Adverse Drug Effects

Differentiating between complicating consequences of HIV infection and toxicities of drugs used in the management of HIV infection is challenging. However, the experience gained with combination antiretroviral (ARV) drugs has led to the recognition of several distinct adverse drug events. These include:

- mitochondrial dysfunction (including lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy);
- metabolic abnormalities (such as fat maldistribution and body habitus changes; hyperlipidemia; hyperglycemia and insulin resistance; and osteopenia, osteoporosis, and osteonecrosis);
- hematologic adverse events from drug-induced bone marrow suppression (anemia, neutropenia, and thrombocytopenia); and
- allergic reactions (skin rashes and hypersensitivity responses).

While individual ARV drugs or classes of ARV drugs are associated with specific toxicities, interaction between ARVs and interactions with other drugs used in the management of HIV/AIDS complications can result in altered pharmacokinetics and additional drug toxicities. The major adverse drug events seen in children and the management of these events are discussed in this supplement, recognizing that experience in children is more limited than in adults. Therefore, the management of complications of pediatric HIV infection, including ARV drug toxicities, requires consultation with a physician experienced in management of pediatric HIV/AIDS. The sections that follow provide an overview of adverse events associated with ARV treatment.

LACTIC ACIDOSIS

Background

Chronic and asymptomatic mild hyperlactatemia (2.1 to 5.0 mmol/L) is relatively frequent among HIV-infected individuals receiving nucleoside analogue reverse transcriptase inhibitors (NRTIs), occurring in approximately 15 to 35% of infected adults receiving ARV treatment, usually for longer than 6 months *[1]*. There are few data available in pediatric patients. In a cohort of 81 HIV-infected Spanish children receiving ARV therapy, asymptomatic mild hyperlactatemia was observed in 17% of children *[2]*. In the U.S., asymptomatic hyperlactatemia was observed in 32% of 127 HIV-infected children receiving highly active antiretroviral therapy *[3]*.

Symptomatic hyperlactatemia is less common (reported in 0.2 to 2.5% of infected adults), and the syndrome of lactic acidosis/hepatic steatosis is rare *[4, 5]*. In a cohort of adults receiving NRTI therapy at Johns Hopkins University between 1989 and 1994, the incidence of the lactic acidosis/hepatic steatosis syndrome was 0.13%; in a more recent cohort of 964 infected adults from France followed between 1997 and 1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a stavudine (d4T)-containing regimen *[6, 7]*. Although lactic acidosis has been described in association with all NRTI drugs, particularly if treatment is over 6 months in duration, therapy with didanosine (ddI) and/or d4T may be more likely to be associated with this syndrome *[8-10]*. Life-threatening and fatal cases of lactic acidosis have also been reported in HIV-infected children *[11-13]*. While uncommon, lactic acidosis is associated with a high fatality rate (33 to 57%).

Lactic acidosis/hepatic steatosis is thought to be secondary to mitochondrial dysfunction induced by NRTI treatment *[14, 15]*. NRTI drugs have varying affinity for mitochondrial DNA polymerase gamma. The relative potency of the NRTIs in inhibiting mitochondrial DNA polymerase gamma *in vitro* is highest for zalcitabine (ddC), followed by ddI, d4T, and zidovudine (ZDV); lamivudine (3TC), abacavir (ABC), and tenofovir disoproxil fumarate (TDF)

have lower affinity for the mitochondrial polymerase *[15-17]*. Inhibition of mitochondrial DNA polymerase gamma can result in inhibition of mitochondrial DNA replication, resulting in impaired synthesis of mitochondrial respiratory chain enzymes, deterioration of oxidative phosphorylation, and depletion of ATP levels. When a cell is unable to generate enough energy through oxidative phosphorylation, anaerobic respiration occurs via conversion of pyruvate to lactate in the cytoplasm. This results in an excess production of hydrogen ions, which can lead first to a cellular, then to a systemic metabolic acidosis if uncontrolled. Lactate clearance normally occurs via the liver or kidneys, but if production is excessive or the organs have pre-existing malfunction, accumulation of lactate and hydrogen ions can result. Thus, both overproduction and underutilization of lactate occur. Steatosis occurs secondary to fatty acid oxidation inhibition, leading to excess hepatic fat production and accumulation of microvesicular lipid droplets in the liver.

Risk factors for lactic acidosis/hepatic steatosis include female gender, high body mass index, chronic hepatitis C infection, African-American ethnicity, use of d4T, prolonged NRTI use, acquired riboflavin or thiamine deficiency, and possibly pregnancy *[4, 7, 9]*. However, there is no proven way to predict who will develop lactic acidemia.

Clinical Features

Onset can be acute or subacute. Cases have occurred as soon as 1 month and as late as 20 months after starting therapy, with a median onset of 4 months in one case series *[4, 18]*. Initial symptoms of lactic acidosis are variable and non-specific; a clinical prodromal syndrome may include generalized fatigue, weakness, and myalgias; gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, and sudden unexplained weight loss); and respiratory (tachypnea and dyspnea) or neurologic symptoms (motor weakness, including a Guillian-Barre–like syndrome of ascending neuromuscular weakness) *[19]*. Features of hepatic dysfunction may be observed, including a tender and enlarged liver, ascites, and encephalopathy; jaundice is unusual, and hepatic enzymes are usually only modestly elevated *[18]*. Patients who are receiving NRTIs and present with this constellation of symptoms should undergo prompt evaluation for lactic acidosis. With progression of lactic acidosis, hepatic and renal failure, clotting abnormalities, seizures, cardiac arrhythmias, and death can ensue.

In HIV-infected adults with this syndrome, lactic acidosis is associated with hepatic steatosis in 69% of patients and pancreatitis in 22% *[1]*. Hepatic steatosis is a common finding on imaging studies or liver biopsy; hepatic necrosis can occur in fulminant cases *[20]*. Laboratory abnormalities include hyperlactatemia, low bicarbonate, increased anion gap (> 16), systemic acidosis (arterial pH < 7.35), and elevated aminotransferases, creatine phosphokinase, lactate dehydrogenase, lipase, and amylase. Arterial or venous lactate levels are generally > 5.0 mmol/L, and serum bicarbonate is decreased in patients with symptomatic lactic acidosis, indicating widespread cellular energy deficit and metabolic decompensation. Lactate levels > 10 mmol/L are life-threatening and have been associated with mortality of > 80% *[21]*. A CT scan may demonstrate an enlarged fatty liver; histologically, microvesicular steatosis is seen on examination of the liver.

Recommendations for Assessment and Monitoring

Routine monitoring of serum lactate levels in asymptomatic patients is not recommended as part of routine clinical practice *[5, 20, 22]*. Patients with mild elevations in arterial or venous lactate levels (2.1 to 5.0 mmol/L) and a normal bicarbonate level are usually asymptomatic, and subsequent progression to the lactic acidosis syndrome is rare. Thus, mild hyperlactatemia in asymptomatic patients does not identify patients who are at greater risk for development of lactic acidosis or hepatic steatosis.

Measurement of serum lactate is recommended only for patients presenting with clinical or laboratory signs or symptoms consistent with lactic acidosis. Clinical symptoms warranting consideration of serum lactate level assessment include new-onset extreme fatigue, vague abdominal pain, sudden weight loss, unexplained nausea or vomiting, peripheral neuropathy, or sudden dyspnea. Additional diagnostic evaluations include assessment of serum bicarbonate and anion gap and/or arterial blood gas (to assess extent of acidosis); amylase and lipase (pancreatitis can accompany severe lactic acidosis); and liver function tests (hepatic steatosis and necrosis can accompany

severe lactic acidosis). Laboratory abnormalities include low bicarbonate, chloride, or albumin levels; raised anion gap; unexpected increases in liver enzymes; or new onset of clinical liver failure.

Sample collection for assessment of lactate is difficult in adults, and even more so in children, as vigorous exercise (e.g., prolonged vigorous crying), poor hydration, and prolonged tourniquet use are associated with falsely elevated results. Blood should be collected without prolonged tourniquet application or fist clenching into a pre-chilled, gray-top, fluoride-oxalate–containing tube and transported on ice to the laboratory to be processed within 4 hours of collection *[18]*. An elevated lactate level should be confirmed with a repeat measurement.

Serum lactate levels of 2 to 5 mmol/L are considered elevated and need to be correlated with symptoms. A confirmed lactate level above 5 mmol/L in the presence of clinical signs or symptoms, or a confirmed level above 10 mmol/L regardless of clinical symptomatology, establishes the diagnosis of NRTI-associated lactic acidosis in a patient receiving such therapy. Measurement of arterial pH to confirm the presence of acidosis is not necessary in most cases.

Management/Treatment (Table 1)

In patients with symptomatic but low level hyperlactatemia (< 5 mmol/L), continuation of therapy including NRTIs is reasonable, but lactate levels should be monitored regularly. In patients with lactic acidosis (i.e., all patients with lactate > 10 mmol/L and symptomatic patients with lactate 5 to 10 mmol/L), ARV and any other potentially contributory drugs should be discontinued. If NRTI therapy is continued in such patients, progressive toxicity may occur, with severe lactic acidosis, respiratory failure, and death.

Therapy is primarily supportive (intravenous fluid support; reduction in oxygen demand and ensuring adequate oxygenation of tissues through sedation and respiratory support, as needed) *[23]*. Although some reports suggest that alkalinizing the blood with bicarbonate infusions to clear or neutralize the lactic acid might improve prognosis, this remains controversial *[23-25]*. Thiamine (vitamin B_1) and riboflavin (vitamin B_2) are both important for mitochondrial function; nutritional deficiencies of these vitamins could predispose the patient to mitochondrial toxicity *[26-30]*. In some uncontrolled case reports, administration of high doses of these vitamins has been associated with improvement in NRTI-associated lactic acidosis. Administration of antioxidants such as vitamins C, E, and K, or of L-carnitine and co-enzyme Q (ubiquinone), has also been reported in case reports to be beneficial. Doses of L-carnitine that have been used for treatment of HIV-infected adults were 50 mg/kg/day divided into three doses and administered by a 2-hour infusion in a 5% glucose solution for 15 days *[31]*. However, there are no controlled data to show efficacy of any of these agents in the treatment of NRTI-associated lactic acidosis.

