generally accepted by the medical community as an effective and proven treatment for the condition for which it is recommended, then the procedure is medically necessary and should be covered by both private insurance and public benefits programs. On the other hand, if the service is rarely used, novel or relatively unknown, it would be considered "experimental" in the absence of authoritative evidence that it is safe and effective.⁷ In making this determination, courts have looked to several factors: the procedure's frequency and success record; the reputation of the practitioners and institutions that perform the procedure; the long-term prognosis of patients who have undergone it; and the extent to which medical science in related areas has developed rapidly.⁸ While the best indicator that a procedure is necessary is its acceptance by the professional medical community as a proven treatment, some different measure of "experimental" may be needed for procedures that are so new and, as a result, relatively unknown, that the medical community has not yet formed an opinion about them. Using this analysis, a court in Florida determined that a liver-bowel transplant for an infant was not experimental because (1) the procedure had been in existence for two years; (2) one provider had an excellent rate of success with the operation; and (3) the particular institution proposing the procedure had a long and excellent reputation.⁹ The court also rejected the insurer's argument that a certain amount of time had to have passed, or clinical trials had to have been completed, before a procedure would become "non-experimental." On the other hand, the Fourth Circuit Court of Appeals (which hears appeals from federal courts in the Carolinas, Virginia and Maryland) held that an insurance company did not abuse its discretion in deciding that an autologous bone marrow transplant with high-dose chemotherapy for epithelial ovarian cancer was experimental or investigative.¹⁰ The court noted that the National Institutes of Health (NIH) considered the procedure experimental, and had recommended limiting

its use to research settings.

When people infected with HIV seek treatments outside of the usual scope, they are often met with the argument that the procedure is "experimental" insofar as they are concerned due to their HIV status. In a New York decision, a man with HIV wanted his insurer to pay for a bone marrow transplant from his identical twin brother.¹¹ Although the insurer claimed that the addition of AZT therapy to protect donor cells from infection made the procedure experimental or investigative, the court rejected this argument and focused on the physician's reputation and familiarity with the procedure, noting, "The addition of AZT... does not transform what is already accepted medical protocol into experimental treatment."¹² The court was also swayed by the physician's assessment that the treatment would be just as effective for treating immunodeficiency as it had been proved to be for other, non-HIV related medical problems. The court recognized this when it stated: "The testimony made clear that both chemotherapy and bone marrow transplants have a sufficient history to support the medical community's conclusion that they are not investigative treatments. This is true notwithstanding the severe side effects of chemotherapy, the significant risk of death from bone marrow transplants and the uncertainty of the results. The consequences of the absence of these treatments is more certain."¹³ Therefore, even though the patient in question was HIV-positive, the likelihood of a successful transplant was deemed to be very strong, and therefore the insurer was precluded from denying coverage.¹⁴

Organ Transplants

On the specific issue of organ transplants, federal regulations vest The United Network for Organ Sharing (UNOS) with responsibility for administering transplants protocol in the United States. As a result, UNOS has implemented policies and procedures that must be met in order for organ allocation and donation to occur.¹⁵ These standards vary based upon the organ in question as well as the individual donors and recipients. However, they also have very specific pre-transplant policies for both donors and recipients who are HIV-positive.¹⁶ UNOS policy requires members to adopt policies for sero-positive donors and recipients, and recommends



screening potential donors for "high risk" groups, then testing potential donors for HIV, using an FDA-approved test. Organs from donors with a positive screening test are not accepted, unless a subsequent test proves the first to have been a false positive. Transplants can be performed in emergency circumstances before the donor is tested, but only with informed consent from the recipient or next of kin. UNOS policy recommends that a potential transplant candidate who is HIV positive but "who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality for immunosuppressive therapy."¹⁷

Although there are no reported decisions dealing specifically with transplants to someone with HIV, there is available case law which supports the position that transplants should not be categorically excluded as experimental simply due to the donee's HIV status. In an administrative hearing, the Massachusetts Division of Medical Assistance rejected the argument that an HIV-positive patient be excluded from the liver transplant list due to his HIV status and thus rejected the claim that transplantation is by definition experimental in people with HIV.¹⁸

