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AIDS EDUCATION
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HIV Clinician

ISSN: 1551-885X

Due to Hurricane Katrina, two issues did not appear. Regular issue numbering will resume with Vol. 19 in 2007.

formerly FACULTY NOTES

Summer 2006 • Vol. 18, No. 2

What do the studies show about STIs in the chronically HIV-1 infected patient?

Ronald D. Wilcox, MD

Structured or Strategic Treatment Interruptions (STIs) are defined as one or more cyclical interruptions in antiretroviral therapy (ART) that are planned with timing pre-specified ideally, although occasionally patients take their own unplanned STIs. A term patients often use is “drug holiday.” This approach to therapy has been evaluated with the hope of decreasing time on drug, therefore decreasing drug toxicities and costs. Multiple studies have evaluated their use in both acutely infected patients and those with chronic HIV infection. There are hundreds of studies addressing this subject and this article reviews merely a few of the more recent and/or relevant studies dealing with the use of STIs in *chronically infected* patients.

STIs in research are usually classified as either timed-cycle STIs, where a predetermined amount of time off ART is then followed by resumption of ART with close

monitoring of viral and immunologic parameters such as HIV viral loads and CD4 counts, or strategies where ART is stopped for a duration of time guided by the patient’s CD4 count.¹ Another term for the second strategy is “pulse” therapy.

The first success with an STI was reported by Lisziewicz in 1999 and involved a German patient who was taken off ART due to complications. The patient, who had two STIs, developed a very strong response in his antiviral HIV-1 specific immune response and was able to stop therapy after the second STI.² For an excellent comprehensive summation of many of the subsequent studies, please refer to the review by The Cochrane Collaboration from 2006.¹

Previous randomized controlled timed-STI cycle studies in chronically infected patients have shown either a decline in HIV-specific CD4 cells or no evidence of significant virologic or immunologic benefit.³⁻⁸ Of concern, these studies

See *STIs*, next page

Inside

8 Nursing

10 Dentistry

12 Pharmacy

14 Nutrition

16 Journal Articles

16 CE Programs

Legal

The aftermath of Schiavo: advance directives update

Linton Carney, JD; Lisa Mirman, JD;
and Lisa Thombly, JD

Over a year has passed since the media frenzy and ensuing legal battle over Theresa “Terri” Schiavo, the woman who became a household name in

March 2005. In the event anyone has forgotten, Schiavo collapsed in 1990 from what doctors suspect was a potassium imbalance.¹ She suffered severe brain damage, and lapsed into a “persistent vegetative state,”² according to sev-

See *Advance directives*, page 4



Medicine

STIs should probably always be avoided if regimen is NNRTI based

STIs, from page 1

have shown some development of resistance, especially when the patient was on an ART regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI). One study by Garcia (2003) with 20 participants contained an intervention arm where hydroxyurea was added to ART therapy and given during five timed STI cycles. This study showed that eight/nine participants in the intervention arm had viral suppression to < 5000 copies/ml at 52 weeks, whereas those who were on ART alone had only four of ten participants with viral suppression at 52 weeks.⁹ A more recent study (n=68) using hydroxyurea during STIs in primary HIV infection did not show this effect but instead showed a deleterious effect of the use of hydroxyurea with CD4 cell increases significantly blunted in the hydroxyurea group.¹⁰

Randomized controlled trials of CD4-guided STIs have also been reported since 2003. The first of these, the STACCATO trial, consisted of three arms: “week on week off (WOWO)” cycling, a CD4-guided arm, and a continuous ART arm. The first arm was discontinued early secondary to a higher virologic failure rate (53%) but there were no reported failures in the CD4-guided arm. Of concern was an increased rate of grade 3 or grade 4 events in the CD4 arm (46% vs 65% vs 44% respectively).¹¹⁻¹³ The BASTA study used a CD4-guided strategy in 69 patients with viral suppression and high CD4 counts (CD4 > 800). At 64 weeks, there was no differ-

ence in participants with CD4 count ≤ 400 as compared to the control group, although the main predictor for a significant decline in CD4 count was the nadir CD4, with greater viral rebound and greater cell loss in those with lower nadirs.¹⁴

The largest study to assess the effectiveness of CD4-guided STIs in chronically infected patients was stopped in January 2006. The Strategies for Management of Antiretroviral Therapy (SMART) study was a multi-national study carried out

There are definitely both risks and benefits to the use of strategic interruptions in anti-retroviral therapy.

by the Community Programs for Clinical Research on AIDS (CPCRA) in collaboration with Regional Coordinating Centers in Copenhagen, London, and Sydney that enrolled patients with CD4 counts > 350 cells/mm³. The patients were randomized into either the Viral Suppression (VS) Strategy arm or the Drug Conservation (DC) Strategy arm. The VS arm assessed the use of ART to maintain viral load as low as possible throughout follow-up as compared to the DC arm, which stopped or deferred ART until the CD4 count dropped below 250 cells/mm³. The episodic ART was

given based on CD4 cell count to increase counts to > 350 cells/mm³ at which point ART was again stopped. The planned enrollment was for 3000 patients per arm with an eight-year-average follow-up. The primary endpoint was HIV clinical disease progression or death and the other key endpoints included severe complications such as cardiovascular or renal or hepatic problems. 33 countries were involved with a total of 318 sites.

