Adverse Drug Effects

Differentiating between adverse 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, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L) is relatively frequent among HIV-infected adults receiving nucleoside analogue reverse transcriptase inhibitors (NRTIs); it occurs in approximately 15%–35% of adults receiving ARV therapy longer than 6 months *[1-3]*. There are few data in pediatric patients. In a longitudinal study conducted in Spain of 80 HIV-infected children, 9 months to 17 years of age, receiving ARV therapy, 29% had asymptomatic mild hyperlactatemia *[4]*. The incidence was 8.7 per 100 patient-years. Younger age at start of ARV therapy was significantly associated with the development of hyperlactatemia. Similarly, in a study conducted in Great Britain of 146 children, those <3 years of age on combination ARV therapy had higher lactate concentrations than those ≥3 years of age on combination ARV therapy and higher than children not on combination ARV therapy, in any age group *[5]*. In the U.S., asymptomatic hyperlactatemia was observed in 32% of 127 HIV-infected children receiving combination ARV therapy *[6]*.

Symptomatic severe hyperlactatemia (>5.0 mmol/L) is less common (reported in 0.2%–2.5% of HIV-infected adults), and the syndrome of lactic acidosis/hepatic steatosis is rare *[7, 8]*. In a cohort of adults receiving NRTI therapy in the United States between 1989 and 1994, the incidence of the lactic acidosis/hepatic steatosis syndrome was 0.13%; in a cohort of 964 infected adults from France followed during 1997–1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a stavudine (d4T)-containing regimen *[9, 10]*. In another cohort of 1,566 adults followed for a total of 4,788 person-years during 1999–2003, only 4 (0.3%) developed lactic acidosis and there was an association with regimens containing didanosine (ddI) and d4T in combination as well as those containing efavirenz *[2]*. Life-threatening and fatal cases of lactic acidosis have also been reported in HIV-infected children *[11-15]*. While symptomatic lactic acidosis is uncommon, it has been associated with a high fatality rate in the range of 33%–57%.

Lactic acidosis/hepatic steatosis is thought to be secondary to mitochondrial dysfunction induced by NRTI treatment *[16, 17]*. 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), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF) have lower affinity for the mitochondrial polymerase *[17-20]*. 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 decreased clearance of lactate occur. Steatosis occurs secondary to inhibition of fatty acid oxidation, leading to excess hepatic fat production and accumulation of microvesicular lipid droplets in the liver.

Risk factors for lactic acidosis/hepatic steatosis described in adults include female gender, high body mass index, chronic hepatitis C infection, African-American ethnicity, prolonged NRTI use (particularly d4T and ddI), coadministration of ddI with other agents, (such as d4T, TDF, tetracycline, or ribavarin), acquired riboflavin or thiamine deficiency, and possibly pregnancy *[21-30]*. However, there is no proven way to predict who will develop lactic acidosis.

Clinical Features

Onset of symptoms associated with lactic acidosis can be acute or subacute. Cases have occurred as early as 1 month and as late as 20 months after starting therapy, with a median onset of 4 months in one case series *[7, 31]*. Initial symptoms 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) *[32]*. Features of hepatic dysfunction may include a tender and enlarged liver, ascites, and encephalopathy; jaundice is unusual, and hepatic enzymes are usually modestly elevated *[31]*. Patients receiving NRTIs who 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, symptomatic lactic acidosis is associated with hepatic steatosis in 69% of cases and pancreatitis in 22% *[1]*. Hepatic steatosis is a common finding on imaging studies or liver biopsy; hepatic necrosis can occur in fulminant cases *[33]*. Laboratory abnormalities with lactic acidosis include hyperlactatemia, low bicarbonate, increased anion gap (>16), systemic acidosis (arterial pH <7.35), and elevated hepatic transaminases, creatine phosphokinase, lactate dehydrogenase, lipase, and amylase. Arterial or venous lactate concentrations are generally >5 mmol/L, and serum bicarbonate is decreased in patients with symptomatic lactic acidosis, indicating widespread cellular energy deficit and metabolic decompensation. Lactate concentrations >10 mmol/L are life-threatening and are associated with mortality of >80% *[34]*. A CT scan may demonstrate an enlarged fatty liver; histologic examination of the liver may reveal microvesicular steatosis.

Recommendations for Assessment and Monitoring

Routine monitoring of serum lactate in asymptomatic patients is not recommended as part of routine clinical practice *[8, 33, 35]*. 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. Mild hyperlactatemia in asymptomatic patients does not predict which patients are at greater risk for development of symptomatic lactic acidosis or hepatic steatosis. In a cross-sectional analysis of 284 patients receiving NRTIs, mild to moderate symptoms of fatigue, abdominal pain, abdominal

bloating, jaundice and vomiting did not correlate with increased lactate *[36]*.

Measurement of serum lactate is recommended only for patients presenting with clinical signs or symptoms consistent with lactic acidosis, e.g., 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 (to assess for pancreatitis); and hepatic transaminases and serum albumin level (to assess for hepatic dysfunction).

Proper blood collection is critical for accurate determination of serum lactate. This may be difficult in children. Vigorous exercise, 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 *[31]*. An elevated lactate level should be confirmed with a repeat measurement.

Serum lactate levels of 2–5 mmol/L are considered elevated and need to be correlated with symptoms. A confirmed lactate concentration of >5 mmol/L in a symptomatic patient or a confirmed lactate >10 mmol/L regardless of clinical symptomatology, establishes the diagnosis of lactic acidosis.

Management/Treatment (Table 1)

Although it is not recommended to measure serum lactate in asymptomatic patients as a routine measurement, if it measured for other indications, and is <2 mmol/L, no alteration in therapy is advised.

