Management of Antiretroviral-Associated Complications

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Objectives

1. Discuss the definition, pathogenesis, diagnosis, and treatment of immune reconstitution syndrome (IRS).
2. Discuss the metabolic changes associated with human immunodeficiency virus (HIV) infection and antiretroviral therapy, specifically dyslipidemia, lipodystrophy, insulin resistance, lactic acidemia, and decreased bone density.
3. Discuss the etiology and mechanisms of these changes.
4. Discuss treatment strategies.

Key Points

1. IRS occurs most often in sicker patients who have a rapid response to therapy.
2. Usually, treatment with antiretroviral medications should continue through IRS.
3. HIV infection and its treatment are associated with a variety of endocrine and metabolic abnormalities.
4. The etiologies of these abnormalities are multifactorial.
5. These abnormalities may result in life-threatening complications and/or increase risk of serious chronic illnesses.
6. These abnormalities may be responsible for nonadherence to antiretroviral therapy.

Overview

Patients first beginning treatment with antiretroviral therapy (ART) sometimes paradoxically become sicker. This outcome is thought to be an immune-modulated reaction to the reconstitution of the previously depleted immune system. The exact nature of this reaction depends on many factors, including the state of the patient’s immune system prior to medications as well as past opportunistic infections. This reaction is commonly known as immune reconstitution syndrome (IRS).

Human immunodeficiency virus (HIV) infection is associated with a wide array of endocrine and metabolic abnormalities, including hypercholesterolemia, hypertriglyceridemia, insulin resistance, diabetes mellitus, osteopenia, osteoporosis, adrenal insufficiency, hypoaldosteronism, thyroiditis, hypogonadism, and hypopituitarism (Figure 1). The pathophysiology of these changes is equally varied and may include direct damage by HIV, opportunistic infection, malnutrition, systemic inflammatory responses, neoplasms, and the complications of HIV therapy. These abnormalities may also increase the possibility of more long-term, secondary diseases, such as cardiovascular disease. Furthermore, adherence to potent ART may be compromised. An understanding of the adverse events and their management will help to maximize the effectiveness of available treatment.

Figure 1. Adverse effects of antiretroviral therapy
**Immune Reconstitution Syndrome**

**Definition**

IRS, the term we will use herein, has been referred to by many names: immune reconstitution disease, immune recovery disease, and immune restoration disease. IRS is a paradoxical worsening of symptoms after the initiation of ART medications.

There is no agreed-upon definition of IRS; however, most experts, including the World Health Organization (WHO), believe that for an illness to be considered IRS it should have the following elements:

- Temporally related to the start of ART—usually within the first 12 weeks.
- Documented improvement of immune status (a 1-log or greater decrease in viral load or a documented increase in CD4 lymphocyte cells). IRS is more likely to occur in those with worse disease at the time of ART initiation (CD4 <50 cells/µL).
- No evidence of new infectious process or drug toxicity.
- Patient has previously been treated for this disease (this is not always consistent because IRS may “unmask” previously undiagnosed illness).
- Clinical evidence of an inflammatory condition.

**Epidemiology/Pathophysiology**

Few prospective studies on IRS have been conducted. Retrospective studies imply that 10% of patients starting on ART will experience some form of IRS. Those more likely to experience IRS are those with a lower CD4 cell count at initiation of ART who exhibit rapid viral suppression and reconstitution of the immune system. Almost all organisms causing opportunistic infections and/or comorbidities with HIV have been associated with IRS. Diagnosis and treatment for the associated infection within a few months of initiating highly active ART (HAART) increases the risk of an IRS. The most common are the following:

- *Mycobacterium* (*Mycobacterium tuberculosis*, *M. avium* complex, and leprosy)
- Cryptococcal disease
- Herpes family viruses: varicella-zoster virus, herpes simplex virus
- Kaposi sarcoma
- Cytomegalovirus
- JC virus
- Noninfectious diseases (sarcoidosis, Guillain-Barré, Graves’ disease)

Paradoxical worsening of disease after initiation of therapy is not unique to ART. IRS has been described in the treatment of tuberculosis. Both syndromes are thought to be related to the increase of various immune cell lines and an increase in the release of interleukins and other immune modulators. It is postulated that the “reawakening” immune system is often dysregulated and can therefore lead to lymphadenopathy, early weight loss, or reactivation of dormant disease.