Following discontinuation of ARV therapy in adults with lactic acidosis, lactate levels return to normal at a mean of 3 months post-discontinuation *[18]*. However, symptoms associated with lactic acidosis may continue or worsen for a longer period after ARV discontinuation. Whether there are long-term sequelae of NRTI-related lactic acidosis is not known.

Following resolution of symptoms, ARV therapy can be resumed. There are insufficient data to recommend whether therapy should be restarted with an NRTI-sparing regimen (e.g., a non-nucleoside reverse transcriptase inhibitor and dual protease inhibitor regimen) or with a revised NRTI-containing regimen. If an NRTI is required for an effective regimen, then the antiretroviral drugs least likely to inhibit mitochondrial DNA polymerase gamma (preferably ABC or TDF; possibly ZDV or 3TC) can be used with caution *[32, 33]*. Reinstitution of therapy including an alternative NRTI should be closely monitored; some clinicians recommend monthly monitoring of lactate for at least 3 months in patients who experienced NRTI-associated lactic acidosis *[18, 20]*.

Special Case: *In Utero* Antiretroviral Exposure

Background

Blanche and colleagues from France reported 8 cases of HIV-exposed but uninfected infants with *in utero* and/or neonatal exposure to either ZDV/3TC or ZDV alone (4 infants each) who developed indications of mitochondrial dysfunction after the first few months of life *[34]*. Two infants exposed to

ZDV/3TC developed severe neurologic disease and died, 3 had mild to moderate symptoms, and 3 had no symptoms but transient laboratory abnormalities. All infants had elevated lactic acid levels.

Further evaluation of mitochondrial toxicity was conducted in 4,392 uninfected or HIV-indeterminant children (2,644 with perinatal ARV exposure) followed within the French Pediatric Cohort or identified within a France National Register developed for reporting of possible mitochondrial dysfunction in HIV-exposed children. Evidence of mitochondrial dysfunction was identified in 12 children (including the 8 cases mentioned above), all of whom had perinatal ARV exposure, representing an 18-month incidence of 0.26% *[35]*. Risk was higher among infants exposed to combination ARV drugs (primarily ZDV/3TC) than ZDV alone. All children presented with neurologic symptoms, often with abnormal MRI and/or a significant episode of hyperlactatemia, and all had a deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy histology. In a separate publication, the same group reported an increased risk of simple febrile seizures during the first 18 months of life among uninfected infants with ARV exposure *[36]*.

However, a retrospective examination of several large cohorts that included over 16,000 HIV-exposed but uninfected children with and without ARV exposure identified no deaths similar to those reported from France or clinical findings attributable to mitochondrial dysfunction *[37]*. Additionally, a clinical review of data from 1,954 living HIV-exposed but uninfected children in the prospective Pediatric AIDS Cohort Transmission Study has not identified any child with ARV exposure who had symptoms that could be attributed to mitochondrial dysfunction *[38]*. The European Collaborative Study also reviewed clinical symptoms in 2,414 uninfected children (1,008 with perinatal ARV exposure) followed prospectively; median length of follow-up was 2.2 years (maximum 16 years) *[39]*. No association between clinical manifestations suggestive of mitochondrial abnormalities and perinatal ARV exposure was found. Of the 4 children with seizures in this cohort, none had perinatal ARV exposure. Thus, there are conflicting data regarding whether mitochondrial dysfunction in HIV-exposed but uninfected children is associated with perinatal ARV exposure. If an association exists, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be weighed against the clear benefit of ARV prophylaxis in reducing transmission of a fatal infection by 70% or more *[40, 41]*. However, children with *in utero* ARV exposure should have long-term follow-up for potential late toxicities, and mitochondrial dysfunction should be considered in uninfected children with perinatal ARV exposure who present with severe clinical findings of uncertain etiology, particularly neurologic findings.

Recommendations for Assessment and Monitoring

Two studies have suggested that mild, transient elevations in plasma lactate may be observed in 85 to 92% of HIV-exposed uninfected infants with perinatal ARV exposure, although moderate elevations (exceeding 5 mmol/L) were seen in fewer infants (26% of 38 infants in one study) *[42, 43]*. The elevations were generally not accompanied by clinical manifestations, and plasma lactate normalized by age 6 months. These studies have involved only small numbers of infants, and generally do not describe the methodology for sample acquisition and processing for the lactate level measurements. The clinical significance of these laboratory findings is unclear, and further studies are needed to validate these findings.

In a child with clinical symptomatology suggestive of possible mitochondrial dysfunction, particularly neurologic signs or symptoms or hepatic disorders, serum lactate should be assayed and further evaluation performed to determine if there are additional signs of a mitochondrial disorder. However, routine monitoring of lactate levels in asymptomatic neonates with ARV exposure is not recommended at this time.

Table 1. Recommendations for Evaluation and Management of Lactic Acidosis Associated with Antiretroviral Therapy

Clinical Findings	Recommendations
Asymptomatic	Routine monitoring of serum lactate levels is *not* recommended.
Clinical symptoms • usually insidious onset of: ➢ generalized fatigue, ➢ weakness, and ➢ myalgias or ➢ gastrointestinal, ➢ respiratory, or ➢ neurologic symptoms; • some patients may present with multi-organ failure, such as: ➢ fulminant hepatic failure, ➢ acute pancreatitis, or ➢ respiratory failure	***Note: if ability to obtain lactate measurement is delayed and this syndrome is suspected, discontinue all antiretroviral drugs pending evaluation.*** **Diagnostic evaluations:** • Serum lactate • Serum bicarbonate, anion gap • Liver function tests • Amylase • Lipase • Arterial blood gas • Imaging studies, such as abdominal ultrasound or CT scan, as indicated (e.g., evaluation for hepatic steatosis, pancreatitis) **Management:** *Lactate < 2.0 mmol/L and normal bicarbonate:* • Continue antiretroviral therapy • Not lactic acidosis; evaluate for alternative etiology of symptoms *Lactate 2.1-5.0 mmol/L (confirm with second test):* • Antiretroviral therapy can be continued, particularly if bicarbonate is normal, but carefully monitor symptoms, serum lactate, and other laboratory values as above; *or* • Alternatively, temporarily discontinue therapy while conducting additional diagnostic work-up *Lactate > 5.0 mmol/L (confirm with second test) or if lactate >10 mmol/L, regardless of symptoms:* • Discontinue all antiretroviral therapy • Supportive therapy (intravenous fluids; reduce oxygen demand and ensure adequate oxygenation of tissues through sedation and respiratory support, as needed) • Anecdotal, although unproven, supportive therapies: ▪ Bicarbonate infusions ▪ High dose thiamine (vitamin B_1) and riboflavin (vitamin B_2) ▪ Oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C) **Following Resolution of Clinical and Lab Abnormalities:** *Antiretroviral therapy can be resumed, either with:* • NRTI-sparing regimen (e.g., a non-nucleoside reverse transcriptase inhibitor and dual protease inhibitor regimen); *or* • A revised NRTI-containing regimen, instituted with caution ▪ Use NRTI less likely to inhibit mitochondria (preferably ABC or TDF; possibly ZDV or 3TC) ▪ Close monitoring (some clinicians recommend monthly monitoring of lactate for at least 3 months)

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HEPATIC TOXICITY

Background

Elevations in liver enzymes with or without clinical hepatitis have been reported in 14 to 20% of HIV-infected adults receiving HAART *[1-5]*. The differential diagnosis of liver dysfunction in an HIV-infected patient is complicated, as abnormalities in liver function are common and may be caused by HIV itself, coinfection with hepatitis B or C viruses or opportunistic infections, malignancies, coexisting conditions (e.g., chronic alcohol use), drug interactions, or drug-induced hepatic toxicity. Hepatotoxicity has been reported with all of the available NRTI, NNRTI, and PI drugs.

NRTI-associated hepatotoxicity is thought to be primarily due to mitochondrial toxicity *[2]*. Lactic acidosis associated with hepatic steatosis is recognized as a rare but serious and potentially life-threatening complication of treatment (see "**Lactic Acidosis**" for a more detailed discussion of the syndrome and its management).

NNRTIs are associated with several types of hepatic toxicity, including asymptomatic elevation in transaminase levels (which can occur early during therapy or, less frequently, with a later onset) and hypersensitivity reaction with hepatitis *[1]*. Although there is debate about whether asymptomatic transaminase elevations are more common with NNRTIs than other drugs, the NNRTIs have been the most common ARV drug class implicated in hypersensitivity reactions (see also "**Hypersensitivity Reactions and Skin Rashes**") *[1, 5-7]*.

In most studies, nevirapine (NVP) is reported to be associated with more hepatotoxicity than efavirenz (EFV) or delavirdine (DLV) *[1, 6-8]*. Asymptomatic transaminase elevations have been reported in 6 to 13% of patients receiving NVP, while symptomatic hepatitis has been reported in approximately 4 to 5% of patients *[5-7, 9, 10]*. NVP-associated symptomatic hepatitis develops during the first 6 to 18 weeks of therapy, and may have associated symptoms of skin rash, fever, and hypotension *[5]*. In adults, this type of reaction has been observed more frequently in females than males and in patients with higher CD4 cell counts (> 250/mm^3 in women, > 400/mm^3 in men) *[5, 7]*. Patients co-infected with hepatitis B or C may also be at higher risk *[10]*. Although rare, this syndrome can progress rapidly to hepatic failure and death within days, and progression can occur even after NVP is discontinued *[11-13]*. NVP should be permanently discontinued in patients who develop severe NVP-associated symptomatic hepatotoxicity. In contrast to hepatic toxicity manifested as asymptomatic transaminase elevations, the development of rash-associated hepatic events does not correlate with elevation from baseline transaminase levels *[5]*.