The study was halted on January 11, 2006. Total enrollment at that time was 5472. The average age at baseline was 46 years old and the demographics of participants included 27% women and 30% blacks. The median baseline CD4 was 596 versus 599 (DC arm versus VS arm) with a median CD4 nadir of 250 versus 252. Similar demographics were also found in HIV RNA < 400 c/ml (71.0% vs 70.8%), prior clinical AIDS diagnosis (24.7% vs 23.4%), ART naivity (4.5% vs 4.8%), years of prior ART (six years for both). When it was found that the primary endpoint of clinical disease progression or death was significantly higher in the DC group than in the VS group (3.7 vs 1.5 events per 100 person-years; RR 2.5 (1.8, 3.6) with $p < 0.0001$), enrollment in the study was halted. When individual groups were analyzed, it was found that men in the DC group had a 2.3 relative risk for the primary endpoint and women a relative risk of 3.4. Blacks were also at higher risk (RR 3.6) as compared to non-black participants (RR 2.0). The rise



in relative risk did not decrease with those participants who had higher baseline CD4 counts nor did it correlate with the nadir CD4 counts (RR 2.9 for those with nadir < 50 as compared to RR 2.6 for those with nadir CD4 > 400). The findings showed that the Drug Conservation (or STI) strategy, as compared to the Viral Suppression strategy, showed an increased risk for HIV disease progression or death; death; serious HIV disease progression; and severe complications (cardiac, renal, or hepatic).¹⁵

There are definitely both risks and benefits to the use of STIs. During STIs, there may be significant viral rebound leading to viral rebound syndrome that may resemble acute retroviral syndrome, including aseptic meningitis, an increased risk of transmission of the virus, and possibly a reseeding of viral reservoirs. Viral suppression generally occurs after re-initiating therapy but there are also reports of viral mutations presenting, especially after the use of NNRTIs. There frequently will be a loss of peripheral CD4 cells that can often be predicted by the nadir CD4 count, although the recent SMART study may refute this finding. Opportunistic infections have been reported in timed-cycle STI trials but not CD4-guided STI trials. The SMART study has clearly shown in a large group of patients that a CD4-guided STI strategy has an increased risk of significant disease progression or death and should be used very cautiously if at all in chronically infected patients. A large randomized similar trial is necessary using a timed-cycle approach with protease-inhibitor based regimens to see if there is any true benefit or

significant drawback to this approach. STIs should probably always be avoided if the patient is on an NNRTI-based regimen, due to the long half-life of the NNRTI giving an increased chance of development of resistance with subsequent loss of the class.❖

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Legal

Consent statutes delineate who makes end-of-life decisions

Advance directives, from page 1

eral neurologists. After a long, bitter, and widely publicized legal battle between Michael Schiavo, Theresa's husband, and the Schindlers, her biological family, Michael Schiavo obtained a court order from the Circuit Court for Pinellas County, Florida, Probate Division, to have Theresa Schiavo's nutrition and hydration tubes removed on March 18, 2005.³ A mesmerized nation watched as Michael Schiavo, the Schindlers, and the judicial and legislative branches of the United States government struggled over the fate of Theresa Schiavo. Theresa Schiavo died on March 31, 2005, thirteen days after her nutrition and hydration tubes were removed following the court order.⁴

Who decides?

The removal of Theresa Schiavo's nutrition and hydration tubes sparked a national debate over issues of life and death. One of the most controversial issues in the Schiavo case was the struggle between Theresa Schiavo's biological family and her husband over the authority to make medical decisions for her in the absence of an advance directive.

Advance directives are legal documents in which patients express their wishes about the kind of health care they want to receive should they become unable to make their own treatment decisions; note that these documents may be called different names in different states.⁵

In the absence of such documents, all states have some form of medical consent statutes that provide guidance as to who can make these decisions.

In Louisiana, if an adult is too incapacitated to make medical decisions for him/herself, then the decision is made by the person's spouse, unless the parties are judicially separated. If the person is unmarried, then the decision is made by an adult child. If the patient has no adult children, parents are to decide. If the parents are deceased, then siblings make the decisions. Finally, if the patient has no siblings, the patient's other ascendants or descendants (like grandparents or grandchildren) have the right to make decisions.⁶ If there is more than one person in any of these classes (for example, if both parents are alive, or the patient has several brothers and sisters), then the decision must be made by all available members of that class.⁷ Note that the Louisiana statute does not provide a mechanism for resolving conflicts when the family members cannot unanimously agree.

In Mississippi, the order of priority for a medical decision-maker is the adult patient's spouse, unless legally separated, an adult child, a parent, or an adult brother or sister.⁸ In contrast to Louisiana, the Mississippi law has a specific provision for majority rule in the event not everyone can agree. Mississippi also prohibits appointing as the medical agent anyone who is an owner, operator, or health care

employee at the facility where the patient is receiving care, unless the medical agent is related by blood, marriage, or adoption.⁹ Thus, a patient may not name an attending physician as a medical agent, even if the patient has no living relatives or friends.

In Arkansas, if an adult patient does not have a valid declaration or health care agent, then the order of priority for a medical decision-maker is the patient's spouse, the patient's adult child (and if there is more than one, then a majority vote), the parents, an adult sibling (if there is more than one, then a majority vote), persons standing *in loco parentis* to the patient, or a majority of the patient's adult heirs at law who participate in the decision.¹⁰ Arkansas, unlike Louisiana and Mississippi, does not specify whether the patient's spouse may make medical decisions for the patient if they are legally separated.

Get it in writing

Medical consent statutes are extremely important because they delineate who makes end-of-life decisions for the patient. The struggle between the two families in the Schiavo case possibly could have been alleviated with the existence of an advance directive. There are two types of advance directives: (1) a durable power of attorney for health care and (2) a living will.