**Management**

Management of IRS is similar regardless of the associated organism. In most cases, HAART should be continued. Only when severe central nervous system (CNS) or pulmonary symptoms are...
seen and considered life-threatening should HAART be discontinued. This scenario is most likely with cryptococcal neoformans or KS. For moderate to severe symptoms, these symptoms can be lessened with adjunctive steroid or nonsteroidal anti-inflammatory drug (NSAID) therapy. Prednisone dosing would be 0.5-1 mg/kg of body weight/day for 5-10 days; dexamethasone is reserved for CNS symptoms and would be 8-10 mg/day divided twice daily for adults and 0.08-0.3 mg/kg/day divided twice daily for children. If steroids are used at higher doses and/or for longer than 5 days, a taper of the medication is recommended to avoid complications of steroid use.

**Mycobacterium-Associated IRS**

*M. tuberculosis* IRS is the most common seen internationally. It will manifest as fever, lymphadenopathy, new findings on chest radiograph, and perhaps weight loss. It is important to distinguish IRS from new-onset disease and/or tuberculosis (TB) that is resistant to the medication regimen that the patient is taking. In TB IRS, cultures of blood, sputum, and/or lymph biopsy samples will be negative for the organism but will show evidence of granulomas and inflammatory reaction. Patients with a previously anergic Mantoux skin test will now exhibit a reaction. TB IRS is more commonly seen in patients who begin HAART within 2 months of initiating TB treatment. It may also be seen in those with previously treated TB. Treatment depends on the severity of illness. Often, continuing HAART and TB treatment is enough for symptoms to subside. If severe pulmonary or CNS symptoms are seen, HAART may have to be temporarily discontinued. Occasionally, steroids (prednisone or dexamethasone) are needed to decrease symptoms. NSAIDS can also be used to alleviate symptoms.

*M. avium* complex-associated IRS often presents with lymphadenitis (painful) and fever. Blood and bone marrow cultures for *M. avium* complex will be negative; lymph aspirates usually show no organism but will show granulomas. Symptoms can be more diffuse, including abdominal pain or lung infiltrates. Treatment includes continuing HAART; incision and drainage of lymphadenitis; and, if severe, corticosteroids. Again, it is usually self-limited disease.

Bacillus Calmette-Guérin (BCG)-associated IRS has been reported in infants or children who have recently received the BCG vaccine prior to initiation of HAART. It may present as drainage and swelling at the site of BCG or ipsilateral lymph swelling. Culture of drainage would reveal BCG strains. Treatment is continuation of HAART and incision and drainage. See “Immunizations and HIV” for updated immunization recommendations.

Finally, limited case reports exist of IRS-associated leprosy. Most were previously undiagnosed cases, limited disease, and amiable to standard treatments. Most experts expect that the incidence will increase as access to HAART in leprosy-endemic areas increases.

**Cryptococcus neoformans-Associated IRS**

Lymphadenitis, CNS manifestations (mass lesions or meningitis), and pulmonary symptoms are the most common presentations of cryptococcus-associated IRS. Most patients have had identified cryptococcal disease prior to HAART initiation and a very low initial CD4 cell count (<50 copies/µL). Patients will often present with headache and neck stiffness despite being on preventive antifungal medications. Lumbar puncture will reveal a high opening pressure but negative cultures. Symptoms typically develop in the first 6 months after HAART initiation. Symptoms will develop more rapidly in severely immunocompromised patients. Treatment includes continuing ART medications, antifungal medications, and anti-inflammatory medications in cases of severe respiratory distress or mental status changes.

**Herpesvirus-Associated IRS**

Many herpetic viruses can cause IRS reactions in immunocompromised patients starting HAART.

Varicella-zoster virus most commonly presents as dermatomal zoster. Zoster is seen more frequently in HIV-positive patients receiving ART than in those who are not taking antiretrovirals (ARVs). Most cases are self-limited and can be treated with acyclovir or famciclovir. Continuation of HAART is recommended.

HSV labialis has been described in pediatric patients initiating HAART as well as adults. Again, symptomatic treatment and continuation of HAART are the recommended treatment, with few serious consequences.

**Kaposi Sarcoma**

Kaposi sarcoma (KS) resurgence has been reported with HAART initiation. Most are in patients with previously diagnosed KS and present within the first 3-8 weeks of
HAART initiation or switch. Those with lower CD4+ cell counts at initiation of HAART are at higher risk for IRS-associated KS. Deaths have been reported, primarily in those with pulmonary complications. HAART can be continued; however, patients should be monitored for new lesions and/or symptoms. Rapidly progressing KS, particularly visceral KS, should also be treated with antineoplastic agents. Such treatment has led to favorable outcomes for patients.

