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New protease inhibitor offers clinicians hope for better salvage therapy

Mary J. Murphy, MD

Tipranavir (trade name Aptivus) received accelerated approval by the FDA in June 2005. Ritonavir-boosted tipranavir (TPV/r) is indicated for use in combination antiretroviral regimens for highly antiretroviral-experienced adults or those with virus resistant to multiple protease inhibitors (PIs). Tipranavir is structurally different from the other currently available PIs. It is a nonpeptide developed from coumarin derivatives. Its unique structure may contribute to a superior resistance profile because of greater molecular flexibility in inhibiting the protease enzyme.

The clinical data supporting the approval of TPV comes from two phase III clinical trials known as RESIST I and II (Randomized Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir). RESIST I was conducted in the US, Canada and Australia, and RESIST II in Europe and Latin America. Boehringer Ingelheim, the maker of tipranavir, sponsored these open-label trials.

The study participants were HIV-1 infected adults with advanced disease who had at least 3-class antiretroviral exposure. They had taken a median of 12 different antiretroviral agents and at least two PI-containing regimens and were failing a PI based-regimen at the time of enrollment. Subjects were randomized to receive either boosted TPV or a comparator-boosted PI based on genotypic screening. The comparator PIs included amprenavir, indinavir,

lopinavir and saquinavir. An optimized background regimen was chosen based on genotype results and antiretroviral history. Enfuvirtide was allowed as part of the optimized background. Treatment response was defined as 1 log₁₀ or greater drop in viral load compared to baseline.

The results of the RESIST trials showed that a significantly greater proportion of patients in the TPV arms achieved a treatment response compared to those taking comparator PIs. The combined 48-week data showed that 33.6% of patients in the TPV arms achieved a virologic response versus 15.3% in the comparator PI arms. Viral loads of < 400 copies/mL were reported in 30.4% in the TPV arms vs 13.8% in the comparator PI arms, and < 50 copies/mL in 22.8% versus 10.2% respectively. The p value was <0.0001.

The inclusion of enfuvirtide further improved the virologic outcome with 48.5% versus 23.9% showing a treatment response in the TPV arms versus comparator PI arms. Among those who were enfuvirtide-naïve and received TPV, 36% achieved virologic suppression to < 50 copies compared to 14% in the comparator PI arms. These results illustrate that better outcomes can be achieved by employing at least two new active agents whenever possible in highly ARV-experienced patients.

The resistance profile of TPV principally involves mutations on four codons: 33, 82, 84 and 90, also known as universal protease associated mutations or UPAMs. The activity of TPV decreases as

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Medicine

In clinical trials, more patients achieved a treatment response

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the number of UPAMs increases. When greater than two UPAMs are present, TPV loses its activity. Resistance to other ritonavir-boosted PIs has been associated in a number of studies with the accumulation of five or more PI resistance mutations. The advantage of TPV seems to be that its activity is conserved in the face of a greater total number of PI mutations, as long as no more than two UPAMs are present.

A Spanish study of over 1300 PI-experienced patients found that nearly 40% had five or more PI mutations but only 5.5% harbored virus with > 2 UPAMs, and this group of patients had a median of ten total PI mutations. This suggests that TPV may be effective in many heavily pre-treated patients with significant PI resistance.

The decision to use TPV should be guided by careful review of genotype results and antiretroviral history. Phenotyping may also be useful. A baseline TPV fold change in IC₅₀ of < 3 fold predicts likelihood of response to TPV. It is important to keep in mind that the efficacy of a salvage regimen depends on the presence of at least two fully active antiretrovirals, so the addition of new agents like enfuvirtide should be considered.

Similar to previously marketed PIs, TPV/r has multiple drug interactions. The P450 enzyme system both inhibits and induces so that some drug interactions may be hard to accurately predict. The net effect on CYP 3A4

is inhibition. Like the other PIs it should not be coadministered with selected agents in the following drug classes: antiarrhythmics, statins, benzodiazapines, antihistamines, ergot derivatives and intestinal motility agents. Patients using oral contraception alone should use a backup method. TPV may increase levels of certain serotonin reuptake inhibitors and erectile dysfunction agents and decrease levels of methadone. It should not be coadministered with rifampin which significantly reduces TPV

Treatment decisions should be guided by careful review of genotype results and patient's ARV history.

levels. The dose of coadministered rifabutin is 150 mg orally every other day. Herbal medicines such as St. John's Wort can lower TPV levels and should be avoided.