A durable power of attorney for health care, sometimes called a durable medical power of attorney, allows the patient to designate a spokesperson during the



patient's period of incompetence. It is not necessary for a person to be suffering from a terminal illness or to be in an irreversible coma for the medical agent to be authorized to make decisions. In contrast, a living will is an individual instruction with regard to artificially prolonging the patient's life. Living wills are also commonly referred to as "Do Not Resuscitate," "Right to Die," or "Natural Death" documents.¹¹ Unlike the durable power of attorney for health care, the living will applies only when two doctors determine that the patient is suffering from either a terminal illness or an irreversible coma, and is unable to make decisions for him/herself. The living will cannot be used if the patient is capable of making health care decisions.

What treatment does a medical power of attorney cover?

In Louisiana, Arkansas, and Mississippi, a medical power of attorney covers any care, treatment, service, or procedure to maintain or diagnose a patient's physical condition.¹² In Arkansas and Mississippi, the laws on durable powers of attorney for health care define health care as both physical and mental health treatment.¹³ However, Louisiana has a special statute allowing advance directives for mental health treatment.¹⁴ Under the Louisiana statute, the patient may set forth instructions regarding mental health treatment in the event the patient is incapable of making his/her own health care decisions, and mental health treatment is necessary. This statute provides rather strict rules for a mental health power of attorney (for example, a physician must certify that s/he

has discussed the options for treatment with the patient), and thus brings into question whether a general health care power of attorney can be used for mental health treatment in Louisiana.¹⁵

Recent developments

The surge of interest about advance directives that followed the Schiavo case prompted many states to initiate or amend legislation. According to the Health Policy Tracking Service, more

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than 100 bills involving living wills and advance health care directives were proposed in the state legislatures of 30 states in 2005.¹⁶ Several states chose to tailor the bills to the circumstances of the Schiavo case, while others simply attempted to clarify ambiguous portions of preexisting advance directives statutes. In the Delta region, two states significantly amended their statutes last year.

New Louisiana legislation regarding Advance Directives

The Human Dignity Act (Act Number 447), which began as House Bill Number 675, was signed by Louisiana's governor on July 11, 2005.¹⁷ This new legislation is eerily similar to the facts surrounding the Theresa Schiavo case. Act Number 447

changes Louisiana's previous living will statute significantly in terms of the definition of spouse, and whether or not nutrition and hydration tubes should be considered artificial means.

The Act defines a spouse as "a person who is legally married to the qualified patient but does not include a spouse who is judicially separated from the patient, is cohabited with another person in the manner of married persons..."¹⁸ The marital status portion of the amendment is significant; a spouse must be someone who is legally married to the patient. In this respect, Act 447 does not considerably change the law; it is well settled that those in relationships outside of marriage have no statutory authority to make medical decisions for their respective spouses unless there is a declaration. Act 447 has significant implications for those who are legally married in particular situations. A person who is separated from the patient or cohabited with another person in the "manner of married persons" would not be considered a spouse under this Act.¹⁹ With regard to the Schiavo case, this amendment would have prevented Michael Schiavo from making medical decisions for his wife because he was living with a woman and had children with her.

Moreover, Act 447 changes Louisiana living wills considerably with respect to whether or not nutrition and hydration should be deemed life-sustaining procedures. Specifically, now patients must initial one of two options: 1) That all life-sustaining procedures, including nutrition and hydration, be withheld or withdrawn so that food and

See *Advance directives*, next page



Legal

HIV clinicians should urge patients to put their wishes in writing

Advance directives, from previous page

water will not be administered invasively, or 2) That life-sustaining procedures, *except* nutrition and hydration, be withheld or withdrawn so that food and water can be administered invasively [emphasis added].²¹ The amendments are noteworthy because now the patient must directly state that nutrition and hydration should be removed with other life-sustaining procedures. Prior to the amendments, the statute permitted patients to make a blanket election that life-sustaining procedures be withheld or withdrawn.

Effective August 15, 2005, Act 447 states that any declaration executed prior to that date, which does not contain an option to specifically initial a choice regarding nutrition and hydration, will not be found invalid *for that reason*, nor will it be presumed that the declarant desires the administration of nutrition and hydration.²⁰ Note that the living will could still be deemed invalid for other reasons. In addition, the last clause of Act 447 law provides that any ambiguity in the statute shall be interpreted to preserve life, because "human life is of the highest and inestimable value through natural death."²¹

While the amendments adopted in Act 447 have changed living wills considerably, Louisiana Senate Bill 40 would have been even more dramatic if ad-

opted. Urged by Theresa Schiavo's brother, Bobby Schindler, a Louisiana Senate panel proposed Senate Bill 40, which would have *required* keeping incapacitated patients alive unless their living wills specified that the patients did not want nutrition or hydration tubes. However, the bill was amended in committee before it passed to require the state to pay medical costs accumulated in providing the patient with nutrition and hydration if the patient's family was unable to pay. Senate Bill 40 was sent back to die in committee without being enacted, probably due to fiscal concerns.

Arkansas legislation

The Arkansas Legislature contemplated issues involving advance directives prior to the Schiavo case, as evidenced with its Rights of the Terminally Ill or Permanently Unconscious Act,²² which went into effect on July 16, 2003. The Act allows the patient, via a living will, to direct the physician to withhold or withdraw life-sustaining treatment not necessary to provide comfort care, or to appoint a health care agent to make life-sustaining treatment decisions. Under the Act, life-sustaining treatment is defined as "any medical procedure or intervention that, when administered to a qualified patient, will serve only to prolong the process of dying or to maintain the patient in a condition of permanent uncon-

sciousness."²³ However, like the new Louisiana law, the Arkansas legislation has special provisions for nutrition and hydration. A patient may initial the portion of the living will indicating that nutrition should be withheld, but only after consulting with the attending physician.²⁴ There is an identical clause regarding hydration, which is separate from the nutrition clause. On the other hand, the law does not require the patient to consult with the attending physician in order to direct that nutrition or hydration *not* be withheld.