In July 2004, Illinois became the first state to enact a law permitting people with HIV to donate organs to others infected with the virus. Recognizing that a diagnosis of HIV and AIDS is no longer a diagnosis of a certain and swift death, Illinois is attempting to prolong the life of people living with HIV while simultaneously increasing the number of organs available for donation. However, there are several obstacles for the new statute to overcome. Under federal law, a person who tests positive for HIV and then knowingly attempts to donate or see any organs shall be fined or imprisoned.¹⁹ In addition, Illinois and any other jurisdictions that might eventually take the same course of action will have to reconcile their new laws with the current protocol employed by UNOS.²⁰

Reconstructive/Cosmetic Surgery

Perhaps one of the most common problematic side effects for people with HIV is lipodystrophy, a redistribution of body fat that includes both fat wasting (in the cheeks, legs and buttocks) and fat accumulation (in the abdomen, face, base of neck and breasts). Estimates of the percentage of patients who experience lipodystrophy range from 20% to 50% of patients on drug regimes, while overall about 4% of patients not on medications suffer from it to some degree. Naturally, age comes

into play as well—older people, whether infected or not with HIV, may experience some "middle age spread."

There are several new treatments available to combat lipodystrophy²¹ but getting them paid for by insurance or public health programs is far from automatic. The initial reaction by most third party payors is to claim that the procedure is cosmetic and therefore not covered. On the other hand, if it can be shown that these surgeries are more than merely cosmetic, and in fact are both medically necessary as well as effective and generally accepted in the medical community, as opposed to experimental, then it may be possible to require insurance benefits programs to pay for these procedures. For example, there are now specific laws on the books in California which state that if the surgery is reconstructive, and not merely cosmetic, and improves function and/or creates a normal appearance, then the surgery must be covered by public health programs and private insurance.²²

While there does not appear to be any specific case law in either Louisiana, Mississippi or Arkansas directly related to HIV/AIDS lipodystrophy surgery, there have been developments from other jurisdictions that can be used to argue for coverage.

In Louisiana, the state health plan is not required to offer comprehensive coverage to every eligible person for procedures that are purely cosmetic. However, this does not include "[s]urgery for the repair or treatment of an injury or a congenital bodily defect to restore normal bodily functions."²³ Therefore, if it can be shown that the deformities caused by lipodystrophy, such as back problems, impaired movement, lack of sleep, compromised confidentiality and stigma as an HIV-positive person, have impaired a person's ability to function normally, then the surgeries may be categorized as reconstructive and not cosmetic, and therefore covered under state health plans.

Under Arkansas law, the state medical assistance program provides for procedures which are deemed "medically necessary" and "appropriate for the diagnosis or treatment of an illness or injury in accord with generally accepted standards of medical practice at the time the service, drug, or supply is provided."²⁴ Coverage of cosmetic procedures in particular is not addressed in the Arkansas statute. Again, if it can be demonstrated that the surgical procedures employed to correct the "buffalo hump" that results from the use of certain protease inhibitors in HIV patients is medically necessary, then it is possible that the medical program will cover the costs associated with such operations.

In contrast, under Mississippi law, there is a statute which excludes coverage of cosmetic procedures for public employees covered under the state health insurance plan except when the treatment is necessary to correct damage which is the direct result of a disease covered by the plan.²⁵ Cosmetic surgery for lipodystrophy caused by HIV appears to be covered then by the Mississippi state health plan by the wording of this statute as long as the treatment is deemed medically necessary to correct the disfigurement.

Similarly, private insurance policies apply their own exclusions, generally taking one of three approaches: excluding cosmetic surgery from coverage without defining it; defining "cosmetic surgery" and excluding it from coverage entirely; or excluding designated cosmetic procedures.

