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HIV & Hepatitis Education Prison Project

HEPP REPORT

HIV & HEPATITIS EDUCATION PRISON PROJECT

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INFECTIOUS DISEASES IN CORRECTIONS

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HEPP Report, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, HEPP Report provides up-to-the moment information HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education. HEPP Report is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

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Long-Term Toxicities Associated with HIV and Antiretroviral Therapy

By Peter J. Piliero, M.D.*, Associate Professor of Medicine, Albany Medical College

Soon after the introduction of the first antiretroviral (ARV) agent, zidovudine (AZT), drug-related toxicities became recognized and well-characterized. Things have since become more complicated; there are now 17 ARV agents in four distinct classes. This has led to both decreased morbidity and mortality from HIV infection due to immune reconstitution and viral suppression, and increasing recognition of both acute and long-term toxicities of ARV therapy (ART). Most clinicians agree that the benefits of ART generally outweigh the risk; however, patients who experience significant side effects sometimes disagree with this. This can lead to patient non-adherence or refusal to take any ART at all for fear of toxicity. Drug toxicities may have both acute and long-term implications to the health of HIV-infected persons.

This report reviews common acute and long-term toxicities of ART. Drug toxicities can be class-specific or ARV-agent specific. Having an understanding of these complications allows clinicians to anticipate potential toxicities, and to communicate about them with their patients. Clinicians should inform patients considering ART what complications they may experience, how to recognize these side effects, and what they should do about them. This proactive approach is likely to lead to a more trusting relationship and improved adherence.[1]

Mitochondrial Toxicity

In recent years, mitochondrial toxicity has been recognized as one of the most serious potential side effects of ART.[2] Mitochondria are the energy-producing factories of our bodies; when mitochondrial production is decreased by inhibition of the cellular DNA polymerase gamma, end-organ toxicity can occur. Mitochondrial toxicity is associated with the use of the nucleoside and nucleotide reverse transcriptase inhibitors, and may lead to a number of clinical problems. These include pancreatitis, peripheral neuropathy, and increased production of lactic acid.

Pancreatitis

Pancreatitis can be an acute complication of ART, even though it may occur after years of stable treatment.[3] This potential fatal complication has been linked predominantly to the use of didanosine (ddI); however, stavudine (d4T) and lamivudine (3TC) have also been associated with pancreatitis. There may be an added potential for pancreatitis when using combinations of these nucleoside reverse transcriptase inhibitors (NRTIs). Importantly, the concomitant use of alcohol increases the risk of pancreatitis. In cases of acute pancreatitis, temporary interruption of ART is recommended. Subsequent resumption should avoid the likely causative agents the patient was taking at the time he or she developed pancreatitis.

Peripheral neuropathy

Peripheral neuropathy usually occurs after prolonged use of NRTIs.[4] This complication is most often associated with the use of the "d-drugs" - zalcitabine (ddC), stavudine (d4T), and didanosine (ddI) (in decreasing order of likelihood). The combined use of two of these drugs has been associated with an even higher incidence of neuropathy. Recognizing neuropathic symptoms early on, and reducing or interrupting the offending agent(s) usually leads to symptom resolution. If patients are maintained on these drugs, progressive and often permanent neuropathy requiring narcotic analgesia may ensue.

Lactic acidosis

Lactic acidosis syndrome (LAS) was first reported in the early 1990s in association with zidovudine (AZT) use, predominantly in obese African-American women. In recent years, the greatest association has been with the use of stavudine (d4T) with or without didanosine (ddI). The nucleoside and nucleotide analogues inhibit mitochondrial DNA production, which leads to an increased breakdown of fatty acids into lactic acid. Inhibition is greatest for the "d-drugs" but also occurs with the other NRTIs.[5]

Patients with LAS generally present with vague constitutional complaints including fatigue, malaise, abdominal pain, and nausea and vomit-

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Long-Term Toxicities...

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ing. Over the course of several weeks, these patients can develop tachypnea, pancreatitis, and/or hepatitis in the setting of progressive acidemia. If unrecognized, death may occur. The clinician considering this diagnosis early on in the setting of vague complaints should obtain an arterial or venous lactate level. A mildly elevated level (2-5 mmol/L) is diagnostic of symptomatic hyperlactatemia, whereas a level >5 mmol/L in conjunction with a reduced arterial pH confirms the diagnosis of LAS. In both situations, interruption of ART until resolution is necessary. Subsequent therapy should, when possible, avoid those drugs most associated with LAS.

Metabolic Complications

Various metabolic complications associated with HIV have now been recognized. These include dyslipidemia, insulin resistance/diabetes (dysglycemia), and osteopenia/osteoporosis.

