Complications of Antiretroviral Therapy: Protease Inhibitors and New Antiretroviral Agents

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INTRODUCTION

Since protease inhibitors (PIs) were introduced in 1995, they have been the cornerstone of potent antiretroviral therapy (ART) combinations. Updated treatment guidelines from the International AIDS Society–USA Panel published in 2002 recommend a PI and 2 nucleoside reverse transcriptase inhibitors (NRTIs) as one of the first-line combination therapies for ART-naïve patients. However, PI-based regimens can be difficult because of multiple times per day dosing regimens, pill burden, and toxicity, all of which can affect the utility of these regimens.

This review is the second of a 2-part series addressing common and emerging complications of ART. Part 1 reviewed antiretroviral mechanisms of action and discussed specific complications of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Part 2 focuses on the metabolic toxicities of PIs, including fat redistribution, dyslipidemia, and insulin resistance. Potential etiologies, treatment options, and impact of metabolic toxicities on cardiovascular risk are explored. Complications associated with recently approved antiretroviral agents are briefly discussed. A section of sample board review questions is provided following the text.

PROTEASE INHIBITORS

FAT REDISTRIBUTION ASSOCIATED WITH PIs

Case Presentation

A 52-year-old man is seen for a routine visit in HIV clinic. He was diagnosed with HIV infection 8 years ago and has been on therapy since that time. He has been stable on combination therapy with zidovudine, lamivudine, and ritonavir-boosted indinavir for the past 2 years. His most recent CD4 cell count was 435/mm³ with a viral load of less than 75 copies/mL. He has been feeling well but complains that despite his daily exercise routine at the gym and a low-fat diet, he has noticed increasing abdominal girth. He realizes that other HIV-infected acquaintances have had similar changes in body habitus and asks if this is the result of HIV infection. He also asks if there are treatments that can successfully reverse these changes.

• What are the suspected causes of fat redistribution in HIV-infected patients?
• What treatment might you recommend for this patient?
• What additional testing would be warranted at this time?

Adverse reactions associated with PIs are listed in Table 1. Recognition of body fat redistribution in HIV-infected patients on PI therapy dates to 1997, soon after these drugs were introduced. In 1998, the first description of a syndrome associated with PIs, including lipodystrophy, dyslipidemia, and insulin resistance, was published. Since that time, the syndrome has been given a number of different names, but an established case definition has been elusive, making formal study difficult and the available data confusing. Lessons from clinical and research experience have clarified that fat redistribution occurs with both PIs and NRTIs. NRTI-related fat redistribution is associated more with lipoatrophy, weight loss, and lactic acidemia. PI-associated fat redistribution commonly manifests as central adiposity (including a dorsocervical fat pad—the so-called “buffalo hump”), dyslipidemias, and insulin resistance. Patients who have never been on ART have been described to have body morphologic changes similar to those seen in both of the above categories, suggesting at least a partial contribution of HIV infection itself. This section focuses on PI-associated body changes. The term fat redistribution is used to refer specifically to morphologic changes, whereas lipodystrophy refers to the entire syndrome of morphologic and metabolic derangements.
### Table 1. Adverse Reactions Associated with Protease Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Brand Name</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir (SQV)</td>
<td>Invirase (hard gel capsule)</td>
<td>GI intolerance, nausea, diarrhea, abdominal pain, and dyspepsia Headache Transaminase elevation Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding episodes in patients with hemophilia</td>
</tr>
<tr>
<td></td>
<td>Fortovase (soft gel capsule)</td>
<td>Headache Transaminase elevation Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding episodes in patients with hemophilia</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Crixivan</td>
<td>Nephrolithiasis GI intolerance, nausea Increased indirect bilirubin Miscellaneous: headache, asthenia, blurred vision, dizziness, rash, metallic taste, alopecia, thrombocytopenia, hemolytic anemia Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding episodes in patients with hemophilia</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>Norvir</td>
<td>GI intolerance, nausea, vomiting, diarrhea Paresthesias Hepatitis Pancreatitis Asthenia Taste perversion Labwork: triglycerides increase &gt; 200%, transaminase elevation, elevated CPK, and uric acid Hyperglycemia Possible increased bleeding episodes in patients with hemophilia</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Viracept</td>
<td>Diarrhea Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding episodes among patients with hemophilia Transaminase elevation</td>
</tr>
<tr>
<td>Amprenavir (APV)*</td>
<td>Agenerase</td>
<td>GI intolerance, nausea, vomiting, diarrhea Rash Oral paresthesias Transaminase elevation Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding episodes in patients with hemophilia</td>
</tr>
<tr>
<td>Lopinavir/ritonavir† (LPV/ir)</td>
<td>Kaletra</td>
<td>GI intolerance, nausea, vomiting, diarrhea Asthenia Transaminase elevation Hyperglycemia Fat redistribution and lipid abnormalities Possible increased bleeding in patients with hemophilia</td>
</tr>
</tbody>
</table>