PI-associated liver enzyme abnormalities can occur any time during the course of treatment. The pathogenesis of PI-associated liver injury is not known. As a class, PIs are extensively metabolized by the liver cytochrome P450 enzyme system. Thus, underlying hepatic impairment may result in elevated PI levels, which could enhance the risk of toxicity; additionally, other drugs (including ARVs) that are metabolized in the liver can affect PI metabolism and hence predispose to toxicity as well *[3]*. The overall incidence of liver enzyme elevations 5 to 10 times the upper limit of normal (ULN) in adult patients receiving PIs ranged from 3 to 18%, but the incidence of symptomatic liver toxicity is lower (1 to 5%). Coinfection with hepatitis B or C viruses has been consistently associated with a greater risk of severe liver injury in patients receiving PIs. Tipranavir (TPV) with low-dose ritonavir (RTV) has been associated with clinical hepatitis and hepatic decompensation, including some fatalities. This toxicity has generally occurred in adults with advanced HIV disease taking multiple concomitant medications. Patients with chronic hepatitis B or C virus co-infection have an increased risk of TPV-associated hepatotoxicity. RTV has been identified as a risk factor for severe hepatic toxicity independent of coinfection with chronic viral hepatitis. However, low-dose RTV used for pharmacologic "boosting" of other PIs has generally not been associated with liver toxicity to the same extent as observed with therapeutic doses of RTV *[3, 10, 11, 14, 15]*. Indinavir (IDV) and atazanavir (ATV) have been associated with a high rate of unconjugated (indirect) hyperbilirubinemia (6 to 40% of patients). This is caused by inhibition of the activity of the hepatic enzyme UDP-glucuronosyltransferase, leading to the development of a reversible, asymptomatic, indirect hyperbilirubinemia that clinically resembles Gilbert's disease and is not associated with hepatic injury. Clinically significant jaundice is less common (7 to 8% of patients treated with IDV or ATV) *[14]*.

A number of large studies have reviewed the incidence of hepatic toxicity and its risk factors in adults receiving antiretroviral treatment. Some of the non-drug associated risk factors that have been identified include elevated baseline serum transaminase enzyme levels at initiation of therapy, fatty liver disease, hepatotropic viruses (e.g., hepatitis B or C viruses), and use of alcohol *[4, 9, 11, 14-17]*.

Physicians should be aware that improvement in immune status with HAART might have a deleterious effect on the course of hepatitis infection in some patients with hepatitis B or C coinfection. Patients with chronic hepatitis B or C may experience a rise in transaminase levels after initiating HAART. This has been attributed to immune reactivation, with a rapid increase in cytotoxic T cells leading to immune-mediated destruction of HBV- or HCV-infected hepatocytes *[3, 18, 19]*. Some ARV drugs, such as lamivudine (3TC) and tenofovir (TDF), are also effective in the treatment of hepatitis B, and discontinuation of these drugs (such as with a change in therapeutic regimen) may result in a flare-up of hepatitis B virus-associated liver disease.

Hepatic Toxicity in Pediatrics

No similar studies have reviewed the incidence of hepatic toxicities and their risk factors in pediatric populations, and a review of the pediatric literature is hindered by the variability in reporting of hepatic events. However, several consistent observations can be made. Early studies with NRTI drugs in pediatric patients with mild to moderate symptoms of HIV disease demonstrated that elevated liver function tests, including increases in serum transaminases (AST and ALT), was a relatively common event in children being treated with NRTI drugs. In an early study of ZDV monotherapy, 12.8% of patients developed ALT > 5 times ULN *[20]*. In a study of

combination NRTI therapies, 4% of the children developed ALT > 10 times ULN *[21]*.

More recent studies with HAART regimens have not demonstrated an increased risk of hepatitis with these combination therapies in pediatric patients. In one study comparing 100 children receiving combination NRTI treatment to 197 children receiving an RTV-containing regimen, the rates of hepatic adverse events were not statistically different: 16% and 17% of the children receiving RTV in combination with ZDV+3TC or stavudine (d4T), respectively, experienced severe hepatic toxicity, compared to 10% of the children who received only NRTIs *[22]*. In a study conducted in a similar study population that included 129 children treated with NVP-containing regimens, rates of hepatic events varied by treatment arm, but ranged from 12 to 18% in the NVP-containing arms *[23]*. There were, however, no treatment discontinuations for any hepatic-related adverse events. In subsequent studies of a spectrum of HAART regimens in a variety of pediatric populations, severe hepatic toxicity has rarely been reported and even more rarely resulted in treatment discontinuation *[24-29]*. Thus, severe drug-related hepatic adverse events may be less common in HIV-infected children than in comparably treated adults, and may be related to lower rates of chronic hepatitis B or C coinfections in pediatric patients.

Monitoring

Monitoring liver function tests as part of routine periodic laboratory evaluations of HIV-infected children remains an important part of standard monitoring. Such monitoring is particularly important in the first few months after initiating antiretroviral therapy or changing therapies, as liver toxicities may be more common early after initiating a new therapy *[6, 30]*. However, liver function abnormalities can occur at any time while on treatment. Patients with early increases in liver enzymes (i.e., within the first 6 weeks) should be monitored more closely to exclude the possibility of hypersensitivity to the drug (e.g., NVP, abacavir [ABC]). On the other hand, if liver enzymes are elevated months after initiation of therapy, lactic acidosis or liver steatosis should be considered. Children who are co-infected with hepatitis B or C viruses should have increased monitoring due to potential interaction of coinfection with development of drug toxicity.

Management

Observations from pediatric studies and adult cohorts *[4, 11, 19]* suggest that HAART regimens generally do not need to be interrupted for asymptomatic mild to moderate elevations in serum transaminases (< 10 times ULN). Evidence of clinical hepatitis or severe hepatotoxicity should trigger an investigation for other causes (e.g., hepatitis A, B, or C) and may result in interruption of ARV therapy. In children with hepatitis B coinfection who are receiving 3TC as a component of HAART for treatment of HIV, continued use of 3TC should be considered, even if 3TC-resistant strains of HIV develop, to avoid flare-up of hepatitis B infection *[11]*. NVP-containing regimens should be discontinued if a patient develops clinical hepatitis. Some experts would consider discontinuation of HAART in patients with hepatic enzyme elevation > 10 times ULN. It is important to note that a clinical picture of acute liver failure may progress rapidly and may require intensive supportive care *[19, 31]*. Reintroduction of the potential offending agent after the resolution of severe hepatic toxicity should be done cautiously, as it may result in a relapse of liver toxicity *[19]*. Rechallenge with NVP or ABC after any episode of acute clinical hepatitis, regardless of severity, is not recommended.

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FAT MALDISTRIBUTION AND BODY HABITUS CHANGES

Background

Changes in body fat distribution (lipodystrophy) have been reported to occur in 1% *[1]*, 10% *[2]*, 18% *[3]*, 29% *[4]*, and 33% *[5]* of HIV-infected children treated with ARVs. Lipodystrophy has been found more commonly in adolescents than in prepubertal children *[3]*. In adults, body habitus changes have been reported to occur in 2 to 84% of patients *[6-9]*. These changes include either loss of subcutaneous fat (peripheral fat wasting, termed lipoatrophy), deposition of fat tissue subcutaneously or in visceral stores (central fat deposition or accumulation, sometimes termed truncal lipohypertrophy), or a mixture of the two. The body habitus changes usually occur gradually, with the full impact not apparent until months after the initiation of combination ARV therapy. Bone mineral loss may be more common in children with lipodystrophy *[10]*.

In lipohypertrophy (central fat accumulation), findings may include central obesity, including the presence of dorsocervical fat accumulation ("buffalo hump"), and increase in visceral adipose tissue (VAT) with increased abdominal girth and increased waist-to-hip ratio. Breast enlargement may occur. Central fat accumulation syndrome may be somewhat more common in women than men *[8]*. The syndrome has been defined in pediatric case series as trunk/arm skinfold ratio > 2 standard deviations from the mean *[5]*, as dual energy x-ray absorptiometry (DEXA)-identified increase in the trunk/total fat or trunk/limb fat ratio *[4, 11]*, or based on the clinical findings described above *[3]*. Increased intra-abdominal adipose tissue (IAT) can be measured with MRI *[11]* or computed tomography (CT) *[12]*. Single-slice cross-sectional measurements allow calculation of total, visceral, and subcutaneous adipose tissue (TAT, VAT, and SAT, respectively).

Lipoatrophy is marked by sometimes dramatic thinning of subcutaneous fat in the face, buttocks, and extremities, with the decrease in peripheral subcutaneous fat on the arms and legs associated with a prominent appearance of peripheral veins. It can be identified by a decrease in the ratio of limb/total fat or limb/truncal fat *[11]* on DEXA scan, by triceps and biceps skinfold thickness below the third percentile for gender and age *[5]*, or based on the clinical evaluation for signs noted above *[3]*. Lipoatrophy has been associated with PI use and use of NRTIs, especially stavudine (d4T) and didanosine (ddI) *[13, 14]*. It has also been associated with very low plasma leptin concentrations *[15]* and low plasma adiponectin concentrations *[16]*, and is postulated to occur from alterations in mitochondrial function caused by NRTIs, especially the dideoxynucleosides d4T, ddI, and zalcitabine (ddC) *[17-19]*. While clearly associated with NRTI (especially d4T) use, older age and lower pretherapy body mass index may be more important risks *[20]*.