Similar to Louisiana's Act 447, the statutory construction of Arkansas's Rights of the Terminally Ill or Permanently Unconscious Act is such that nutrition and hydration are not necessarily deemed life-sustaining treatments. This broad definition of life-sustaining treatment seems to encompass nutrition and hydration; the administration of such could both "serve only to prolong the dying process" or "maintain the patient in a condition of permanent unconsciousness." Nevertheless, the aforementioned Act setting forth the requirements for a living will expressly separates the nutrition and hydration directives from the life-sustaining treatment directive.

Mississippi legislation

Mississippi Senate Bill 2420 was approved by the governor on April 4, 2005.²⁵ The new

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law amended the 1972 Lindsay Miller-Beth Finch Organ Recovery Act, a law that required every licensed acute care hospital in Mississippi to have a protocol for identifying potential organ donors, including a procedure for family consultation. While this portion of the Act remains unchanged, the 2005 amendments make clear that declarations by the organ donor through a will, Durable Power of Attorney for Health Care, Living Will, or Mississippi's Anatomical Gift Law are exempt from family consultation. Thus, an individual's decisions recorded in one of these documents takes precedence over any decision by family members.²⁶

Part 2 of the 1972 Lindsay Miller-Beth Finch Organ Recovery Act was not affected by the 2005 amendment. Part 2 allows the patient to give his/her medical agent the authority to make end-of-life decisions.²⁷ If the patient does not want to give the medical agent this authority, the patient may give specific directions with respect to life-sustaining treatment. Under Part 2(6), the patient has the choice of whether or not to prolong life, while Part 2(7) contains specific instructions regarding artificial nutrition and hydration.²⁸ If the patient chooses *not* to have his/her life prolonged under 2(6), then Part 2(7) mandates the withdrawal of nutrition and hydration unless the patient specifically requests it. Similarly, if the patient chooses to have his/her life prolonged under Part 2(6), then Part 2(7) requires the administration of nutrition and hydration unless the patient directs that nutrition and hydration should be withdrawn.²⁹ The language of this portion of the

Act is significant when compared to Louisiana and Arkansas statutes, because it presumes that a patient who wants life-sustaining treatment withdrawn would also want nutrition and hydration withdrawn, and vice versa. In this respect, the Mississippi law suggests that nutrition and hydration is life-sustaining treatment, which is in direct contravention to the Louisiana and Arkansas statutes as they now stand.

Conclusion

The Theresa Schiavo case generated newfound interest in advance directives. Issues involving advance directives are pertinent to patients who are infected with HIV/AIDS because they may become seriously ill earlier in their lives as compared to those without the virus. Clinicians should encourage their clients to consider advance directives, preferably when they are in good health, to avoid potential nullity of the directives. HIV-associated dementia presents issues of competence, which may become especially important with regard to advance directives. Particularly in Louisiana, where the relevant law requires that ambiguities be resolved in favor of life, a client *in extremis* who executes a living will that rejects hydration and nutrition may have his/her wishes thrown into question due to issues of competency. Moreover, clinicians in Louisiana and Arkansas should be prepared to discuss nutrition and hydration, since the laws in those states require that the issues be specifically addressed by the patient.

Thus, while advance directives do not solve all of the potential complications with respect

to end-of-life decisions, they can provide safeguards to ensure the patient's wishes are carried out.❖

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6. LSA-R.S. 40:1299.58.5.
7. *Id.*
8. Miss. Code Ann. §41-41-211.
9. *Id.*
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11. Labeling a living will a "Do Not Resuscitate" (hereinafter DNR) order is misleading. DNR orders are written by doctors to indicate that a patient should not be resuscitated, because the order reflects the patient's expressed wishes, or because the patient will not benefit from resuscitation. A DNR is simply an order that the patient should not receive cardiopulmonary resuscitation (CPR). A DNR can supplement a living will and durable power of attorney for health care. Ethics in medicine, Washington University School of Medicine, February 22, 1999: "Do Not Resuscitate Orders." Available at <http://depts.washington.edu/bioethx/topics/dnr.html>.
12. ACA §20-13-104, MS ST §41-41-201, LSA-C.C. Art. 2997.
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17. Act. No. 447, amending and reenacting LSA-R.S. 40:1299.58.2(14) and (15) and 1299.58.3(C)(1) and (3) and to enact LSA-R.S. 40:1299.58.2(16) and 1299.58.10(E).
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21. *Id.*
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28. *Id.*
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Nursing

Community-acquired pathogen can signal need for HIV test

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Community-acquired methicillin-resistant *staphylococcus aureus* (CA-MRSA) is a pathogen that is spread by direct contact. It can thrive on the immunocompromised host and be cultured in persons living with HIV/AIDS who have skin and soft tissue infections (SSTIs) that would be considered trivial in other people. It is sometimes the AIDS- or HIV-related symptom that triggers the initial access to health care.

CA-MRSA is ugly and it hurts. It can be a rosacea-like facial rash with unsightly pustules accompanied by a CD4 count below 50 and a viral load above 100,000, as in one actual case that was successfully treated with Benzacilin and, of course, antibiotic prophylaxis for pneumonia and *Mycobacterium avium* complex (MAC), as well as a HAART regimen. The patient continues to do well three months later.