CPK = creatine phosphokinase; GI = gastrointestinal.

*Oral solution contains propylene glycol, contraindicated in pregnant women, children < 4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole.

†Oral solution contains 42% alcohol.
Clinical Features, Risk Factors, and Etiologies

The clinical spectrum of fat redistribution includes peripheral lipodystrophy of the face, limbs, and buttocks, as well as central lipohypertrophy within the abdomen, breasts, and in the dorsocervical region. In spite of these often dramatic and cosmetically disfiguring changes, a patient’s weight most often remains stable, consistent with the concept of overall redistribution of adipose tissue.9

It has been estimated that approximately 50% of patients exhibit at least 1 lipodystrophic feature within 12 to 18 months of initiating ART. The median time to onset appears to be shorter for those taking ritonavir-boosted regimens as compared with unboosted PIs.10 Reports of overall prevalence rates of PI-associated fat redistribution have ranged from 2% to 84%, the wide range emphasizing the lack of a consensus definition, and making prevalence impossible to accurately characterize.11 Rates vary depending on the source and manner of reporting (ie, patient self-report versus physician). Although body composition changes have been objectively measured with dual energy X-ray absorptiometry (DEXA) and computed tomography (CT), these expensive tests are not routinely performed as part of patient care outside of a study setting.

Risk factors for the development of fat redistribution have been identified in several large cross-sectional and prospective cohort studies and include increasing age, body mass index gain, amount and duration of immune recovery, and duration of antiretroviral treatment (PI and NRTI).12,13 Additional factors may include female gender, low body weight prior to therapy, and use of boosted PIs.14,15 The biological basis for PI-associated fat redistribution is unclear. Hypotheses implicate pathways in adipogenesis and glucose handling, with recent studies exploring roles of sterol regulatory element–binding proteins, cytoplasmic retinoic acid–binding protein-1, low-density lipoprotein (LDL) receptor–related protein, and the glucose transporter 4 (GLUT-4) enzyme.16,17

Clinical Implications and Treatment Options

Although a causal link has not been established, changes in adipose with or without other metabolic derangements (eg, hyperlipidemia, insulin resistance) may place patients at high risk of premature coronary disease and other vascular complications. In addition to these potential risks, patients find the changes associated with fat redistribution cosmetically disfiguring and socially stigmatizing. This has been observed to impact adherence and lead to virologic and clinical failure.

In the absence of a precise understanding of the etiology of fat redistribution, treatment is aimed at cosmetic improvement. No guidelines exist for the initiation of treatment, nor is there good evidence for the durability of any specific intervention. Severity of a given feature, patient comfort, and presence of multiple cardiovascular risk factors are all acceptable reasons to attempt therapy.