Dyslipidemia

Abnormal serum lipids have been noted since the beginning of the HIV epidemic. In the pre-ART era, patients commonly had hypocholesterolemia and hypertriglyceridemia as a function of their wasted hypercatabolic state, combined with increased pro-inflammatory cytokines.[6] However, the highly active ART (HAART) era has been associated with a dyslipidemic profile consisting of high total and LDL cholesterols, elevated triglycerides, and a low HDL cholesterol. Although some patients may exhibit all three of these abnormalities, many will only have abnormalities in either the cholesterol or triglyceride fractions. The fraction most affected usually depends on the ARV agent(s) used (for example, ritonavir (RTV) predominantly affects triglycerides). The effect on lipids is most pronounced with protease inhibitors (PIs), followed by non-nucleoside and then nucleoside reverse transcriptase inhibitors.

The dyslipidemic profile is associated with an increased risk for atherogenesis, raising concern that as patients live longer due to HAART they may experience an increased risk for coronary or cerebral vascular morbidity and mortality.[7] Multiple cohort studies comparing the frequency of coronary and/or cerebral vascular disease in HIV-infected patients with matched HIV-uninfected controls have shown an increased incidence of disease in those with HIV infection. Identification and management of individuals with dyslipidemia is now an essential part of HIV care. Guidelines are now available.[8]

Dysglycemia

Disorders of glucose metabolism, or dysglycemia, were one of the first metabolic complications of ART identified.[9] Initial reports of new-onset hyperglycemia, including episodes of diabetic ketoacidosis, were linked to the use of protease inhibitors (PIs). Subsequent cohort studies have confirmed this association, which is largely due to acquired insulin resistance.[10] Patients with HCV co-infection appear to be at greater risk of developing this complication.

Diagnosis is usually performed through periodic fasting glucose determinations or by a two-hour oral glucose tolerance test. Glycosylated hemoglobin levels are usually normal even in the setting of insulin resistance. Treatment depends on the severity of the hyperglycemia, with mild cases responding to dietary intervention and exercise, moderate cases responding to insulin-sensitizing agents such as the glitazones, and severe cases responding to insulin therapy. Modifying the regimen by replacing the PI with a non-PI agent may also be successful.

Disorders of Bone Metabolism

More recently, disorders of bone metabolism have been recognized as another long-term complication seen in HIV-infected patients.[11] Osteopenia and osteoporosis have both been described in patients on ART, but predominately in those on HAART. The etiology of these changes has not been delineated, although there is a suggestion that the HIV-1 protease inhibitors may contribute to this process by affecting osteoclast or osteoblast differentiation. Diagnosis is made by standard DEXA scanning, although at this time routine DEXA scanning of all HIV patients is not indicated. However, for those with other risk factors for osteoporosis, such as family history, hypogonadism, smoking, and corticosteroid use, screening DEXA scanning should be considered. Preliminary studies have shown that alendronate is effective at treating osteoporosis in these patients.

Lipodystrophy

One of the most disconcerting toxicities increasingly recognized in the past three years is lipodystrophy, a disturbance in the way the body produces, uses, and distributes fat.[12] Patients with long-term HIV infection, especially those treated with antiretroviral therapy, may exhibit changes in body morphology due to changes in fat distribution. Although these changes are usually not associated with medical complications, the disfigurement can be psychologically disabling.

Various cohort studies have estimated that up to 50% of patients suffer from lipodystrophy. Two patterns have emerged. Lipoatrophy, or subcutaneous fat loss, is seen most commonly in the face, extremities, and buttocks. Lipohypertrophy, or increased fat deposition, is seen predominantly in the abdominal region ("paunch"), dorsocervical region ("buffalo hump"), and breasts. Patients often have a combination of the two types of dysmorphic features.

The pathogenesis of fat maldistribution remains elusive. Retrospective cohort studies have defined characteristics associated with development of lipodystrophy: these include an age >40 years, nadir CD4 cell count, Caucasian race, and antiretroviral use. More recently, a prospective study of ARV-naïve patients initiating therapy showed an association between development of lipoatrophy and use of a stavudine-containing regimen, and lipohypertrophy and the use of a PI-containing regimen. These investigators also defined a pattern to changes in body morphology occurring after initiation of therapy. Specifically, patients gained fat and lean mass during the first 24 weeks of therapy, followed by progressive loss of extremity fat while preserving gained central abdominal fat over the next 72 weeks of therapy.[13]

No definitive treatment for fat maldistribution exists, though different approaches have been tried. For lipoatrophy, several studies have shown that substitution of either zidovudine (AZT) or abacavir (ABC) for stavudine (d4T) may be associated with increases (albeit small) in subcutaneous fat, compared to continued declines in those remaining on stavudine (d4T). For lipohypertrophy, replacement of the protease inhibitor with a reverse transcriptase inhibitor may be useful.[14]

Cosmetic surgical options to treat facial lipoatrophy include a variety of methods of soft tissue augmentation. Although none of these procedures are specifically FDA-approved for this indication, some are FDA permissible as off-label use of approved agents. Bioabsorbale materials used for soft tissue augmentation include Zyplast collagen, human cadaveric dermal tissue (Cymetra), or fascia lata (Fascian) polylactic acid (Newfill), hyaluronic acid (Perlane) and fat transfers. Permanent options include implants, liquid injectable medical grade silicone (Silikon-1000), and polymethylmethacrylate (Artecoll).