Hyperlipidemia (elevated cholesterol and triglycerides) has been noted more commonly in children with body habitus changes in some, but not all, of the small case series reported in children *[2-5, 21]*. Insulin resistance may be found along with the body habitus changes, but hyperglycemia is rare. These biochemical changes frequently occur in the absence of changes in body habitus. In a study of 614 HIV-infected adults treated with PIs, metabolic abnormalities (alterations in glucose metabolism, hypertriglyceridemia, or hypercholesterolemia) occurred in 60% of 164 adults without lipodystrophy and in 74% of 300 persons with lipodystrophy *[22]*.

While not always the case *[22]*, lipohypertrophy is more commonly associated with insulin resistance than is lipoatrophy *[8, 16]*. Lipoatrophy (with or without central fat accumulation) is more strongly associated with low plasma adiponectin levels, but not with insulin resistance *[16]*.

Use of PIs, especially indinavir (IDV) *[23]*, has been implicated in the pathogenesis of lipohypertrophy and insulin resistance *[24]*. PIs and NRTIs can interfere with differentiation of pre-adipocytes to adipocytes, and the combined effect is different than the effect of each drug alone *[25]*. Use of a PI plus lamivudine (3TC) was associated with a syndrome of lactic acidemia, weight loss, and a dorsocervical

fat pad *[14]*. Cholesterol and triglyceride concentrations are higher in persons treated with PIs than in those without PI exposure *[26]*. Insulin resistance and changes in lipid metabolism (all clinically related to lipodystrophy syndrome) have been associated, through different mechanisms, with nelfinavir (NFV) *[27, 28]*, IDV, ritonavir (RTV), amprenavir (APV) *[29]*, efavirenz (EFV) *[30]*, testosterone oversecretion *[31]*, interleukin-6–associated inflammation *[32]*, and impaired growth hormone secretion *[33]*. Mitochondrial dysfunction from NRTI use has also been implicated as a possible cause of lipodystrophy syndrome *[34, 35]*.

As with obesity in children without HIV, genetic and developmental characteristics, interacting with diet *[36]* and drug exposure and duration *[37]*, may be important in development of the metabolic and body habitus changes of the lipodystrophy syndrome *[38]*. In a comparison of serum lipids, glucose homeostasis, and abdominal adipose tissue distribution in 50 HIV-infected children ages 3 to 18 years in Toronto, serum cholesterol, LDL cholesterol, and triglycerides were statistically significantly higher in 30 PI-treated children compared with 20 children not treated with PIs *[21]*. However, glucose homeostasis was more closely associated with Tanner stage than with HIV therapy, and VAT to SAT ratio (i.e., lipohypertrophy) was most closely associated with patient age *[21]*. In another study, insulin resistance in the adipose tissue was present to similar degree in 6 children with HIV-associated lipohypertrophy and 6 obese children without HIV infection, but such insulin resistance was not found in 8 children with HIV but without lipohypertrophy *[39]*.

Assessment and Monitoring

There are currently no modalities recommended for routine assessment and monitoring for the lipodystrophy syndrome. Anthropometric measurements of potential usefulness include waist circumference, waist-to-hip ratio, and triceps skinfold thickness. Appropriate age, gender, and race standards exist for many of these measurements, and studies have measured the extent of abnormality in these characteristics in children with HIV *[5, 11]*. However, data are lacking on sensitivity, specificity, and predictive value of these tests in identifying patients with lipoatrophy or lipohypertrophy. Their use requires considerable training of personnel to achieve reproducible results. While promising because of low cost and safety, routine use of anthropometric measurements cannot yet be recommended to identify fat maldistribution syndromes in children with HIV infection.

While single-slice MRI and CT scanning can accurately measure TAT, VAT, and SAT, there are no studies that take age, gender, race, and nutritional status into account to allow for appropriate standardization and interpretation of the results. Both methods are expensive, and CT scanning has the added disadvantage of radiation exposure. Bioelectrical impedance analysis (BIA) can be used to measure whole-body composition, but it cannot be used to measure regional distribution of body fat, which is key to identifying the lipoatrophy or lipohypertrophy syndromes. DEXA scanning has been used by some investigators, but it cannot differentiate VAT from truncal SAT, and appropriate normal reference standards are not available; interpretation of results can be quite misleading. Ultrasound can be used for 3-dimensional measurements of adipose and lean body tissue, but there are no data on this modality in children.

Treatment

Because there are multiple potential causes of the fat maldistribution syndrome, the effectiveness of an intervention will depend on matching appropriate treatment to underlying cause. No therapy has proven to be of benefit in large numbers of affected patients, and there are few data on treatment outcomes in children. Studies in children are needed before specific treatments can be recommended. Such studies should use standardized definitions of the syndrome and follow-up measurements, control for the effect of normal development (Tanner stage), and perhaps compare diet and exercise to other possible interventions.

The syndromes of peripheral fat wasting, central fat deposition, and the metabolic syndromes that may accompany body habitus changes are not mutually exclusive. In fact, many patients whose clinical picture is most obviously marked by central fat deposition also have peripheral fat wasting upon careful measurement. Exact definitions of the metabolic syndromes and body habitus changes associated with HIV and ARV therapy are still evolving. Lack of standard definitions is a

particularly important issue when trying to evaluate potential effects of treatment.

Metabolic abnormalities and, to a lesser extent, truncal fat accumulation can be partially reversed by switching patients from PIs to NVP or EFV *[40]*, although such a switch may be associated with breakthrough viremia and should be undertaken cautiously *[41, 42]*. Diet and exercise may also help reverse these fat maldistribution and body habitus abnormalities *[43, 44]*.

Because of the association of lipoatrophy with the use of certain NRTIs, avoidance of d4T and especially the combination of d4T and ddI may help in prevention or treatment.

Other experimental interventions for patients with body fat changes associated with HIV and its therapy include insulin-sensitizing medications such as metformin *[45, 46]* and thiazolidinediones *[47]*; hormones, including growth hormone and testosterone *[48];* and surgery *[49]*. Since exercise and diet *[43, 44]* and metformin and exercise *[45, 46]* both improve the abnormalities of lipohypertrophy/metabolic syndrome, a trial comparing diet *[50]* and exercise with drug therapies such as metformin or rosiglitazone is needed. Such trials in children would need to control for age and developmental (Tanner) stage, as well as for the impact of the intervention.

Changes in appearance may be slow to resolve even after changes in therapy, and the choice between loss of viral control and change in appearance may be difficult, especially for adolescents.

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HYPERLIPIDEMIA

Background

Derangements in lipid metabolism, as evidenced by elevated total cholesterol, triglycerides (TG), and low density lipoprotein cholesterol (LDL-c) and decreases in high density lipoprotein cholesterol (HDL-c) occur frequently in HIV-infected adults, particularly those receiving PIs *[1-10]*. Proposed explanations for PI-associated dyslipidemia include abnormalities of retinoic acid metabolism, impaired lipid clearance, impaired adipogenesis, apolipoprotein abnormalities, and increased hepatic TG, fatty acid, and sterol synthesis *[11]*. Among the PIs, the incidence of hypertriglyceridemia is the highest with ritonavir (RTV) (2.6-fold higher than the other PIs) and lowest (or absent) with atazanavir (ATV) *[1, 7, 12]*. There are few published reports on the effects of PIs on lipid levels in children and adolescents. In a recent Swiss retrospective study of 66 PI-treated children, the initiation of RTV therapy resulted in a doubling of both total cholesterol and TG levels *[13]*. Nelfinavir (NFV) administration resulted in increases in total cholesterol levels, but not in TG *[13]*. Among the NRTIs, stavudine (d4T) is most commonly associated with hyperlipidemia *[5]*. Nevirapine (NVP) and, to a lesser extent, efavirenz (EFV) may actually increase HDL-c levels over time and have potentially antiatherogenic effects *[14]*.

While the risks associated with hyperlipidemia in adults are well documented and HIV PI therapy is associated with increased cardiovascular disease (CVD), there are no studies documenting a relationship between elevated cholesterol levels in children and an increased risk of premature death, as in adults *[13-20]*. Persistent dyslipidemia in children, however, is likely to lead to premature CVD, with evidence of atherosclerotic disease similar to that seen in children heterozygous for familial hypercholesterolemia (FH) *[13, 20]*. The National Cholesterol Education Program (NCEP) classification of fasting cholesterol levels in children and adolescents is listed in **Table 2** *[16, 17]*.

Table 2. NCEP Classification of Fasting Cholesterol Levels in Children and Adolescents *[16, 17]*.

Category	Total Cholesterol	LDL Cholesterol
High	>200 mg/dL	>130 mg/dL
Borderline	170-199 mg/dL	110-129 mg/dL
Acceptable	<170 mg/dL	<110 mg/dL
Triglyceride levels below 200 mg/dL are considered acceptable.		

Monitoring

For HIV-infected adolescents and adults, the adult ACTG guidelines outline recommendations for evaluating and monitoring patients who are initiating HAART or are currently on ARV medications *[21]*. A fasting (12 hour) lipid profile, including total cholesterol, HDL-c, and TG, with calculation of LDL-c, is recommended before initiating ARV therapy and should be repeated every 3 to 6 months *[21, 22]*. In adult patients with advanced HIV disease and immune deficiency, changes in lipoprotein metabolism include decreases in total cholesterol, LDL-c, and HDL-c and increases in TG *[14]*. Monitoring of the ratio of total: HDL-c or the non-HDL–c fraction (total cholesterol minus HDL-c) may be more useful with advanced disease or significant hyperlipidemia *[14]*. In certain circumstances, monitoring of random (non-fasting) lipid profiles may be useful as a screening mechanism when obtaining fasting specimens is problematic, such as for children who live a great distance from the clinical setting or in infants or young children. If non-fasting TG or total or LDL cholesterol are elevated, then fasting levels should be determined on a schedule similar to that outlined above for adolescents and adults. Many laboratories now offer direct LDL-c measurements that permit assessment in non-fasting samples. This is another option in cases where fasting samples are difficult to obtain.

