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Inside

Implications and management of xerostomia in the HIV-infected patient

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The average person produces at least 500 ml of saliva over a 24-hour period. Salivary flow rates vary considerably during any one 24-hour period depending on the demand or the current physiologic status of the patient. Saliva consists of two components that are secreted by independent mechanisms: First, a fluid component that includes ions, produced mainly by parasympathetic stimulation; second, a protein component arising from secretory vesicles in acini and released mainly in response to sympathetic stimulation. Excitation of salivary glands stimulates salivary secretion, but the effects of the parasympathetic nerves are stronger and longer-lasting.

Salivary gland disease presents clinically as parotid gland enlargement; xerostomia, or dry mouth, is also present. Oral dryness can profoundly affect quality of life, interfering with basic daily functions such as eating, speaking and sleeping. Reduction of salivary volume and subsequent loss of the antibacterial properties of saliva may accelerate infection, tooth decay and periodontal disease. Additional oral symptoms may include soreness, adherence of food to buccal surfaces, fissuring of the tongue, and dysphagia. In addition to the appearance of dental caries, angular cheilitis associated with candidiasis may exist. The taste buds also may be abnormal, resembling those of patients with idiopathic hypogeusia, and their numbers decrease. Gross accumulation of plaque may exist.

With the use of highly active antiretroviral therapy (HAART), the pattern of oral manifestations in people living with HIV disease has changed. The prevalence of salivary gland disease, however, has increased significantly. Salivary gland disease can arise in 4% to 8% of adults and children with HIV infection. The principal clinical features of salivary gland disease in HIV infection are as follows: HIV salivary gland disease with associated xerostomia and salivary gland enlargement, Kaposi's sarcoma causing salivary gland enlargement, non-Hodg-

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Immune reconstitution disease (IRD) is increasing; recognition important

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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

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Most cases of SGD show regression when HAART is implemented

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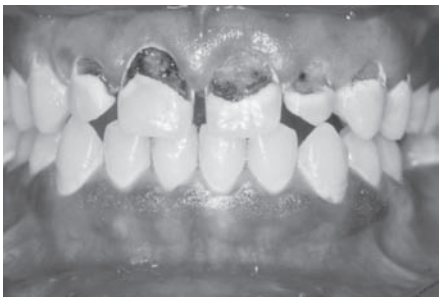
kin's lymphoma; intraglandular lymphadenopathy, and acute suppurative sialadenitis.

HIV salivary gland disease (HIV-SGD) is a distinct disorder characterized by recurrent or persistent major salivary gland enlargement and xerostomia. The parotids are most frequently affected, often with profound bilateral enlargement. Salivary gland disease tends to arise in late HIV infection, but it can occasionally be the first manifestation of HIV disease. A higher male-to-female ratio of involvement has been reported, but this probably reflects the epidemiology of the patients who have been reported. Although the exact pathophysiology remains uncertain, theories concerning the origin of SGD include lymophoepithelial lesions, cysts involving the salivary parenchyma, interglandular lymph nodes, and an inflammatory infiltrate similar to that seen in Sjögren's syndrome. The clinical picture of HIV-SGD mimics that of Sjögren's syndrome; however, there are distinct histopathologic and serologic differences between the two disorders. Patients with HIV-SGD generally do not have anti-Ro or anti-La antibodies. The minor salivary gland histopathology of HIV-SGD is generally similar to that of Sjögren's syndrome, in that it is dominated by perivascular, periacinar, and periductal lymphocytic infiltrates; however, the majority of the infiltrating T cells are CD8. Multicystic lymphoepithelial lesions may also occur, but cystic change can also arise from intraglandular ductal obstruction by hyperplastic lymphoid tissue.

Greenspan described the possible relationship between SGD and T-lymphocyte CD8+ cell infiltration in the gland. The role of viral etiology in SGD has been discussed in the literature. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have primarily been considered as the agents most likely responsible for salivary gland disease,



although multiple studies have failed to show evidence of these viruses in SGD. The diffuse infiltrative lymphocytosis syndrome (DILS) is characterized by lymphocytosis and visceral lymphocytic infiltration, affecting the salivary glands and lungs (lymphocytic interstitial pneumonia). The diagnostic criteria for DILS includes HIV seropositivity documented by enzyme linked immunoassay (ELISA) and Western Blot, bilateral salivary gland enlargement, or xerostomia persistent for more than six months, and histologic confirmation of salivary or lacrimal granulomatous or neoplastic involvement. Most importantly, patients who carry a diagnosis of DILS have a four-fold risk of developing non-Hodgkin's lymphoma.

If a patient has dry eyes and mouth accompanied by SGD similar to that with Sjögren's syndrome, a full workup for connective tissue disease or other immune deficiencies should be performed. The susceptibility to caries in HIV infection remains controversial. Some authors back the theory of increased susceptibility secondary to general and local immune suppression and diminished salivary output, while others do not find any variation when compared to control groups. Overall it appeared that patients with more advanced HIV disease showed a higher caries rate. Xerostomia independent of HIV-SGD may arise in HIV infection as a consequence of some nucleoside analog HIV reverse transcriptase inhibitors or protease inhibitors, by an unknown mechanism. Didanosine induces xerostomia; in fact, xerostomia may be seen in up to one third of patients taking it. Up to 7% of patients using protease inhibitors may have xerostomia.

Enlargement of the salivary glands is often left untreated. Close observation is the mainstay of treatment, once other factors of enlargement (e.g., malignancy) have been ruled out. Assessment of salivary function should be performed during an initial dental exam. Palpation of the major glands and milking of the major glands should be a standard part of the comprehensive head and neck examination

of HIV-positive patients. When progressive glandular enlargement is evident, function has to be confirmed by milking the involved gland and observing flow. If minimal or absent flow is seen, further flow studies might give an objective assessment of function loss. Purulent discharge from the ducts suggests acute infection and appropriate treatment should be administered. If SGD is acute, the workup should include ruling out a tumor, infection (viral or bacterial) or sialolithiasis. Asymptomatic enlargement should be monitored and salivary flow assessed during recall visits.

Lubricating agents in the form of gels, mouthwashes, lozenges, and toothpastes have been used, with varying results, to relieve the symptoms of xerostomia. Sugar-free gum or sugar-free candies may help to increase salivary output, but they may be inconvenient and affect patient's compliance. Commercial artificial saliva, available by prescription, also may alleviate the discomfort.

Therapeutic Management

Pilocarpine. Pilocarpine is a parasympathetic agonist of acetylcholine muscarinic M3 receptors and thus stimulates secretion by exocrine glands such as the salivary, sweat, lacrimal, and respiratory mucous glands; the contraction of smooth muscle; and the motility of the gastrointestinal and urinary tracts, gall bladder, biliary ducts, and bronchi. These latter effects have dissuaded some clinicians to use pilocarpine. Pilocarpine is readily absorbed from the gastrointestinal tract, and peak plasma concentrations are reached within approximately one hour. Pilocarpine is metabolized by the liver and excreted principally by means of the kidneys, with the elimination half-life being approximately one hour. Systemic pilocarpine will increase exocrine gland secretion and may also give rise to adverse side effects that reflect its other cholinergic actions.

Cevimeline. Cevimeline (±) cis-2-methylspiro [1,3-oxathiolane-5,3'-quinuclidine] mono-hydrochloride, hemihydrate; SNI-2001; Evoxac) is a quinuclidine analog of acetycholine with a high affinity for M3 muscarinic receptors both of lacrimal and salivary glands but a low affinity for equivalent M2 receptors on cardiac and lung tissue. Cevimeline increases lacrimal and salivary flow in normal rats and mice, in xerostomic mice with relevant autoimmune disease, and in rats with xerostomia secondary to irradiation. Therapy with cevimeline, 30 mg 3 times daily, seems to be well tolerated and provides substantive relief of xerostomia symptoms, whereas a dosage of 60 mg 3 times daily, although providing symptomatic relief, was associated with an increase in the occurrence of adverse events, particularly gastrointestinal tract disorders. Cevimeline is metabolized principally in the liver and excreted through the kidneys and has a half-life of approximately 5 hours (far greater than that of pilocarpine); however, the adverse effects of cevimeline mirror those of pilocarpine. It has been suggested that cevimeline may have clinical application in the management of xerostomia secondary to irradiation, HCV infection, and drug therapy, but additional data are clearly required.

> The two currently used cholinergic agents have not been approved for use in the pediatric population.

Most cases of SGD will show regression when antiretroviral therapy is implemented. This applies for asymptomatic cases with absence of salivary dysfunction. Radiation therapy has been effective in reducing glandular size in adults, but carries a high risk for malignancy in children. Surgical treatment for SGD is mainly esthetic when the enlargement interferes with daily activities. This approach consists of partial gland resection or ablation and is reserved for only the most severe and disfiguring cases.

The two currently used cholinergic agents, pilocarpine and civemeline, have not been approved for use in the pediatric population. Children with xerostomia require an aggressive oral hygiene protocol, anticipatory guidance, implementation of fluoride treatments as necessary (twice a year as a minimum) and caries control. Use of fluoride trays might be considered with severe hypo function. Recall visits should be scheduled every three to five months in children with salivary dysfunction due to their increased susceptibility to caries.❖

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Effects of long-standing xerostomia

Salivary gland enlargement
Oral mucosal soreness
Dry, sore cracked lips
Oral candidiasis
Increased frequency of cervical caries
Gingival and periodontal diseases
Depapillation of tongue (burning tongue)
Trouble eating, swallowing and speaking
Dysgeusia (bad taste)

Drugs that may give rise to xerostomia

Protease Inhibitors
Didanosine
Disopyramide
Dideoxyinosine
Diuretics
Antipsychotics
Tricyclic antidepressants
Serotonin reuptake Inhibitors
Antihistamines
Antiemetics
Decongestants
Bronchodilators
Appetite suppressants
Omeprazole
Lithium
Amphetamines

Commonly used Topical Fluoride Products (over the counter and by prescription)

OTC FLUORIDE
- 0.05% Sodium Fluoride Rinse
- 0.04% Stannous Fluoride Gel

PRESCRIPTION FLUORIDES
- 0.2% Sodium Fluoride Rinse
- 1.1% Sodium Fluoride Gel
- Prevident 5000 + Dentrifice FI gel

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unclear, it is important for clinicians to recognize it, especially since it may have unusual manifestations compared to the classic presentation of HIV-related opportunistic 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 associated 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 coinfected 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 peri-

cardial 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 granulomas 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 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.

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

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, porphyira 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

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of this syndrome involves a brisk inflammatory 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.❖

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How valuable is HIV rapid testing in expanded prevention efforts?

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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 nation-wide (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]

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 pricewise 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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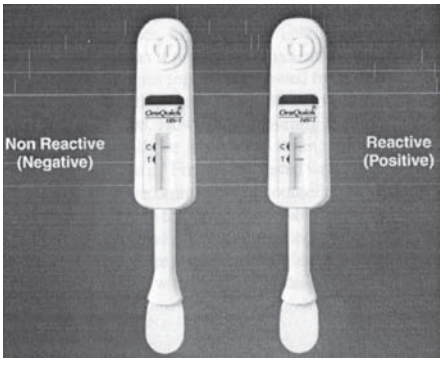

OraQuick Rapid HIV-1 Antibody Test nonreactive and reactive results. Source: The Annals of Pharmacotherapy, April 2004, Volume 38.