For buffalo humps that cause disfigurement, neck pain, or sleep apnea, liposuction may be effective. Human growth hormone has also been shown to decrease buffalo hump and excess abdominal fat.[15] However, high cost and tolerability issues have led few patients to use this approach. Once ongoing research establishes the definitive cause of fat maldistribution, more specific therapeutic options can be developed.

Hepatotoxicity Unrelated to Chronic Viral Hepatitis

Previous articles in HEPP Report have extensively covered the effects of chronic HBV and HCV in patients with HIV (go to www.hivcorrections.org). However, hepatotoxicity occurs in HIV-infected patients even in the absence of chronic viral hepatitis. Some of these are acute drug toxicities, such as those seen with

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Letter from the Editor

Dear Correctional Colleagues:

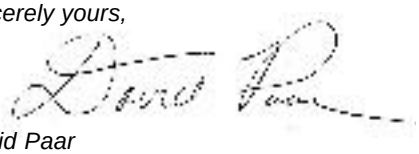
In this month's main article, Dr. Peter Piliero discusses mitochondrial toxicity, which is responsible for many of the long-term complications of antiretroviral therapy. These complications, along with the development of viral resistance, are the primary reasons for delaying the initiation of antiretroviral therapy in HIV-infected patients. This delay provides the opportunity and time to establish an effective provider-patient relationship and to educate patients about the risks and benefits of antiretroviral therapy. Such an approach will lead to improved acceptance of and adherence to antiretroviral therapy, as well as earlier recognition of complications that can be addressed by appropriate changes in antiretroviral therapy.

In this month's spotlight, Drs. Bhupinder Mann and Joseph Bick describe the sudden appearance of SARS and its effect on an unprepared public and health care system. Although fear may be the first response to life-threatening emerging infectious diseases, rational plans of response that are informed by facts are the only ways to respond to and contain emerging pathogens. It is unclear what the magnitude of the SARS problem will be in the United States. But it is clear that all heath care facilities, including prisons and jails, should develop a plan to contain and treat this infection if and when it appears at our doorsteps.

After reading this issue, you should be familiar with toxicities associated with antiretroviral therapies, including common toxicities across drug classes and with specific agents. You should also be familiar with issues relating to the SARS virus, including how it is transmitted, symptoms, making a diagnosis, and what to think about when implementing a plan in a correctional facility.

As always, please contact us with your suggestions and comments.

Sincerely yours,



David Paar

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In accordance with the Accreditation Council for Continuing Medical Education Standards for Commercial Support, the faculty for this activity have been asked to complete Conflict of Interest Disclosure forms. Disclosures are listed at the end of articles. All of the individual medications discussed in this newsletter are approved for treatment of HIV and hepatitis unless otherwise indicated. For the treatment of HIV and hepatitis infection, many physicians opt to use combination antiretroviral therapy which is not addressed by the FDA.

A Correctional Perspective on Severe Acute Respiratory Syndrome (SARS)

Bhupinder Mann, M.D. and Joseph Bick*, M.D.*

Editor's note: *Bhupinder Mann, M.D., is a Mayo Clinic-trained hematologist/oncologist who spent several years working in correctional health at the California Medical Facility in Vacaville, CA. Dr. Mann is currently a Senior Consultant in Medical Oncology at the National Cancer Centre of Singapore, and has firsthand experience with the SARS epidemic.*

The sudden global emergence of Severe Acute Respiratory Syndrome (SARS) has sickened over 8,000 individuals, crippled health care delivery, and has had a devastating impact on the economy. The causative agent, a novel Coronavirus, is not previously known to cause disease in humans. Thus far, no specific treatment, vaccination or reliable and readily available diagnostic tests are available. Exactly where we are in the course of this epidemic is not yet clear.

Transmission

Most infections have been acquired by close contact with a symptomatic individual. The virus has been cultured from nasopharyngeal secretions and stool, and has been shown to remain viable for several hours outside the body on plastic and other surfaces. It appears that respiratory droplets are the primary source of transmission. However, large clusters have been documented to result from nebulizer-generated aerosols and fecal-oral transmission (traced to damaged sewage system in an apartment complex).

Symptoms

The incubation period ranges from two to 16 days; the average is six days. Common symptoms include fever (100%), chills, rigors, myalgias, cough (>50%) and sputum, sore throat, coryza, nausea, vomiting, diarrhea (20-30%). Seventy percent of patients have moderate lymphopenia, and 45% have mild thrombocytopenia.

At the time of initial presentation, 70-80% of patients demonstrate varying patterns of air-space consolidation on CXR. Hypoxemia requiring ICU care develops in 20-30% of cases. The mortality rate appears to be dependent upon age, with an overall death rate of 14-15% and as high as 55% in those over 60 years of age.