Epidemiology

CA-MRSA has become more recognized as a community-acquired pathogen causing primary infections in healthy children and adults since the 1980s. About 20 years ago, CA-MRSA infections were first noted in the IVDU population in Detroit (Chambers, 2001). In 1999, the deaths of four healthy children brought CA-MRSA to national attention (CDC, 1999). More recently, it has been identified in specific populations such as inmates, Native Americans, military recruits, homeless youth, and competitive athletes (Tufts and Harman, 2006) and has

emerged as a worldwide problem (Vandenesch et al, 2003). Older CA-MRSA patients tend to be poor, addicted, and/or chronically ill with diabetes or AIDS (Frazee, et al, 2005)

Pathophysiology

CA-MRSA infections are genetically distinct from typical nosocomial MRSA infections. The Pantone-Valentine Leucocidin (PVL) gene is responsible for production of a toxin which can cause necrosis of the skin or severe necrotizing pneumonia. (Naimi, 2003.) Further, CA-MRSA infections are usually resistant only to beta-lactams, and usually only cause SSTIs, whereas hospital-acquired MRSA (HA-MRSA) is multi-drug resistant, causes much more serious infections and must be treated with vancomycin or alternately linezolid (Aberg, et al, 2006).

Related factors

Related factors in primary infections include poor hygiene, minor trauma, or diminished skin integrity, which is so often found in AIDS-related dermatoses such as eosinophilic folliculitis, dermatophytes, psoriasis, or eczema. Therefore, treatment should include bathing and shampooing with antibacterial cleanser, the usual skin protective precautions recommended with pruritis, and moisturization. Adequate oral liquids during summer months are essential.

Recurrent hidradenitis suppurativa is not considered an opportunistic infection, however it might serve as a red flag for early detection of HIV if it raises the index

of suspicion of the primary care provider who questions immunosuppression in a patient, especially if a high risk profile exists. Rarely do oral antibiotics without incision and drainage clear this infection and often removal of the apocrine sweat glands must be accomplished to prevent further infection. The surgery referral is almost a reflex, but first there should be further investigation into constitutional symptoms, as well as an HIV test.

Symptoms and complications

Patients with CA-MRSA will often present with the chief complaint of "spider bite." This will be based on a lesion which is surrounded by bright erythema and tenderness. There may be a central pustule as well. Depending on the degree of immunosuppression, the lesion will rapidly progress to form an abscess and cellulitis. There may have been preceding red lesions which hurt or itched. The surface is usually intact. In follicular pustules, a tiny central pustule may extend below the surface forming abscesses or, in rare cases, violaceous hidradenitis-like plaques with pus-filled pockets of scar tissue caused by excoriations that may obscure the primary lesions.

If patients are experiencing flu-like symptoms, followed by rapid progression of blistering necrosis, pain, and systemic toxicity, they should be referred to the emergency department with a possible diagnosis of necrotizing fasciitis. CA-MRSA has the potential to cause this life-threatening complication. MRSA also occurs in mastitis, wound infections, and



pyodermas. Complications of skin and soft tissue infections with untreated or incorrectly treated MRSA include bone and joint infections. Septicemia and endocarditis associated with high mortality have been diagnosed in IV drug users. There is not always a focus of infection in such cases (Aberg, 2006). Hospitalization is indicated when systemic toxicity accompanies staphylococcal skin infection, or if the infection is advancing or other complications exist such as necrotizing fasciitis or compartment syndrome.

Differential diagnosis

The following list will provide a guide to help differentiate skin lesions. Testing will help establish it further.

- Fungal lesion
- Eosinophilic folliculitis
- Herpes simplex, herpes zoster
- Cutaneous hypersensitivity reaction to drugs
- Deep vein thrombosis in calf, swelling with cellulitis
- Syphilis
- Pyogenic granuloma
- Angiosarcoma
- Kaposi sarcoma
- Bacillary angiomatosis

Treatment

MRSA is characteristically resistant to all beta-lactam antibiotics, including penicillins, cephalosporins and carbapenems. Community-acquired MRSA is usually sensitive to tetracyclines, rifampin, quinolones, and clindamycin. Trimethoprim-sulfamethoxazole is often active against MRSA as well, but usually reserved for less serious infections. Any lesion larger than 5.0 cm in diameter should be incised and drained and sent for Gram stain and culture and sensitivity.

To reduce recurrence of CA-MRSA infection, several effective strategies exist:

- Treatment may be augmented with mupirocin ointment, administered intranasally (bid for 5 days to 4 weeks).
- Rifampin (300 mg bid po for 5 days) may be added to any of the recommended antibiotic regimens.
- Throughout antibiotic therapy, daily bathing with an antimicrobial agent, such as Hibiclens, is recommended.
- Any household or close contacts should be treated with mupirocin ointment, as they may be asymptomatic carriers of CA-MRSA.

The patient may require pain medication. Start with anti-inflammatory agents. Augment with a narcotic only for breakthrough pain.

Patient education

The patient should be informed that his/her infection is contagious and other people should not be allowed to touch the affected areas without gloves on. Careful attention to handwashing, bathing and shampooing are also important in personal hygiene, as well as cleaning the bathtub after bathing with a bleach solution. Adherence to antibiotics must be stressed and strategies for reducing missed doses explored. Often there will be a plan for wound care which will need to be carried out with help from a family member or a home health nurse. Instructions should be carefully written down. Supplies for the wound care should be provided or assistance in procuring them obtained. This should include an antibacterial agent such as Hibiclens. Hydrogen peroxide can be poured directly into an infected wound but is not recom-

mended for a wound without slough. This process needs to be kept as simple as possible. Avoid the use of tape on skin. Wounds must be wrapped securely if a heating compress is to be applied. The patient should be instructed that any clothing, linen or reused binders that have come into contact with the wound must be laundered in hot water with detergent.