Resistance exercise has been shown to reduce truncal fat and total body fat, but also has been associated with increased peripheral fat wasting.18 Subcutaneous or intralesional growth hormone has been used to reduce intra-abdominal adiposity and the size of dorsocervical fat deposits. However, it has been observed to worsen lipodystrophy and precipitate hyperglycemia and is costly.19 Metformin and thiazolidinediones continue to be evaluated as therapies for morphologic changes. In general, these therapies should be used with caution and only in the context of documented concomitant insulin resistance.

Surgical procedures such as lipectomy or liposuction have been performed with improvement in appearance; however, anecdotal reports have described fat reaccumulation following such procedures.20 Successful use of polyactic acid (“polyfill”) injections to treat facial lipodystrophy has been reported.21 Patients describe increases in adipose thickness, but these interventions are costly and painful. Most insurance companies will not pay for surgical procedures to correct even severely disfiguring cases of fat redistribution.

In patients with severe morphologic changes, improvement in fat redistribution has been described after discontinuation of PI. Studies examining the substitution of a PI with nevirapine have demonstrated improvement in body shape and in quality of life as determined by a scoring system.22 Studies involving swapping out a PI for abacavir, efavirenz, or nevirapine have yielded conflicting results.23,24 Although CD4 counts and viral suppression may be preserved after switching off of PI therapy, the modest and very slow improvements in lipodystrophy that have been observed do not warrant routine use of this strategy.

METABOLIC COMPLICATIONS ASSOCIATED WITH PIs

Case Presentation, Continued

Given the association of dyslipidemia and impaired glucose tolerance with fat redistribution, you decide to test this patient with a fasting lipid panel and oral glucose tolerance test. His lipid panel returns with the following results: total cholesterol, 260 mg/dL; high-density lipoprotein (HDL), 28 mg/dL; LDL, 150 mg/dL; and triglycerides, 520 mg/dL. His 2-hour glucose level obtained with oral glucose tolerance testing was 190 mg/dL. Hemoglobin A1c was 7%.
• What type of lipid abnormalities are observed with PI therapy?
• What can you tell this patient about his cardiovascular risk?
• What are monitoring guidelines for patients starting ART with respect to lipids and glucose?

Body fat redistribution in patients on PI therapy usually is associated with other metabolic features that include dyslipidemia and insulin resistance. These abnormalities are more common in individuals with significant fat redistribution. As with fat redistribution, risk factors for these other metabolic changes include increasing age and total duration of ART. Likewise, etiologies for HIV-related metabolic changes are incompletely understood, but pathways involved in adipogenesis and glucose handling are implicated.

Dyslipidemia

Prior to PI therapy, dyslipidemia had been described in HIV-infected patients. The characteristic lipid profile included elevated triglycerides and decreased total cholesterol with decreased HDL and LDL levels. These changes were particularly typical of patients with low CD4 cell counts and more advanced disease, and were thought to be due, in part, to increased levels of plasma interferon-α.25 With the advent of PI therapy, new alterations in lipids were observed, including hypertriglyceridemia and hypercholesterolemia with increased LDL and very-low-density lipoprotein and no significant change in HDL level.26 Prospective data suggest that PI-associated hypertriglyceridemia occurs within 3 to 5 months of starting therapy, and that the prevalence of hyperlipidemia in PI-treated patients exceeds 25% at 1 year.27,28 In early studies of ritonavir on HIV-uninfected patients, participants developed increased levels of cholesterol, triglycerides, lipoprotein(s), and apolipoprotein B after only 2 weeks of therapy, illustrating that cholesterol, triglycerides, lipoprotein(s), and apolipoprotein B are thought to be due, in part, to increased levels of plasma interferon-α. With the advent of PI therapy, new alterations in lipids were observed, including hypertriglyceridemia and hypercholesterolemia with increased LDL and very-low-density lipoprotein and no significant change in HDL level.26 Prospective data suggest that PI-associated hypertriglyceridemia occurs within 3 to 5 months of starting therapy, and that the prevalence of hyperlipidemia in PI-treated patients exceeds 25% at 1 year.27,28 In early studies of ritonavir on HIV-uninfected patients, participants developed increased levels of cholesterol, triglycerides, lipoprotein(s), and apolipoprotein B after only 2 weeks of therapy, illustrating that abnormalities appeared to be related to ART as opposed to being a direct effect of HIV.29 In a cohort study, PIs were associated with a 2.8-fold risk of hypercholesterolemia and a 6-fold risk of hypertriglyceridemia.30 Ritonavir is particularly associated with increased levels of total cholesterol and triglycerides, although all PIs—with the exception of atazanavir—share this side effect.31