Conclusion

Standards are being developed by state and federal law to evaluate access by HIV-positive patients to treatments which were once deemed experimental. While we await the development of these clearer standards, practitioners can assist their patients by phrasing recommendations in ways that allow access rather than raising challenges by third party payors such as Medicaid or private health insurers. When recommending procedures outside of the usual scope of treatment, practitioners should be prepared to document the frequency in which the procedure is used, as well as its success, and anticipate additional challenges based on the patient's HIV status. Particularly for lipodystrophy, unless procedures are deemed restorative rather than cosmetic, they will remain out of the price range for most patients. Some of the new medications claim not to cause lipodystrophy but it is unclear whether switching treatment regimes can reverse these symptoms. Of course, the new regimes may bring their own side-effects, raising new issues about health coverage. ♦

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Nursing

How valuable is HIV rapid testing in expanded prevention efforts?

Pat Gootee, FNP

For the past 20 years of the AIDS epidemic, few can disagree that HIV testing has been labor intensive, costly, and somewhat frustrating, as many who get tested never return for the results. Return rates have been variable in different locations and populations, and under different circumstances. For instance, in a North Carolina study, Landis et al.¹ reported that only 42% of those tested returned for results and that only 51% returned nationwide (U.S.) Yet in a study by Washington University in St. Louis, looking at the differences between anonymous vs confidential testing, Berger, et al.² reported that 80% returned for results. Until now, a two-week turnaround was the norm for getting results of an HIV test.

In April, 2003, the CDC expanded currently recommended strategies to prevent new infections of HIV. The four components of this initiative are: 1) incorporate HIV testing as part of routine medical care, 2) implement new testing strategies that take place outside of traditional medical settings, 3) prevent new infections in partners of people infected with HIV, and 4) decrease current rates of vertical transmission.³

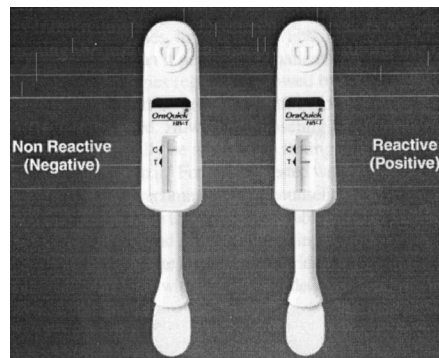
One of the most important tools in this initiative is the new rapid HIV test from OraSure Technologies, Bethlehem, PA.⁴ OraQuick was approved by the FDA for use on whole blood (via finger stick or venopuncture) in November of 2002, and received CLIA waiver in January, 2003, as a procedure of "moderate complexity." On March 25, 2004, the FDA approved expanded use of OraQuick on saliva. Less than a week prior to this announcement, FDA approved OraQuick for whole blood detection of HIV-2 (found mostly in western Africa). If the use of OraQuick on oral fluids receives CLIA waiver (which it likely will by print time), 170,000 sites in the U.S. will be available to use the test, including the 33,000 sites currently approved for the test.⁵

OraQuick rapid testing has been under use and study in various point-of-care settings in India, Democratic Republic of Congo, Ivory Coast, Botswana, Ghana, Vietnam, Honduras, the Dominican Republic and Brazil, as well as cities within the US: Chicago, Houston, and Washington, DC.^{6,7,8,9,10,11,12,13,14,15}

In African countries with multiple viral subtypes of HIV, the results of a blinded

retrospective study of stored sera from patients in STD, tuberculosis and prenatal clinics showed that all of the known HIV+ and all of the HIV- patients were accurately diagnosed, resulting in 100% sensitivity and specificity using a rapid HIV 1 and 2 test.⁷

Another study was conducted in Botswana as a result of the World Health Organization's recommendation to test tuberculosis patients. This study was to determine the utility of the OraQuick HIV Assay for the detection of HIV antibodies in sputum. Of 377 patients, 84% were HIV+ by serum Elisa. Of this positive group, OraQuick Assay detected HIV in 98.4% in gingival secretions. When the OraQuick Assay was applied to sputum specimens, the results were comparable.⁹



OraQuick Rapid HIV-1 Antibody Test nonreactive and reactive results. Source: The Annals of Pharmacotherapy, April 2004, Volume 38.