Dental management of HIV-infected children and adolescents

Reprinted from *HIV Clinician* Spring 2004

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As the HIV/AIDS pandemic continues, an increasing number of the world's pediatric population is becoming infected with the virus. According to the United Nations AIDS Program, in the year 2003 alone, 2.5 million children in the world became infected with HIV and more than 500,000 died.

With the advent of better methods of detection and better therapies, we are beginning to see HIV-infected children surviving longer, and thus coming under the care of a host of affiliated medical personnel, including dentists. These new treatments and newer mechanisms for assessing patients have enabled them to live longer, often with prolonged periods of severely depressed CD4 cell numbers. During these times, they are also acquiring more opportunistic infections. Some of these infections have a predilection to the oral cavity. Thus, oral health has become very important to physicians and dentists managing children with HIV infection.

The dental literature suggests that children with HIV infection are at greater risk for dental caries than children without HIV infection. This is especially true for nursing caries. The risk for dental caries and gingivitis is related to many factors. Already present are the well-recognized issues related to socioeconomic factors, lack of caretaker oral health knowledge, and behaviors such as frequent use of nursing bottles. However, other factors are also present that increase the risk for plaque diseases in the child with HIV infection. These include progressive immune compromise, effects of medications on salivary physiology and oral flora, and caries-promoting effects of oral medications.

Furthermore, some HIV-infected children suffer from progressive developmental delay and failure to thrive, which necessitates the prolonged use of nursing bottles to deliver adequate nutritional supplementation. Unfortunately, these supplements also contain very high concentrations of sugars. In these children in particular, oral dysfunction results in poor oral clearance of foods and medications, which can also increase caries risk. This article explores the clinical guidelines relating to dental standards of care for the primary care practitioner and will serve as a brief update on oral care management of children and adolescents with HIV infection.

COMMON ORAL LESIONS IN THE HIV-INFECTED PEDIATRIC PATIENT

Lesions may occur in any area of the mouth and oropharynx. At times, there may be lesions of different etiologies present. These lesions may occur singly or in multiples. Etiologic agents may be viral, such as herpes, cytomegalovirus (CMV) and Epstein-Barr virus (EBV), or bacterial or fungal organisms. Lesions caused by antiretroviral medications have been reported. Kaposi's sarcoma as a manifestation of HIV in children is very rarely reported in Western countries.

A. Oral Candidiasis

The most common soft-tissue lesion in children with HIV infection is oral pseudomembranous candidiasis. Erythematous candidiasis is also commonly observed in children with HIV infection.

A number of factors may influence the risk for candidiasis in children. Feeding behaviors and nutritional requirements that increase the frequency of fermentable carbohydrates intake (e.g., formula, juices, milk, dietary supplements), especially when delivered with bottles, support the growth of candidiasis.

Oral rinsing, nutritional and medication management, and cleansing the entire mucosal and gingival tissue area beginning at birth may help control oral *Candida* and delay the progression of oral candidiasis. In infants and small children, candidal lesions can be treated by swabbing with nystatin. Antifungal medications may also be required (See Table 1 on page 11 for antifungal medications).

Growing evidence shows that prolonged and chronic use of antifungal medications has limitations, such as resistant strains, toxicity, and deleterious effects on immature organ systems. Furthermore, both the sucrose in some antifungal preparations and the juice or milk that may be added to ensure adherence will increase the risk of caries. Elimination of the feeding bottle by weaning to a cup as early as possible may reduce candidiasis risk and frequency. Rarely, children with severe immune compromise may require much higher dosages of antifungal medication to successfully treat oral thrush. This should be prescribed in conjunction with a pediatric HIV specialist.

B. Angular Cheilitis

Angular cheilitis is commonly observed in children with HIV infection. It is diagnosed on the basis of its clinical appearance. It appears as erythema or fissures at the commissures of the lips and frequently accompanies intra-oral candidiasis. In patients with deeply pigmented skin, depigmentation may occur at the site of angular cheilitis. Cytologic smears are often negative for fungal hyphae, as angular cheilitis may represent poor diet and poor feeding in addition to fungal infection. Observation of the response of the lesions to antifungal therapy is important in confirming the role of *Candida* in the etiology of this lesion.

C. Parotid Swelling

Parotid swelling is the second most commonly reported oral lesion. It is usually asymptomatic and bilateral and spontaneously resolves and recurs. The reason for the swelling is not well understood; possible explanations include lymphocytic infiltration and non-HIV viral super infections. The differential diagnosis of parotitis also includes bacterial infection, blocked salivary ducts, lymphoma, and leukemia. In contrast to candidiasis, parotid swelling does not seem to be a marker of poor outcome

D. Caries and Gingivitis

The dental literature suggests that children with HIV infection are at greater risk for dental caries and gingivitis than children without HIV infection. The increased risk is due, in part, to baby-bottle tooth decay, progressive immunodeficiency, effects of medications on salivary flow and oral flora, developmental delay, and/or failure to thrive. Extrinsic factors such as diet, inadequate oral hygiene, socioeconomic status, lack of caregiver knowledge, and frequent use of the bottle while going to sleep may be additional risk factors. HIV infection, changes in saliva and

xerostomia contribute to the severity of plaque-related diseases. Dental eruption can be delayed in children with HIV infection.

E. Xerostomia

Diminished salivary secretion, known as xerostomia, has been observed in pediatric patients and can cause dental caries. The frequency is unknown, and the etiology is not clear. Xerostomia is difficult to assess; symptoms include dry stools, low urine volume, high fluid consumption, eating of "watery, loose" foods, and complaints of dry mouth. The administration of gamma globulin and didanosine (ddI) has been suggested as a possible cause for xerostomia in some children.

In some patients, a complex similar to Sjôgren's syndrome has been described, and the histologic appearance of cystic benign lymphoepithelial lesions has been reported.

F. Aphthous Ulcers

Aphthous ulcers in children with HIV (estimated prevalence <10%) can present serious problems, such as pain and impaired ability to eat. Diagnosis is based on characteristic clinical appearance of painful, round-to-oval, yellow-white ulcers surrounded by a halo of erythema. In addition to prolonged course, size and location may be atypical. Antiretroviral therapy with zalcitabine (ddC) has been suggested as an etiologic factor. Most aphthous ulcers in children with HIV resolve spontaneously. A short course of oral prednisone may provide symptomatic relief and hasten recovery.

Thalidomide has been shown to be effective for the treatment of non-resolving aphthous ulcers in HIV-infected patients, however serious teratogenic effects associated with thalidomide have been documented in pregnant women. In female adolescents capable of bearing children, thalidomide should only be used when 1) all other options have been exhausted, 2) the patient is known not to be pregnant, and 3) the patient is known to be using effective methods of birth control. Thalidomide is only available through a special access program. A pediatric HIV specialist should be contacted before enrolling a patient in such a program.

G. Herpetic Stomatitis

Herpetic stomatitis is a common viral infection in the pediatric population, regardless of HIV status. This lesion, however, can be especially severe in the child with HIV infection. The course of an infection may be longer than normally observed (10-14 days), the lesions may be more aggressive, and they may recur more frequently. Diagnosis of typical recurrent herpes simplex ulceration can be made by recognizing the typical clinical appearance. Herpes labialis appears as a crop of vesicles that coalesce and form an irregular ulcer on the vermilion of the lips or peri-oral skin. Intra-oral recurrent herpes simplex infection presents as a localized crop of vesicles that characteristically form only on keratinized mucosa.

Herpetic stomatitis in immune-competent hosts is self-limited and usually does not require treatment. However, in children with HIV, it may require treatment with topical, oral, or intravenous acyclovir depending on the severity of the lesions and the immune deficiency of the child.

H. Hairy Leukoplakia

Hairy leukoplakia has been reported in HIV-infected children, but it is rare. It most commonly presents as a white, ragged, corrugated, or irregular lesion involving the lateral and dorsolateral tongue. Lesions may be unilateral or bilateral. Hairy leukoplakia is caused by infection of the lesional epithelial cells with Epstein-Barr virus (EBV). It may or may not resolve, and its prognostic significance is unknown.

I. Linear Gingival Erythema

Linear gingival erythema (LGE), most commonly associated with the upper and lower anterior dentition, has been observed in pediatric patients. Based on clinical experience, it has been determined that approximately 10% of children with HIV have this condition. These lesions usually do not cause clinical problems or interfere with nutrition. LGE is limited to the soft-tissue periodontium and characteristically appears as an erythematous linear band. There also may be punctate erythema, which extends onto the alveolar mucosa. In most cases of LGE, bleeding is seen after gentle probing.

J. Periodontitis

Necrotizing ulcerative periodontitis (NUP) and other destructive diseases of the periodontium, such as atypical necrotizing ulcerative gingivitis (ANUG), are rarely described in studies of children in the United States. There may be a higher risk of these diseases in adolescents with HIV infection.

CONSIDERATIONS FOR PREVENTION AND TREATMENT PLANNING

Given the multitude of risk factors associated with oral problems, prevention is essential. Providing rehabilitative dental care is very challenging for these families and the dental care team. We have observed that once caries begins in the child with AIDS, it is difficult to control progression. Further, we have observed that appointment compliance, both medical and dental, for these families is poor. Providing proper preventive oral health care and treatment of oral disease as part of good primary medical care decreases the risk of oral infection, eliminates pain and suffering, and promotes good oral and general health in all HIV patients.

Another role of treatment of oral disease is primary detection of HIV infection. For example, candidiasis which persists after early infancy may indicate undetected HIV infection. Preventive measures provided by the child's caregiver and the medical-dental team are especially critical for the child with HIV infection (see Table 2 on page 11).

Dental sealants, optimal systemic and topical fluoride, and fluoride varnish supplementation are keys to preventive strategy. Dental therapy based on effective home care and management of nutrition and medication can give a sense of accomplishment to caregivers. The patient's oral hygiene and the condition of the soft tissues usually reflect the degree of the caregiver's and the patient's ability to adhere to the specified home care regimen.

Anticipatory guidance should begin during the prenatal period and continue during infancy as part of the comprehensive primary care for the pregnant mother and her child. Well-child care should include discussions of bottle-feeding issues and oral hygiene. Additional recommendations can be obtained from the American Academy of Pediatric Dentistry guidelines.