**Cytomegalovirus**

Cytomegalovirus (CMV) causes primarily ocular complications in patients with a CD4 cell count less than 100 cells/mm$^3$. Cases present similar to primary disease: painless floaters, blurred vision, photophobia, decreased visual acuity, or ocular pain. Examination of the fundus will show marked inflammatory response. In rare cases, systemic disease can also occur. Incidence of IRS is high: up to 63% in those known to have CMV ocular disease prior to HAART initiation. Nontreatment can have high morbidity, including loss of sight. Patients should continue HAART, and steroid treatment should be initiated because it decreases complications. Many patients with previously diagnosed disease are already on CMV medications, and these should be continued at therapeutic doses (see chapter on opportunistic infections).

**JC Virus**

The JC virus is associated with progressive multifocal leukoencephalopathy in patients with AIDS. As many as 20% of patients can experience worsening neurologic symptoms with the initiation of HAART. Imaging of the brain with contrast may reveal enlarging lesions. Onset of IRS-associated JC is 3-8 weeks after HAART initiation. Continuation of HAART and adjunctive steroid therapy for severe cases usually leads to resolution in 3-6 months. Some fatalities have been reported, however.

**Noninfectious IRS**

Several different autoimmune diseases have been associated with IRS. Guillain-Barré, sarcoidosis, autoimmune thyroiditis, and Graves’ disease have all been reported. They present 3-12 weeks after HAART initiation, strengthening the evidence that they are IRS-associated illnesses. Sarcoidosis may, however, present up to 12 months after the start of therapy. Most patients had been previously diagnosed with sarcoidosis that had become inactive as the patient’s CD4 lymphocyte count deteriorated. Hence, this reactivation of disease appears to be related to the reconstitution of the immune system. IRS-associated sarcoidosis responds well to adjunctive steroid therapy. Any autoimmune illness previously quiescent secondary to immune suppression can be expected to flare as immune reconstitution takes place. Should this occur, steroids are one possible treatment.

**Metabolic Changes Related to ART**

Treatment of HIV with HAART has changed the natural history of the infection and has allowed children infected at birth to live into adulthood. HIV has become a chronic illness that requires lifelong treatment and care. HAART, however, is associated with the development of adverse effects that include hyperlipidemia, lipodystrophy, insulin resistance, lactic acidemia, and bone changes. These conditions may be associated with long-term complications such as risk for coronary artery disease in patients with persistent hyperlipidemia. Some of these conditions can also be stigmatizing and related to decreased adherence to ART. These complications and their treatment are discussed next.

**Dyslipidemia**

Dyslipidemia refers to changes in lipid metabolism, particularly increases in total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) cholesterol levels and increases of high-density lipoprotein (HDL) cholesterol levels in the blood. By unclear mechanisms, dyslipidemia can be caused by HIV disease independent of ART. These changes are also associated not only with protease inhibitors (PIs) but also with nonnucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs) in adult patients.

An estimated 20%-50% of children receiving HAART will have lipid abnormalities, including elevations in TC and LDL. Among 280 children evaluated by the European Paediatric Lipodystrophy Group, 27% of children had elevated TC and 21% had elevated TG, resulting in an overall prevalence of dyslipidemia of 38%.

Cross-sectional cohort studies comparing children treated with PI-containing and non-PI-containing HAART regimens revealed elevations in TC and LDL cholesterol in those patients receiving PIs. TG levels were elevated in some patients but may normalize after several months of therapy. Although PIs as a class of ART are most
associated with elevated TG and TC levels, atazanavir (ATV) is less likely to cause changes in serum lipids. Patients who had hyperlipidemia with the use of other PIs may have normalization of lipid levels with the use of ATV. When ATV is used in combination with low-dose ritonavir, however, dyslipidemia is more common. NRTIs, particularly D4T ( stavudine), have also been implicated in increasing cholesterol and triglycerides. Tenofovir, an NRTI, is associated with fewer metabolic aberrations than stavudine. NNRTIs seem to be least likely to increase lipid levels.