Treatment of dyslipidemia in HIV-infected patients has been clarified by recent recommendations from the Infectious Disease Society of America (IDSA) and AIDS Clinical Trials Group (ACTG). The guidelines urge evaluation and management of patients based on the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).32 Per these guidelines, risk should be assessed and the intensity of intervention should be tailored to the degree of risk. Diet and exercise measures are encouraged for all patients. When pharmacotherapy is necessary, the guidelines recommend pravastatin or atorvastatin for elevated LDL and gemfibrozil or fenofibrate for triglyceride levels greater than 500 mg/dL. These medications are effective at treating hypertriglyceridemia and hypercholesterolemia, although data regarding safety and efficacy within the HIV-infected population are limited. Pravastatin is the safest in its class for patients on PIs because it does not compete for the same cytochrome metabolic pathway. Simvastatin, lovastatin, and atorvastatin are metabolized by cytochrome P450_3A, which is inhibited by PIs, although low doses of atorvastatin have been used safely in clinical trials.33 Use of antiretroviral agents, statins, and fibrates together can lead to elevated levels of plasma statins and resultant myopathy. According to the IDSA/ACTG guidelines, risk factor reduction is paramount, and when pharmacotherapy is required, it should be prescribed with utmost attention to potential drug interactions and close observation for complications.

Hyperglycemia and Diabetes Mellitus

In June 1997, the US Food and Drug Administration issued a public health advisory reporting 83 cases of new-onset hyperglycemia or worsening pre-existing diabetes in HIV patients taking PIs.34 Although a causal relationship has not been established, the prevalence of diabetes mellitus and impaired glucose tolerance in patients on PIs is approximately 8% to 10% and 10% to 46%, respectively.35,36 Insulin resistance appears to be more closely associated with visceral adiposity but can occur in patients without fat redistribution. The median onset to development of hyperglycemia (or diabetes) after initiation of PI use is 60 days.37 The association between PIs and insulin resistance is supported by studies of indinavir in normal subjects who developed insulin resistance after 4 weeks of treatment.38

For treatment of hyperglycemia, metformin and thiazolidinediones have been used. Early studies of metformin in PI-treated patients have been encouraging. A small study (25 patients) showed improvement in insulin resistance, visceral abdominal fat, and body weight after 3 months of metformin therapy.39 Although mild diarrhea was the most common adverse effect of metformin in this study, physicians should be aware of the increased

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risk of lactic acidemia with use of metformin in conjunction with NRTIs. In 30 patients with ART-associated lipodystrophy, rosiglitazone for 24 weeks resulted in improved insulin sensitivity but was accompanied by statistically significant increases in triglycerides. Careful use of these drugs is warranted while systematic investigation continues.

**Treatment of Severe Metabolic Toxicity with “Drug Swapping”**

In cases in which metabolic derangements are difficult to manage, switching to the PI atazanavir or switching off of PI therapy are both reasonable options. Based on early data, atazanavir appears to be less offensive with regard to dyslipidemia compared with other PIs, including lopinavir/ritonavir and nelfinavir. In fact, in a recent study, lipid abnormalities were essentially erased when patients switched to atazanavir-based PI regimens.

Therapy with the NNRTI nevirapine has been shown to alter lipid profiles—usually with a modest increase in total cholesterol, little change in triglycerides, and a trend toward increasing HDL. Studies in which PIs in combination regimens were replaced with nevirapine have shown that after 6 to 12 months, dyslipidemia, glycemia, and insulin resistance all improved without compromising HIV suppression. The primary lipid effect was a decrease in triglyceride levels without significant change in cholesterol levels.