Management

The policy statement by the American Academy of Pediatrics emphasizes dietary changes and exercise as the cornerstones in the management of dyslipidemia in children without HIV infection *[17]*. As in adults with HIV-infection, these lifestyle changes may be difficult to achieve in some pediatric patients with HIV *[23]*. An adequate trial period of 6 to 12 months should be given to these management strategies, except in those patients at high risk for pancreatitis (patients with TG greater than or equal to 500 mg/dL), in whom prompt intervention may be required *[24-26]*. If these efforts fail to produce the desired response, drug therapy for dyslipidemia should be considered. Persistence after an adequate trial of lifestyle changes of total cholesterol > 200 mg/dL or LDL cholesterol > 130 mg/dL, especially with a positive family history of premature CVD or 2 or more positive risk factors (including smoking), merits drug therapy, although present experience is limited to children over 10 years of age *[17]*.

There are few prospective studies of lipid-lowering therapy in adults with HIV infection and no published studies in pediatric patients with HIV infection *[7, 23, 27-30]*. Recently, the Adult ACTG Cardiovascular Disease Focus Group developed preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving ARV agents *[21]*. The available classes of drugs used to treat hyperlipidemias include the HMG-CoA reductase inhibitors (statins), fibrates, niacin, and bile acid sequestering agents (**Table 3**). Recently approved, ezetimibe (Zetia) is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related phytosterols. There is limited pediatric information, but ezetimibe appears to be safe and effective when combined with dietary interventions and statins in children over the age of ten without HIV infection. The bile acid sequestrants such as cholestyramine and colestipol have been widely studied in children, but are not recommended in HIV-infected patients because they are poorly tolerated and have the potential for significant interference with the absorption of ARV agents and vitamins *[21]*. Niacin is associated with many side effects, such as cutaneous flushing, pruritis, and hepatotoxicity. In addition, niacin causes insulin resistance and should be used with caution in patients taking PIs *[21]*.

The most widely prescribed lipid-lowering agents for adults with HIV infection are the statins. The effectiveness of the statins in decreasing cholesterol and TG has ranged from 25 to 60% and 10 to 15%, respectively *[7, 28-31]*. There are multiple drug interactions involving the statins and the PIs and NNRTIs. Lovastatin and simvastatin should not be used because the PIs significantly increase serum concentrations of these agents by inhibiting CYP3A4 isoenzyme activity, thereby increasing the likelihood of toxicity *[21, 32, 33]*. Pravastatin appears to be the least affected by CYP3A inhibition, and is the preferred agent when combined with the PIs *[32]*. Atorvastatin metabolism is moderately inhibited; it should be used with caution at reduced doses. The risks associated with elevated statin concentrations are significant and include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. NVP and EFV are CYP3A inducers and may decrease statin concentrations significantly *[21, 34]*.

There are currently two statins that can be recommended for use in pediatric patients taking ARV agents: pravastatin (preferred) and atorvastatin (alternative) *[35-42]*. Approved pravastatin dosing in children is 20 mg/day for children ages 8 to 13 years and 40 mg/day for adolescents 14 to 18 years of age (manufacturer prescribing information). Atorvastatin has been studied in children over the age of 10, in whom doses of 10 to 20 mg/day have been used safely. The manufacturer's prescribing information was obtained in pediatric patients with FH, who generally had modest improvements in lipid parameters *[37, 41]*. Therapy with pravastatin and atorvastatin should be initiated at the lowest possible dose and titrated to response every 4 weeks or at longer intervals as needed to reduce cholesterol levels to the acceptable range. Treatment goals are for LDL-c levels < 130 mg/dL and TG levels < 150 mg/dL. Liver function tests and creatine kinase levels should be monitored prior to institution of statin therapy, every 12 weeks during therapy, and whenever dosages are increased. Long-term safety and efficacy of the statins in children has not been established. The statins are teratogenic and should not be used in female patients who may become pregnant.

The fibrates, which include gemfibrozil and fenofibrate, are alternative agents useful in patients with elevated TG levels. These agents lower TG levels by 30 to 55%, but have only a modest effect on HDL-c and mild effects on LDL-c *[7, 18, 31]*. In patients with severe refractory hyperlipidemia, a combination of statins with fibrates may be required. However, this combination is associated with an increased risk of myopathy and rhabdomyolysis, and should be avoided if possible *[21, 23, 31]*. Gemfibrozil is not approved for use in children, and very limited dosing information is available. Published data, limited to 2 case reports and one small study of children with nephrotic syndrome, suggest that improvements in lipid profiles can be safely achieved in children with gemfibrozil at doses ranging from 150 to 300 mg twice a day *[43-45]*. There have been no studies of potential drug interactions between these agents and ARV therapies.

When virologically appropriate, another approach in the management of dyslipidemia associated with HIV infection is to switch ARV therapies from those containing PIs to those with the NNRTIs EFV or NVP. This strategy has been studied in a number of adult patients with varying success *[19, 22, 46, 47]*. The overall trend in these studies has been no change or modest increases in HDL-c and no change or modest decreases in TG *[47]*. Recently, the results of the first pediatric switch study were reported; 17 children in the study well-maintained on a PI-containing regimen were changed to an EFV-containing regimen *[48]*. The authors were able to show significant improvements in fasting cholesterol, LDL cholesterol, TG, and cholesterol/HDL ratio *[48]*. However, in this small study, mean baseline levels for cholesterol were only 203 mg/dL (+/- 50), mean LDL-c 124 mg/dL (+/- 42), and only 2 children had triglyceride levels slightly above 200 mg/dL *[48]*. Whether similar improvements would be seen in pediatric patients with significantly elevated lipid parameters is not known at this time. Another strategy would be to switch to the new PI atazanavir, which has been shown to reverse lipodystrophy in some adult patients *[49]*. Limitations to this approach are that the drug is not approved for children, and no dosing information is available for this age group.

Recommendations

Children on combination ARV therapy should have serum lipids monitored at baseline, before a new agent is introduced, and at least every 6 months. Dietary changes and exercise should be the first strategies initiated in children with ARV-related hyperlipidemias. For those patients unresponsive to adequate trials (6 to 12 months) of dietary changes and exercise or for patients at high risk for pancreatitis, other management strategies may be necessary, including changes in ARV regimens or the use of lipid-lowering agents. Changes in ARV therapy regimens have been studied primarily in adults but have had varying success rates and may not be appropriate for patients who are well maintained on their current regimens. However, in a child with hyperlipidemia unresponsive to dietary measures, a change in ARV therapy to a regimen less likely to cause hyperlipidemia may be considered, taking into account the potency of the regimen and the possibility of drug resistance. Alternatively, the use of statin agents such as pravastatin can be initiated in an attempt to decrease elevated LDL-c to the target goal of < 130 mg/dL or TG of < 150 mg/dL. In patients who have failed conservative approaches, the risks of new treatment-related toxicities and virologic relapse that could occur with changes in therapy must be weighed against the potential risks of drug interactions and toxicities associated with the use of lipid-lowering agents *[22]*.

Table 3. Classes of Drugs Used to Treat Hyperlipidemias

Drug Class	Effects	Agents	Pharmacologic Considerations	Side Effects
Statins	LDL ↓ HDL↑ TG ↓,↑	Pravastatin (Pravachol) Fluvastatin (Lescol) Atorvastatin (Lipitor) Lovastatin (Mevacor, Altocor, generic) Simvastatin (Zocor) Rosuvastatin (Crestor)	Preferred agent–less drug interaction Alternative–use with caution Alternative–use with caution Not recommended–AUC increased with PI Not recommended–AUC increased with PI Not recommended–insufficient data	Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis
Bile acid sequestrants	LDL ↓ HDL↑ TG same,↓	Cholestyramine (Questran, generic) * Colestipol (Colestid) Colesevelam (WelChol)	Potential interference with absorption of antiretroviral medications for this class of agents	Unpalatable gastrointestinal side effects such as bloating and constipation
Nicotinic acid	LDL ↓ HDL↑ TG ↓	Nicotinic acid (niacin, generic) Extended/sustained release nicotinic acid preparations (Niaspan, Slo-Niacin)	Causes insulin resistance and may pose additional problems if PIs are used	Cutaneous flushing and pruritus (less with extended-release preparations); hepatotoxicity
Fibrates	LDL ↓ HDL↑ TG ↓	Gemfibrozil (Lopid, generic) Fenofibrate (Tricor) Clofibrate (Atromid-S, generic)	Combination of fibrates with statins may result in myopathy and rhabdomyolysis; should be avoided if possible	Serious toxicities include bone marrow suppression and myositis
Cholesterol absorption inhibitor	LDL↓ HDL same TG↓	Ezetimibe (Zetia)	Additional benefit to patients on statins with primary hypercholesterolemia (not studied with PIs)	Well tolerated
Stanol ester margarines	LDL↓	Benecol*	Dietary adjunct	Well tolerated
Psyllium	LDL↓	Metamucil*	Dietary adjunct	Well tolerated

* FDA approved for use in children

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HYPERGLYCEMIA AND INSULIN RESISTANCE

Background

Insulin resistance without fasting hyperglycemia, asymptomatic fasting hyperglycemia, new onset diabetes mellitus, and exacerbations of pre-existing diabetes have all been reported in patients treated with ARV therapy *[1-3]*, especially *[4]* but not exclusively *[5]* with PI-containing regimens. Incidence estimates of 3 to 17% are suggested for hyperglycemia in adults, with median onset approximately 60 days following initiation of ARV therapy. Insulin resistance is associated with increased free fatty acids *[6]* and is a common accompaniment of the lipodystrophy/fat maldistribution syndromes, which may occur in up

to 33% of children treated with PIs *[7]* or stavudine (d4T) *[5]*. New onset clinical diabetes occurs only rarely in children or adolescents treated with PIs *[8]*. While insulin and glucose abnormalities may resolve with change from PI therapy, the abnormalities may persist in some patients.