There are some drug interactions with TPV that are distinct from those seen with most of the other PIs. It reduces levels of the NRTIs abacavir, didanosine EC and zidovudine, although no dose adjustments are considered necessary. Administration of TPV and didanosine should be separated by two hours. TPV significantly reduces levels of other

PIs including amprenavir, indinavir, lopinavir/r and saquinavir. **Coadministration of TPV/r with other PIs should be avoided.** Aluminum and magnesium-containing antacids interfere with TPV absorption and they should be given apart. Fluconazole significantly increases TPV levels and doses of fluconazole greater than 200 mg/day are not recommended. Coadministration of loperamide results in both decreased TPV and loperamide levels and dose adjustments have not been established at this time. Clarithromycin levels may be decreased by TPV but no dose adjustment is recommended.

TPV shares many of the usual side effects common to the PI class. The occurrence of nausea, vomiting and diarrhea with TPV/r was similar to the comparator PIs in the RESIST trials. However, TPV was associated with higher rates of liver toxicity including liver-related fatalities. Patients with chronic hepatitis B and C were at higher risk of severe liver toxicity. Patients with moderate to severe hepatic insufficiency should not receive TPV. All patients should be monitored carefully for liver toxicity, especially those with underlying chronic hepatitis.

Lipid elevations were also more frequent with TPV versus comparator PIs and lipid profiles should be closely followed. Rash may occur with TPV and seems to be more common in women. TPV contains a sulfa moiety and should be used with caution in sulfa-allergic individuals. TPV is pregnancy category C.



TPV is available in 250 mg pink soft gelatin capsules. The recommended adult dose is 500 mg (two capsules) given with 200 mg of ritonavir twice daily. It should be taken with food. A high fat meal increases absorption. Unopened bottles should be refrigerated. After opening, it can be stored at room temperature.

TPV/r will be studied in antiretroviral-naïve adult patients and in the pediatric population. Given its significant drug-drug interactions and toxicities, it will likely remain a drug that is chosen later on in antiretroviral sequencing.❖

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Mary J. Murphy, MD, is Medical Director, HIV Outpatient Program (HOP), Medical Center of Louisiana at New Orleans; Assistant Professor, Section of HIV/ID, Department of Medicine, LSU Health Sciences Center; and a faculty member of Delta Region AETC.

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Mental Health

Insomnia: A simplistic approach to a complex problem

Guillermo Urrutia, MD

Insomnia is a frequent complaint heard by clinicians who treat HIV patients. Depending on the severity of the problem, the insistence of the patient, and the ability of the clinician to rule out the presence of one or more predisposing and precipitating factors for the lack of sleep, a series of treatment measures are prescribed. These may vary from giving reassurance, recommending sleep hygienic measures and teaching relaxation techniques to using agents that depress central nervous system (CNS) functions at one or several levels. These medications have the potential of causing harmful side effects and consequences, mostly dose related. About 30% of the general population will experience sporadic problems with sleep, which usually respond well to treatment, and of those afflicted, only 10 % will suffer from chronic insomnia, a condition that presents more serious treatment challenges.¹

Sleep physiology proposes an apparently simple model. However, many of its mechanisms are still not fully understood. The theory is that melatonin, a hormone secreted by the pineal gland in a circadian fashion, controls our sleep. The changes generally coincide with environmental darkness. The binding of melatonin to receptors widely distributed through the CNS synchronizes the circadian rhythms, attenuating the CNS-generated alerting signals.² During the night, retinal photorecep-

tors stimulate the production of melatonin through an increment in nor-epinephrine secretion,³ and the wakeful drive is turned off. During the day, the opposite situation occurs, melatonin levels decrease, and we are awake. Alterations of the circadian pattern can occur, but it takes time before the CNS can make the adjustments. Melatonin production decreases with advancing age, and therefore, people in their sixties will sleep less than their younger counterparts.