From January to July 2002, the CDC evaluated 5771 women in the labor and delivery units of four hospitals in Chicago for a study known as Mother Infant Rapid Intervention at Delivery (MIRIAD). Three hospitals used point of care testing and one used hospital laboratory HIV testing: 513 (9%) of the 5771 women were deemed eligible for rapid HIV testing; 380 (74%) of these 514 gave informed consent and enrolled in MIRIAD. A total of 225 women were tested at the three hospitals using point of care testing and 155 were tested at the hospital using laboratory testing.¹⁴

Standard enzyme immunoassay and when necessary, Western blot testing, confirmed 100% of the rapid test results. Three women were identified as HIV infected and given antiretroviral therapy during labor and delivery, along with their infants

after delivery. None of these infants became HIV infected.¹⁴

Turnaround time at the three hospitals using rapid point of care testing was 30 minutes to 2.5 hours, and the hospital using laboratory testing ranged from 3.5 hours to 16 hours. The findings in this report show that the new CDC initiative aimed at reducing perinatal HIV transmission is complemented by rapid point of care testing for women who are not screened during prenatal care, or do not receive prenatal care.¹⁴

There are three rapid HIV tests currently approved by the FDA and commercially available for use in the United States: OraQuick Rapid HIV I/II Antibody Test, Reveal Rapid HIV-1 Antibody Test, and Uni-Gold Recombigen HIV Test. Only OraQuick Rapid HIV test is CLIA waived and needs only a timer with the test.¹⁶ The test kit includes an internal control so it is not necessary to run external control specimens. The test also requires no refrigeration.¹⁶

For waived tests, there are no federal requirements for personnel, quality assessment or proficiency testing.¹⁶ They can be done in laboratories, clinical settings such as doctors' offices, HIV counseling and testing sites, mobile vans, and health fairs. To perform only waived tests, an organization must obtain a certificate of waiver from the CLIA program and follow the manufacturer's instructions. More information can be obtained at www.phppo.cdc.gov/clia/moderate.asp.

This sounds easy, but has anyone looked at error rates in non-laboratory personnel performing a rapid HIV test?

The CDC recently assessed 99 personnel with no laboratory experience performing two different types of rapid HIV tests. All participants received written instructions and one half also received a short demonstration. Error rates ranged from 2.1% to 4.6% with and without the demonstration. The number of invalid tests were greatly reduced when participants received a demonstration. The CDC recommends continued monitoring of HIV rapid testing in non-laboratory settings.¹⁷

What about using OraQuick Rapid Antibody Testing for HIV infected patients with various levels of exposure to antiretrovirals?

The CDC also conducted a study using a cohort of known and unknown HIV status.¹⁵ One hundred volunteers at low risk for HIV infection and 101 HIV I-infected patients were recruited from an



ongoing HIV natural history study. Four HIV-infected subjects tested negative with Ora-Quick. Twenty subjects were randomly selected from the remaining 97 HIV-infected participants and their serum was tested with OraQuick and a gp41 EIA as well. Results: OraQuick was reactive with oral mucosal transudate and sera from 97 of 101 HIV-infected subjects and 0 of 100 subjects who were uninfected (sensitivity and specificity, 96 and 100% respectively). 79% of the HIV-infected subjects were taking HAART on the OraQuick study. The four OraQuick false-negative subjects had undetectable viral loads at the time of the study and had been initiated to HAART early on in their diagnosis.¹⁵

How does OraQuick compare price-wise with standard HIV testing in a laboratory?

A phone survey of a local reference lab revealed that the standard ELISA would cost \$79 and confirmation by Western Blot costs \$252.¹⁸ However, one case of 100 OraQuick Rapid HIV I/II tests costs \$14.50/test and \$20 for the control tests which were discarded every three weeks or 100 tests. When ordering 5 cases (500 tests), the cost of the single test was \$12.¹⁹ In Louisiana, local STD and HIV outreach testing sites are free of charge to the patient and sent to the state laboratory at the Louisiana Department of Health.