A number of randomized, controlled trials have shown improvements in dyslipidemia after a PI was replaced with abacavir, although this option has been less attractive virologically. Studies in which a PI was replaced with the NNRTI efavirenz have yielded conflicting results. Decisions to switch therapy are complicated and should be guided by expert advice.

**Sequelae of Metabolic Toxicity: Is Cardiovascular Risk Increased?**

The largest study addressing the risk of ART on cardiovascular and cerebrovascular (CV-CV) morbidity and mortality followed 36,766 HIV-infected patients in the Veterans Affairs (VA) system between 1993 and 2001. The authors found slight declines in CV-CV events and a sharp decline in overall mortality, and refuted the hypothesis that ART (of any type) is associated with increased risk of CV-CV disease. Likewise, no association with PI use was observed in a case-control study of HIV-infected Kaiser patients, although cases did have a higher rate of cardiovascular events compared with HIV-negative controls. Increased rates were not associated with PI or other antiretroviral exposure.

Many other studies have found associations between ART and cardiovascular disease, including a French cohort study of patients who received treatment with PIs. The incidence of myocardial infarction (MI) per 10,000 patient-years increased 3-fold when therapy lasted up to and beyond 30 months. Results from the newest trial by the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group support the French findings. This prospective observational study of 23,468 patients on combination ART demonstrated a 26% relative increase in the rate of MI per year of exposure during the first 4 to 6 years of use. Large scale trials with adequate control populations and longer-term follow-up are required to better characterize risk, although the aforementioned VA and Kaiser studies provide some reassurance. In all of these studies, it is important to keep in mind that the absolute risk of MI was low, and any risk must be weighed against the clear mortality benefit of combination ART.

In summary, as patients with HIV live longer, the risk of cardiovascular disease increases. This risk may be compounded by the combination of traditional factors, the metabolic impact of ART, and HIV disease itself. Given these circumstances, close monitoring of all HIV-infected patients for cardiovascular risk is warranted. Prior to initiation of ART, patients should have a thorough cardiovascular assessment and counseling on risk factor reduction. While on ART, appropriate monitoring includes fasting lipid and glucose levels at baseline, after the first 6 to 12 weeks of treatment, and every 3 months during the first year of therapy. If values are reassuring during this time, monitoring can be done on a yearly basis unless interim symptoms occur. It is safe to say that the benefits of ART at this time clearly outweigh the risks, and attention to other modifiable risk factors such as smoking cessation should be paramount in counseling sessions.

**Follow-up Discussion of Case**

The patient is started on pravastatin 10 mg once daily and gemfibrozil 600 mg twice daily for his dyslipidemia, and metformin 500 mg twice daily for impaired glucose tolerance. He is continued on the same antiretroviral regimen. Six months later, his total cholesterol level is 190 mg/dL, LDL is 130 mg/dL, HDL is 35 mg/dL, and triglyceride level is 280 mg/dL. A random glucose level sampled at this time is 90 mg/dL and hemoglobin A1c is 6%. He has lost 10 lb, and although results of his physical examination appear unchanged, he reports a perceived improvement in visceral adiposity.
NEW ANTIRETROVIRAL AGENTS

New drugs for the treatment of HIV are coming to market rapidly and may offer equal or better efficacy with fewer side effects. The PI fosamprenavir is a more bioavailable and less toxic formulation of the previously approved PI amprenavir. The new formulation may renew interest in this agent, which is attractive from a resistance-profile standpoint, and has previously been of limited utility due to pill burden and side effects. In addition, the fusion inhibitor enfuvirtide differs from other antiretrovirals by targeting a novel viral protein, gp41, and may hold promise for patients unresponsive to previously approved agents.\(^{52}\) This medication, the first parenterally administered drug, has attendant toxicities of subcutaneous injection site reactions, and an unexplained association with bacterial pneumonia.\(^{52}\)

Adverse reactions associated with newer antiretroviral agents are listed in Table 2. The true toxicity profiles of these and other new drugs will be understood only with more widespread use.