It is unknown if subclinical insulin resistance may be associated with growth delay in patients on therapy for HIV infection, but even in the absence of therapy, some HIV-infected children with growth delay were shown to have *in vitro* resistance to insulin-like growth factor-1, growth hormone, and insulin *[9]*. In general, oral glucose tolerance tests may identify insulin resistance in the absence of fasting hyperglycemia, and insulin resistance without fasting hyperglycemia has been found to cause growth delay in children with cystic fibrosis *[10]*.

Most patients with insulin resistance, with or without fasting hyperglycemia associated with ARV therapy, will remain overtly asymptomatic. In adults, insulin resistance may lead to early atherosclerosis. It is unclear if ARV-associated insulin resistance has the same effect in children, as this has not been studied in children or adolescents.

Recommendations for Monitoring

When starting PIs, guardians and patients should be educated about symptoms of overt diabetes mellitus (polyuria, polyphagia, polydipsia, weight loss). Patients with signs of overt diabetes mellitus or ketoacidosis should certainly be evaluated with appropriate testing, including fasting blood sugar and, possibly, oral glucose tolerance tests.

For patients with fat maldistribution syndromes or with risk factors for type 2 diabetes mellitus, fasting blood glucose measurements may identify fasting hyperglycemia (fasting blood glucose > 110/dL). In addition, oral glucose tolerance tests may identify insulin resistance in the absence of fasting hyperglycemia.

Routine fasting or random blood glucose or hemoglobin A_{1c} measurements are not routinely indicated in asymptomatic patients without other risk factors for type 2 diabetes mellitus. For adults, the International AIDS Society-USA recommends a fasting blood glucose measurement before starting treatment with PIs, at 3 to 6 months after institution of therapy, and yearly while on therapy *[11]*. Fasting blood glucose measurements may be difficult to arrange in the outpatient setting and will not identify insulin resistance without fasting hyperglycemia, and routine measurement of fasting glucose in asymptomatic children being treated with PIs is of unproven benefit. Therefore, routine fasting blood glucose measurements are not recommended for children.

For ease of ordering or because laboratory "panels" are less expensive, blood glucose measurements are sometimes sent with a panel of laboratory tests, even in the absence of signs or symptoms of diabetes. Such testing may result in identification of elevated random glucose concentration in some patients. Random glucose measurements repeatedly greater than 140 mg/dL should be followed by measurement of fasting glucose. If the fasting glucose value is repeatedly greater than 110 mg/dL, further testing might be needed, as noted above.

Treatment

For patients with symptomatic diabetes mellitus, studies are currently assessing the benefit of switching a PI component of a multi-drug regimen to another ARV agent, such as nevirapine, efavirenz, or abacavir. Definitive data are not yet available. Treatment with oral insulin-sensitizing agents or insulin is instituted as required.

For patients with glucose abnormalities associated with lipodystrophy, an exercise program combined with a moderate-fat, low-glycemic-index, high-fiber diet is indicated; this can reverse several aspects of lipodystrophy, including mild to moderate insulin resistance *[12]*. Change from PI therapy might also be indicated in this setting.

For patients with insulin resistance without fasting hyperglycemia, or for those with asymptomatic fasting hyperglycemia, no recommendation can be made as to whether or not ARV regimens should be changed. Other factors, including virologic and immunologic response to therapy and remaining treatment alternatives, must be taken into consideration when evaluating the possibility of a change in therapy. Substitution of the PI component of a multi-drug regimen is of unproven benefit in this circumstance.

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OSTEOPENIA, OSTEOPOROSIS, AND OSTEONECROSIS

Background

Decreased bone mineral density (BMD) is now recognized as one of the emerging metabolic complications of HIV infection in adults and children *[1, 2]*. Osteoporosis is characterized by severe loss of bone mass and disruption of skeletal microarchitecture, which can lead to increased risk of spontaneous atraumatic and traumatic fractures of the bone *[3]*. Osteopenia refers to a thinning of the bone that can precede osteoporosis. The temporal linkage of increased recognition of these conditions in HIV-infected individuals with increased use of HAART has suggested a potential relationship to antiretroviral therapy. In a cross-sectional study, a 2-fold increase in the incidence of osteopenia and osteoporosis was observed in HIV-infected adults receiving combination therapy including PIs compared to HIV-infected adults not receiving PIs *[4]*. Evidence for a decrease in bone formation and an increase in serum markers of bone resorption has been demonstrated in HIV-infected adults receiving potent antiretroviral therapy, particularly PIs *[5, 6]*.

A postulated mechanism for decreased BMD due to PI therapy is inhibition of the hepatic CYP450 enzyme that mediates vitamin D metabolism to its most potent circulating metabolite, part of an essential process for vitamin D control of calcium homeostasis *[3, 7]*. However, BMD changes have also been observed in HIV-infected adults receiving antiretroviral regimens without PIs, such as tenofovir (TDF) or stavudine (d4T) in combination with lamivudine and efavirenz; the changes in BMD were associated with increased lactate levels, suggesting possible NRTI-associated mitochondrial toxicity *[8]*. Osteoporosis has been linked to mitochondrial deletions in young men without HIV infection, some of whom had asymptomatic hyperlactatemia but few other clinical features of mitochondrial disease *[3, 9, 10]*.

Data on BMD in HIV-infected children are limited. In a study of bone metabolism markers in 35 HIV-infected children receiving HAART, 5 HIV-infected antiretroviral-naïve children, and 314 HIV-uninfected control children, HAART-treated children were found to have lower spine BMD values than HIV-infected children on no therapy or uninfected children, whereas spine and total body BMD were similar in HIV-infected untreated and

uninfected children *[11]*. Additionally, total body BMD was lower in HAART-treated children who had lipodystrophy than in those without lipodystrophy. Serum markers of bone formation and resorption were also higher in HIV-infected children receiving HAART, indicating increased rates of bone turnover.

However, a higher than expected prevalence of reduced BMD has also been described among HIV-infected children and adults not receiving antiretroviral drugs, suggesting that HIV infection itself may also be a contributing factor, possibly through immune activation and cytokine production, direct infection of osteogenic cells, or HIV-related changes in endocrinologic function *[1, 3, 6, 12-14]*. For example, a number of cytokines are known to regulate bone resorption or formation, including platelet-derived growth factor, interleukin-1 and -6, and tumor necrosis factor *[15]*. Some of these cytokines are also increased in HIV-infected individuals; for example, tumor necrosis factor and interleukin-6 are increased with HIV infection, and are known to induce differentiation of bone marrow precursors into osteoclasts, which would favor bone resorption *[3, 16]*. It is likely that the changes in BMD observed in HIV-infected individuals may be multifactorial, with changes potentially induced by HIV infection itself exacerbated by treatment with certain antiretroviral agents.

Other bone-related complications have been reported in HIV-infected adults, including osteonecrosis and rare reports of compression fractures of the lumbar spine *[3, 16, 17]*. Avascular necrosis of the bone (osteonecrosis) refers to ischemic death of the cellular constituents of bone, generally at the epiphyseal or subarticular bone region; while it most commonly occurs at the femoral head of the hip, it can involve other areas, including the humeral head, femoral condyles, and the scaphoid and lunate bones of the wrist *[1]*. Avascular necrosis of the hip was first reported in an HIV-infected adult in 1990, before the advent of potent antiretroviral therapy *[18]*, although more recent reports have suggested that incidence may be increasing in adults *[1]*. Avascular necrosis of the hip (Legg-Calve-Perthes disease) was reported in a small series of HIV-infected children in 2001 *[19]*. It does not appear that avascular necrosis is associated with a specific antiretroviral regimen, but it has been linked to corticosteroid use in some patients *[1]*. Other factors associated with osteonecrosis in HIV-infected adults include alcohol abuse, hemoglobinopathies, hyperlipidemia, and hypercoagulability states *[17]*. The occurrence of hyperlipidemia with osteonecrosis suggests at least an indirect link between antiretroviral therapy and the occurrence of decreased bone density in HIV-infected patients; however, prospective clinical studies will be required to establish this association.

Because childhood and adolescence are critical periods of bone development and growth, inhibition of bone mineral accrual has potentially serious consequences for the growing child *[13]*. It is unknown whether children are more sensitive to potential bone effects of HIV infection or more sensitive to drugs that might produce adverse effects on bone metabolism. TDF, a nucleotide analogue, causes decreased BMD in animals, particularly when used in high doses for prolonged periods in juvenile macaques. A phase I study of TDF in treatment-experienced HIV-infected children with advanced disease conducted at the National Cancer Institute included serial DEXA scans, which indicated that over half of the children had abnormal BMD prior to receiving TDF. After 48 weeks of TDF therapy, a decrease in BMD of > 6% from baseline was seen in 5 of 19 (26%) children, higher than has been reported in similar studies in adults *[20]*.