The problem with insomnia is that melatonin only functions as a "sleep gate" and it can be superseded by a host of factors. An effort should be made in every patient to find other factors that may be causing, or enhancing, the sleep disturbance.

Individual factors that predispose to insomnia include an increase in sympathetic nervous system hyperactivity, which causes hyper reactivity to stress, excessive worries about sleep, and about the unhealthy consequences of insomnia. Frequently, patients have negative expectations about their sleep adequacy and have a poor sense of how much sleep time they get.⁴ Emotional factors, such as anxiety, depression and stressful life events are causes of insomnia, and sustained emotions over time may condition the development of chronic insomnia. It is interesting that most patients with insomnia do not have daytime sleepiness, which suggests that a neurophysiologic abnormality is responsible for the decreased homeostatic response

to sleep loss.⁵ In some cases, patients complain about poor quality of sleep independently of the duration of sleep time.

Another group of problems that may precipitate insomnia is related to medical and psychiatric conditions, to the use of drugs (both prescribed and illicit), and to frequent changes in work schedules. Patients with Parkinson's and Alzheimer's diseases frequently have problems with initiating and maintaining sleep (microarousals). A large number of patients with chronic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia and neuritis often suffer from insomnia. Hormonal changes that stimulate the CNS, such as hyperthyroidism and hyperadrenocorticism induce poor sleep. Menopausal women, particularly those who suffer hot flashes and night sweats, have decreased sleep efficiency. Gastro-esophageal reflux disease may cause frequent awakenings. Psychiatric diseases such as major depression, generalized anxiety disorder and post-traumatic stress disorder are well known to cause insomnia, mostly when associated with obsessive-compulsive features or panic attacks. Stimulant drugs with abuse potential such as amphetamines, methylphenidate, pemoline and caffeine, and non-prescribed drugs such as cocaine and heroin, cause wakefulness by delaying onset of sleep, and increasing sleep fragmentation. Many medications not frequently suspected of causing insomnia, such as antihypertensive and antiarrhythmic drugs, b-block-



ers like propranolol and pindolol, corticosteroids, theophylline, lovastatin and nasal decongestants, often keep patients awake at night. Among the antidepressants agents, monoamine oxidase (MAO) inhibitors and many of the serotonin uptake inhibitors (SSRI), like fluoxetine, paroxetine, fluvoxamine, venlafaxine and bupropion, may delay sleep initiation.⁵ Some anti-viral medications utilized in the treatment of HIV disease may cause vivid dreams and insomnia at the beginning of their use, but as a group, they are not associated with sleep disturbances in a significant way.⁶

Behavioral factors may cause or perpetuate chronic sleep loss, such as keeping a sedentary lifestyle, napping during the day, consumption of caffeine-containing drinks in excess or less than six hours before bedtime, reading in bed, engaging in strenuous physical or emotional activities shortly before bedtime, and maintaining inadequate bedroom physical conditions of light, sound and temperature. Drinking alcohol may help induce sleep, but after a few hours it causes interruption and fragmentation of sleep. The association of alcohol and sleeping medication has a similar effect. Worrying about inability to sleep, and maintaining negative expectations about it can induce a self-perpetuating process of insomnia.⁴

Of the situations described, the three found most frequently among patients with HIV disease are worry, depression, and abuse of alcohol or drugs. It is therefore not surprising that the number of patients who complain about sleep difficulties in HIV clinics is larger than in the general popu-

lation.⁶ Because the treatment of HIV and its complications involves taking many medications, and patients with HIV often suffer with varying degrees of poor general health and weakness, the prescription of sedative agents must be carefully considered due to possible undesirable consequences such as addiction and side effects. On the other hand, lack of sleep represents a challenge for a patient's quality of life and its relief is important.

In HIV patients, insomnia is often associated with worry, depression and abuse of alcohol or drugs.