Take home message

To all unsung heroes in the uphill primary care march on morbidity and mortality among the masses: "I have a spider bite" just may be code for "I got AIDS."❖

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Dentistry

Is HIV a risk factor for complications of dentoalveolar surgery?

Kishore Shetty, DDS, DDPH

Patients who are infected with immunodeficiency virus (HIV) suffer progressive deterioration in immunity as indicated by a fall in the T-helper (CD4) cell count. Studies suggest that in such patients the risk of wound infection increases as the immune status deteriorates. Pronounced immunosuppression (CD 4+ T cells < 200/ul) has been associated with a higher risk of postoperative complications. Immunologically-compromised patients are unable to generate sustained, controlled, and effective immune responses when subjected to external trauma. Consequently, it has been suggested that the risk of complications in HIV-positive patients subjected to surgical procedures in the maxillofacial region is presumably higher than in HIV-negative patients (Table 1). The purpose of the study described below was to perform a preliminary test of the hypothesis that patients infected with HIV have an increased risk of complications after oral surgery in comparison with HIV-negative patients.

Methods

The study was carried out at the HIV Outpatient Clinic and the Charity Hospital Dental Clinic at the Medical Center of Louisiana in New Orleans. The records of all HIV-infected patients who underwent any dental surgical procedures at the Oral and Maxillofacial Surgical Unit from 1999 to 2004 were reviewed. Patients were identified through the clinic discharge database. In a matched design, HIV+ patients were compared with respect to surgical outcomes in the highly active antiretroviral therapy (HAART) era. The plan was to review selected surgical procedures (extractions, impactions, biopsies, pre-prosthetic and implant surgery, and benign tumor excisions) among more than 86 HIV+ patients in the period June 1999 to June 2004 and then cases matched 1:1 to randomly selected HIV-patients (controls) on type, year, location of surgery, gender and age of surgery. Demographic and clinical information was entered into a database that included: indication for surgery, type of

surgical procedure, emergent or elective surgery, pre-procedure antibiotics, CD4 count, viral load, white blood cell (WBC) count and platelet count. Peri-operative and post-operative events were recorded as complications if they were described in the medical records as a complication or untoward event on or before the follow-up visit. An event was classified as a complication if it met one of the following criteria: (a) re-hospitalization; intra-operative complication (either surgical or anesthetic); (b) clinically apparent bleeding; (c) post-operative fever lasting more than 72 hours; (d) clinical diagnosis of infection requiring antibiotic treatment of routine prophylaxis; (e) other clinically significant events.

Results

The adjusted rates of infectious and hematological complications in major dentoalveolar procedures were higher among the HIV-positive patients than among the HIV-negative individuals. However, a logistic regression analysis demonstrated that controlling for known risk factors eliminates the significant difference in complication rates between the two groups. The most important risk factors for complication of surgery in HIV-positive individuals were high viral load and absence of antiretroviral treatment (Table 2).

Discussion

In recent medical studies, HIV-1 RNA concentration was highly predictive of the rate of decline of CD4 lymphocyte counts and of progression to AIDS and death. Because of a strong association between viral load and clinical outcome, viremia is thought to be central to the pathogenesis of HIV disease. Viremia is an indicator of active viral replication requiring continuous re-infection and destruction of CD4 lymphocytes and the total number of virus-producing cells. Patients will develop opportunistic infections or progression to AIDS and death sooner if they have a high viral load because of the greater rate of virus production, which will quickly and severely impair the ability of and capacity to replenish CD4 lymphocytes. The widespread use of HAART has led to a

sustained reduction in AIDS-related morbidity and mortality.

The number of HIV-positive patients seeking dental care continues to rise and it is very important to base dental care on sound scientific principles and not on outdated assumptions. Improving the viral and immune status of patients receiving HAART will have a significant impact on improving the clinical outcomes and decrease the complications after dentoalveolar surgery. ♦

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Table 1. Maxillofacial/Dental Literature Review

Author	# HIV Patients	Procedure Performed	Variable (s) Examined	Results for HIV patients	Control Group
Robinson 1992	8	Extraction of teeth	Infection rate Localized alveolitis	Post extraction complications 3%	HIV-negative Patients
Porter 1993	38	Extraction of teeth	Infection rate	Post extraction complications 3.7%	HIV-negative Patients
Glick 1994	331	Extraction of teeth	CD4	Post extraction complications 4.1%	None
Dodson 1994	44	Extraction of teeth	Localized alveolitis Infection rate	Higher postextraction complication rate	HIV-negative Patients
Schmidt 1995	20	Reduction of mandibular fracture	Infection rate	Higher overall rate of postoperative infection	HIV-negative Patients
Dodson 1997	76	Extraction of teeth	CD4, CD8, CBC	Post extraction complication rate in HIV + was high CD 8 count was a predictor of risk	None
Carey 2001	10	I&D odontogenic infection	Intensity of ICU care	More intensive hospital stay	HIV-negative

Table 2: Logistic Regression Model for identifying the risk factors for complications relating to dentoalveolar surgery (statistically significant)**