Diagnosis

The initial diagnosis of SARS relies on suspicion based on a patient's history. Specifically asking patients about their history of travel to affected areas, visits to an affected health care facility, or history of casual social contact with a suspected or probable case is critical.

Relying on initial symptoms alone, it is hard to differentiate SARS from any other flu-like illness. Since a reliable, rapid diagnostic test is not presently available, clinicians must rely on symptoms, signs, and exposure/travel history. Many patients develop an ARDS-like clinical picture. Suspect cases should receive a chest x-ray, pulse oximetry, and blood cultures. Gram stain of sputum and testing for other respiratory viruses such as influenza should be performed.

RT-PCR can rapidly document the presence of coronavirus RNA. Antibody response is now known to develop over time in serum; however, the sensitivity and specificity of these tests has not yet been established. Specimens from suspect cases should be saved for further testing, and acute and convalescent serum samples should be obtained from individuals who meet the SARS case definition (see Table 1).

Infection Control

Appropriate precautions need to be taken while evaluating suspected patients, starting from the point of triage. Patients with suspicious symptoms should be provided with a surgical mask upon arrival. When possible, suspect cases should be evaluated in a designated area.

Control of the epidemic relies on quarantining exposed individuals and tracing their contacts. Institutionalized individuals who may have been exposed, and their caretakers, should have their temperature checked regularly.

Clinicians and others who work in health care settings need to adhere to strict respiratory and contact precautions. All individuals should undergo mask fit testing. Staff need to learn the proper methods for putting on, removing, and disposing of personal protection gear. Those evaluating suspect cases should use standard precautions (hand washing), airborne precautions (N-95 respirator), and contact precautions (gowns and gloves). Hospital disinfectants including those based on quaternary ammonium, phenol and alcohol, are highly active against coronaviruses.

During an outbreak, patients and caretakers should remain separated from others in order to minimize the chance of spread to other patients and health care workers. Also, the number of social visitors into the facility needs to be restricted, elective procedures should be delayed, and the number of staff caring for SARS patients should be limited.

SARS in the United States

In the United States SARS has occurred in people with a history of travel to countries with SARS. In the U.S., casual contact with SARS patients has not resulted in transmission of the causative virus. Efforts to prevent SARS in this country have focused primarily on screening for illness in those arriving from areas with high rates of SARS. At this time, the Centers for Disease Control and Prevention (CDC) does not recommend quarantine of persons arriving from areas with SARS.

Correctional Facilities

Currently, those of us working in correctional facilities might feel somewhat protected from the SARS epidemic. However, many believe that this virus will continue to circulate, and that the number of cases (including those in the U.S.) will increase. Respiratory viruses such as influenza tend to wane in the warmer months and return with the colder weather. The Directors of the National Institutes of Allergy and Infectious Diseases (NIAID) and the CDC have stated that they believe that SARS will persist and amplify in the years to come.

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TABLE 1: SARS Case Definition

Severe respiratory illness

- Temperature of >100.4º F (>38º C), and
- One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), and
  - radiographic evidence of pneumonia, or
  - respiratory distress syndrome, or
  - autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

AND

Epidemiological criteria

- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community transmission of SARS, or
- Close contact* within 10 days of onset of symptoms with a person known or suspected to have SARS

** Close contact is defined as having cared for or lived with a person known to have SARS or having a high likelihood of direct contact with respiratory secretions and/or body fluids of a patient known to have SARS. Examples of close contact include kissing or embracing, sharing eating or drinking utensils, close conversation (<3 feet), physical examination, and any other direct physical contact between persons. Close contact does not include activities such as walking by a person or sitting across a waiting room or office for a brief period of time.*

HIV 101

Common Toxicities Among ARVs

AGENT	POSSIBLE CLASS TOXICITIES	ADDITIONAL TOXICITIES
NRTI		
Abacavir (ABC; Ziagen)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Hypersensitivity reaction
Didanosine (ddI; Videx)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Pancreatitis, peripheral neuropathy
Lamivudine (3TC; Epivir)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Pancreatitis
Stavudine (d4T; Zerit)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Peripheral neuropathy, pancreatitis, hepatoxicity
Zalcitabine (ddC; Hivid)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Pancreatitis, peripheral neuropathy, oral apthae
Zidovudine (AZT; Retrovir)	Mitochondrial toxicity (pancreatitis, peripheral neuropathy, lactic acidosis) and lipodystrophy	Anemia, leukopenia, neutropenia, myositis
NtRTI		
Tenofovir (TDF; Viread)		Lactic acidosis
NNRTI		
Delavirdine (DLV; Rescriptor)	Hepatotoxicity; potential to cause rash	
Efavirenz (EFV; Sustiva)	Hepatotoxicity; potential to cause rash	Hyperlipidemia
Nevirapine (NVP; Viramune)	Hepatotoxicity; potential to cause rash	
PI		
Amprenavir (APV; Agenerase)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	
Indinavir (IDV; Crixivan)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	Hepatitis
Nelfinavir (NFV; Viracept)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	
Ritonavir (RTV; Norvir)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	Hepatitis
Saquinavir (SQV; Invirase, Fortovase)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	
Lopinavir/Ritonavir (LPV/RTV; Kaletra)	Hyperglycemia, hyperlipidemia, and lipodystrophy. Increased risk for osteopenia and osteoporosis.	