COMPONENTS OF A PRIMARY CARE VISIT

1. Include and document a complete oral/dental evaluation as part of the initial or intake examination and

See *HIV+ Children,* page 10

HIV+ Children, from page 9

thereafter at three-month intervals or as necessary.
2. Assure continuity of oral/dental care, especially when problems are detected on routine examination. At least one study of a group of HIV-positive patients has shown that HIV-positive patients have more caries than HIV-negative siblings. HIV-positive patients are less likely to be able to comply with dental appointments, even though they may be receiving medical attention.
3. Take a developmental approach to changing behaviors that cause or promote dental/oral disease when working with families who have limited parenting skills.
4. Support caregivers in their effort to deal with feeding issues such as the inappropriate use of bottle-feeding to induce sleep.
5.Track families with severe dental problems and provide follow-up for affected children, their siblings and future siblings.
6. Refer for dental treatment immediately if signs or symptoms of caries are noted.
7. Routine dental care:
A. HIV-positive children should receive normal dental care based on their general ability to undergo treatment procedures, not their HIV status. It is not uncommon (5%-10% of the general pediatric population exhibit some degree of nursing caries) for a 2-3 year old to require comprehensive dental care for nursing caries or rampant caries.
B. For HIV-positive patients, there is an additional risk produced by the use of cario-genic medications. Medications containing cariogenic substances (simple sugars) such as nystatin rinses and troches can cause dental caries which may result in rapid formation of dental abscess and cellulitis, especially in the case of deciduous/primary teeth. Primary teeth have relatively thin enamel (the outer layer of the tooth) and relatively large pulp chambers. These two characteristics of primary teeth create a potential for rapid destruction of tooth structure and abscess/cellulitis with frequent applications of cariogenic foods (including milk, formula, juices and nutritional supplements) and/or medications such as nystatin rinses, troche, or any medication containing cariogenic sweeteners. Medications which cause decreased salivary flow will increase the potential for caries formation; these include didanosine, dronabinol, foscarnet, interferon alpha-2A. Consider fluoride supplements such as "over-the-counter" fluoride rinses when using cariogenic medications, especially if there is evidence of existing caries or restored teeth (the most accurate indicator of high-risk status for future dental caries).
C. Young children and older phobic children may require behavioral management techniques such as outpatient sedation or general anesthesia. Behavior assessments must be made by a pediatric dentist to determine their ability to cooperate in an outpatient setting when their treatment plan calls for major dental restoration.
8. Include the dental care providers in the health care provider team.
A. Dental care providers will supply knowledge and expertise in the areas of preventive and restorative dental care.
B. Being part of the team will supply them with updated medical information to help assure safe delivery of dental care.
C. Dental care providers can help train other members of the team to recognize oral lesions.❖

This article is based on the HIV Clinical Guidelines for the Primary Care Practitioner, New York State Department of Health AIDS Institute.

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See next page for related table.

Table 1: ANTIFUNGAL THERAPIES FOR ORAL CANDIDIASIS

Antifungal Medications for Pediatric Population with Oral Candidiasis	
Agent	Dosage
Topical	
Oral nystatin suspension	2 to 5 Ml, 4 to 6 times/day
Clotrimazole troches	10-mg tablet, 3 to 5 times/day
Systemic	
Flucanozole	3 to 5 mL, 4 to 6 times/day
Itraconazole	100 mg/day orally for children>3 years of age
Ketoconazole	5 to 10 mg/kg/day

Table 2: ORAL HEALTH PREVENTIVE STRATEGIES FOR HIV-INFECTED PEDIATRIC PATIENTS

Oral Health Preventive Strategies by Age	
Age Group	Preventive Strategies
Infants	Supervised use of bottles for feeding or pacification, management of cariogenic medication
Children	Dental sealants, optimal systemic and topical fluoride, fluoride varnish supplementation, management of nutrition and medication, low frequency and chronicity of fermentable carbohydrate intake (e.g., juices, milk, dietary supplements.
Adolescents	Removing residue of food and medicine through rinsing with water or mechanical cleansing, management of nutrition and medication, addressing barriers that prevent adolescents from accessing care.

For information about HIV treatment guidelines, HIV drugs, and HIV clinical trials, vsit **aidsinfo.nih.gov**

With HAART success, managing dental caries is again important

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For at least the past twenty years, much attention has been given to the oral opportunistic infections that affect persons with AIDS. With the number of cases of AIDS in decline, the identification and management of conventional oral disease, i.e. dental caries, returns as an important health consideration for persons living with HIV (PLWH). The recent Surgeon General's Report, Oral Health in America, defines an oral disease as any condition of the mouth that interferes with daily activities such as eating, swallowing, and speaking. Dental caries, or tooth decay, is considered the most common oral disease, affecting more than 90% of all adults in the United States. Dental caries is an infectious disease caused by cariogenic microorganisms metabolizing fermentable carbohydrates provided in dietary intake. Studies using germ free animals has shown that caries does not occur without bacterial infection.

Streptococcus mutans is the most virulent cariogenic microorganism, with lactobacilli, enterococci and actinomycetes contributing to a caries-tolerant environment. Streptococcus mutans appears to spread vertically in the populations, primarily by close contact between mother and child, even through breast-feeding. Persons with higher fermentable carbohydrate amounts in their diet, for example by consumption of beverages that contain sucrose, will have higher titers of cariogenic bacteria in the mouth. Human genetic studies in which participants must avoid sucrose consumption (i.e. hereditary fructose intolerance and intestinal sucrase deficiency) support the hypothesis that sucrose does have a great impact on both colonization of the teeth by cariogenic bacteria, and the development of dental caries.

The dental caries process begins with the loss of calcium ions from the surface apatite crystals that form the bulk of the three calcified tissues of a tooth: enamel, dentin, and cementum. Alternately under normal conditions, enamel demineralization is dynamically compensated for by remineralization, a dynamic process when favorable conditions are present in the mouth. Do PLWH have increased dental caries risk secondary to compromised host immunity? Are other risk factors prevalent in PLWH? What precautions should PLWH take to reduce the risk for dental caries?

Besides cariogenic dietary considerations, PLWH may have increased risk for dental caries by association with modified salivary factors. Saliva has buffering capacity to reduce acidity, and contains immuno-globulins, specifically salivary IgA, as well as innate non-immunoglobulin factors. Chronically low salivary rate is one of the strongest indicators for increased risk for caries prevalence, probably by the loss of the protective features listed above. Alterations in oral saliva production may be pathologic from HIV infection and salivary gland dysfunction, or may result from the xerostomic side effects of certain medications. Medications that inhibit cholinergic signaling pathways in salivary tissues decrease the production of saliva, and include antidepressant and antianxiety medications that PLWH may be taking.

Conservative management of caries-active individuals includes behavioral modification, fluoride varnishes, fluoride rinses, chlorhexidine rinses, and combined chlorhexidine rinses and occlusal sealants. All health care providers should be attentive to those behaviors that contribute to this oral infectious disease. PLWH must be motivated by all health providers to engage in behaviors that will reduce morbidity. The most effective self-regulatory behavior is tooth brushing with a fluoridated dentifrice. Lessons in effective tooth-brushing technique should be given, preferably with direct supervision of a person's technique with feedback for improvement. Xylitol chewing gum has been shown to be effective in reducing cariogenic risk, but the proposed mechanism of Xylitol's effectiveness is unclear. PLWH may be encouraged to use this product. Tobacco cessation programs should be recommended for those who smoke or use smokeless tobacco products. Mothers of children with HIV should be advised of feeding habits that will prevent caries. Dental sealants, polymers that adhere to the grooves and fissures of teeth, are very effective in preventing pit and fissure caries in children.

Nutritional counseling should include recommendations to prevent dental caries. Twenty-four hour diet recall interview, three-day diet diary, and food frequency questionnaires should be considered when conducting HIV early intervention assessments. Sugar consumption in high frequency should be avoided, unless caloric intake is severely compromised without such. In such cases, behavioral modification to reduce caries should be emphasized. Doctor-prescribed fluoride gels and varnishes provide topical protection against cariogenic microorganisms, and dental referrals can determine the best product for the PLWH to receive. The appropriate fluoride regimen would include semi-annual topical application of a fluoride varnish containing 22,600 ppm of fluoride to a noncavitated carious lesion, or more frequently as indicated. Daily fluoride application at home should include a fluoride dose of 5,000 ppm, as a NaF or APF preparation. Some researchers question the use of topical antimicrobial agents such as 0.12% chlorhexidine rinse as a "shotgun suppression of the entire microbiota," yet caries reduction has been reported with regular use of such products. Further research to target specific cariogenic microbes with such products is needed.

Attention to salivary function should be given to PLWH, with treatment of salivary dysfunction as indicated. A review of medications with anticholinergic effects should be conducted as a part of primary care, to identify those with increased risk for caries. There is no conventional therapy to enhance salivary secretions for those with salivary gland disease. However, there are two drugs approved as secretogogues for persons with radiation-induced salivary gland hypofunction and Sjôgren's syndrome, pilocarpine (Salagen®) and cevimeline. These drugs activate muscarinic receptors in the salivary gland to secrete saliva, but they do not address the underlying inflammatory processes or tissue pathology that induces the hyposecreation.

In addition to screening for oral opportunistic infection, persons living with HIV should be informed of the value of preventing dental caries to improve their health, reduce complications from odontogenic infections, and improve health outcomes.❖

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The role of clinical pharmacist is pivotal in HIV outpatient clinics

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One of the major outcomes of the application of highly active antiretroviral therapy (HAART) to HIV disease, is the dramatic decrease in opportunistic infections that often accompany untreated or poorly treated HIV infections, thereby making this disease a chronic but manageable infection, amenable to long-term ambulatory care management.

The gains of HIV pharmacotherapy notwithstanding, problems with long-term toxicities due to antiretroviral therapy remain a concern, sometimes causing a parallel increase in hospital admissions. As this transition into long-term ambulatory care occurs within the prevailing atmosphere of lifelong polypharmacy, pharmacists, as gatekeepers for patients' medications, are placed in a position to offer unique services.

As the healthcare provider most accessible to the general public, and especially HIV-infected patients in-between their provider visits, ambulatory care pharmacists can play a pivotal role in optimizing HIV therapies. This can be done through their understanding of the pharmacology, side effects, issues affecting adherence for each individual patient, and drug-drug interactions associated with each patient's combination therapy. When ambulatory care pharmacists are trained to effectively communicate this information to other members of the healthcare team through formal and informal HIV updates, as well as one-on-one consults to providers, patients, significant others and caregivers, improvements in clinical and virologic outcomes can be achieved for HIV-infected patients.

One such area where pharmaceutical care services can be optimized is through an assessment of the overlapping toxicities that tend to occur or be exacerbated when different combinations of drugs are offered to an individual patient. Since most current pharmacy computer software is able to list active and inactive medications on the patient profile, ambulatory care pharmacists are well-positioned to assist the provider in assessing to what extent individual drugs being administered to the patient may have caused or exacerbated toxicity. The tables shown here attempt to offer guidance on such overlapping adverse toxicities as they occur in HIV-infected patients undergoing HAART therapy along with concomitant drugs that cause similar toxicities. Hopefully their use will assist providers of HIV care to achieve better overall treatment outcomes.❖

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Table 1: **HIV-related drugs with overlapping toxicities***

a) Drugs that cause bone marrow suppression

AZT
Cidofovir
Cancer chemotherapy
Dapsone
Flucytosine
Ganciclovir
Hydroxyurea
Interferon-a
Pentamidine
Pyrimethamine
Ribavirin
Sulfadiazine
Trimethoprim-sulfamethoxazole (high doses)
Trimetrexate

b) Drugs that cause nephrotoxicity

Adefovir (now removed from clinical trials)
Aminoglycosides
Amphotericin B
Foscarnet
Indinavir
Pentamidine

c) Drugs that cause pancreatitis

Didanosine
Ethanol
Lamivudine (in children)
Pentamidine
Valproic acid

* Concomitant administration of agents not recommended or if unavoidable, close clinical monitoring suggested.