The treatment of patients with sleep difficulties involves a three-pronged approach: 1) A detailed review of all predisposing and precipitating factors of insomnia. 2) A careful investigation of sleep patterns, habits and schedules that may include the input and cooperation of sleep partners, after which the education of the patient may start, and corrective measures can be implemented. 3) A judicious use of sleep-inducing agents. Clear therapeutic goals must be set for this treatment. A word of caution is indicated here. Strictly speaking, the use of sleep-inducing agents is not physiologic, because their action consists of a non-specific depression of the CNS, and because they promote dependency. Some of them, like the sedating anti-histaminics

(diphenhydramine) or the sedating antidepressants (trazodone and amitriptyline), work for short periods of time and can be useful when a few nights of sleep is all that is desired. They have strong anti-cholinergic effects and can be a problem in elderly male patients with large prostate glands. It has been demonstrated that their efficacy disappears after several weeks, and after that only the placebo effect remains.⁷ Sedation that sometimes lasts until the following morning is another problem. The incidence of falls and hip fractures increases with the use of all cortical depressing agents because of the ataxia they cause. Transient amnesia and disorientation have been observed, particularly in the elder population.⁸

FDA-approved sleeping medications are GABA receptor antagonists such as benzodiazepines with short half lives, and nonbenzodiazepine compounds with even shorter ones. Both groups interact with GABA receptors increasing the inhibitory effects of this neurohormone. The benzodiazepine compounds and their half lives are: triazolam (Halcion®)—1.7-5 hours; temazepam (Restoril®)—3.5-18.4 hours. They compare favorably with older compounds of the same class, such as estazolam (ProSom®/Eurodin®)—10-24 hours; flurazepam (Dalmane®)—47-100 hours; and quazepam (Doral®/Dormalin®)—70-90 hours. The nonbenzodiazepine drugs include zaleplon (Sonata®)—1 hour; eszopiclone (Lunesta®)—6 hours; and zolpidem (Ambien®)—2.5 hours. It has been reported that the possibility of addiction is decreased by a strict adherence to the prescribed doses, and that

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Relief of insomnia is important for HIV patient's quality of life

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nonbenzodiazepine medications are even less addictive as long as the recommended doses are followed. All of these compounds produce rebound effect when discontinued, and all of them affect the CNS in varying degrees, causing ataxia and somnolence, side effects that occur more frequently in the elderly.^{8,9} Recently a long-acting zolpidem (Ambien C-R) has been marketed. The hypnotic effect of this presentation lasts for 6 hours. This enhances the duration of sleep time, but also prolongs the presence of side effects. Other benzodiazepine drugs, like clonazepam (Klonopin®), alprazolam (Xanax®) and lorazepam (Ativan®) are frequently used with the purpose of inducing sleep, but that is not the intended indication of these drugs, and they are not more efficient than the ones approved by FDA.¹⁰

The use of over-the-counter agents such as kava, L-tryptophan and St. John's wort should be discouraged because of "insufficient scientific evidence" of efficacy, and also because of the serious side effects and toxicity they may cause,¹¹ as well as possible drug interactions with HAART.

In another category, there is ramelteon (Rozerem®), a new melatonin receptor binding agent which increases levels of endogenous melatonin, and whose affinity for the melatonin receptors

is more potent than that of the hormone itself.¹² It appears that it does not bind with GABA, serotonin, acetylcholine, glutamate, noradrenaline or with other neuropeptides, cytokines or opiates, therefore does not cause most of the side effects of the benzodiazepines, and also does not create addiction.¹³ It provides a large supply of melatonin, a feature particularly desirable to elderly patients, who usually have lower levels of the hormone. Although its pharmacologic action is more physiologic than that of the benzodiazepine antagonists, it does not seem to be strong enough to treat more severe forms of insomnia. Not enough experience has been accumulated with this agent, and the existing data, which were generated by the pharmaceutical company that manufactures the medication, need to be validated by independent observers. If these findings are confirmed, this medication may turn out to be the agent of choice in milder cases of insomnia, mostly in elderly patients, and in insomniac patients with current substance abuse problems.