Adapted from Bartlett, et al. 2001-2002 Medical Management of HIV Infection; and Sande, et al. The Sanford Guide to HIV/AIDS Therapy, 2002, Eleventh Edition.

SARs... *(continued from page 4)*

If this scenario unfolds, management of patients presenting with what appears to be a routine viral syndrome or community-acquired pneumonia will become much more problematic. Even now, the staff and visitors of correctional facilities are a potential source for the introduction of SARS into a jail or prison. One can easily imagine how rapidly this illness might overwhelm a vulnerable population crowded together in a congregate living environment.

Implementing a Plan

The worldwide experience with SARS has allowed us to strategize for the likely eventuality of SARS in our practice settings. The following questions should be kept in mind while preparing a plan to manage SARS in the correctional setting.

- Can you obtain enough masks for all patients and staff who may need them?
- Do you have the ability to do fit testing?
- Can you isolate (or at a minimum cohort) all suspect cases?
- Is custodial staff prepared to control inmate movement?
- Do you have adequate contracts with outside agencies to provide appropriate medical services?
- Will you be able to feed inmates and continue other necessary programs in the event of controlled movement?
- Do you have enough health care staff to ensure the provision of necessary services in the event of an outbreak?

**Disclosures: Nothing to disclose.*

Ask the Expert

Case Study: 38-year-old Woman With Persistent Flu-like Symptoms

Case presentation and discussion by Stephen Tabet, MD, MPH, Assistant Professor of Medicine, University of Washington, and Director, Northwest Correctional Medicine Education Program. A collaboration with the Northwest AIDS Education and Training Center, with Stephen Tabet, MD, and Kate Willner, trainer.

CASE: *A 38-year-old woman presents to the prison infirmary with flu-like complaints consisting of myalgias, abdominal pain, and nausea. Her medical history is significant for Class A2 HIV disease. She has had no HIV-related illnesses except for chronic, mild diarrhea. Her CD4 T-cell count is 512 (32%), and HIV RNA by bDNA is less than 50. Her antiretroviral regimen consists of stavudine (d4T), lamivudine (3TC), and indinavir/ritonavir (IDV/RTV). Her only other illness is asymptomatic chronic hepatitis C virus (HCV) infection. She first reported to the infirmary one week ago, complaining of one week of flu-like illness. Total time since onset is two weeks. On examination today, the patient appears moderately ill. Her blood pressure is 112/64, pulse 105, respirations 22, and temperature 37.1 C. Her right upper abdomen is tender to palpation. Because there has been no improvement in her symptoms, her medical care provider decides that further investigation is warranted.*

If this were your patient, what would you be concerned about right now, and how would you proceed to make the diagnosis?

DISCUSSION: It was fortunate for this woman that the alert infirmary provider did not send her back to her room to wait a little longer for the "flu" to resolve. The provider in this case promptly checked a battery of laboratory tests. The patient's urinary analysis was leukocyte esterase trace-positive and positive for ketones. Serum AST (92 units), ALT (118 units), total bilirubin 1.7 (units), and amylase normal. BUN/creatinine were 27/1.6 units, and electrolytes were Na 139 units, Cl 104, K 4.3, and HCO3 12.; The anion gap (AG) was computed as follows:

AG = (Na + K) - (Cl + HCO3) or AG = Na - (Cl + HCO3)
AG normal value < +/- 12mEq/L
or < 16 mEq/L if potassium concentration is used to calculate value

The result is 23. The correct diagnosis for this woman's illness is gap acidemia.

The medical provider held the patient's medications and sent her to the hospital for further evaluation and treatment.

In the hospital, the medical team obtained a serum venous lactic acid level, following the ACTG Guidelines Protocol (http://aactg.s-3.com/members/psmet.htm). The reading was 6.1 mmol/L (normal is 0.5 to 2.5 mmol/L at this institution). An ultrasound of her abdomen revealed hepatomegaly with fatty infiltration. A diagnosis of severe nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidemia with hepatic steatosis was confirmed and the patient's antiretroviral medications were discontinued.

What is the most likely cause of anion gap acidosis in this patient?

An acidosis can be caused by several things. Medication-induced renal tubular acidosis and chronic diarrhea can cause an acidosis, but not a gap acidosis, as seen here. Sepsis can cause lactic with an anion gap, but this patient did not appear to have sepsis clinically. This patient's gap acidosis was caused by medication-induced lactic academia.