****Cotrimoxazole**
** Cotrimoxazole causes a 40% increase in the plasma concentrations of lamivudine and so may increase lamivudine toxicity such as headaches, myalgia and neutropenia. Monitor closely upon concomitant use.

d) Drugs that cause hepatotoxicity

Delavirdine
Efavirenz
Fluconazole
Isoniazid
Ketoconazole
Nevirapine
Nucleoside reverse transcriptase inhibitors
Protease inhibitors
Rifabutin
Rifampin

e) Drugs that cause rash with or without pruritis

Abacavir
Cotrimoxazole
Dapsone
NNRTIs
Amprenavir

f) Drugs that cause diarrhea

Clindamycin
Didanosine
Nelfinavir
Ritonavir
Saquinavir
Lopinavir/ritonavir

g) Drugs that cause ocular toxicity

Isoniazid (optic neuritis and optic atrophy)
Cidofovir
Ethambutol
Lamivudine (uveitis in children)
Rifabutin

h) Drugs to avoid in patients with peripheral neuropathy (provider should assess risk to individual patient and take action as needed)

Single Ingredient drugs
Didanosine (Videx, ddI)
Nitrofurantoin (oral)
Nitrofurantoin macrocrystal (oral)
Nitrofurantoin sodium injection
Stavudine (Zerit, d4T)
Zalcitabine (Hivid, ddC)

Multiple ingredient drugs
Didanosine/calcium carbonate/magnesium salt (oral)
Didanosine/magnesium salt/sodium citrate (oral)
Nitrofurantoin/hexylresorcinols/cetrimonium (oral)
Nitrofurantoin/nitrofurantoin macrocrystal (oral)
Nitrofurantoin/pyridoxine HCL (oral)
Nitrofurantoin/tetracaine (oral)
Sulfadiazine/nitrofurantoin (oral)
Sulfadiazine/nitrofurantoin/phenazopyridine (oral)
Sulfamethizole/nitrofurantoin (oral)

Table 2: **Drug interactions with anti-*Pneumocystis carinii* pneumonia agents**

Drug	Major adverse reactions	Interactions
Atavoquone	Transaminase elevation, rash, fever	Increases levels of ZDV
Dapsone	Rash, nausea/vomiting, anemia, methemoglobinemia, neuropenia, thrombocytopenia, transaminase elevation	Increases levels of trimethoprim and dapsone that may increase both the pharmacologic and toxic effects of both drugs. Rifampin increases metabolism of dapsone while ddI decreases absorption of dapsone and may lead to failure of dapsone prophylaxis. Avoid.
Pentamidine	Nephrotoxicity, hyperglycemia, transaminase elevation, hyperkalemia, neutropenia, thrombocytopenia, pancreatitis, potentially life-threatening ventricular arrhythmias	Foscarnet: increased risk of nephrotoxicity, severe hypoglycemia and hypocalcemia. Avoid drugs that cause or exacerbate pancreatitis such as ddI.
Primaquine	Hemolysis (especially in G6PD-deficiency). Fever, rash, methemoglobinemia, transaminase elevation.	
Clindamycin	Diarrhea, nausea, vomiting, pseudomembraneous colitis, rash, fever, transaminase elevation	Opiates and diphenoxylate may worsen diarrhea. Kaolin-pectin antidiarrheals decrease absorption of clindamycin. Patient needs close monitoring.
Trimethoprim-sulfamethoxazole	Skin: erythema multiforme (Stevens-Johnson syndrome, rare), generalized skin eruptions, epidermal necrolysis, exfoliative dermatitis, photosensitivity, urticaria, pruritus. Nausea, vomiting, transaminase elevation, neutropenia, thrombocytopenia and fever.	Increased prothrombin time for patients on warfarin. Increases levels of dapsone and half-life of phenytoin due to protein binding.

Source: Adapted from multiple sources, mostly from Pharmacist's Drug Handbook 2002, American Society of Health Systems Pharmacists, Bethesda, Maryland and the DHHS Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington, DC. Department of Health and Human Services (DHHS) and the Henry J. Kaiser Foundation, February 4, 2002.

Thalidomide for recurrent apthous ulcerations

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Kishore Shetty, DDS

Recurrent apthous ulcers (RAU) are the most common oral ulcerative disease, affecting 10-15% of the general population. Clinically, RAU presents as extremely painful, shallow ulcerations with an erythematous halo on unattached oral mucosa. First described by Hippocrates in 400 BC, the disease is identified by several names by the lay public and professionals: canker sores, cold sores, apthous stomatitis. RAU have been reported in 2-4% of HIV-seropositive patients and are more frequent in advanced stages of their disease. Accurate diagnosis of oral lesions in the HIV-seropositive patient may require biopsy in combination with a clinical examination and patient history.

The pathogenesis of RAU involves a predominantly cell-mediated immune response in which tumor necrosis factor plays a major role. A monoclear (lymphocytic) cell infiltrate in the epithelium in the preulcerative stage is followed by a localized papular swelling. The painful papule then ulcerates and a fibrinous membrane covers the ulcer, which is infiltrated mainly by neutrophils, lymphocytes and plasma cells.

RAU are often quite painful, may lead to difficulty in speaking, eating, and swallowing, and may negatively affect patients' quality of life. In patients with advanced HIV disease, apthous ulcers may exacerbate weight loss. While most apthae are small and heal within 7-10 days, larger ulcers can persist for weeks or months. Consequently, therapy for the disease of RAU should address both healing and the prevention of new ulcers.

The primary goals of therapy for RAU are relief of pain, reduction of ulcer duration, and restoration of normal oral function. Secondary goals include reductions in the frequency and severity of recurrences and maintenance of remission. Table I illustrates the topical and systemic agents for RAU approved by the FDA. Topical medications can achieve the primary goals but have not been shown to alter recurrences or remission rates, especially in cases of large apthae in HIV-positive patients. This necessitates the use of systemic medications. The agents listed in Table I have had limited success in the management of major apthous ulcers in the HIV-positive patient.

There has been renewed interest in the therapeutic potential of thalidomide despite its known teratogenic effects in humans. Of primary interest to patients with HIV infection are results demonstrating the healing of oral apthous ulcerations. Furthermore, thalidomide has suggested benefit in the management of HIV-associated wasting and may alter tumor necrosis factor alpha, known to induce the expression of HIV by infected cells.

History of thalidomide

Thalidomide was first introduced as Contergan in 1956 in West Germany as a sedative. Because of its presumed safety and anti-emetic effect, thalidomide was given to pregnant women suffering from morning sickness and for nausea associated with influenza. Between its introduction and removal in late 1960s from the market, thousands of babies were born with severe deformities, most notably vestigial, often flipper-like limbs, as well as malformed internal organs. The teratogenic effects of thalidomide became known and the drug was withdrawn from the world market in 1961.
During the period when it was being prescribed to expectant mothers, it was found that thalidomide also had some anti-inflammatory effects. In 1964, a physician in Israel was confronted with a patient with erythema nodosum leprosum (ENL), one of the many manifestations of leprosy. ENL is characterized by painful skin nodules and nerve damage. With few other options, his doctor administered thalidomide, some of which remained in a local hospital pharmacy. Within a few days, the nodules vanished and did not come back as long as the drug was continued.

Worldwide use over the past 30 years has confirmed thalidomide as the preferred treatment for moderate to severe ENL in men and women without childbearing potential, and this application led to its availability in the United States for many years on a compassionate-use, investigational basis for the treatment of ENL.
This immunomodulatory activity of thalidomide provided the rationale for continued research in numerous disorders such as RAU.

Mechanism of action

The mechanism of action of thalidomide is not fully understood, and it may be related to immune modulation, cytokine inhibition, and/or antiangiogenesis. Importantly, the drug is not mutagenic, cytostatic, or myelosuppressive. In healthy male volunteers, thalidomide, 200 mg for four days, induced a significant decrease in a circulating T-helper to T-suppressor cells ratio, compared with pretreatment values. The decreased helper-to-suppressor cell ratio resulted from a significant decrease in the percentage and absolute numbers of circulating T-helper cells and an apparent increase in the percentage and absolute numbers of T-suppressor cells. Thalidomide also inhibits TNF–alpha production by accelerating the degradation of messenger RNA encoding the protein.

Pharmacokinetics

Thalidomide is absorbed slowly from the gastrointestinal tract. The extent of absorption is proportionate with the dose at lower doses, but at doses higher than 200 mg, a flattening of peak concentration is observed, with an associated delay in the time to peak concentration. Peak plasma concentrations occur three to four hours after drug administration. The effects of administration with food on the peak concentration and extent of absorption are minor, increasing or decreasing by less than 10%.

Thalidomide is not hepatically metabolized to any appreciable extent. The primary degradation pathway for thalidomide appears to be nonenzymatic spontaneous hydrolysis in blood and tissue, but metabolism by aromatic hydroxylation has also been observed.

The mean elimination half-life of thalidomide is approximately five to seven hours and is not altered by dose or after multiple dosing. Total body clearance in healthy volunteers is 10.41+/-2.40 L/h. Renal clearance is 1.15ml/min, indicating mainly nonrenal elimination. Urinary excretion of thalidomide is small, with 0.7% of the dose excreted unchanged in urine; 0.02% is excreted as 4-OH-thalidomide 12 to 24 hours after the dose. There is also no evidence to suggest that age, gender, or race affects

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the pharmacokinetic parameters of thalidomide.

Thalidomide and recurrent apthous ulcerations

The National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group evaluated the activity of thalidomide as therapy for oral apthous ulcers in HIV-infected patients in a double blind, randomized, placebo-controlled study. Of 57 patients included in the analysis, 28 received placebo and 29 received thalidomide, 200 mg orally once daily at bedtime for four weeks. Overall, 26 (90%) of the 29 patients in the thalidomide group had a complete or partial response at the end of week four, compared with only seven (25%) of 28 patients in the placebo group. Complete resolution was achieved in some patients within as little as one week after the start of therapy, although the median time to complete healing among responding patients was 3.5 weeks. In addition, quality–of-life measures clearly show that thalidomide reduced pain from the apthous lesions and improved the patient's ability to eat. A retrospective analysis evaluated the efficacy of thalidomide for recurrent apthous stomatitis in 25 immuno-competent patients receiving initial doses of 50 to 100 mg/d. Treatment duration ranged from one to 55 months. Of the 25 patients, six demonstrated complete healing and were able to stop treatment without recurrence. An additional 10 patients responded and remained in clinical remission with low-dose thalidomide.

Neuropathy associated with thalidomide is manifested by painful paresthesia of the hands and feet, often accompanied by sensory loss in the lower limbs. Irreversible neuropathy may result if treatment is continued too long or signs of motor dysfunction develop. Neuropathy limits long-term use of thalidomide. Most reported cases occurred at dosages of 100-300 mg/day given for more than six months.

The National Institute of Dental and Craniofacial Research and the National Institutes of Health have recently announced a multi-site clinical trial to test the effectiveness of a topically applied formulation of thalidomide. The researchers predict that the topical thalidomide, when applied in a dosage of 20 mg, will effectively heal and reduce the pain associated with apthous ulcers, without causing the side effects of a systemic dose of the drug

Therapy with thalidomide requires teaching patients to identify the early signs of neuropathy and to understand the risk of teratogenicity. Prickling, tingling, numbness, or pain in the extremities suggests the need for an examination by a physician. Patients should be evaluated at baseline and monthly for the first three months, after which examinations for manifestations of neuropathy should continue periodically. Sensory nerve action potential (SNAP) testing should be performed at baseline and every six months. All patients, pharmacists, and physicians must participate in the System for Thalidomide Education and Prescribing Safety (STEPS) program. Patients must meet eligibility criteria to receive the drug. Informed consent must be obtained to ensure education about contraceptive measures for men and women, the frequency of pregnancy testing, and the symptoms and evaluation of peripheral neuropathy.❖

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See next page for related table.

Evidence-based practice: implications for social work in AIDS care

Reprinted from *HIV Clinician* Winter 2002

Valerie Gordon-Garofalo, MSW, PhD

New mandates require social workers to engage in "evidence-based practice." What does this new terminology mean, and how does it change social work practice and the delivery of HIV/AIDS-related social services?