In summary, HIV rapid testing with OraQuick holds out the hope of providing a tool in the CDC's recent initiative to decrease infection rates with HIV in many settings, including perinatal transmission in not only the western world, but in developing countries as well. ♦

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Pat Gotee is a nurse practitioner in the HIV Outpatient Program (HOP) of the Medical Center of Louisiana and corrections liaison for Delta Region AETC.

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International Volunteer Opportunities for HIV Clinicians

200 short-term volunteer healthcare providers are needed to improve the quality of care provided to over 500,000 HIV patients in developing countries.

Using clinical mentoring techniques, volunteers provide HIV bed-side training to local healthcare providers.

International Center for Equal Healthcare Access (ICEHA) is a network of physicians and nurses who volunteer technical assistance on HIV care and infectious diseases to clinics in developing countries.

ICEHA's clinical mentoring program was developed specifically for the rapid scale-up of skills of the local healthcare staff, strengthening the quality of healthcare delivered in developing countries so that countries can fight the HIV epidemic from within.

More information, including a volunteer application, is available online at www.iceha.org or by emailing Katie Graves-Abe at kgravesabe@iceha.org.



Dentistry

International collaboration on oral health and disease in AIDS

Janet Leigh, BDS, DMD

(This is the first of two reports on the 5th World Workshop on Oral Health and Disease in AIDS held in Thailand on July 6-10, 2004.)

In the mid-eighties, a small group of oral health care providers and researchers recognized the growing significance of oral health and disease in the HIV/AIDS epidemic.

In 1987, a workshop was organized and held in San Diego with the intention to set the pattern for international collaboration in standardizing the classification of oral lesions related to HIV infection, recognizing the significance of oral lesions in HIV, leading research into the mechanisms behind these manifestations and sharing methods of treatment of oral lesions. The general aims have remained the same over the past 17 years and a format was developed to encourage participation of all delegates, in order to facilitate the exchange of both research and clinical knowledge. Information gathered and questions identified at the workshops have helped direct and shape research issues for the past 15 years.

As the HIV/AIDS epidemic grew, the need for sharing knowledge in regional epicenters was recognized. In 2000, the fourth World Workshop was held in South Africa, and in 2004, the fifth World Workshop was held in Thailand.

The dental faculty, led by Dr. Wangrangsimakul, of Prince of Songkla University, took on the mammoth task of organizing the international meeting, which was deliberately set for the first week of July so that participants could then go on to the AIDS meeting in Bangkok. Three months before the start of the workshop, political unrest broke out in the province where the meeting was scheduled and the difficult decision to cancel the meeting or move locations had to be made. The government of Thailand proved its strong commitment to the fight against AIDS and the workshop was moved to the beautiful island of Phuket. This was achieved with the active involvement of the Ministry of Public Health of Thailand, the Ministry of Education, and even the Governors of Songkla and Phuket.

On July 6, 2004, individuals from 27 nations, including seven representatives

from LSU Health Sciences Center, gathered at the Pearl Village Resort for the opening ceremonies. Welcoming remarks were made by Dr. Kaeyuraphan, the Minister of Public Health, Mr. Chaibangyang, the Governor of Phuket, Dr. Petersen of the World Health Organization, and Professor Stephen J. Challacombe, the chair of the International Steering Committee.

A decision was made from the outset of this meeting that a declaration should be developed to promote greater understanding of the importance of oral health in HIV disease.

The Phuket declaration was developed and is as follows:

The participants of the 5th World Workshop on Oral Health and Disease in AIDS which took place 6-10 July 2004 in Phuket, Thailand, welcomed the initiative to analyze the evidence on HIV/AIDS related oral disease and the implications for prevention and public health programs.