In adults there is a strong association between elevated TC and LDL levels and the development of atherosclerosis and cardiovascular disease. As children are living longer and using more complex regimens, the recognition and treatment of this disorder is becoming more important. The assessment of dyslipidemia must include information about other risk factors for coronary heart disease. Such risk factors include the following:

- A family history of hypercholesterolemia (elevated TC levels >240 mg/dL or 6.3 mmol/L)
- Hypertriglyceridemia (triglyceride level >500 mg/dL or 5.6 mmol/L)
- Low HDL levels (<40 mg/dL or 1.1 mmol/L)
- Hypertension (blood pressure greater than the 95th percentile for height or history of antihypertensive medications)
- A family history of premature coronary heart disease (in males younger than 55 years or females younger than 65 years)
- Age (older than 45 years for males, older than 55 years for females)
- Cigarette smoking

**Management of Dyslipidemia**

In adults the management of dyslipidemia begins with lifestyle changes. These changes include decreased fat intake, increased exercise, smoking cessation, decreased alcohol consumption, and weight loss if appropriate.

Dietary changes and exercise are important in the management of dyslipidemia in children as well. Increased dietary fiber, especially soluble fiber, has a modest cholesterol-lowering effect. Monounsaturated fats lower LDL cholesterol levels while maintaining or increasing HDL cholesterol levels. Foods that contain monounsaturated fats include olive oil, avocados, and many kinds of nuts (such as cashews) and seeds (such as sesame). An adequate trial period of 6-12 months should be given to these management strategies, except in patients at high risk for pancreatitis (TG >500 mg/dL).

If lifestyle changes are ineffective, drug therapy for dyslipidemia may be needed. Less is known about the available agents used to treat dyslipidemia and the long-term risks associated with lipid abnormalities in children with HIV infection. The available classes of drugs used to treat hyperlipidemias include the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, niacin, bile acid-sequestering agents, and cholesterol absorption inhibitors (ezetimibe).

The statins are the lipid-lowering drugs of choice for children with HIV infection. There are multiple drug interactions between this class of medications and ARVs, particularly PIs and NNRTIs. Lovastatin and simvastatin administration with PIs is contraindicated because PIs inhibit CYP3A4 isoenzyme activity, resulting in significantly increased serum concentrations of these agents’ increasing the potential for toxicity. Toxic effects include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Pravastatin is preferred for use in patients receiving PIs because pravastatin’s pharmacokinetics are minimally affected by PIs. NNRTIs are CYP3A inducers and may decrease statin concentrations; thus, higher statin doses may be needed to achieve the desired effect.

There are currently two statins that can be recommended to use in pediatric patients taking ARV agents: pravastatin (preferred) and atorvastatin (alternative). Therapy with pravastatin and atorvastatin should be initiated at the lowest possible dose and titrated to response at intervals of at least every 4 weeks as needed to reduce cholesterol levels. Short-term toxicities in children and adolescents include elevations of hepatic transaminases without clinical hepatotoxicity. These elevations are usually mild, asymptomatic, and reversible. Patients should be instructed to recognize symptoms of idiosyncratic hepatotoxicity and rhabdomyolysis. Statins are teratogenic but may be used in female patients who might become pregnant with adequate counseling about teratogenicity. Effective contraception should be prescribed to those patients who are sexually active.

Patients with HIV/AIDS who have elevated LDL and whose triglyceride levels are above normal (200-500 mg/dL)
dL or 2.2-5.6 mmol/L) may use pravastatin at a dose of 10-40 mg per day or atorvastatin at 10 mg per day, because these drugs are least likely to interact with ARV medications. Patients with triglyceride levels above 500 mg/dL (5.6 mmol/L) regardless of LDL cholesterol levels may be treated with gemfibrozil 600 mg twice daily or fenofibrate 54-160 mg per day. There are no established pediatric doses for these medications.

**Lipodystrophy**

Lipodystrophy is a clinical syndrome characterized by changes in body habitus attributable to fat redistribution and may be associated with many metabolic derangements, including dyslipidemia and insulin resistance. Some of these metabolic derangements are addressed separately in this chapter. The changes of lipodystrophy can include the loss of subcutaneous fat, termed lipoatrophy; deposition of fat tissue subcutaneously or in visceral stores, referred to as lipohypertrophy; or a combination of the two conditions. Lipodystrophy occurs in as many as 33% of children and is more common in adolescents than in prepubertal children. Body habitus changes occur gradually and may not become apparent until months after initiation of combination ART.