Clinical Features/Assessment and Monitoring

Bone strength is measured by means of bone quantity and quality. Bone quantity is measured by BMD, which is a common surrogate marker for bone strength *[16]*. BMD can be measured by DEXA or by newer measurements such as quantitative ultrasound. There is no recommendation at the present time for routine measurement of serum or urine bone markers or bone density assessment in asymptomatic HIV-infected children or adults. Measurements of bone density included as part of clinical trials of new antiretroviral agents may generate data that will be useful in developing recommendations for monitoring bone density in the clinical setting. Children who develop severe decreases in BMD may present with atraumatic fractures or back pain, similar to what is observed with osteoporosis in adults.

Children with osteonecrosis often come to the attention of the clinician due to persistent limp or hip pain with Legg-Calve-Perthes disease or periarticular pain in other affected areas, such as the shoulder. Physical exam may reveal periarticular

tenderness or decreased range of motion of the affected joint. Plain radiographs and magnetic resonance imaging (MRI) are the most useful modalities for diagnosis of osteonecrosis and for identifying the stage and extent of the pathologic process *[17]*. Radionuclide bone scan and computed tomography may be considered if the earlier tests are negative but the clinical suspicion of disease is high *[17]*. It should be noted that asymptomatic disease with abnormal MRI findings was identified in 4% of a cohort of HIV-infected adult patients, although the prevalence of asymptomatic disease in the general population has not been investigated *[17, 21]*.

Management/Treatment

Specific prophylaxis or treatment recommendations to prevent more significant osteoporosis have not been developed for HIV-infected patients with osteopenia, but HIV-infected children with pre-existing hyperlipidemia or wasting syndrome or those requiring treatment with corticosteroids may be at enhanced risk for developing decrease in BMD *[19]*. Based on experience in the treatment of primary osteoporosis, it would be reasonable to suggest adequate intake of calcium and vitamin D and appropriate weight-bearing exercise, and for HIV-infected adolescents, avoidance of alcohol and smoking. At least one study in HIV-infected adults reported no beneficial effect on BMD of withdrawal of PI therapy *[3, 22]*.

Consultation with a pediatric endocrinologist might be considered for those children who have significant or clinically evident decreases in BMD (e.g., atraumatic fractures). When fractures occur or osteoporosis is documented, more specific and aggressive therapies with investigational drugs such as bisphosphonates might be considered; however, studies of these drugs have only been done in HIV-infected adults *[23]*. Bisphosphonates (clodronate disodium, pamidronate, zoledronic acid), given intravenously or as subcutaneous infusions, have been used in clinical trials of children with non-HIV chronic illnesses that are associated with osteonecrosis and severe bone pain *[24-27]*. These studies of bisphosphonates have demonstrated no significant short-term toxicity and were successful in decreasing bone pain, enhancing new bone formation, decreasing pathological fracture, and increasing patient mobility.

The early stages of osteonecrosis may be managed conservatively (e.g., decreased weight bearing on the affected joint and use of analgesic as needed) *[17]*. However, as in patients without HIV infection who have avascular necrosis, some patients who do not initially require surgical intervention may later develop significant arthritis and require surgery *[28, 29]*. Children who present with more advanced stages of disease, with radiologic findings such as subchondral collapse or femoral head destruction, require surgical intervention, which can include core decompression, bone grafting, vascularized fibular grafting, intertrochanteric osteotomies, or total joint replacement *[3, 17, 19]*.

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HEMATOLOGIC COMPLICATIONS

Background

Hematologic complications occur frequently in children with HIV infection and may be due to a variety of causes that must be differentiated to facilitate effective management. Children with advanced or untreated HIV infection may develop bone marrow suppression or autoimmune phenomena, resulting in anemia, neutropenia, and/or thrombocytopenia. AIDS-related conditions, such as disseminated Mycobacterium avium complex, cytomegalovirus, or lymphoma, may contribute to hematologic abnormalities. Finally, adverse reactions to drugs, both ARV agents and supportive medications, may also lead to cytopenia of any or all hematologic cell lines. Because combination ARV therapy has become the standard treatment recommendation, it has become increasingly difficult to identify the contribution of newer drugs to hematologic adverse reactions. Hematologic complications resulting from these non-ARV–associated conditions obviously require different therapeutic strategies, and initial efforts should be made to identify the causative factors.

Anemia is one of the most common problems that develop in HIV-infected children receiving ARV therapy. As noted above, anemia may be ascribed to HIV infection itself, HIV-related conditions, or to ARV or other drug therapy. Anemia as a

consequence of drug therapy is seen most commonly with ZDV treatment, but may occur with other agents as well. In PACTG 152, 9.4% of children receiving ZDV developed anemia (hemoglobin < 7.5 g/dL), compared with 3.9% and 4.8% of children receiving ddI and ddI combined with ZDV, respectively *[1]*. More recent clinical trials of combination ARV therapy have identified less anemia in study patients receiving ZDV, possibly due to the use of lower doses of ZDV or more effective treatment of the underlying HIV infection *[2]*. Not surprisingly, anemia was also the most significant adverse event noted in PACTG 076 during the use of ZDV in neonates in the setting of prevention of mother-to-child transmission *[3]*.

As with anemia, the problem of neutropenia in HIV-infected children receiving ARV therapy is common, and identifying causality may be difficult. In the experience of many pediatric HIV experts, the definition of clinically significant severe neutropenia in the HIV-infected child differs markedly from the criteria that apply to an otherwise healthy child or to a child with a hematologic malignancy. HIV-infected infants and children appear to tolerate lower absolute neutrophil counts with infrequent, but not absent, complications. Few children with HIV suffer infectious complications of neutropenia unless it is quite severe (absolute neutrophil count < 250 cells/mm^3) and prolonged. Neutropenia has been frequently observed as a complication of ARV therapy, and is most often attributed to the use of ZDV; however, the contribution of other agents is difficult to determine. In PACTG 152, neutropenia was observed in 9.9% and 26.8% of children in the ddI and ZDV therapy arms, respectively *[1]*. In PACTG 300, a comparative trial of ddI, ZDV/ddI, and ZDV/3TC, the most common toxicity was neutropenia, occurring in 6.1% of patients *[4]*. Though study patients received a variety of regimens, PACTG 382, a study evaluating the combination of EFV, NFV, and NRTIs, identified neutropenia in 12% of participating children *[2]*. Similarly, in PACTG 377, a study enrolling NRTI-experienced children to receive one of 4 regimens without ZDV (combinations of d4T, 3TC, NVP, and NFV), neutropenia was reported in 9 to 23% of patients in each treatment arm *[5]*. In other cases, neutropenia may be attributable to bone marrow suppression secondary to non-ARV drug toxicity, as can be seen with trimethoprim-sulfamethoxazole, ganciclovir, rifabutin, or hydroxyurea. Children with advanced HIV infection may require multiple drugs with potential for bone marrow suppression.

Thrombocytopenia (platelet count < 100,000 cells/mm^3), like anemia and neutropenia, is relatively common in children with HIV infection *[6]*. Although thrombocytopenia may occur in conjunction with ARV therapy, it also occurred in up to 30% of untreated children with HIV infection in older surveys of pediatric HIV/AIDS. Severe thrombocytopenia occurred in 2% of children receiving ddI, ZDV/ddI, or ZDV/3TC therapy in PACTG 300, but was present at entry into study in 2.2% of enrollees *[7]*. Children with undiagnosed and untreated HIV infection may present with thrombocytopenia as the first manifestation of disease. This, in fact, appears to be much more common than the development of thrombocytopenia secondary to ARV therapy *[8, 9]*. Thus, thrombocytopenia may resolve once ARV therapy is initiated.

Recommendations for Monitoring

Routine monitoring of complete blood count (CBC) with differential and platelet count is recommended for all HIV-infected children. Children at risk should be evaluated for conditions such as hemoglobinopathies that may contribute to hematologic adverse events. CBC with differential and platelet count should be performed at regular intervals based on the child's level of disease and past medical history. This may be monthly for children with more severe disease or who have recently changed regimens, or every 3 to 4 months for those who are asymptomatic and tolerating therapy well. It may be appropriate to monitor children receiving ZDV more frequently than children receiving non-ZDV–containing regimens.

Children with decreasing hematologic parameters should be evaluated for other pathophysiologic processes that might result in or contribute to anemia, neutropenia, or thrombocytopenia. If opportunistic infection, secondary malignancy, nutritional deficiency, or worsening HIV status is unlikely, the child's drug regimen should be reviewed for ARV and non-ARV drugs with potential for bone marrow suppression.

Management

Management of anemia or neutropenia attributable to ARV drugs such as ZDV or non-ARV drugs such as trimethoprim-sulfamethoxazole or rifabutin

depends to a large extent on the therapeutic options available to the individual child. As more drugs become available in pediatric formulations, it may be most reasonable to switch the presumed culprit drug for another drug of the same class in children who have several options for treatment. In those children who have limited therapeutic options because of either known HIV resistance or previous intolerance, a simple switch may not be possible. Similarly, a health practitioner caring for a child who has achieved an excellent response with one ARV regimen may not want to risk loss of that antiviral effect by changing to another regimen. In such cases, management of the bone marrow suppression may require other medical intervention.

The hemoglobin level at which intervention should occur is not entirely clear. Hemoglobin < 7.0 or 8.0 g/dL is generally considered significantly low enough to warrant evaluation and treatment, but symptoms of anemia may be minimal even at this level. Children with anemia attributable to ARV agents seldom require cessation of therapy and often respond to erythropoietin *[9]*. A dose of 50 to 200 IU/kg/dose given 3 times weekly is usually adequate. For children in whom thrice-weekly erythropoietin injections are unacceptable or ineffective, regular transfusions may be both beneficial and cost-effective *[10]*. Given the current options in ARV therapy, it is unlikely that children with drug-associated anemia will have to resort to transfusions except in the setting of severe, acute anemia. Attention to adequate nutrition and iron supplementation, if appropriate, may also be of value.