Risk Factor	Odds Ratio	(95% CI)
Viral Load	2.33 **	(1.25 ± 3.89)
HAART	2.45 **	(1.32 ± 3.68)
Ethnicity	1.97	(1.01 ± 2.45)
Age	1.68	(0.95 ± 2.67)
Hematocrit	1.20	(0.87 ± 1.56)
Platelet Count	0.99	(0.89 ± 1.44)
WBC Count	0.89	(1.11 ± 1.34)
Gender	0.78	(1.22 ± 1.56)
HIV infection	0.67	(0.34 ± 2.04)



Pharmacy

Update: Black box warnings for FDA-approved antiretrovirals

Tina Edmunds-Ogbuokiri, PharmD, FASCP

Adverse drug reactions (ADRs) continue to be a leading cause of death all over the world and in the United States. A major factor that contributes to the increased risk of ADRs after drug approval by the Food and Drug Administration (FDA) is the fact that drugs are studied in selected populations for limited periods of time. In HIV infection, this period has been shortened because of the so-called “fast-track” approvals carried out in order to make these agents quickly available for the treatment of this deadly and incurable disease. While expediting the availability of new medications for treatment of HIV-infected patients (who often have limited options) through this fast-track process, it becomes necessary that post-marketing surveillance strategies remain in place to provide data on adverse drug events that may be reported when the drugs become available to a wider population of patients and providers. Such new data are often brought to the attention of providers and patients through the “black box warnings.”

The so-called “black box” is a prominently displayed boxed warning added to the labeling of drugs or drug products by the Food and Drug Administration (FDA) when serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury. Derived from both clinical trials data and post-marketing surveillance data, black box warnings are an important part of how the FDA evaluates, communicates and manages drug benefits and risks and conveys these findings to healthcare providers for optimal medication management in all patients, including HIV-in-

ected patients. The intent of this article is to review and update the black box warnings of antiretroviral agents, as presented through the Department of Health and Human Services Guidelines of May 2006, for the use of antiretroviral agents in the treatment of adults and adolescents with HIV infection.

Warnings associated with the non-nucleoside reverse transcriptase inhibitors

Nevirapine (Viramune) is the only non-nucleoside reverse transcriptase inhibitor that carries a pertinent black box warning information in its product labeling. The indication and usage section now recommends against using this drug in women with CD4+ cell counts > 250 cells/mm³ (and men with CD4+ cell counts >400 cells/mm³) at the time of initiation of the drug, unless the benefit far outweighs the risks. This recommendation is based on higher observed risk of serious liver toxicity in patients with higher CD4+ cell counts prior to initiation of therapy. Females have a three-fold higher risk of symptomatic liver toxicity than males and females with CD4+ cell counts > 250 cell/mm³ have a 12-fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts of < 250 cells/mm³. In addition, the revised package insert now includes literature given to patients to inform them about the risk associated with use of nevirapine in the treatment of HIV infection. The May 2006 guidelines specifically state as follows: “Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported. Patients may present with non-specific prodromes

of hepatitis and progress to hepatic failure. Women with CD4 counts > 250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection are at considerably higher risk of hepatotoxicities. Severe life-threatening and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings and organ dysfunction have occurred with nevirapine treatment. Patients should be monitored intensively during the first 18 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity and skin reactions. A 14-day lead-in period with nevirapine 200mg daily must be followed strictly. Nevirapine should not be restarted after severe hepatic, skin or hypersensitivity reactions.”

Warnings associated with the nucleoside reverse transcriptase inhibitors

Tenofovir (Viread) or in combination with emtricitabine (Truvada)

Lactic acidosis and severe hepatomegaly with steatosis have been reported, including fatal cases, with the use of nucleoside analogs alone or in combination with other antiretroviral agents.

Tenofovir is not indicated for the treatment of chronic hepatitis B (HBV) infection; safety and efficacy in patients with HIV/HBV co-infection have not been established.

Severe acute exacerbations of hepatitis B have been reported in patients who discontinued tenofovir; hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV co-infected patients.



If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.

Stavudine (Zerit, D4T)

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors alone or in combination with other antiretroviral agents.

Fatal lactic acidosis has been reported among pregnant women who received the combination of stavudine and didanosine with other antiretroviral combinations.

Stavudine and didanosine should only be used during pregnancy if the potential benefit clearly outweighs the potential risk.

Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.

Zidovudine (AZT, Retrovir) or in combination products (Combivir and Trizivir)

This agent can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including and especially among, advanced HIV patients.

Prolonged zidovudine use has been associated with symptomatic myopathy.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside antiretroviral agents alone or in combination.

Zalcitabine (Hivid, ddC)

Zalcitabine can cause severe peripheral neuropathy. Use with caution among patients with pre-existing neuropathy, for instance due to diabetes or other diseases, as well as other drugs that cause neuropathy.

In rare cases, zalcitabine can cause pancreatitis. Therapy should

be withheld until pancreatitis is excluded.

Rare cases of hepatic failure and death have been reported among patients with underlying hepatitis B infection.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside antiretroviral agents alone or in combination.

Warnings associated with the protease inhibitors

Tipranavir (Aptivus)

When co-administered with ritonavir, 200mg twice daily, tipranavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities.

Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

Ritonavir (Norvir)

Co-administration of ritonavir with certain non-sedating antihistamines, sedative-hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious and life-threatening adverse events because of possible effects of ritonavir on hepatic metabolism of certain drugs.