Patient self-report and physical examination by an experienced clinician are generally sufficient for the diagnosis of lipodystrophic changes.

**Lipoatrophy**

Lipoatrophy is characterized by thinning of subcutaneous fat in the face, buttocks, and extremities. A decrease in peripheral subcutaneous fat on the arms and legs results in a prominence of peripheral veins. Skinfold thickness near the triceps and biceps below the third percentile for sex and age further characterizes this condition. DEXA can be used to demonstrate a decrease in the ratio of limb/total fat or limb/truncal fat. Whole-body MRI can be used to compare SAT in the trunk and extremities. In an individual patient, features of lipohypertrophy and lipoatrophy can occur concurrently.

Many studies suggest that lipodystrophy is more highly associated with HAART than with the pathogenesis of HIV disease itself. PIs have been most strongly implicated in the development of lipohypertrophy and its associated metabolic derangements. These changes can also be seen in PI-naïve patients. Thus, the body habitus changes of lipohypertrophy are related to an interrelation between patient genetic and lifestyle factors combined with HIV infection and its therapy. In contrast, lipoatrophy may be more specific to HIV infection and its treatment, specifically the use of NRTIs. Stavudine, didanosine, and zalcitabine are most strongly implicated in the development of this complication, which is postulated to be related to mitochondrial toxicity leading to a change in fat metabolism or even fat cell apoptosis or cell death.

**Treatment**

Diet and exercise are perhaps the most effective approach to increase the muscle-to-fat ratio and reversing the fat maldistribution and body habitus abnormalities of...
lipohypertrophy. Data on pharmacologic interventions are lacking. Hormone therapy has been attempted in some studies, particularly the use of testosterone, growth hormone, or steroids. Cosmetic surgery has also been employed. If therapy permits, changing from a PI-containing regimen may have some benefit. Because lipoatrophy is associated with use of certain NRTIs, avoidance of stavudine and didanosine is the most effective approach to lipoatrophy prevention. Discontinuation of PI therapy does not lead to improvement in lipoatrophy. Substitution of NRTIs less strongly associated with mitochondrial toxicity such as abacavir or tenofovir may improve limb fat, but if the regimen change is delayed, the improvement in peripheral fat may be slower and less complete. Any change in ART must be balanced against the risk of decreasing the effectiveness of the regimen and subsequent resurgence of HIV-associated illnesses.

Many studies have examined the effect of lipodystrophy on HIV-infected adults. Although not as abundant, some research regarding lipodystrophy in HIV-infected children suggests that children, especially prepubertal, are less susceptible to lipoatrophy syndrome than postpubertal adolescents and adults. In fact, it has been suggested that puberty-related changes may precipitate the development of lipodystrophy in some children taking HAART. These changes are not merely cosmetically significant; patient awareness of the disfiguring side effects of ART can be a significant hindrance to adherence. Also, lipodystrophy’s worldwide recognition causes some patients to fear stigmatization.

**Hyperglycemia and Insulin Resistance**

HIV disease and HIV treatment can alter glucose homeostasis. ARV therapy, especially PI-containing regimens, impair glucose tolerance as reflected in the following conditions:

- Insulin resistance without fasting hyperglycemia
- Asymptomatic fasting hyperglycemia
- New-onset diabetes mellitus
- Exacerbations of preexisting diabetes

However, distinguishing the contributions of ART to impaired glucose homeostasis from those of HIV disease is difficult.

ARV-associated hyperglycemia occurs in 3%-25% of adults receiving HAART, with a mean onset of 60 days after initiation of ARV therapy. The mechanism of hyperglycemia and insulin resistance in patients on ART is unknown and probably multifactorial. PIs can directly affect insulin resistance through the inhibition of insulin-stimulated glucose transport. NRTIs may contribute by increasing the VAT to SAT ratio, thereby altering fat and energy metabolism.

Insulin resistance occurs when there are higher circulating levels of insulin than are needed for maintaining normal glucose homeostasis. This condition occurs at the level of skeletal muscle, liver, and adipose tissues, which develop decreased sensitivity to the effects of insulin. Insulin resistance has often been associated with use of PIs. Studies performed on HIV-negative patients treated with PIs demonstrated definite signs of insulin resistance. However, several factors might contribute to insulin resistance, including changes in fat distribution (VAT:SAT ratio), age, and body mass index. Patients who acquire insulin resistance may have a higher risk of type 2 diabetes mellitus. There may also be an increased risk of atherosclerotic disease.