Generally, mild to moderate neutropenia (absolute neutrophil count > 250 cells/mm^3 in children older than 3 months) in the absence of associated signs or symptoms that warrant concern, such as persistent fever or focal or generalized infection, is not an indication for immediate reduction or cessation of therapy. In some children, neutropenia represents a manifestation of their HIV disease and may improve with enhanced suppression of HIV replication resulting from a change in ARV regimen. If a patient is clinically stable but significant absolute neutropenia persists (absolute neutrophil count < 250 cells/mm^3), altering the ARV regimen or instituting therapy with granulocyte colony stimulating factor (G-CSF) should be considered. If neutropenia does not improve within 1 week of instituting G-CSF, the dose can be increased. The response to G-CSF is highly variable, but most patients achieve an adequate neutrophil count at doses of 5 to 10 μg/kg given once daily, although doses as high as 20 μg/kg have been used *[11]*.

When thrombocytopenia is severe (< 20,000 cells/mm^3) or clinically significant bleeding occurs, treatment with intravenous immunoglobulin (IVIG) is indicated (1 g/kg/day for 2 to 3 consecutive days). An alternative treatment utilizes an intravenous preparation of anti-D antibody (WinRho SDF), 50 μg/kg administered every 4 to 6 weeks. Anti-D therapy requires a smaller infusion volume, can be administered more rapidly, and may improve platelet counts in patients who have failed to respond to IVIG *[12, 13]*. Anti-D therapy should not be administered to children who are Rh(D) negative. If immunotherapy fails, a course of corticosteroids may be beneficial or, as a last resort, splenectomy may be considered in some children.

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HYPERSENSITIVITY REACTIONS AND SKIN RASHES

Background

Skin rashes and hypersensitivity reactions are a potential concern following administration of any medication. While skin rash may accompany a hypersensitivity reaction, hypersensitivity reactions may also occur in the absence of a rash.

Clinical Manifestations

In general, most cutaneous adverse events following the use of antiretroviral agents are mild or moderate, occur within the first few weeks of therapy, and resolve spontaneously following drug discontinuation. Rashes are usually maculopapular eruptions or urticarial. Notable exceptions include the more severe and potentially life-threatening drug rash syndromes, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, rash associated with abacavir (ABC)-associated systemic hypersensitivity reaction, and the drug rash with eosinophilia and systemic symptoms (DRESS) reported with NNRTIs (see **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**) *[1, 2]*. In some children, medications may be continued or reintroduced safely despite the presence or history of a rash, as spontaneous resolution of the rash may occur despite continued use. However, discontinuation is appropriate and rechallenge is contraindicated when the medication causes one of the severe/life-threatening manifestations, follows the administration of ABC, or if the rash is accompanied by systemic symptoms.

As with HIV-1 infected adults, experience in HIV-1 infected children reveals the NNRTIs to have the highest prevalence of cutaneous adverse events. Rash develops in approximately 17% of nevirapine (NVP) recipients; 6 to 8% are severe (Grade 3: vesiculation or ulcers; Grade 4: exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, or moist desquamation) and require treatment discontinuation *[3]*. Rash usually occurs during the first 2 to 4 weeks of treatment, rarely occurs after 8 weeks of therapy. The rash is usually maculopapular, confluent, and erythematous. It most commonly involves the arms and trunk. More severe cutaneous involvement can take the form of life-threatening Stevens-Johnson syndrome/toxic epidermal necrolysis, reported in approximately 0.3% of infected children receiving NVP.

Management of Cutaneous Eruptions and Hypersensitivity Syndrome

Continuing NVP in the presence of mild or moderate rash during the lead-in phase may result in spontaneous resolution of the rash. However, since progression of the rash may occur with continued administration of NVP, patients with rash require close monitoring. NVP should be permanently discontinued in children who develop severe rash (Grade 3 or 4), cutaneous bullae or target lesions, mucosal lesions, or systemic symptoms consistent with hypersensitivity. Rechallenge with NVP in children with more severe NVP adverse effects may result in more rapid onset of rash, and there is a

potential that the rash or other manifestations may be more severe and even fatal. There is no evidence that corticosteroids given during the lead-in phase can prevent NVP-associated rashes. If NVP is discontinued because of mild or moderate rash, restarting NVP after the rash has resolved may be considered with close monitoring.

Cross-reactivity among NNRTIs may occur. However, in children with mild or moderate rash without mucosal involvement or systemic symptoms, substitution of an NNRTI other than NVP, such as efavirenz (EFV), may be done with caution. It would be prudent to avoid current NNRTIs in children who develop the more severe adverse effects following receipt of NVP. Cutaneous reactions may occur in patients receiving EFV. In general, these reactions are less severe than those with NVP, and resolution of the rash during treatment continuation is common. However, if EFV-associated rash is severe, or is accompanied by mucosal or systemic symptoms, EFV should be permanently discontinued.

Rash has also occurred in children receiving antiretroviral regimens containing NRTIs alone, with or without ABC *[4]*, or in combinations with PIs *[5-8]*. Amprenavir and fosamprenavir are sulfonamides and have the potential for cross-reactivity with other sulfa drugs; they should be used with caution in patients with a prior history of sulfa hypersensitivity.

Enfuvirtide (T-20), an HIV-1 fusion inhibitor, is administered by subcutaneous injection. Injection site reactions occur in nearly all patients who receive T-20 (98% in published clinical trials) *[9, 10]*. The injection site reactions include induration, erythema, and subcutaneous nodules or cysts. Most reactions are reported as mild or moderate in intensity. In adult patients, the injection site reactions have resulted in treatment discontinuation in < 3% of patients receiving T-20. Histopathologically, the lesions are interstitial granulomatous drug reactions *[11]*. The lesion usually resolves in < 7 days.

Rotating injection sites, avoiding existing injection site reactions, and following manufacturer's instructions for injection may reduce the severity of injection site reactions with enfuvirtide. Injections into the arm appear to be associated with fewer or less severe injection site reactions than those following injection into the abdomen or thigh. Analgesics may be needed when injection sites are painful.

Hypersensitivity Syndrome

While rash is common with many hypersensitivity reactions, hypersensitivity to antiretroviral medications can result in numerous other symptoms, with or without rash. The hypersensitivity reactions of most concern with antiretroviral drugs include those associated with ABC and NVP. ABC causes a potentially fatal systemic illness characterized by fever, rash, nausea, vomiting, diarrhea, fatigue, flank or abdominal pain, myalgia, and arthralgia *[12]*. The skin rash, which is often maculopapular or urticarial, is often clinically unimpressive, and only occurs in about 70% of cases. Respiratory symptoms, such as pharyngitis, cough, or dyspnea, may also be noted. Less common symptoms include adenopathy, mucositis, myocarditis, hepatitis, and nephritis. The combination of acute onset of both respiratory and gastrointestinal symptoms shortly after initiating ABC therapy is more typical of the hypersensitivity reaction than a concurrent infectious illness such as influenza or rotavirus, which more typically involve symptoms in only one organ system. Laboratory abnormalities may include atypical lymphocytosis, eosinophilia, thrombocytopenia, and elevated creatine phosphokinase, creatinine, and liver function tests.

Hypersensitivity reactions to ABC occur in 0 to 14% (average 3.7%) of patients *[12]*. ABC hypersensitivity occurs more frequently in treatment-naïve patients, Hispanic or African-American patients, and patients with specific genetic markers (HLA-B*5701, HLA-DR7, and HLA-DQ3) *[12, 13]*. Hypersensitivity reactions to ABC occur most commonly early in therapy, usually in the first 6 weeks of exposure to ABC. The median time to develop the reaction following initiation of therapy is 8 days (range 1 to 160 days). Rash is typically the presenting complaint and is usually mild initially. Other findings suggestive of ABC hypersensitivity include:

1. involvement of multiple organ systems, resulting in a constellation of symptoms;
2. acute onset with worsening of symptoms after each dose of ABC; and
3. occurrence of symptoms in the first few weeks after initiating ABC *[12]*.

If ABC is continued, the symptoms increase and worsen. Discontinuation of ABC will usually result in improvement in a few days, although symptoms may continue to worsen for 1 to 2 days after ABC is discontinued. ABC should never be restarted

following a hypersensitivity reaction, as anaphylactic-like reactions (some fatal) with hypotension, renal failure, and/or bronchoconstriction and respiratory insufficiency have occurred within hours of rechallenge *[14]*. Treatment is supportive. Antipruritics and corticosteroids do not appear to help.

A hypersensitivity syndrome has also been reported with NVP. Systemic symptoms such as fever, myalgia, arthralgia, hepatitis, and eosinophilia may be noted as part of the NVP hypersensitivity reaction. These symptoms may precede or occur without a skin rash. The hypersensitivity reaction is most commonly noted early in therapy; it is unusual after 8 weeks of treatment. Permanent discontinuation of NVP should be considered for any patient with or without rash, and use of currently available NNRTIs should be avoided. Reactions may worsen temporarily after drug discontinuation. Treatment is supportive. Use of corticosteroids does not prevent NVP hypersensitivity *[14]*.

Unexplained hypersensitivity reactions have been reported in clinical trials with T-20 *[9, 10]*. This syndrome may include fever, rash, and shortness of breath. T-20 should be discontinued if the hypersensitivity reaction occurs. Rechallenge is contraindicated as the syndrome has recurred with rechallenge.

Conclusions

In addition to antiretroviral medications, HIV-1 infected children receive many other medications with a potential for hypersensitivity reactions and/or rash. Trimethoprim-sulfamethoxazole, beta-lactam antibiotics, and anti-tuberculosis therapy may be responsible for rashes in HIV-infected children who are or are not receiving antiretroviral therapy *[15]*. Concomitant medications may confound efforts to identify the offending medication in the HIV-infected child with a drug rash.

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