Evidence-Based Practice (EBP) is a process by which social workers and other practitioners pose treatment-planning questions, search for the current best practices, and deliver interventions based on sound guidelines (Gibbs, 2002). It is simply making practice decisions on the best available research evidence or, in their absence, utilizing well-formulated standards of care.

While new graduates of MSW and other health science programs will be proficient in gathering evidence for practice, those who have been working in agencies for a few years may not understand this new jargon or the requisite implementation process. In fact, a recent study showed that social workers in the work force tend not to engage in evidence-based practice, know what it means, or understand what it entails (Mullen & Bacon, 2000). However, social workers are very interested in applying these methods once explained, and implementing evidence-based practice is easy.

Steps in EBP

The process of evidence-based practice follows several steps, according to Gibbs (2002), who adapted for social work the framework that medical doctors use (Sackett, Richardson & Haynes, 1997). The following is a condensation.

Asking answerable questions. EBP is best applied when social workers can access technology to consult the current best evidence quickly. Converting information needs into specific questions allows us to guide a computer search or seek other consultation as the situation is unfolding and soon enough to guide our decisions about treatment options (aka "just in time"). A good question, like a good treatment plan, is always developed with the client's input and has four components. It identifies (1) the client type and problem, (2) what you might do to address the problem, (3) alternative action steps, and (4) what you want to accomplish. The clinician generally asks questions that address one or more of five dimensions: treatment effectiveness, prevent-ion, assessment, description, or risk. Especially important are how these aspects of practice apply differently to diverse client types (e.g., for men vs. women, low income vs. affluent, those with higher levels of education vs. those who are minimally educated), with different units of attention (e.g., for individuals vs. families, groups, or organi-zations), and in different settings (e.g., in-home vs. agency or clinic). An example of a question that addresses effectiveness might be (1) If a newly diagnosed African-American female client shows signs of depression, (2) is referred to a psychoeducational group, (3) or given individual cognitive-behavioral counseling, (4) which will result in a return to normal-level functioning most effectively? Questions resemble the traditional treatment plan

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Table 1

Topical Agents for Recurrent Apthous Ulcers

Amlexanos	Most effective for minor ulcers
Antibiotics	May be used as a rinse for patients with multiple ulcers
Chlorhexidine Gluconate	Effectiveness is unpredictable
Corticosteroids	Superpotent strength formulations are most effective

Systemic Agents for Recurrent Apthous Ulcers

Colchicine	Suppressive therapy Limited by GI toxicity
Dapsone	Suppressive therapy Requires careful laboratory testing
Pentoxifylline	Least toxic suppressive therapy Controlled efficacy studies are needed
Thalidomide	Acute treatment for patients with ulcerations unresponsive to topical therapy

Table reproduced with modifications from Eisen 2001

Once-daily dosing: do the benefits outweigh the concerns?

Reprinted from *HIV Clinician* Summer 2002

Paul Monier, MD

There is no doubt that highly active antiretroviral therapy (HAART) has favorably affected the treatment of HIV-infected patients. Patients who are able to strictly adhere to and tolerate an antiretroviral regimen clearly benefit in terms of both symptoms and disease progression.

However, this favorable response is often tempered by the complexity of the treatment schedule employed, as well as by toxicities of individual antiviral agents. These factors lead to non-adherence, the rate of which has been estimated to be as high as 50%.[1] Recognizing this, a major goal in the treatment of HIV infection has been simplification of the complex dosing schedules that have become commonplace in treating this illness. Several strategies have been employed to this end, including combination medications, the development of agents with longer half-lives, and the exploitation of pharmacokinetic interactions between agents to boost drug levels and allow for reduced dosing frequency and easier dosing requirements. The latter two strategies have played a major role in the evolution of once-daily dosing of HAART, which has recently come to the forefront as another means of achieving greater adherence.

Suboptimal adherence with medications is the most common impediment to a successful outcome in treating an HIV-infected individual.[2] Lack of adherence not only leads to inadequate viral suppression, but also places the patient at increased risk for the development of drug resistance, thus limiting future treatment options. It is generally accepted that compliance rates of >95% are required for optimal efficacy of HAART. In one study, rates of virologic failure, defined as HIV viral RNA levels of >400 copies/ml, were 30% higher in patients who were 90-95% adherent with their medications than in those who were >95% adherent.[3] As would be expected, the percentage of successful outcomes drops as compliance decreases. Patients cite many reasons why they are unable to adhere to their medications, including forgetfulness, inconvenient dosing schedules, heavy pill burdens, drug intolerance and adverse effects.[4] The higher rates of mental illness and substance abuse frequently seen in HIV-infected populations only add to the problem of noncompliance. It is hoped that once-daily dosing of HAART will positively impact adherence by directly influencing medication-related problems such as inconvenient dosing, as well as by providing treatment schedules that can conceivably be followed by typically nonadherent patients. Studies have shown that once-daily dosing in the treatment of hypertension is only somewhat better than twice-daily dosing but superior to regimens that require medication be taken three times per day,[5] whereas accuracy of dose timing was much better in the once-daily group than that seen in the twice-daily group. Similar results have been shown in studies assessing compliance in patients being treated for diabetes.[6] Whether this can be extrapolated to the use of antiretroviral agents remains to be seen. All of this aside, HIV providers need to understand that nonadherence is a multifactorial problem and although a step in the right direction, once-daily dosing will not be a "magic bullet" that resolves all adherence issues.

The number of once daily options has recently expanded and will continue to do so. FDA-approved agents available for once daily use in treating HIV infection include efavirenz, didanosine, tenofovir and amprenavir when combined with low dose ritonavir (RTV). Agents currently FDA approved for twice daily dosing but under evaluation for once-daily use include lamivudine, nevirapine, other RTV-boosted protease inhibitors, and abacavir. Investigational agents that will be taken once daily include atazanavir, stavudine XR, and emtricitabine, as well as other agents less further along in development. Several studies cite success using various combinations of available agents in treating HIV infection, and more data is certain to evolve. Several combinations consisting of two nucleoside reverse transcriptase inhibitors (NRTI) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an RTV-boosted protease inhibitor (PI) from Table 1 could be used to construct a once-daily antiretroviral regimen. It should be noted, however, that tenofovir and didanosine should only be used together with caution, if at all, because of an interaction that leads to potentially toxic levels of didanosine. The most studied once daily combination consists of efavirenz, didanosine, and lamivudine.[7,8] In one cohort, 77% of 75 patients achieved an HIV viral RNA <50 copies/ml with a concomitant mean rise in CD4 cell counts of 199/ml. Similar results were reported in another trial which evaluated the same regimen in 40 additional patients. Several RTV-boosted PI-based regimens have been evaluated[9-11] using various combinations containing low dose ritonavir added to either amprenavir, saquinavir, indinavir, or lopinavir. In addition, a once daily triple NRTI regimen anchored by abacavir is likely to evolve as well.

The advantages of once-daily dosing of HAART are clear. Less frequent dosing should lead to improved adherence and ultimately to more successful outcomes. In addition to improved symptoms related to viral suppression, many patients would also be expected to experience a psychological boost resulting from the impact once daily dosing could have on lifestyle, as well as a general sense of well being as treatment becomes more simplified. Other advantages include, in some cases, reduced cost and a greater ability to employ directly observed therapy (DOT), which has proven useful in certain populations such as patients who are incarcerated and those in drug rehabilitation programs.[12]

No new treatment strategy can be employed without concerns and once-daily HAART is certainly no exception. First of all, there is a lack of data to support its use as optimal treatment in terms of efficacy and durability of viral suppression when compared to standard dosing. Preliminary data appears favorable in this regard but is based mostly on observational cohort studies. Randomized comparative trials are needed to address this issue. Until more data are available, providers may want to be selective in choosing patients who are prescribed once-daily regimens, focusing on those with less advanced disease states or those whose lifestyles preclude more frequent dosing. Another commonly asked question concerns missed doses. If a patient taking once-daily HAART were to miss his or her scheduled medications, a 48-hour interval could elapse between doses, potentially allowing viral replication and possible resistance formation as drug levels fall below the IC50 for that agent. Because of this, it is suggested that drugs that have long half-lives and are therefore "forgiving" if doses are missed should be used when constructing these types of regimens. Examples of such agents include the NNRTI's efavirenz and nevirapine, as well as amprenavir when boosted with ritonavir. Based on some pharmacokinetic

models, missed dosing doesn't appear to be any more of a problem with these agents when used once daily than when standard dosing is used. However, this concept of "forgiveness" is not completely understood and the clinical effects of missing doses of a once-daily regimen are not known and will be further complicated by interpatient variability, the role of intracellular concentrations of medications, and drug-drug interactions. Another concern with once-daily HAART is pill burden. This is particularly a problem with the PI-based regimens, which can require as many as 12 pills to be taken all at once. Whether this is an improvement over standard dosing of PIs, which usually requires 5-6 pills be taken twice daily, remains to be seen. For NNRTI-based regimens, pill burden is less of an issue, although no studies demonstrate whether 4-5 pills taken one time per day is an improvement over one pill twice daily; i.e. Trizivir.® Many clinicians have also raised the question of whether taking more pills once daily will be associated with a greater incidence of adverse effects. It seems reasonable to expect that the PI-based regimens are likely to be associated with more gastrointestinal side effects such as nausea and vomiting. In a study comparing once-daily HAART containing ritonavir-boosted saquinavir with an efavirenz-based regimen, there was a significantly higher discontinuation rate in the saquinavir-ritonavir arm with 34% of these patients experiencing nausea, vomiting, or diarrhea.[13] It should be noted that these toxicities are more likely to occur using the soft gel formulation of saquinavir. This has lead to a renewed interest in the use of Invirase® (the hard gel formulation of saquinavir) in lieu of Fortavase®, combined with ritonavir, a regimen that would be less likely to induce gastrointestinal-related complaints.

The evolution of once-daily dosing of HAART is another positive advance in the treatment of HIV-infected patients. Complex treatment schedules and adverse effects of medications have tempered the incredible success seen in patients who are able to adhere to and tolerate HAART. And although improvement in terms of viral suppression, immunologic response and symptoms is clearly desirable, it is often achieved at the expense of quality of life which is affected by dosing schedules, pill burdens and side effects. Once-daily dosing has the potential to positively impact quality of life. However, as with any new treatment strategy, there are real concerns and once-daily HAART should be used judiciously. One certainly does not want to sacrifice efficacy for the sake of convenience. In addition, whether or not more pills taken once daily will lead to better adherence than fewer pills taken twice daily is not clear. Like most decisions faced in treating HIV infection, the choice to use once-daily therapy needs to be based on individual patient characteristics and in all likelihood will be well suited for some, while less than ideal for others.❖

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approach, taught in almost all schools of social work and used in most HIV/AIDS case management and mental health agencies.

Tracking down best practices. The most efficient way to locate evidence of effective treatment options is to run a computer search. This requires access to electronic databases or Internet search engines and skill in searching them. It is beyond the scope of this article, but instruction in conducting computer-based evidence searches is available through many channels. Schools of social work are offering continuing education workshops, as are HIV/AIDS social work conferences. As well, soon to be released is an excellent guide from Brooks/Cole Publishing (Gibbs, 2002). Other information is quickly becoming available through journal articles, web-based information, and clinical guide books (Corcoran, 2000).