Lactic academia and mitochondrial toxicity in HIV infection

The mitochondria are the body's battery packs, producing and storing adenosine triphosphate (ATP) through a (non-lactate-producing) process of cellular respiration and breaking it down when energy is required. The number of mitochondria in cells of any particular tissue varies, depending on tissue energy requirements. Cells of relatively quiescent tissue may contain only a few mitochondria; the cells of tissues with higher energy requirements - such as muscle, liver, and nerves - may contain thousands of mitochondria. Mitochondria have their own DNA strands (mtDNA) that are replicated by the enzyme polymerase gamma (pol gamma). Pol gamma is very similar to the HIV polymerase reverse transcriptase.

NRTIs that inhibit HIV reverse transcriptase may also interfere with polymerase gamma, apparently causing mutations in the replicating mitochondria. Mitochondria do not have a mechanism for correcting replication mutations caused by the NRTIs. As the number of non-functioning mitochondria increases, the cell loses some of its ability to produce energy from the non-lactate-producing respiration process. A "back-up" (lactate-producing) anaerobic energy production system is activated. Lactate, which is a by-product of anaerobic respiration, is released from the cell into surrounding tissues and the bloodstream, where in healthy persons, it is cleared mainly by the liver. The anaerobic process is not intended by nature to be the cell's primary energy source; rather, it is for times when extra energy is required - during exercise, for example. A person with compromised mitochondria seems to be using this reserve system for daily energy and may not be not clearing lactic acid sufficiently. Thus, NRTIs can precipitate abnormalities, dysfunction, then toxicity, especially in someone with liver damage.

Mitochondrial dysfunction leads to varied pathology and is not easy to predict. HIV disease alone can cause a variety of abnormalities. This is a list of selected *in vivo* manifestations of NRTI-associated mitochondrial toxicity:

- Neuromuscular - Myopathy: zidovudine (AZT); Polyneurophathy: zalcitabine (ddC), didanosine (ddI), stavudine (d4T)
- Hepatic/GI - Steatosis, lactic acidosis: zidovudine (AZT) didanosine (ddI), stavudine (d4T), zalcitabine (ddC); Pancreatitis: didanosine (ddI), stavudine (d4T)
- Hematologic - Pancytopenias: zidovudine (AZT)
- Nephrologic - Proximal renal tubular dysfunction: adefovir (Hepsera)
- Metabolic - Lipodystrophy (new theory): stavudine (d4T)

Why are so many different tissues affected?

Some thoughts are that 1) each tissue may have different NRTI kinetics (tissue levels of drugs may differ); 2) each tissue may have different activation enzymes (levels of active drug may differ); 3) each tissue may have different underlying proportion of mutant mtDNA; 4) it is known that NRTIs vary in their ability to inhibit mtDNA polymerase; 5) the role of mitochondria may be more or less important in certain tissues.

The Food and Drug Administration (FDA) reported 106 cases of lactic acidemia through June 1998. There were 46 cases associated with the use of a single NRTI (mainly AZT) and 61 cases associated with a combination of NRTIs including d4T, ddI, or AZT. In 69% of these cases, hepatic steatosis was present. There were 20 fatalities (85% female; 65% females obese). The French reported 11 cases in 867 (0.84%) patients over 18 months: d4T/ddI (n=7); d4T/3TC (n=2); d4T (n=2). Hepatic steatosis was present in four of five biopsies. There was one fatality. Four of the patients had HCV co-infection. They report treating lactic acidemia with riboflavin and carnitine.

Treating Mitochondrial Toxicities

Effective treatments still need to be evaluated. Current theories of

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Ask the Expert... *(continued from page 6)*

treatment focus on assisting the respiratory chain function with 1) Coenzyme Q - electron transfer with complex* III (portions of the ATP electron transport chain in the mitochondria), 2) riboflavin - a cofactor for electron transport complexes I and II, or 3) L-carnitine, a shuttle mechanism for fatty acid transport across the mitochondria. These have shown varying efficacy in uncontrolled trials to date. Challenges in studying mitochondrial toxicity (MT) include the lack of cell line or animal model to reliably predict MT. *In vitro* models may provide important information but experience with fialuridine (FIAU) and recently with lodenosine (FddA) shows that clinical experience is the most reliable indictor.

Hepatic Steatosis

Hepatic steatosis is a frequent finding at biopsy, most often attributed to alcohol, obesity, diabetes, or drugs. If fatty acid oxidation in hepatic mitochondria is impaired, triglycerides may accumulate as small lipid vesicles in hepatocytes. Acute microvesicular steatosis can be very serious, leading to liver failure and death.