CONCLUSION

Antiretroviral agents for HIV infection have increased length and quality of life, but also they have been linked to numerous adverse effects that carry substantial morbidity and mortality risks. The type and timing of treatment will be increasingly influenced by these adverse effect profiles. Additional research should help to better understand the biological bases for toxicities, as well as identify risk factors and markers that can predict and diagnose adverse reactions. An increased awareness of potential toxicities should help clinicians balance the risk-benefit ratio of antiretroviral regimens and further improve survival and quality of life for HIV-infected patients.

REFERENCES

4. Chen D, Misra A, Garg A. Clinical review 153: Lipodys-

Table 2. Adverse Effects Associated with New Antiretroviral Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class/Date Available</th>
<th>Known Adverse Reactions</th>
<th>Other Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide (Fuzeon)</td>
<td>Fusion inhibitor/March 2003</td>
<td>Injection site reactions, insomnia, headache, dizziness, nausea, eosinophilia</td>
<td>2 cases of hypersensitivity have been reported; higher rates of bacterial pneumonia were reported in phase III studies</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva)</td>
<td>PI/October 2003</td>
<td>Rash, nausea, diarrhea, hyperlipidemia, transaminase elevation</td>
<td>Active metabolite amprenavir is metabolized by the cytochrome P4503A4 isoenzyme and may alter concentrations of other drugs metabolized by this pathway</td>
</tr>
<tr>
<td>Atazanavir (Reyataz)</td>
<td>PI/June 2003</td>
<td>Jaundice (~10% of patients), nausea, diarrhea, transaminase elevation</td>
<td>Has not been found to cause significant elevations in total cholesterol, LDL, or triglycerides</td>
</tr>
<tr>
<td>Emtricitabine (Emtriva)</td>
<td>NRTI/July 2003</td>
<td>Headache, diarrhea, nausea, rash, skin discoloration (hyperpigmentation of palms and soles)</td>
<td>Extent of mitochondrial toxicity unknown</td>
</tr>
</tbody>
</table>


LDL = low-density lipoprotein; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
Complications of Antiretroviral Therapy


Complications of Antiretroviral Therapy


The following questions review both parts of the 2-part series, *Complications of Antiretroviral Therapy* (Hospital Physician Infectious Diseases Board Review Manual, Volume 9, parts 2 and 3).

1. A previously healthy, 49-year-old HIV-infected man presents with a 2-week history of malaise, nausea, anorexia, and diffuse abdominal discomfort. The patient has had no recent fevers, chills, or diarrhea. Six weeks previously, the patient’s antiretroviral medications had been changed due to persistent HIV viremia on therapy. His current medications include lopinavir/ritonavir, didanosine, and stavudine at standard doses. On physical examination, the patient is alert but ill-appearing. His blood pressure is 120/70 mm Hg, and his respiratory rate is 28 breaths/min. Lungs are clear to auscultation. The abdomen is diffusely tender without rebound or guarding. There is no rash or embolic stigmata. A CD4 count drawn 2 weeks ago was 358 cells/mm³. What test is most likely to uncover the source of this patient’s symptoms?
   (A) Two sets of peripheral blood cultures
   (B) CT scan of the abdomen with intravenous contrast
   (C) Serum lactate level
   (D) Antiphospholipid antibody screen

2. One week after initiation of new ART, a 41-year-old, HIV-infected woman reports extremely vivid dreams, some of which seem like nightmares. She has experienced no hallucinations, suicidal thoughts, or depressive symptoms. Review of her records shows that she recently was prescribed efavirenz, lamivudine, and zidovudine. Results of her physical examination are unremarkable. It is surmised that this symptom is most likely associated with efavirenz therapy. The most appropriate course of action at this point would be to:
   (A) Discontinue all therapy and initiate a new regimen that does not include efavirenz
   (B) Obtain cerebrospinal fluid by lumbar puncture to rule out herpes simplex encephalitis
   (C) Measure serum lactate level
   (D) Reassure the patient that this is a common side effect that will likely diminish with time and encourage exercise and bedtime relaxation techniques