The participants from 27 countries emphasized that oral health is an integral part of general health and wellbeing. They expressed concern about the growing burden of oral disease related to HIV/AIDS which particularly affects developing countries with low availability of programs and services for oral health.

Participants took note of the following documents essential to improved health and disease control in the 21st Century:

- *The WHO World Oral Health Report 2003*
- *The WHO World Health Report 2003—Shaping the future*
- *The WHO Global Health—Sector Strategy for HIV/AIDS, 2003-2007*
- *United Nations Global Strategy Framework on HIV/AIDS 2001*
- *Coogan MM, Sweet SP (eds.) Oral manifestations of HIV in the developing and developed world. Oral Diseases 2002; 8 (Suppl. 2).*

The participants hereby affirm their commitment to oral health and general health as a basic human right and resolve to support the work carried out by national and international health authorities, research institutions, non-governmental organizations and civil society for the effective control of HIV/AIDS related oral disease. In particular, the following areas of work should be strengthened:

(a) provision of systematic epidemiological information on oral health conditions associated with HIV infections;

- (b) promotion of research into understanding oral disease related to HIV and identification of the most indicative oral manifestations of HIV/AIDS;*
- (c) integrating oral health into national health surveillance systems which record HIV/AIDS related health conditions;*
- (d) dissemination of information on HIV/AIDS related oral disease, care and prevention through every possible means of communication;*
- (e) training of primary health workers in screening and provision of first-level care in HIV/AIDS related oral disease;*
- (f) access to health facilities and provision of oral health care and health promotion for the improvement of quality of life of people infected by HIV, emphasizing the inter-relationship between oral health and general health;*
- (g) development of positive attitudes towards oral care of HIV/AIDS patients by health workers.*

The development of the Phuket Declaration set an exciting tone for the meeting and the following three days were packed with morning plenary sessions, afternoon workshops and poster presentations. Six plenary sessions were given, covering 1) Current Perspectives in Epidemiology and Management of HIV disease, 2) Pathogenesis of HIV and Vaccine Research, 3) Oral Lesions and HIV Disease, 4) Innate and Specific Mucosal Immunity in HIV Infections, 5) Bacterial and Fungal Infections Associated with HIV Infection, and finally, 6) Viruses Associated with HIV.

The first session on Current Perspectives in Epidemiology and Management of HIV Disease set the tone and pace for the entire meeting. An excellent review of the global epidemiology of HIV and its implications given by Dr. Ungchusak was followed by a talk by Mr. Thanprasertsuk on HIV/AIDS Status and Trends in Asia and the Pacific Region. Of the one million infected individuals in the Asia-Pacific region, the epidemic trends tend to be concentrated in "at risk" populations of injecting drug users and sex workers. Dr. Phanuphak followed this with an examination of the impact of the epidemic on Thailand and the differences between the "older" epidemic in northern Thailand versus the "newer" epidemic in the south. The comparison of the two epidemics was particularly thought provoking, demon-



strating how old problems can morph into new changing challenges requiring flexible and adaptable approaches. Thailand is the only country in Asia that has a policy to treat tens of thousands of HIV-infected people with HAART. As a result of generic drug manufacturing within the country, a fixed dose combination of stavudine, lamivudine and nevirapine costs only \$1 per person per day. This allowed the Thai government to increase the coverage of free ARV from 12,000 patients in 2003 to 50,000 in 2004. This was followed by a sobering presentation on the HIV epidemic in India, with 4.5 million individuals infected, by Dr. Solomon and then Dr. Petersen from WHO, who shared with us the action program of WHO toward control of HIV/AIDS.

The next plenary session focused on the HIV virus with an in-depth review of HIV pathogenesis by Dr. Jay Levy from San Francisco. This was followed by a presentation of original work by Dr. Laurie Bergmeier of Professor Tom Lehner's laboratory, involving innate and adaptive immunity in protection against HIV infection. The use of a cytotoxic lymphocyte response in vaccination against HIV is difficult due to the rapid mutation of the virus. This has led the Lehner group to focus on other possible methods of vaccination, including innate immunity, targeting the vaginal and rectal mucosa to elicit a response at the site of infection, stimulating a broadly based adaptive immune response and finally, developing allo-immunity in susceptible individuals.