Resuming antiretroviral therapy

This patient improved after two days in the medicine intensive care unit, and an additional four days in the acute care ward. She returned to the facility and was seen in the infirmary for follow up. At one month, her labs were rechecked and results showed Na 137, Cl 106, and CO2 21. At two months, post-discharge her electrolytes were normal, and she was no longer acidemic. However, the patient's HIV RNA increased to 16,000 units (it had been undetectable) and her CD4 count was 392 units (down from 512 units). The patient was hesitant to restart antiretroviral therapy, and since her viral load and CD4 are at acceptable levels for now, the bottom line for this patient is "wait and see." When she does require therapy, NRTIs previously used in her treatment regimen will not be used and an NRT-sparing regimen will be considered.

Summary

If lactic acidemia is not specifically looked for, it may not be diagnosed in time. The disease varies in presentation, and its common symptoms - nausea, vomiting, fatigue, myopathy, abdominal pain, and recent weight loss - are also symptomatic of HIV disease itself. There are currently limited diagnostic tests for toxicity and a serum specimen to measure for lactic acid must be drawn carefully according to protocol.

Reference

AACTG Metabolic Guidelines for Hyperlactatemia and Lactic Acidosis, http://aactg.s-3.com/metabolic/lactic.pdf

For a list of references please email Kate Willner at kwillner@u.washington.edu

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Long-Term Toxicities... *(continued from page 2)*

hypersensitivity to nevirapine (NVP). One under-recognized toxicity is non-alcoholic steatohepatitis (NASH). NASH may be seen in HIV-uninfected patients and is usually associated with obesity, diabetes, or certain medications, and can progress to cirrhosis if untreated. In HIV-infected patients, NASH has been reported to occur in those with prolonged hypertriglyceridemia and insulin resistance, usually secondary to HAART. These patients present with sustained, mild-to-moderate elevations in serum transaminases (AST or ALT) with no serologic or virologic evidence of chronic HBV or HCV infection. Hepatic ultrasound or CT scan will show a pattern consistent with fatty liver. Liver biopsy will show steatosis with or without fibrosis or cirrhosis. Treatment involves therapy for the hypertriglyceridemia or insulin resistance, abstinence from any alcohol intake, use of antioxidants such as vitamins C and E, and in some cases alteration of the current ARV therapy to remove the agents contributing to hypertriglyceridemia or insulin resistance.[16]

Conclusion

The ART era has been a miraculous time for many patients with HIV infection and for those providing care. For patients with access to ARV therapy, HIV/AIDS has the potential to become a manageable, chronic disease. However, there are many prices to pay for this, including a lifetime need for complex medical regimens associated with acute toxicities. In the last few years, we have learned that there are chronic complications of both ARV therapy and prolonged survival with HIV infection. Some of these complications can be immediately life-threatening, whereas others have implications for patients' future morbidity and mortality. In either case, patients and health care providers must recognize that these long-term complications exist. Importantly, health care providers need to understand how to diagnose and manage these complications in order to provide optimal long-term care to their patients with HIV infection.

Suggested reading:

M Schambelan, et al. Management of Metabolic Complications Associated With Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society-USA Panel. JAIDS 2002, 31: 257-75.

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Save the Dates

Legal Issues in Correctional Health Care
Sponsored by NCCHC and the American Bar Association Criminal Justice Section
June 27-28, 2003
Chicago, Illinois
Call: 773-880-1460
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The United States Conference on AIDS
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New Orleans, Louisiana
Call: 202-483-6622
Visit: www.nmac.org

HIV Minifellowship for Correctional Health Care Providers
Sponsored by the University of Texas Medical Branch and HEPP Report, Brown University
September 22-24, 2003
Providence, Rhode Island
Call: 409-747-8769
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Inside News

Save the Date: "Texas" Minifellowship
The annual HIV Minifellowship for Correctional Health Care Providers will be held in Providence, Rhode Island, on September 22, 23, and 24, 2003. Sponsored by the University of Texas Medical Branch and HEPP Report, the conference will feature discussions by leading correctional care providers and infectious disease specialists. Topics will include HIV epidemiology, opportunistic infections, HIV/HCV co-infection, mental health issues, guidelines for initiating and modifying ARV, and ethical issues. Call 409-747-8769 or email pwelsh@utmb.edu to register.

Number of Syphilis Cases in NJ Triples
The number of New Jersey men diagnosed with syphilis has more than tripled in the last three years, and the rise in numbers could be due to increased risky behavior, ultimately leading to more HIV infections, according to the Bergen Record. The number of syphilis cases decreased throughout the 1990s but has spiked since 2000. New Jersey Health Department officials report that 121 men (mostly men who have sex with men) and 48 women were diagnosed with syphilis in 2002. *Bergen Record, 5/4/03*

Many Minorities With HIV Not Taking HAART
An analysis of 200 HIV-infected patients who died at a Texas hospital in between 1995 and 2000 found that more than half of them were not taking HAART. Despite the availability of HAART, only 48% of patients who died in 1999-2000 were taking HAART at the time of death, according to the authors. The main reasons the patients were not taking the drugs were an inability to adhere to the regimen, an HIV diagnosis less than six months prior to death, or an inability to tolerate the drugs due to underlying liver disease. The study also found that many of the HIV-infected individuals who were not receiving HAART were minorities. *Journal of Clinical Infectious Diseases, 2003;36(8):1030-1038*