In summary, the approach to treatment of insomnia must be geared to investigate the medical, psychological and environmental factors that may impede normal sleep. This search must be followed by a process of patient education about the physiology of sleep in order to teach sleep hygienic measures and behavior-

al techniques to achieve relaxation, as well as to reassure the patient. And lastly, one may consider the use of sleep-inducing drugs, keeping in mind possible side effects and the risk-benefit ratio that will justify their use. Treatment must be individualized and the use of the medication should be limited to mutually-agreed-upon periods of time, using the medications on an as needed basis with close follow-up of the patient. ♦

Guillermo Urrutia is Staff Psychiatrist, HIV Outpatient Program, Medical Center of Louisiana at New Orleans and Associate Clinical Professor of Psychiatry, LSU Health Sciences Center.

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Nursing

Has the rapid test made a difference in perinatal transmission?

Pat Gootee, MSN, BCFNP

Estimated new infections of HIV for adults and adolescents have remained steady at 40,000 annually in the US for the last half of the AIDS epidemic.¹ New infections in infants born to infected mothers have dropped drastically since the "076 Protocol"² (1994 and 1995 US Public Health Service recommendations for preventing mother-to-child HIV transmission) became standard practice in prenatal care during the last ten years. Compared to the estimated 1750 HIV-infected babies born each year in the early 90s to the 280-370³ born annually in recent years, U.S. prevention efforts appear successful in prevention of mother-child HIV transmission. However, nearly 40,000 (1%) women who gave birth in the US during 1999-2001 did not receive prenatal care, according to data from the National Vital Statistics report.⁴ In addition, the CDC reports that 12% of pregnant HIV-infected women don't receive prenatal care, and 10% of those women found to be HIV positive later didn't get tested before giving birth.⁵

Yet, even with the widely accepted standard of care of the 076 Protocol for preventing mother-to-infant transmission in 98% of babies born to HIV+ mothers, 40% of mothers of infected infants were unaware of their status.⁶ Can perinatal rapid HIV testing of mothers whose HIV status is unknown at the time of delivery prevent the current incidence of perinatally

infected infants? Can the US further decrease the preventable and costly (on many levels) transmission of HIV to infants?

In 2003, after FDA approval of a CLIA-waived rapid HIV test⁷ and a mandate from the CDC which required states to apply this new tool of rapid HIV testing in labor and delivery suites throughout the US, the state of Louisiana joined the campaign to eliminate perinatal transmission by identifying previously unknown HIV+ mothers. Loui-

**We will only
know in hindsight
whether our efforts to
protect all age groups
have been effective.**

siana's HIV surveillance reports are available for 2004, and by August 2006, the 2005 state HIV statistics should be available. Efforts by the Louisiana Department of Health and Hospitals are ongoing to identify health care facilities in the state which need education about the use of perinatal rapid HIV testing.⁸ Once all private and public hospitals routinely offer rapid testing to laboring women whose HIV status is unknown, the belief is that perinatal transmission will be as rare as any other preventable childhood disease. We will not know for some time if this prevention method is success-

ful in eliminating infant HIV, but studies in other areas of the US and other countries illustrate the possibility.

In November 2004, the American College of Obstetricians and Gynecologists (ACOG) expanded their recommendations for "Prenatal and Perinatal HIV Testing."⁹ They recommended the "opt-out" approach for testing patients. The opt-out approach is the strategy in which universal HIV testing with patient notification is a routine component of prenatal care. A pregnant woman is notified that she will be tested for HIV as part of the routine battery of prenatal blood tests unless she declines. This approach eliminates the requirement to obtain specific informed consent and has a much higher (85-98%) rate of testing than the "opt-in" approach (25-83%), which was the foundation for most state laws and regulations in effect in 2004."