Sources for gathering information include: libraries (both public and university), Delta ETC and other ETC web sites, websites related to social work practice and/or HIV/AIDS care, professional associations and their on-line and printed journals, and internet search engines. The Delta ETC website provides access to medical resources and their related behavioral components through searchable databases, such as PubMed, NLM Gateway, and MedScape. University and medical school library databases are available on a limited basis to non-affiliated professionals. Field instructors of social work interns share full library privileges, including Internet account access, which allows off-site database search. Of particular interest to social work practitioners are the Silver-Platter databases: Social Work Abstracts, PsychInfo (psychology-based), SocioFile (sociology-based), and ERIC (education-based). Purchasing portable databases for agency use is an option. A less expensive option may be database sharing through a consortium or resource network arrangement. We should also advocate for social work relevant database inclusion in HIV/AIDS information clearinghouses.

Critically appraising the evidence. According to Gibbs (2002), this

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Complication risks of invasive procedures on HIV+ patients

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Kishore Shetty, DDS

Complications may result from dental procedures in any healthy individual. There is an abundance of literature on the risks of prolonged postoperative bleeding, delayed wound healing, alveolitis, oral wound or distant site infection whenever dental procedures are performed. However, there is very limited published scientific evidence available to guide clinicians in regard to possible increased risks of oral procedures associated with the HIV status of the patient. A review conducted in 2000 by the Agency for Healthcare Research and Quality concluded that only a few studies have been reported, and only two types of procedures, root canal therapy and simple extractions, have been investigated. This article is an attempt to review the scientific literature since then, and make general recommendations. This review also lists treatment planning guidelines to help the dental provider while providing care to the HIV-positive patient.

Dental Extractions

Immunologically-compromised patients are unable to generate sustained, controlled and effective immune responses when subjected to external trauma. This universally accepted notion is in turn reflected by the high risk of postsurgical complications in these subjects. Consequently, it has been suggested that the risk of complications in HIV-positive patients subjected to dental extractions is presumably much higher than in the general population.

In 1997, Dodson reported finding no difference in a prospective study of complication rates between HIV-positive and HIV- negative patients undergoing tooth extractions at Grady Memorial Hospital, Atlanta, from 1993 to 1996. Post extraction complications that varied in prevalence between the studies included persistent bleeding, persistent pain, localized alveolitis, local wound infection and delayed wound healing However, a retrospective study conducted by the same author in 1988-89 at the Veterans Affairs Medical Center, San Francisco, found that the postextraction complication rates among groups of HIV-positive patients were higher and that the risks increased with increased levels of immune suppression. When these results were adjusted for age, preoperative antibiotic coverage and tobacco use, the difference in complication rates was no longer statistically significant. Two other studies found no significant difference between postoperative complications in the HIV-positive and HIV-negative groups, although the HIV-positive groups tended to have more complications. Nevertheless, across all studies, the postoperative complications were rather minor, and were treated on an outpatient basis.

Implant Surgery

Although there has been relatively little research on the effects of providing dental implants for individuals with HIV, it appears that implant surgery can be successfully provided for many patients. Experts have suggested that there is no difference in the rate of postoperative complications or osseous integration for implant patients with or without HIV infection. Treatment planning must be done on an individual basis in therapeutic partnership between providers and patient.

Endodontics and Apex Surgery

It has been suggested that endodontics and apex surgery in HIV-positive patients should be carried out early, and that the management approach is conditioned by the symptoms, the existence of prior endodontics, the importance of the affected tooth, the oral condition of the patients, and state of immune suppression. The incidence of complications derived from conventional endodontics in the HIV-positive patient is similar to that reported in the general population. Consequently, it has been suggested that no special precautions are required in HIV-positive individuals, and prophylactic antibiotics and anti-inflammatory medication are not recommended unless indicated.

Periodontal treatment

The treatment of periodontal lesions is complex, for the aims of management range from immediate control of pain and gingival bleeding during the acute phase of the process, to the elimination of infectious etiologic agents, prevention of tissue destruction, and the promotion of gingival health. The measures adopted basically comprise local mechanical treatment, the administration of antimicrobials, and the maintenance of oral hygiene. Although mechanical treatment produces transient iatrogenic bacteriemia, the risk of sepsis is fortunately not increased, and symptomatic complications only exceptionally arise.❖

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Treatment planning guidelines for use by dental providers who are providing care to HIV-infected patients

- The medical history should include determination of CD4 counts and viral loads and a review of all drugs that the patient is taking.
- All surgical procedures should be performed in a manner that minimizes bleeding and avoids introducing oral pathogens into the deeper fascial planes and oral spaces.
- Antibiotics should be used judiciously in patients with HIV disease. The clinical decision to prescribe antibiotic therapy should be made on an individual basis. Routine antibiotic prophylaxis is contraindicated.
- If the neutrophil count in a patient is <500 cells/mm^3, the dental provider should administer antibiotics pre-operatively and post-operatively in consultation with the primary care provider.
- For HIV-patients with heart valve abnormalities or other indications for increased risk of bacterial endocarditis, dentists should use the standard protocol established by the American Dental Association and the American Heart Association.
- Oral surgery should be postponed, if possible, when hemoglobin levels decrease to 7.0g/dL or below.
- An increased bleeding time (>9 minutes) indicates a need to assess quantitative and qualitative platelet function.
- Elective dental extractions in HIV-patients who have a platelet count <50,000/mm^3 should be delayed until the primary care provider can be consulted and appropriate treatment strategies are selected.
- The treatment of periapical lesions should be early and aggressive in patients with HIV infection, in order to avoid exacerbations in advanced stages of the disease.

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step implies applying a "hierarchy of evidence," whereby one rates the evidence provided. Studies that use comparison or control groups, probability sampling, clearly defined treatment approaches, adequate numbers of participants, valid and reliable measures, and appropriate statistical analyses are, of course, rated higher than those which do not employ such rigor. A parallel appraisal of feminist, qualitative studies requires examining the validity of interpretations and participant involvement in the research process.

When there is not sufficient evidence in a search of the professional literature to justify one treatment or assessment method over another, one should first turn to sanctioned standards of care or practice guidelines, then rely on supervisory or peer consultation and one's own practice wisdom.

Applying the Results. In this step, the clinician must decide the extent to which evidence gathered applies to the decision at hand. Are the clients similar enough to those described/studied? What about access to the preferred interventive strategies? Practitioner strength in delivering the identified best practice?

Evaluating Performance. Keeping adequate records, documenting service delivery and client satisfaction, and evaluating outcomes is a necessary part of EBP. Social work successes tend to be anecdotal (Vallianatos, 2000). Needed, instead, is clear documentation of service eligibility; clearly articulated rationales for service structure and components; the use of structured assessment tools for identifying individual risk factors and assigning clients to service level; evidence-based interventions, derived from clinical efficacy trials; and documentation and evaluation of program outcomes, to justify the results of programs (Voourlekis, Ell, Nissly, Padgett, & Pineda, 2001). Most, if not all, of these components are present in our state and regional HIV/AIDS service systems. Evidence that social work interventions are effective must be documented in-house, shared with funders and client stakeholders, discussed in consortia, presented in professional forums, and published for those outside the field. For example, task-centered brief treatment works, as do case management and discharge planning in HIV inpatient settings (Vallianatos, 2000), but if evidence is not made public, it cannot be viewed as best practice.

Ways to implement EBP in HIV/AIDS care

Becoming motivated. Gibbs (2002) states that for social workers, the motivation toward EBP will probably come from our dedication to do no harm, our determination to make better practice decisions, and our commitment to collaborate with our

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How common illicit substances interact with antiretroviral agents

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Tina Edmunds-Ogbuokiri, PharmD, FASCP

Recent reports in the literature have brought more attention to the life-threatening interactions, including deaths, that have occurred when protease inhibitors were combined with illicit drugs such as ecstasy (MDMA) and GHB (gamma-hydroxybutarate) (Harrington 1999).

Although protease inhibitors have dramatically improved the prognosis for many HIV-infected patients, they are associated with numerous adverse effects including increases in serum glucose, triglycerides, lipodystrophy, hepatitis, nephrolithiasis and a large variety of GI side effects (Flexner, 1998).

In addition, protease inhibitors can cause serious adverse reactions and interactions when administered in combination with other substances, including illicit drugs, whose metabolism may be altered as a result of the inhibitory effects of the PIs on the cytochrome P450 enzyme system.

Illicit substances most commonly abused include cocaine, marijuana, methamphetamine, ecstacy, heroin, methadone, ketamine, crystal and GHB.

As a result of the myriads of side effects that could follow use of these substances (see listing of side effects for ecstasy at end of article), combination of these substances with protease inhibitors especially increases the likelihood of an overdose due to these agents, for example, ecstasy.

Cocaine has been reported to increase the speed at which HIV replicates while combination of the protease inhibitors with marijuana increases levels of tetrahydrocannabinoids in the blood.

Because combination of methamphetamine with ritonavir (Norvir) causes an increase in the potency of ritonavir, two to three fold, the likelihood of overdose with methamphetamine is increased.

Concomitant use of ketamine in the presence of the protease inhibitors causes hepatitis, while ritonavir decreases plasma levels of heroin by 50%.

Potency of methadone is decreased in the presence of ritonavir, indinavir (Crixivan) and nevirapine (Viramune), while methadone increases the potency of ritonavir by 50%.

Nevirapine was demonstrated to reduce plasma methadone levels and to precipitate opiate withdrawal in patients who were maintained on methadone for narcotics addiction (Altice, 1999).

More recent studies have reported decreases in the amount of stavudine (Zerit) and didanosine (Videx) absorbed from the digestive tract into the bloodstream in the presence of methadone.

Table 1 gives the highlights of most of the side effects that may be exacerbated by the use of ecstasy or MDMA, a powerful street drug recently associated with fatal drug interactions when co-administered with ritonavir.

Drug interactions between opioid analgesics and protease-inhibitor antiretroviral agents

Since most opiates are substrates of the CYP450 enzyme system, when they are coadministered with cytochrome P450 enzyme inhibitors such as the protease inhibitors, erythromycin and clarithromycin, marked increases in serum levels can occur, patients should be monitored for oversedation and initial dosages should be decreased by 50%.

Patients abusing opiate drugs are at risk of toxicity when co-administered with these agents and should be counseled appropriately (Maurer et al. 1993).

Table II lists metabolic pathways of frequently abused drugs potentially affected by co-administration with the protease inhibitors.❖

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Table 1: **Side effects of Ecstasy (MDMA) that may be exacerbated when used along with conventional drugs with similar side effects**

Bradycardia
Faintness
Euphoria
Dysphoria
Headache
Innsomnia
Drowsiness
Pruritis
Rash
Decreased libido
Nausea and vomiting
Urinary retention
Visual disturbances
Respiratory depression
Physical and psychological dependencce

Source: Centers for Disease Control and Prevention. Multistate outbreak of poisonings associated with illicit use of gamma hydroxybutarate use-New York and Texas, 1995-1996. MMWR Morb Mort Wkly Rep. 1997; 46:281-283.

See next page for related table.

HIV in pregnancy: an update of current recommendations

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Ronald D. Wilcox, MD

On November 22, 2002, the CDC came out with the latest version of its recommendations for the use of antiretrovirals in pregnancy. The following is a summation of parts of the report.

When deciding on a treatment regimen for a pregnant women, one must take into account the benefits of therapy versus the risks of adverse events to the fetus, newborn, and woman.