Saquinavir (Fortovase, Invirase)

The low bioavailability of both saquinavir hard gel (Invirase) and soft gel (Fortovase) make them less desirable as sole PIs. The manufacturer currently recommends that all saquinavir be used as boosted PIs with ritonavir (Norvir). Since the hard gel capsule (Invirase) appears to have a better gastrointestinal tolerance than the soft gel preparation (Fortovase), it is preferred by some clinicians and patients. In a recent announcement from the manufacturer

(Roche Laboratories), Fortovase has recently been discontinued and will no longer be available (at least in the US market).

Invirase as saquinavir hard-gel capsules and tablets, as well as Fortovase (saquinavir soft gel capsules), are not bioequivalent and cannot be interchangeable.

Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase.

Diligent recognition and application of the recommendations of black box warnings and other adverse drug reactions will assist providers in optimizing regimens for HIV-infected patients and, by so doing, improve our achievement of the desired clinical and immunological outcomes for patients with this challenging infection. ♦

REFERENCES AVAILABLE UPON REQUEST

The second part of this article will appear in the next issue of HIV Clinician.

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Nutrition

Do your patients use complementary and alternative therapies?

Ginger Bouvier, MEd, LDN, RD

Complementary and alternative therapies are a group of diverse medical and health-care systems, practices, and products that are not presently considered to be part of conventional medicine.

Complementary therapies are used *in conjunction with* conventional medicine. An example of complementary therapy is the use of acupressure bands to help alleviate nausea associated with chemotherapy.

Alternative therapies are used *in place of* conventional medicine. An example of alternative therapy is the use of a special diet to treat cancer instead of undergoing recommended chemotherapy, radiation, or surgery. In the first decade of the AIDS epidemic in the United States, little or no treatment was available for people with HIV/AIDS. Alternative therapies were widely sought by people looking for ways to control HIV and their symptoms. Despite effective antiretroviral (ARV) therapies today, many people with HIV/AIDS seek complementary and alternative therapies for a variety of reasons: symptom control, HIV control, and to feel a sense of control.

In the scenario below, what should a clinician do if this was his/her patient?

28 yr old male patient with CD4=280, HIV viral load < 50 copies/ml.

Your patient, Joe, tells you that he knows that his anti-

retroviral (ARV) therapy has been keeping his viral load at an undetectable level and increasing his CD₄ count, but he tells you that he has decided to stop taking antiretroviral medication and only use “natural” therapies to treat his HIV disease. Joe states he is taking a half cup of coconut oil daily because he heard it has antiviral properties. He is also taking an antioxidant tablet and a multivitamin daily. Joe asks what other “natural” therapies you would recommend to help control his HIV.

What are the main issues in the above scenario?

1. Joe has stopped his ARV despite his acknowledgement that the ARV therapy was working.

It would be important to discuss with the patient the reason(s) he stopped his ARV therapy, and determine whether there is a problem that can be resolved. There are a variety of factors, such as side effects, scheduling problems, disclosure issues, financial burden, difficulty with access, and lack of faith in the medicine or the medical team, which can lead to a patient's decision to stop ARV.

2. Joe seems comfortable telling you that he has stopped ARV therapy.

It seems as though you and Joe have developed an honest, trusting patient-provider relationship. Although you may disagree with Joe's decision to stop his ARV therapy, it is helpful to recognize Joe's honesty with you regarding his decisions and

actions. As a provider, you might ask Joe, “What can I do to help you better understand the risks of stopping ARV therapy and why I am concerned about what you are doing?”

It is important to acknowledge the common goal you both share: maintaining Joe's optimal health. At the very least, both you and Joe must take the time to fully understand each other's beliefs and the reasoning behind them.

3. Joe also seems comfortable telling you that he is taking alternative therapies and is looking to you for recommendations on alternative therapies.

Again, it is helpful to recognize Joe's honesty with you regarding his decisions and actions. Many patients with HIV use complementary and alternative therapies because it gives them a sense of control over their health care. While not every treatment decision a patient makes is worthy of support, the patient's opinions and health are. It is helpful to discuss the patient's use of complementary and alternative therapies in a non-judgmental fashion, otherwise he/she may be reluctant to tell you about any such decisions in the future. In many instances, patients who are determined to use complementary and alternative therapies will do so even if their health care providers disapprove.

Patients should use the following questions to guide them when considering or using complementary and alternative therapies:



1. What do I hope to get out of this therapy?
2. Is this therapy used by other people with HIV/AIDS?
3. Am I able to speak with any of these individuals about their experience?
4. Is there any scientific research about this therapy in HIV disease?
5. Are there any side effects to this therapy?
6. Where can I get this treatment and will it be regularly available?
7. Are there any interactions between this treatment and anything else I'm taking?
8. What is the cost of this treatment and can I reasonably afford it?
9. Is this treatment potentially harmful?
10. Is this therapy regulated by a professional body or government?

Joe is using alternative, not complementary, therapy.

Since Joe is taking coconut oil and vitamins *instead of* ARV therapy and you want Joe to resume his ARV therapy, a compromise may be Joe's use of complementary therapy. If you do not find any potential harm or problems with Joe's alternative therapies, it may be possible to get Joe to agree to use his "natural" therapies along with ARV therapy.

Building a cooperative relationship with patients means working and communicating honestly and respectfully with each other to meet the common goal of maintaining the patients' optimal health.❖

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HIV Clinician is published four times a year by
Delta Region AIDS Education and
Training Center (AETC), 136 S. Roman St.,
New Orleans, LA 70112.
Phone 504-903-0788, Fax 504-903-7893

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Non-commercial reproduction of this newsletter is encouraged. The opinions expressed are those of the authors and are not necessarily those of the Delta AETC. The Delta AETC is funded through the Ryan White Care Act by HRSA Grant 6-H4AHA00059-04-04.

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