Study: How Often Should Liver Biopsy Be Performed?
A study in the Journal of Hepatology found that an interval of at least four to five years is needed between liver biopsies to detect significant changes in patients with mild liver disease. One hundred and eighty patients with histologically proven chronic hepatitis C were studied. The authors concluded that fibrosis progression is very slow in patients with mild chronic hepatitis C, but that it appears to be accelerated in the later stages of disease. Increasing age and daily alcohol consumption are the main factors associated with significant fibrosis. *Journal of Hepatology, 2003;38(3):307-314*

Study: Methadone and Pegasys Interactions and Safety
Researchers from Johns Hopkins University presented results at the Digestive Disease Week (DDW) 2003 conference of a four-week study evaluating interactions between methadone and Pegasys. Methadone exposure increased by 10%-15% during the first four weeks of taking both medications together, but the study found that methadone did not have an impact on the pharmacokinetics or pharmacodynamics of Pegagys. The authors concluded that dose modifications of Pegasys are not required and the combination of the drugs is safe and well tolerated. *NATAP (www.natap.org), 5/20/03*

Man Has HIV Superinfection
A man has been infected with two different strains of HIV, researchers report in the May 2, 2003 edition of AIDS. Although the immunological response to HIV-1 infection is believed to impede "superinfection" with a second virus, study authors report that this is not always the case. About four months after infection with drug-resistant clade B virus, the patient was infected by a second drug-sensitive wild-type virus from the same subtype. His viral load then jumped from 34,000 copies/mL to almost 200,000 copies/mL. *AIDS 2003; 17:F11-F16 and Reuters, 5/19/03*

Study: Evaluation of 24-Hour Viral Response to HCV Combination Therapy
At the DDW 2003 conference in Florida, researchers from the University of Vienna presented results of a prospective evaluation of 24-hour viral response in predicting outcome of treatment with Pegasys and ribavirin. While the 12 or 24 week response is more accurate at predicting ETR and SVR, the authors concluded that the 24-hour viral response rate is a sensitive predictor of the response to therapy, and may be useful in certain situations.
NATAP (www.natap.org), 5/21/03

Resources

New OHRP Guidance on the Involvement of Prisoners in Research
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/prisoner.htm
The Office for Human Research Protections (OHRP) on May 23,2003 posted a new guidance document on the OHRP website: "OHRP Guidance on the Involvement of Prisoners in Research." The new document replaces the prisoner research guidance document titled "OPRR Guidance on Approving Research Involving Prisoners" from May 19, 2000.

SARS Resources

- **Centers for Disease Control and Prevention:** *www.cdc.gov/ncidod/sars/*
- **World Health Organization:** *www.who.int/csr/sars/en/*
- **New England Journal of Medicine:** (SARS content is posted free for all visitors) *http://content.nejm.org/early_release/sars.dtl*
- **CDC Public Health Training Network Satellite Broadcast & Webcast:** Includes archived webcast and presenters' slides. *www.phppo.cdc.gov/PHTN/webcast/sarsII/*

Self-Assessment Test for Continuing Medical Education Credit

Brown Medical School designates this educational activity for 1 hour in category 1 credit toward the AMA Physician's Recognition Award. To be eligible for CME credit, answer the questions below by circling the letter next to the correct answer to each of the questions. A minimum of 70% of the questions must be answered correctly. This activity is eligible for CME credit through December 31, 2003. The estimated time for completion of this activity is one hour and there is no fee for participation.

1. Mitochondrial toxicity has been primarily associated with:
   (a) PIs
   (b) NRTIs
   (c) NNRTIs
   (d) NRTIs and NNRTIs

2. Mitochondrial toxicity can lead to:
   (a) Pancreatitis, peripheral neuropathy, and lactic acidosis
   (b) Pancreatitis, dyslipidemia, and hepatitis
   (c) Lactic acidosis, dyslipidemia, and pancreatitis
   (d) Lipodystrophy, peripheral neuropathy, and lactic acidosis

3. Cohort studies have estimated that up to 70% of patients suffer from lipodystrophy.
   (a) True
   (b) False

4. HIV-infected patients with non-alcoholic steatohepatitis (NASH) can present with sustained, mild-to-moderate AST or ALT elevations, even in the absence of serologic evidence of chronic HBV or HCV.
   (a) True
   (b) False

5. Preliminary studies have shown that the following medication might be effective for the treatment of HIV-infected patients with osteoporosis:
   (a) Calcitonin
   (b) Alendronate
   (c) Raloxifene
   (d) Calcium supplements

6. The dyslipidemic profile includes the following except:
   (a) High LDL cholesterol
   (b) Elevated triglycerides
   (c) Pancreatitis
   (d) Low HDL cholesterol

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