In February 1994, the Pediatric AIDS Clinical Trials Unit (PACTU) introduced the results of Protocol O76, a regimen consisting of the use of AZT alone, starting with oral AZT beginning after the first trimester, then IV AZT during labor, followed by oral AZT for the infant for the first six weeks of life. This protocol showed a 70% decrease from 22.6% transmission to 7.6%. The incidence of AIDS in children has dramatically decreased since the introduction of the results from this study. Monotherapy during pregnancy was the standard of care for many years but, with current data, the standard of care is now the use of combination therapy. The current recommendations are primarily designed for use in the United States at this time.

Recommendations regarding antiretroviral choices for treatment must take into account the possible dosing changes resulting from physiologic changes associated with pregnancy, potential drug effects on the pregnant woman, and potential effects on the fetus. The decision should be made after discussion of the known and potential unknown risks with the pregnant patient. During pregnancy, a woman's gastrointestinal time is slowed down; fat and body water are increased with subsequent increase in blood flow to the organs; plasma protein levels are decreased; and there are changes in the physiology of both the liver and the kidney. Potential harm to the fetus depends on the type of drug, the amount ingested, the amount that crosses the placenta, the gestational age at exposure, and the genetics of the mother and fetus. Data are limited as to the long-term effects of fetal exposure to most antiretrovirals, including possible carcinogenicity.

The current recommendations for initiation of antiretrovirals in pregnant patients are based on the same parameters as those for non-pregnant patients or for those with a viral load ≥ 1000 copies/ml regardless of their immunologic or clinical status. One study has shown a decrease in HIV transmission from 9.8% to 1.0% in women whose baseline viral load was less than 1000 copies/ml while on antiretroviral therapy, usually consisting of AZT monotherapy in this select group. The placental passage of AZT is excellent, whereas that of other antiretrovirals is variable, leading to the recommendation that all regimens used to treat during pregnancy should include AZT whenever possible. AZT is metabolized within the placenta into its active triphosphate form, which may explain the protective effects it has in ways other than just the lowering of maternal viral load. This may be unique to AZT; it was not seen in studies of ddI or ddC. Initiation may be postponed until after the first ten to twelve weeks of gestation. Dual nucleoside therapy with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor should be given as standard-of-care, with mono- or dual-therapy regimens reserved for those women with baseline viral loads < 1000 copies/ml. Treatment with efavirenz

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Table 2: **Metabolic pathways of frequently abused drugs potentially affected by human immunodeficiency virus-1 protease inhibitors (adapted from Harrington, 1999)**

FREQUENTLY ABUSED DRUG	Metabolic Pathway Used (P450 Isoenzyme)
Opiates	
Methadone, Alfentanyl, Fentanyl	Cytochrome P450 (CYP3A4)
Meperidine	Cytochrome P450 (CYP3A4?)
Codeine, hydrocodone, oxycodone	Cytochrome P450 (CYP2D6)
Heroin, Morphine, hydromorphone	Glucoronidation?
Propoxyphene (Darvon)	Cytochrome P450 (CYP2D6)
Benzodiazepines	
Diazepam (Valium)	Cytochrome P450 (CYP3A4, CYP2C19)
Alprazolam, clorazepate, estazolam, flurazepam, midazolam, triazolam	Cytochrome P450 (CYP3A4)
Other drugs prone to abuse	
Marijuana, dronabinol, zolpidem	Cytochrome P450 (CYP3A4)
Slidenafil (Viagra)*	Cytochrome P450 (CYP3A4)
Cocaine**	Hydrolysis by plasma cholinesterase.

*AUC of slidenafil (Viagra) is increased 2-11 fold in the presence of all protease inhibitors; patients should not exceed 25mg in any given 48 hour period.
**Cocaine increases the speed at which HIV-1 virus replicates and so worsens overall prognosis by abolishing gains made by antiretroviral therapy. Metabolism of cocaine should not be affected by protease inhibitors.

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(Sustiva) should be avoided during the first 12 weeks due to findings of significant teratogenicity seen in rhesus macaques. Women who are on therapy with good viral load suppression (<1000 copies/ml) at the time of conception should continue with their current regimen, avoiding efavirenz, with consideration of adding or substituting AZT into the regimen. Women who are not virally suppressed on a regimen should have resistance testing considered and change of their regimen to decrease their viral load to less than 1000.

Women with no or minimal prenatal care with no prior therapy at the time of labor have four treatment options recommended: a single dose of nevirapine at the onset of labor with a single dose given to the infant at age 48 hours; oral AZT with 3TC during labor with one week of the combination therapy for the infant; IV AZT intrapartum with six weeks of AZT for the infant; or combination of the first and third regimens mentioned. The first three regimens are based on previous studies showing a decrease in transmission while the fourth regimen is a theoretical regimen. Of concern with the use of two-dose nevirapine is the development of NNRTI resistance mutations in 19% of antiretroviral-naive women and 15% of those who were on antiretrovirals but received an additional dose of nevirapine at the time of delivery; the development of this resistance was associated with "significantly higher viral loads and lower CD4 counts."

The greatest change in the current recommendations is in the section regarding resistance testing. The incidence of resistance mutations in the therapy-naive patients varies by the type of assay and the geographic area. RT gene resistance mutation rates frequently are > 10% in surveyed areas in the Western Hemisphere with primary resistance rates for protease inhibitors ranging from 1-16%. The International AIDS Society USA Panel and EuroGuidelines Group for HIV-1 Resistance currently recommend that *all* pregnant women with a detectable viral load (usually > 1000 copies/ml) have resistance testing performed to maximize efficacy of therapy.

There definitely are some concerns with the use of antiretrovirals in pregnancy. A retrospective Swiss study of 37 pregnant HIV-infected women revealed preterm delivery in 10 of 30 deliveries. This rate did not differ between women who received a protease inhibitor or not. The European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study investigated 3,920 mother-child pairings; there was a 2.6-fold increase odds of preterm delivery in patients on HAART with those on antiretrovirals before pregnancy having twice the chance of preterm delivery compared to women who initiated HAART in the third trimester. A contrasting study in the USA by the PACTU of 1,472 women with 78% receiving HAART during pregnancy showed no association with preterm delivery; the highest rate was in women who received no antiretroviral therapy.

HAART therapy with a protease inhibitor (PI) has been associated with the development of hyperglycemia and new-onset or exacerbation of diabetes mellitus, as has pregnancy. It is not know at this time if there is an increased incidence of these complications in pregnant patients on a PI-containing regimen.

Of concern also is the development of mitochondrial toxicity from the nucleoside analogues, with the incidence in descending order occurring with ddC > ddI > d4T > 3TC, AZT, and abacavir. Some of the clinical disorders associated with the mitochondrial toxicity include cardiomyopathy, neuropathy, lactic acidosis, hepatic steatosis, pancreatitis, and myopathy. The lactic acidosis and hepatic statosis have been shown to have an increased incidence in women. In 1999, Italian researchers reported a fetal death at 38 weeks gestation in a mother taking d4T-3TC who had a severe lactic acidosis. There have also been reports of three maternal deaths due to lactic acidosis on combination therapy with d4T-ddI; all women were on this regimen at the time of conception and continued throughout pregnancy. Caution with close monitoring must be given in women who remain on this regimen during pregnancy.

The use of AZT has been shown as mentioned above to decrease the transmission rate. The data from the Antiretroviral Pregnancy Registry has not shown any increased risk for congenital abnormalities among women who received AZT nor have there been long-term neurologic, developmental, or growth differences in uninfected children.

The incidence of transmission based on the mode of delivery has also been studied extensively. Several studies done early before the advent of viral load testing and HAART therapy showed a 55-80% reduction in transmission when an *elective* cesarean section is performed as compared to a vaginal delivery. The data for non-elective cesarean sections has not shown a significant decrease in transmission. The current recommendation is that an elective cesarean section should be offered to all HIV-infected pregnant women whose HIV viral load is > 1000 copies/ml at the time of delivery. Maternal morbidity and mortality are greater when a cesarean section is performed, so when a mother's viral load < 1000 copies/ml, the decision concerning a cesarean section rests on other criteria and not HIV.

In summation, the report recommends the use of antiretrovirals in all HIV-infected pregnant women. Resistance testing for any pregnant woman with HIV with a detectable viral load is encouraged. AZT monotherapy or dual therapy should be reserved for those women with a baseline viral load < 1000 copies/ml; all others should receive HAART with AZT as one of the components with a goal of a viral load < 1000 copies/ml at the time of delivery. Efavirenz and hydroxyurea should be avoided during the first trimester and ddI and d4T together should be used cautiously. Cesarean section should be offered to those women without ideal viral load suppression near the time of delivery.❖

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Understanding drug-drug interactions in HIV management

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Recent technologies within the last decade have resulted in our understanding a huge body of knowledge and information concerning the cytochrome P-450 isoenzymes present in the human body, and thus created an awareness of the many life-threatening interactions with such commonly prescribed drugs as the newer antihistamines and cisapride. A basic knowledge of the substrates, inhibitors and inducers of this enzyme system assists providers in predicting drug interactions that may become clinically significant. Apart from the processes of induction and inhibition, other factors that may affect microsomal drug metabolism include hepatic disease, state of nutrition, age, the presence of some endogenous chemicals, and genetic polymorphism. So far, as many as 30 human cytochrome isoenzymes have been identified. The major ones responsible for a majority of drug metabolism include CYP3A4, CYP2D6, CYP1A2 and the CYP2C subunits. This article, which will be continued in a later edition of this newsletter, will present fundamental concepts necessary for an appreciation of the role of these enzymes in drug-drug interactions as they relate to antiretroviral therapy. Pharmacologically, there are two broad classes of drug interactions, namely the pharmacokinetic and pharmacodynamic drug interactions. Interactions are described as pharmacokinetic when the action of one drug alters the serum concentration of another drug by changing any of the following processes: drug liberation, absorption, distribution, metabolism and excretion. Pharmacodynamic interactions are described simply as those interactions that may alter the overall clinical response expected from use of the drugs by altering the efficacy and often toxicity of the drugs. It could be synergistic (mostly positive, i.e., the positive antiretroviral response seen when zidovudine is combined with lamivudine) or it could be negative (antagonistic, i.e., use of zidovudine and ganciclovir causing additive bone marrow suppression or concomitant use of d4T and ddI causing additive neuropathy).

Defining pharmacokinetics: relationship to drug-drug interactions

Pharmacokinetics is simply defined as the study of the processes of drug action through the various processes of liberation, absorption, distribution, metabolism and excretion, often referred to as the LADME system. As a result of this broad definition and the involvement of several key processes, numerous possibilities abound for potential pharmacokinetic drug interactions. For instance, any circumstance that alters gastric pH can affect the absorption of many drugs. This is particularly important for patients receiving palliative care, many of whom may have hypochlorhydria which is common in advanced HIV disease and AIDS and may lead to suboptimal absorption of pH-dependent medications such as ketoconazole (Nizoral), itraconazole (Sporonox) and indinavir (Crixivan). Since fluconazole (Diflucan) is readily absorbed independent of gastric pH, it is often the azole of choice when an azole antifungal is indicated for the treatment of several opportunistic infections.