Insulin resistance can be diagnosed through a combination of physical and laboratory findings, such as polydipsia, polyphagia, polyuria, and increased fasting blood glucose level or a suspicious glucose tolerance test. If insulin resistance is suspected, an intravenous insulin tolerance test can be conducted to verify the diagnosis. Treatment of insulin resistance includes dietary changes, sensible weight reduction, and exercise. Medical management includes metformin at 500 mg twice daily and if feasible, cessation of PI use in ART.

**Lactic Acidosis**

ART can lead to alterations in mitochondrial function, resulting in the generation of excess lactic acid. Increases in serum lactate levels can range from asymptomatic mild elevations (2.1-5.0 mmol/L) without serum acidosis, referred to as hyperlactatemia, to severe lactic acid elevations (>5.1 mmol/L) with serum acidosis, or lactic acidosis.

Chronic, asymptomatic increases in serum lactate levels are relatively common among HIV-positive adults and children receiving NRTIs. As many as 15%-35% of adults and 29%-32% of children receiving ART for longer than 6 months may have asymptomatic increases in serum lactate levels. NRTIs inhibit mitochondrial replication
by disrupting mitochondrial DNA and oxidative phosphorylation. Stavudine, especially in combination with didanosine, has been implicated most commonly. In vitro studies have demonstrated that zalcitabine, followed by didanosine, stavudine, and zidovudine, has the highest affinity for mitochondrial DNA polymerase. Lamivudine, abacavir, emtricitabine, and tenofovir have lower affinity for this enzyme. Inhibition of mitochondrial DNA polymerase results in impaired synthesis of mitochondrial respiratory chain enzymes, deterioration of oxidative phosphorylation, and depletion of ATP levels. When the demand for energy is greater than what a cell can generate through oxidative phosphorylation, anaerobic respiration produces lactic acid and therefore excess hydrogen ions. When the production of hydrogen ions is greater than the clearance, a systemic metabolic acidosis can occur.

The more serious syndrome of lactic acidosis can occur abruptly after months or years of NRTI treatment. The clinical presentation of lactic acidosis can be acute or subacute. The health care worker should maintain a high index of suspicion for this diagnosis so that prompt evaluation and management can be implemented.

Symptoms typically occur a median of 4 months after starting therapy. Patients with lactic acidosis may be asymptomatic or may present with vague and nonspecific complaints. A prodrome may include generalized fatigue, weakness, and myalgias. Later, gastrointestinal, respiratory, and neurologic symptoms can occur: nausea, vomiting, abdominal pain, shortness of breath, tachypnea, and motor weakness. Hepatic failure occurs in some patients with lactic acidosis and may be associated with tender enlargement of the liver, ascites, and encephalopathy. More serious manifestations include cardiac arrhythmias, hypotension, shock, and even death.

Although there are identified risk factors for the development of lactic acidosis, there is no proven way to predict who will develop lactic acidosis. Routine monitoring of serum lactate levels in asymptomatic patients is not recommended. Mildly elevated serum lactate levels of 2-5 mmol/L should be correlated with symptoms. Patients with mild elevations in arterial or venous lactate (2.1-5.0 mmol/L) and a normal bicarbonate level are usually asymptomatic, and subsequent progression to the lactic acidosis syndrome is rare.

A confirmed moderately elevated lactate concentration of greater than 5 mmol/L in a symptomatic patient or a confirmed severely elevated lactate greater than 10 mmol/L regardless of clinical symptoms establishes the diagnosis of lactic acidosis and requires prompt evaluation and intervention.

Measurement of serum lactate levels is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis. Additional diagnostic evaluations include assessment of the following:

- Serum bicarbonate and anion gap
- Arterial blood gas to assess extent of acidosis
- Amylase and lipase to assess for pancreatitis
- Hepatic transaminases and serum albumin level to assess for hepatic dysfunction
- Imaging studies, such as abdominal ultrasound or computed tomography scan to evaluate for hepatic steatosis and/or pancreatitis

### Treatment

Treatment includes supportive care and correction of acid-base imbalance or other possible underlying causes. Supportive therapy may include intravenous fluids,
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sedation, and respiratory support as needed to reduce oxygen demand and to ensure adequate oxygenation of tissues. Administration of bicarbonate to neutralize the lactic acid remains controversial. Anecdotal therapies to treat lactic acidosis include the administration of the following:

- High doses of riboflavin (vitamin B2) and thiamine (vitamin B1)
- Oral antioxidants, such as vitamins C, E, and K, or l-carnitine and coenzyme Q

Studies determining the efficacy of any of these agents in the treatment of NRTI-associated lactic acidosis are lacking.