ACOG also recommended routine universal repeat testing in the third trimester in areas with high HIV prevalence among women of childbearing age (0.5% or greater). Criteria for repeat testing include a history of sexually transmitted infections, illicit drug use, the exchange of sex for money or drugs, multiple sex partners during pregnancy or a partner known to be HIV positive or at high risk, signs or symptoms suggestive of acute HIV infection at any time during pregnancy, and those women who previously declined testing earlier in pregnancy. Finally,

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Nursing

The “opt-out” approach results in a higher rate of HIV testing

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ACOG recommended offering rapid testing during labor with OraQuick Rapid HIV-1 Antibody test which is feasible in obstetric settings and delivers accurate and timely (20-40 minutes) test results.¹⁰

Between April 2002 and June 2005, a large inner-city teaching hospital in Philadelphia identified 259 women in labor whose HIV status was unknown. All were tested with rapid HIV tests, with 62 patients receiving the expedited enzyme-linked immunosorbent assay (ELISA) and 197 receiving the OraQuick rapid HIV-1 antibody test. Four women had positive tests and three were confirmed by Western Blot test. Knowing this information provided an opportunity for their health care team to administer antiretroviral prophylaxis and to incorporate other obstetric interventions to decrease HIV transmission to these infants. One of the ELISA+ women proved to be Western Blot negative; her infant was treated for one week with oral zidovudine before those test results were known. Another mother testing positive with OraQuick was found to be actively using cocaine during her pregnancy and perinatally. She presented to the labor and delivery suite in early labor with ruptured membranes of more than four hours, an HIV viral load of 60,000 copies/mL (discovered later). She declined to have a cesarean delivery. The mother did receive intravenous zidovudine three hours prior to

delivery plus one dose of nevirapine, and the infant received oral zidovudine for the first six weeks of life. The infant's HIV DNA PCR result was negative at 24 hours after birth, however, the test at age two months was positive with an HIV RNA over 100,000 copies/mL. The HIV+ women with their infants were referred to HIV specialists for follow-up and ongoing care.¹¹

The CDC-sponsored Mother-Infant Rapid Intervention at Delivery (MIRIAD) Study group¹² examined the use of rapid testing (OraQuick) or enzyme immunoassay (EIA) in 4,849 prenatal patients with unknown HIV status in a multistate hospital study. Data from this study showed a sensitivity for OraQuick of 100% and a specificity of 99.9%. This study identified 34 HIV+ women at a prevalence of 7/1000 with a positive predictive value of 90% compared with 76% of EIA.

In a study published in *AIDS* in January 2006, “Perinatal HIV Counseling and Rapid Testing in Tijuana, Baja California, Mexico,” the seroprevalence and correlates of HIV infection were discussed.¹³ From March to November 2003, pregnant women attending Tijuana General Hospital who consented to participate in the study had a rapid HIV test (Determine HIV-1/2: Abbott Diagnostics, North Chicago, IL). A confirmatory EIA and Western blot were performed and demographic and risk factor data were obtained.

A total of 1529 (92.5%) of the 1653 women who attended prenatal care and 1068 (95.2%)

of 1122 women in labor consented to participate. HIV seroprevalence was significantly higher among women screened during labor (12/1068, 1.1%) compared with those tested while receiving prenatal care (5/1529, 0.33%). HIV-infected women were significantly more likely to have risk factors (to have used injection drugs, cocaine, methamphetamine, etc., to have more sex partners, to not have received prenatal care, and to have a partner who used injection drugs, etc.) Methamphetamine was independently associated with the risk of HIV infection.

According to the Mexican National Center for AIDS Prevention (CENSIDA), Baja California including Tijuana has the highest rate of AIDS in Mexico. Yet the surveillance revealed only an HIV prevalence during pregnancy of 0.09%, while findings at Tijuana General Hospital show that this estimate underrepresented the true HIV prevalence in this region. Only 60% of the 426 women who delivered every month had received prenatal care. Additionally, the prenatal HIV test and treatment to prevent maternal fetal transmission were not fully implemented.¹⁴

A total of 17 women tested positive and all were confirmed by EIA and Western blot, resulting in a prevalence of 0.65%. HIV seroprevalence did not differ by marital status, education or maternal age when compared with women who tested HIV negative. Counseling and rapid HIV testing was well received during labor. Women with posi-



tive tests in labor were counseled and administered intravenous zidovudine. Infants born to HIV-infected women were given oral zidovudine for six weeks. Infants exposed to HIV were followed at the pediatric HIV clinic at Tijuana General Hospital. No further outcomes were reported in this study other than that appropriate prevention interventions were administered.¹⁵