3. PIs are associated with which of the following metabolic complications?
   (A) Increased very-low-density lipoprotein cholesterol
   (B) Hyperglycemia
   (C) Hypocalcemia
   (D) All of the above

4. A 28-year-old HIV-infected man presents to the emergency department with flank pain, nausea, dysuria, hematuria, and fever. He has no prior history of urinary tract infection or renal calculi. A careful history reveals a change in his ART 8 weeks previously. He reports being somewhat dehydrated due to vigorous exercise in warm weather. On physical examination his temperature is 101.8°F. He has marked right costovertebral angle tenderness. Results of chest and abdominal examinations are normal. Urinalysis reveals leukocytes too numerous to count. Unidentified crystals are seen on microscopic examination. Which one of the following antiretroviral agents is most likely associated with this complication?
   (A) Abacavir
   (B) Indinavir
   (C) Tenofovir
   (D) Lopinavir/ritonavir
ANSWERS AND EXPLANATIONS

1. (C) Serum lactate level. Lactic acidemia associated with NRTI therapy is relatively common (8%–21%). It is most frequently seen with exposure to stavudine and is exacerbated when stavudine is used in combination with didanosine. Once the diagnosis is established by documenting an elevated serum lactate level, discontinuation of the offending medication and supportive therapy generally is adequate. Rare fatal cases have been reported when the serum lactate level exceeds 10 mmol/L. Vitamin supplementation has been used anecdotally. A high clinical index of suspicion is warranted in caring for patients taking agents from the nucleoside analog class, which encompasses most current HIV treatment regimens.

2. (D) Reassure the patient that this is a common side effect that will likely diminish with time and encourage exercise and bedtime relaxation techniques. Approximately 50% of patients beginning efavirenz experience mild central nervous system effects, but most of these patients can continue therapy. All patients receiving new prescriptions for efavirenz should be warned in advance of the typical adverse effects, including sleep disturbance, abnormal dreams, anxiety, dizziness, impaired concentration, drowsiness, and depression. Switching drugs should be considered if symptoms are especially severe or if they persist despite supportive measures. In patients with a history of mental illness such as depression or anxiety, clinicians should consider a psychiatric assessment and initiation of antidepressive therapies prior to initiation of efavirenz. It is worthwhile ensuring that the patient is taking the medication on an empty stomach, as administration concomitant with food increases levels of the drug, and most likely, its associated side effects.

3. (B) Hyperglycemia. A wide array of metabolic abnormalities have been associated with PI therapy. Hyperglycemia and frank diabetes mellitus are associated with a number of HIV-associated medications, most frequently with PIs. Changes in insulin sensitivity are associated with visceral adiposity, another common HIV medication-associated syndrome. Blood glucose levels should be monitored in patients taking PIs. The dyslipidemia associated with PI therapy is characterized by elevated triglycerides and decreased total cholesterol with decreased very-low-density lipoproteins. HDL cholesterol is either decreased or unchanged. Calcium abnormalities have not been reported as a significant side effect of PI therapy. Recommendations regarding the management of glucose and cholesterol disturbances associated with HIV treatment can be found at the Infectious Diseases Society of America Web site (www.idsociety.org).

4. (B) Indinavir. Therapy with the PI indinavir predisposes patients to nephrolithiasis and pyelonephritis. A major risk factor for indinavir-associated kidney stones is dehydration, accounting for the recommendation that patients on indinavir drink at least 2 L of water daily. In isolation, this complication may be treated with aggressive hydration and pain control; recurrent nephrolithiasis may be an indication to switch therapy.

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