Dr. Deborah Greenspan started the next plenary session with an overview of oral lesions of HIV/AIDS in industrialized nations. The impact of Highly Active Antiretroviral Therapy has been seen in a reduction of many, previously common, oral lesions, although there is evidence of an increase in salivary gland disease, oral warts, and possibly squamous cell carcinoma. The recurrence of oral lesions in patients on HAART was discussed as a possible indicator of failure of therapy, either following development of drug resistance or patient non-compliance.

The comparison of oral lesions in developing countries was then made in the following talk by Dr. Rangannathan, As in the US and Europe, oral candidiasis is the most commonly occurring lesion, but there are large numbers of cases of periodontitis, oral ulcers and oral hairy leukoplakia. Dr. Tim Hodges then presented original work on Thalidomide for palliation of Kaposi's Sarcoma in Malawian children. This plenary session was concluded by a talk by Dr. Robinson who examined the public health implica-

tions of oral disease in HIV/AIDS. The problem of HIV-specific oral lesions was addressed, in addition to the oral diseases not specific to HIV, and the impact of these on the approaches to health promotion with respect to HIV-positive individuals.

The fourth plenary session tackled the important area of innate and specific mucosal immunity in HIV infections. An excellent overview on the current status of oral mucosal immunity was presented by Dr. Challacombe, with Dr. Pope presenting work on Dendritic cells and HIV infection and Dr. Weinberg on Beta-Defensins and HIV infection.

An addition to this plenary session included a presentation on funding opportunities for research and also training. Scientific opportunities were discussed by Dr. Nokta of the National Institute of Dental and Craniofacial Research and Dr. McDermott of the Fogarty International Center discussed research and training opportunities with particular emphasis on international collaborations. Dr. Petersen discussed the role of the World Health Organization in supporting research and collaborations, and finally, Dr. Phanuphak presented an example of successful international collaboration with the development of the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) which was established in 1996.

On the final day, the plenary sessions focused on bacterial, fungal and viral infections associated with HIV. Dr. Phanuphak of Thailand started with a presentation on the skin and oral lesions associated with HIV disease in Thailand. This was followed by a lecture by Dr. Ploenchon on prevention and treatment of opportunistic infections in Thailand. Mycobacterium tuberculosis is the most common infection followed by fungal infections, Pneumocystis carinii pneumonia and Cryptococcus. Dr. Paul Fidel then presented an update on Candida host interactions with original research performed at Louisiana State University Health Sciences center. The session was rounded out with a presentation on Lipid-Mediated Dialogues between host and pathogen by Dr. Agabian of San Francisco.

The final plenary session focused on viruses in HIV disease. Dr. Teo of the UK gave a detailed overview of viruses in the oral cavity in HIV disease. Dr. J. Webster-Cyriaque then followed with her original work on Expression and Oral Manifestation of EBV and HHV8. The session was continued with an examination of the

Biology of HPV in HIV Infection by Dr. Palefsky of San Francisco and finished with an overview of anti-viral factors in saliva by Dr. Sharon Wahl.

The pace of these plenary sessions was brisk and the quantity of work presented or reviewed in the three days was immense. All of the presentations stimulated a great deal of questions and feedback among audience members and many lively dialogues started in the sessions were continued at lunch and tea.

Afternoons were dedicated to interactive workshops, which reflected the collaborative efforts of this group. Prior to this meeting, lists of questions or topics of interest to be addressed in each workshop were created by individuals working in the field of oral health in HIV. These questions and the answers generated will be presented in a continuation of this article about the 5th World Workshop on Oral Health and Disease in AIDS. ♦

Janet Leigh is Associate Professor, LSU School of Dentistry; Director, HIV Dental Clinic of MCLNO; and Dental Director, Delta Region AETC.

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Executive Editor
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Editor
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