There are many point-of-care opportunities where HIV rapid testing has proven to be a useful tool in identifying previously unknown HIV-positive persons: jails and correctional institutions, emergency departments, STD clinics, in-patient services and out-patient services.¹⁶

As with everything in the HIV world, we will know only in hindsight whether our efforts have been effective in preventing new infections in all age groups by employing "Prevention for Positives" recommendations, identifying all HIV-positive pregnant women, and administering appropriate treatment for them and for their infants. ♦

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Pat Gootee is Nurse Practitioner, Division of HIV, LSUHSC School of Medicine HIV Clinic, University Medical Center, Lafayette, Louisiana, and a faculty member of Delta Region AETC.

Clinical Consultation for Health Care Providers

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Dentistry

Oral KS case is successfully treated by dental professionals

Alicia Rose Hathorn, DMD

Kaposi sarcoma (KS), the most common malignancy in HIV-infected persons and an AIDS-defining condition, is a neoplasm of endothelial cells involving the skin, oral cavity and occasionally internal organs. KS initially appears as flat, pigmented lesions of red or brown color and can develop into nodules or tumors along lines of skin cleavage. Patients with HIV should have regular skin examinations to detect any beginning growth of shaded plaques. Common skin regions include the soles of the feet, genital and perirectal areas, behind the ears, nose and eyelids. Most KS lesions are raised but some cutaneous lesions are faint pink macules that are difficult to recognize.

Oral involvement can present as red, blue or purple single or multiple lesions in various stages. Lesions may be flat and barely visible and extend to large, raised nodular lesions with ulceration and hemorrhage. The most common sites in the oral cavity are the hard and soft palates. Lesions can also be found on the gingiva, tongue, buccal mucosa and the oropharynx. They can become very painful and interrupt the patient's speech and food intake.

Since KS is of vascular origin, it must be distinguished from other similar clinical lesions such as hematomas, hemangiomas, pyogenic granuloma, or bacillary angiomatosis. Diagnosis is made by histological examination from a biopsy. Two types of biopsies

can be performed to diagnose KS and rule out other lesions. An incisional biopsy is the removal of a part of a lesion for gross and microscopic examination. An excisional biopsy is the removal of the entire lesion for gross or microscopic examination. There are three histopathologic stages of KS: patch, plaque, and nodular. Early patch stage may resemble granulation tissue. The endothelial cells that line blood vessels are enlarged and may protrude into the lumen. The vessels are dilated and more numerous and contain lymphocytes, plasma cells, macrophages, and extravasation of erythrocytes. In the plaque and nodular stage, peripheral spindle cells are present. They are often dilated and contain intra- and extracellular hemosiderin pigment. The spindle cell formations are irregular and extend in all directions.

The therapies involved are numerous and with the complex biology of this malignancy, successful complete regression has proven difficult. Local therapy helps control individual lesions with cryotherapy or intralesional injections of vinblastine. The patient with very few lesions or a slowly progressing disease may benefit from local therapy. Oral lesions may be susceptible to vinblastine but lesions may recur and treatment is limited. Radiation therapy has been used to treat local areas of skin and oral involvement, but success is based on the extent of cutaneous involvement and overall health of the patient. Systemic chemotherapy is indicated for extensive

lesions or a rapidly progressing disease. The goals of chemotherapy are to reduce functional impairments, control symptomatic disease and induce the regression of skin lesions. Many options exist so it is very important to maintain communication between the patient's physician or nurse practitioner and choose a treatment option that best suits the patient's needs.

The American Cancer Society estimated that fewer than 2,500 new cases of Kaposi sarcoma will occur in the U.S. in 2005. The incidence of KS peaked in 1989 among men ages 20-54 and, in 2005, has dropped 10% since the rate was reported in 1994. The ACS has suggested that the decrease of KS after 1989 and since the advent of HAART in 1996 is due to behavioral changes in sexual activities which have reduced the transmission of HIV and HHV-8 (Human Herpes Virus-8). HHV-8 was discovered in 1994 and is now known to be present in all forms of KS. It is a member of the gamma herpesvirus group with the Epstein-Barr virus. Evidence suggests that HHV-8 must be present for KS to develop.