Drug-disease interactions

Drug interactions may arise because of changes due to HIV disease itself. As HIV-infected persons advance in their illness, often oral absorption of foods and drugs is compromised due to changes in gastric pH that accompany HIV enteropathy, a syndrome that describes the effect of advancing HIV disease on the gastrointestinal system. Diarrhea tends to be common in HIV disease and may result from a variety of causes, namely gastrointestinal disturbance following side effects of several of the most commonly used antiretroviral agents, and the presence of concurrent opportunistic organisms, bacterial, protozoal and viral infections that tend to be more common as the disease advances and the immune system weakens. The occurrence of diarrhea, especially if frequent and poorly controlled as in patients with cryptosporidiasis (a disease entity that is almost impossible to eradicate since none of the agents used for symptomatic treatment have shown persistent efficacy in clinical studies), may jeopardize absorption of all drugs because of the decreased transit time and may cause drug regimens to be less efficacious.

This will lead subsequently to less than optimal clinical outcomes and in some instances may predispose the patient to sub-therapeutic drug levels that may herald the emergence of resistant strains of the virus in patients still taking antiretroviral agents.

HIV-infected persons in palliative care are more likely to suffer from an increase in susceptibility to adverse events, such as a higher incidence of allergic reactions to sulfonamides and other drugs, than patients in the early stages of their disease. Other physiological components of advancing AIDS/HIV disease include the malabsorption which is the hallmark of enteropathy and predisposes the patient to changes in body weight that often reflect changes in volume as well as distribution of both fat and muscle tissue. This in turn may affect the dose-related efficacy of drugs, for example, the agents used in the treatment of tuberculosis and mycobacterial avium complex disease. Also frequently reported at this stage of illness are decreases in serum albumin, which in turn may alter the efficacy of drugs such as phenytoin when used in the management of patients with toxoplasmosis or sulfamethoxazole when used both as treatment and in the prophylaxis of patients with pneumocystis carinii pneumonia.

Other changes also occur in drug metabolism with advancing disease. These include changes due to hepatitis, frequently a co-infection in this population, especially those who were intravenous drug users (IVDUs), as biliary disease makes it necessary to adjust both the doses, and often the dosing intervals, of drugs that are mostly metabolized through

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the liver such as rifampin, isoniazid, ketoconazole, and to be selective in the choice of such medications. Changes in the renal elimination of drugs also occurs with advancing disease and can be especially important for renally-cleared antiretrovirals such as zidovudine, lamivudine, didanosine, zalcitabine and stavudine, antiviral agents such as ganciclovir and cidofovir, antifungal agents such as amphotericin B, and antibacterial agents such as the aminoglycosides.

Changes in immune status that may affect drug responses to antimycobacterial medications (such as the tuberculostatics) or management of opportunistic infections (such as mycobacterium avium complex) have frequently been reported in patients with advancing disease. As a general rule, there is an increased incidence of drug toxicity as well as drug sensitivity, for example with use of the neuroleptics (chlorpromazine and prochlorperazine), which may necessitate a decrease in the usually recommended doses in order to avoid undue toxicity.

When to suspect a drug-drug interaction in a patient with HIV disease

As a general rule, patients experiencing exaggerated toxicities on usual doses of medications or manifesting treatment failure, in the absence of factors such as resistance or poor adherence/compliance, may be suffering from an unidentified drug-drug interaction. In order to monitor for such drug interactions, a careful review of the patient's medication profile is necessary. Clinicians should become familiar with the agents most often associated with significant drug-drug interactions and measures to circumvent them when necessary. Regimens with enzyme inducers such as rifampin or enzyme inhibitors such as ritonavir should be noted and checked against a list of other agents metabolized by those same enzyme pathways.

Fortunately, the majority of drug-drug interactions are minor in nature and do not require extensive changes to the patient's drug regimen. However, the minority population of drug interactions that can be clinically important may offset treatment goals and outcomes in patients when these remain unrecognized or unaddressed, leading to sub-optimal drug levels of various drugs and so to treatment failures, often due to emergence of drug resistant strains of the virus.

Drug-food interactions of clinical significance

It is well established that the presence or absence of food or certain beverages may significantly affect the bioavailability of a number of medications. A variety of mechanisms including changes in pH, formation of unabsorbable cation complexes, increased solubility of drugs, interference with gut metabolism, as well as a decrease in the motility of the gut, may be at play. Table 1 (next page) lists some of the more common food-drug interactions and simple strategies to circumvent them.

Changes in the renal elimination of drugs also occur with advancing disease and HIV-associated nephropathy (HIVAN), which can disproportionately affect male African-Americans with a previous history of IV drug use. Such changes can be especially important for renally-cleared antiretrovirals such as zidovudine, lamivudine, didanosine, zalcitabine and stavudine; antiviral agents such as ganciclovir and cidofovir; antifungal agents such as amphotericin B; and antibacterial agents such as the aminoglycosides.

A second installment of this article will appear in a future issue of this publication. It will discuss interactions between antiretroviral agents, psychotropic agents and street drugs.❖

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Evidence-based Practice, from page 22

clients. Mullen and Bacon (2000) found that social workers are open to using clinical practice guidelines and empirically informed practice as long as it is perceived as helping clients. EBP can provide a source of clinical knowledge that improves practice. It gives us the opportunity to combine the best of science available with clinical experience to better serve a wide variety of clients (Sexton, 1999).

Standards of care. Standards of care are important reference tools for the profession and serve as evidence of best practice (Vallianatos, 2000). These guides tend to be user-friendly and are more accessible to practitioners than research findings published in journals. Clinical practice guidelines are often formulated by professional organizations and government agencies, prescribing how clinicians are to assess and treat clients. Sometimes the guides are based on research findings, but oftentimes they are based on professional consensus (Mullen & Bacon, 2000). An excellent example is the Ryan White Title 1 Standards of Care for Case Management. The Service Delivery Committee of the New Orleans Regional AIDS Planning Council developed the practice guide through consensus. The committee, comprised of agency and practitioner representatives, as well as members of the affected community, used a combination of theory, published research evidence, practice experience, expert consultation, and service utilization data derived locally to create the document.

Consultation, training and continuing education. Social workers tend to rely more heavily on consultation than upon reviewing professional literature. Social workers seek direction and guidance from supervisors and other consultants and respect authority, practice wisdom, and experience (Gambill, 1999; Gambill, 2001; Mullen & Bacon, 2000). Important resources for dissemination of EBP knowledge within social work agencies, then, are colleagues who engage in practice research and/or are familiar with current literature (Mullen & Bacon, 2000). Inservices, training programs, certificate and continuing education coursework, and conferences

are excellent ways for social workers and other health care associates to become informed of empirically supported interventions. Some "just in time" learning modules are available on-line, through universities, licensing bodies, professional organizations, and for-profit agencies, such as pharmaceutical companies.

Collaboration with Schools of Social Work. Aside from consultation and education/training programs, schools of social work provide access to library reference and journal materials and can assist agencies in program and service evaluation. Faculty have research skills that can be of value to agencies and auton-omous clinicians, and often have masters and doctoral students available to collect and analyze data. Such services can be provided as formal program evaluation or informal assistance. Noted in the literature is the value of university-based research centers in developing policies and evidence-based practices (Iwaniec & McCrystal, 1999).❖

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Drug-drug Interactions, from page 26

Table 1: Important food-drug interactions and strategies to circumvent them

- Ketoconazole (Nizoral) and itraconazole (Sporonox): Increase in gastric pH due to agents such as antacids, H_2 blockers, proton-pump inhibitors and non-enteric-coated formulations of ddI impairs absorption of ketoconazole, absorption is optimal at gastric pH. Take 2 hours apart or use alternative antifungal agent (MMWR 1999: 48:[RR-10]:47); rifampin decreases activity of both drugs, INH decreases effect of ketoconazole; terfenadine and cisapride (both now removed from the market) lead to ventricular arrhythmias and concurrent use should be avoided
- Administration of acidic beverages such as 240mls of orange juice, tomato juice, ginger ale, grapefruit juice or cola drinks in the presence of achlorhydria of advanced HIV disease will enhance azole bioavailability especially for ketoconazole. When hypochlorhydria is severe, each 200mg of ketoconazole should be dissolved in 4ml of 0.2N hydrochloric acid. A straw should be used to avoid contact with teeth.
- Oral fluoroquinolones: Avoid dairy products, elemental minerals and heavy nutritional supplements: take fluoroquinolones 2 hours before or 6 hours after these items.
- Interactions with Protease Inhibitors (PIs) and the Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs): (As a general rule, use of ketoconazole with these agents is not advised due to a large number of potentially significant drug-drug interactions, fluconazole is preferred) (see tables 2 and 3).
- Indinavir: levels increased 68%—reduce indinavir dose to 600mg q 8h; SQV levels increased 3-fold—no dose change required; RTV increases ketoconazole levels>3 fold—use < 200mg ketoconazole/day. APV levels increased 31% and ketoconazole levels increased 44%—dose implications not clear; NFV—no dosage change, NVP levels increase 15%-30% and ketoconazole levels decreased by 60%, combination is not recommended. The interactions between ketoconazole and efavirenz have not been studied and so no recommendations can be made at the present time (for more detailed information consult the most recent package inserts of ketoconazole and the various drugs).

Table 2: Common Inducers of Cytochrome P450 Enzyme System

Enzyme	Known Inducers
CYP3A4	Carbamazepine (Tegretol), rifampin (Rifadin), Phenobarbital, phenytoin (Dilantin), efavirenz (Sustiva), nevirapine (Viramune), prednisone, rifapentine, troglitazone (Rezulin)
CYP1A2	Cigarette smoke, ritonavir (Norvir), omeprazole (Prilosec), charcoal-smoked foods, cruciferous vegetables
CYP2C9	Carbamazepine (Tegretol), ethanol, phenytoin (Dilantin), rifabutin (Mycobutin), ritonavir (Norvir), rifampin (Rifadin)
CYP2C19	Rifabutin (Mycobutin), rifampin (Rifadin)
CYP2D6	Pregnancy
CYP2E1	Ethanol, ritonavir (Norvir), isoniazid (INH)

Table 3: Common Inhibitors of Cytochrome P450 Enzyme System

Enzyme	Known Inhibitors
CYP3A4	Ritonavir (Norvir), nelfinavir (Viracept), Amprenavir (Agenerase), Indinavir (Crixivan), propoxyphene (Darvon), saquinavir (Fortovase), ketoconazole (Nizoral), itraconazole (Sporonox), erythromycin, grapefruit juice, nefazodone (Serzone), fluvoxamine (Luvox), fluoxetine (Prozac), diltiazem (Cardizem), verapamil (Calan), clarithromycin (Biaxin), omeprazole (Prilosec)
CYP1A2	Ciprofloxacine (Cipro), grepafloxacin (Raxar), fluvoxamine (Luvox), fluoxetine (Prozac), nefazodone (Serzone), Enoxacin (Penetrex)
CYP2C9	Amiodarone (Cordarone), clopidrogel (Plavix), fluvastatin (Lescol), fluvoxamine (Luvox), fluoxetine (Prozac), fluconazole (Diflucan), miconazole (Monistat), metronidazole (Flagyl), trimethoprim/sulfamethoxazole (Bactrim/Septra)
CYP2C19	Ticlopidine (Ticlid), fluvoxamine (Luvox), fluoxetine (Prozac)
CYP2D6	Ritonavir (Norvir),* sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), quinidine, thioridazine (Mellaril), cimetidine (Tagamet), amiodarone (Cordarone), diphenhydramine (Benadryl), haloperidol (Haldol), ticlopidine (Ticlid)
CYP2E1	Cimetidine (Tagamet), isoniazid (INH), watercress

* the only PI with CYP2D6 inhibitory activity

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