Changing ART Regimens
The decision to modify ART depends on clinical symptoms and the presence of acidosis.

Restarting ART
After adults with lactic acidosis discontinue ART, lactate concentrations return to normal in about 3 months. If lactate levels are not available, ART should not be resumed until symptoms completely resolve, often not before 6-8 weeks. After resolution of symptoms, ARV therapy can be reinstituted. An NRTI-sparing regimen (i.e., an NNRTI and dual PI regimen) may be selected. If an NRTI is required for an effective regimen, then cautiously select NRTIs least likely to inhibit mitochondrial DNA polymerase. These include zidovudine and non-thymidine analog NRTIs: abacavir, tenofovir, lamivudine, and emtricitabine. Patients should be followed up with monthly monitoring of clinical status and lactate levels for at least 3 months.

Bone Density Disorders
Osteopenia, osteoporosis, and osteonecrosis are the most significant bone disorders affecting patients with HIV and AIDS. Osteopenia and osteoporosis represent decrease in bone mineral density (BMD). Osteonecrosis results in the cell death of various bone components, including fat marrow and mineralized tissue, as a result of impaired blood supply to the bone. Such abnormalities have been observed in both adults and children. Bone loss in children can be particularly serious because most bone creation takes place before the age of 30 years. The etiologies of bone loss are unclear. Some evidence points to HIV infection itself, whereas some evidence suggests that treatment regimens are the cause. Still other evidence suggests that ART might be protective. The pathogenesis seems to be multifactorial. Figure 4 shows some factors that may contribute to decreased BMD in HIV-infected patients.

A DEXA scan is used to assess BMD. Individual results are often summarized as a T score, which refers to the number of standard deviations above or below the mean BMD of a young adult (usually about age 30) at peak bone density. The WHO criteria for osteoporosis are based on T scores from DEXA scans:

- T score greater than –1 is normal.
- T score between –1 and –2.5 indicates osteopenia.
- T score less than –2.5 indicates osteoporosis.

As the T score declines below 0, the risk of fracture increases continuously. The BMD data may also be summarized as Z scores, which are similar to T scores but are normalized to patients who are the same age as the subject. Several recent studies have shown significant decreases in BMD in HIV-infected children, both on and off ART. Up to 66% of children in one study were found to have bone loss on DEXA scan.

When osteopenia is evaluated, vitamin D deficiency and hormonal imbalance must be ruled out, along with renal pathology. Management may include weight-bearing exercise, decreased
alcohol consumption, smoking cessation, and vitamin D and calcium supplementation. Some suggest the use of alendronate at a dose of 5-10 mg per day. Alendronate acts by inhibiting osteoclast bone resorption.

**Conclusion**

Treatment with HAART has dramatically changed the natural history of HIV infection by allowing HIV-infected children to now survive for many years into adulthood. However, the use of HAART is associated with the development of metabolic alterations, each of which may independently affect the patient’s health and quality of life. Some metabolic abnormalities when combined, such as visceral fat accumulation, hyperlipidemia, and insulin resistance, which are components of the metabolic syndrome, can dramatically increase the individual’s risk for heart disease, diabetes mellitus, and stroke. For early diagnosis of these complications, patients should be screened for metabolic abnormalities regularly. Screening can often be accomplished through thorough history taking and physical examination. Many of the first-line treatments for metabolic abnormalities include diet and lifestyle changes. Such changes should be encouraged for all HIV-infected patients on ART. The effect of these adverse effects on adherence is extreme. For some, the task of having to take medicines every day for the rest of their lives without missing a dose is daunting. The difficulty is compounded by the idea that these medicines cause such adverse physical reactions, especially the cosmetic changes. There is still stigma attached to HIV, and the fear that members of the community can identify someone’s serostatus simply by noticing lipoatrophy can be socially debilitating. Patients and health care workers must understand the adverse effects of ART as well as their management. This understanding is paramount in maximizing the effectiveness of adherence counseling as well as maximizing the benefits of available treatment regimens.

**References**