CASE PRESENTATION:

A 37-year-old white male presented to the dental clinic on referral from his nurse practitioner (NP). His NP had noted on his referral form the presence of an oral lesion on his palate and requested a biopsy. Patient stated that his last dental appointment had been ten years ago and a filling was done at that time. Since that time, he has had occasional pain in



the muscles around his face and neck and an occasional headache. He stated his gums bled when he brushed his teeth and he had difficulty cleaning due to the lesion. His recent lab results revealed an undetectable viral load, CD4 count of 174. Upon oral exam, patient had carious lesions present on teeth #2, 4, 5, 15, 30, and 31. Patient had a raised and nodular palatal lesion slightly left of the midline. The lesion was 1 cm in width, 2 cm in length and 1.5 cm in height towards his occlusal plane. The lesion extended towards his soft palate and exhibited a red to purple color. There was an aphthous ulceration present on the tip of the lesion that was painful to the patient and making it difficult for him to eat. Three other red, flat lesions were present: on the maxillary tuberosity distal to #2, apical to #12 and a third on his uvula and soft palate. Externally, the patient did have multiple purple colored lesions on his face and neck. The lesions were slightly raised and rough in texture. The patient stated the lesions did extend to his upper body and waist, and a biopsy was scheduled. The area chosen for biopsy was a 1cmx1cm area mesial to the largest nodular portion of the palatal lesion. Patient was anesthetized with 2 carpules 2% xylocaine with 1:100,000 epinephrine. An incisional biopsy was performed to remove an elliptical portion of the lesion. Care was taken to obtain enough normal tissue structure for comparison. The piece of tissue was placed in a formalin fix and sealed. Hemorrhage was minimal and an electrocautery unit was set on coag with a power of 8 for hemostasis. After the procedure, patient stated that

he felt good and was dismissed from the clinic. Eleven days later, patient presented for a dental cleaning and the surgical area was healing nicely with granulation tissue. The 1.2x0.8x0.6cm soft tissue was sent for diagnosis. Microscopic examination revealed a highly vascular soft tissue lesion with the vessels being from capillary to artery size. An endothelial projection was associated with the vessels, some of which displayed the typical "stag-horn" architecture for the

Performing biopsy on suspicious oral lesions is our best defense against malignancy in the HIV patient.

lesion. The diagnosis was malignant Kaposi sarcoma. A copy of the diagnosis was given to the patient's NP and the patient was informed. The decision for treatment was left to the NP, who contacted the cancer center. Patient has been seen three times in the dental clinic since and is undergoing chemotherapy for the KS. At the patient's last appointment, the main oral lesion has become smaller in both height and width. The remaining oral lesions have less pigment associated with them, as have most of the patient's external lesions. The patient stated he feels great and is continuing chemotherapy and his dental visits with us.

Today, new HAART regimens are being produced and length-

ening the progression to AIDS. The treatments of opportunistic infections are ever-changing, but Kaposi sarcoma is still present in the AIDS population. While ten years ago the medical community was treating HIV/AIDS with a lack of knowledge about the etiology of opportunistic infections (OIs), we are now treating HIV/AIDS as a chronic illness and have learned a significant amount of information about the OIs. While behaviors are changing and the incidence of KS is decreasing, the dental professional still is a very important participant in the HIV patient's health care. Being a secondary support for primary health care providers in maintaining patients' compliance and an active role in their health care is the responsibility of the dental provider.

Performing biopsies on suspicious lesions for diagnosis still is one our best defenses against malignancies in the HIV patient. We all should strive for quality of care for our patients, while increasing their quality of life.❖

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Alicia Rose Hathorn, DMD, is Assistant Professor, University of Mississippi School of Dentistry, and Coordinator/Provider, CrossRoads Dental Clinic.



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