For symptomatic patients with normal serum bicarbonate and lactate concentrations <2 mmol/L, no change in therapy is indicated. If lactate concentrations are confirmed to fall between 2.1–5.0 mmol/L, the replacement of ddI and d4T components of ARV therapy by other medications should be considered.

For symptomatic patients with repeated measurements of lactate >5 mmol/L, or for any patient with a confirmed value >10 mmol/L, ARV therapy and any other potentially contributory drugs should be stopped and treatment for lactic acidosis initiated *[37]*. If NRTI therapy is continued in such patients, progressive toxicity may occur, with severe lactic acidosis, respiratory failure, and death.

Therapy of lactic acidosis is primarily supportive, and includes a combination of intravenous fluids as well as sedation and respiratory support as needed, to reduce oxygen demand and ensure adequate oxygenation of tissues *[38, 39]*. Although some reports suggest that alkalinizing the blood with bicarbonate infusions to clear or neutralize the lactic acid might improve prognosis, this remains controversial *[39-41]*. 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 *[42-47]*. 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 *[11]* 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 *[48]*. However, there are no controlled data to show efficacy of any of these agents in the treatment of NRTI-associated lactic acidosis.

In adults with lactic acidosis, lactate concentrations return to normal at a mean of 3 months following discontinuation of ARV therapy *[31]*. However, symptoms associated with lactic acidosis may continue or worsen for a longer period after ARV discontinuation. It is not known whether there are long-term sequelae of NRTI-related lactic acidosis.

Following resolution of symptoms, ARV therapy can be resumed. There are insufficient data to recommend restarting 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, the drugs least likely to inhibit mitochondrial DNA polymerase gamma (preferably ABC or TDF; possibly ZDV, 3TC, or FTC) can be used with caution *[20, 49, 50]*. ddI and d4T should be especially avoided. Patients should be closely monitored; some clinicians

recommend monthly monitoring of lactate for at least 3 months in patients who experienced NRTI-associated lactic acidosis *[31, 33]*. The recurrence rate of symptomatic hyperlactatemia has been estimated to be 45.5 cases per 1000 patient-years of NRTI rechallenge but lower rates may occur for patients rechallenged with two compared to three mitochondria toxicity-sparing NRTIs *[49]*.

Special Case: *In Utero* Antiretroviral Exposure

Background

Blanche and colleagues from France reported 8 cases of HIV-exposed 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 *[51]*. 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 concentrations.

Among 4,392 perinatally HIV-exposed 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, 12 children had evidence of mitochondrial dysfunction (including the 8 cases mentioned above), all of whom had perinatal ARV exposure, representing an 18-month incidence of 0.26% *[52]*. 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 significant 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 *[53]*. A case report from Italy describes a child with perinatal exposure to ZDV who developed neonatal encephalomyopathy, anemia and hyperlactatemia and muscle biopsy showed mitochondrial damage *[54]*.

A retrospective review of several large U.S. cohorts that included over 16,000 perinatally HIV-exposed uninfected children with and without ARV exposure identified no deaths similar to those reported from France or clinical findings attributable to mitochondrial dysfunction *[55]*. Additionally, a review of data from 1,954 living HIV-exposed uninfected children in the prospective Perinatal AIDS Cohort Transmission Study has not identified any child with ARV exposure with symptoms attributable to mitochondrial dysfunction *[56]*. The European Collaborative Study also reviewed clinical symptoms in 2,414 uninfected children (1,008 with perinatal ARV exposure) followed prospectively for a median length of 2.2 years (maximum 16 years) *[57]* and found no association between clinical manifestations suggestive of mitochondrial abnormalities and perinatal ARV exposure. Four children had seizures, but none of them had been exposed to perinatal ARV therapy.

A retrospective review of 1,037 uninfected children born to HIV-infected mothers, enrolled in Pediatric AIDS Clinical Trials Group protocols 219 and 219C, was undertaken to identify children who developed signs of possible mitochondrial dysfunction by 3 years of age. Twenty children (1.9%) had signs suggestive of possible mitochondrial dysfunction but none had mitochondrial histological or enzymological studies or cerebral MRI to make a definitive diagnosis of mitochondrial dysfunction. Three of the children had no exposure to antiretroviral drugs *in utero* or perinatally. As compared to children without abnormalities, cases were significantly more likely to have first been exposed to 3TC or the combination of ZDV and 3TC in the third trimester of pregnancy *[58]*.

A preliminary observational study of 75 HIV-uninfected infants exposed to combination ARV therapy *in utero* and to ZDV for 6 weeks after birth showed that treated infants had greater increase in mitochondrial DNA levels during the first 6 weeks of life compared with control infants born to HIV-uninfected women. The ARV-exposed infants had persistence of the elevation and concurrent decrease in mitochondrial RNA after ZDV discontinuation, which suggested that significant changes in blood mitochondrial proliferation and gene expression take place during and after ARV exposure *[59]*.

Thus, there are conflicting data regarding the association of mitochondrial dysfunction in HIV-exposed but uninfected children with perinatal ARV exposure. If such 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 perinatal HIV transmission by 70% or more *[60-63]*.

Recommendations for Assessment and Monitoring

Routine monitoring of lactate levels in asymptomatic neonates with ARV exposure is not recommended at this time as the significance is unclear.

Two studies involving small numbers of infants, suggested that mild, transient elevations in lactate may be observed in 85%–92% of HIV-exposed uninfected infants with perinatal ARV exposure, although moderate elevations (>5 mmol/L) were seen in fewer infants (26% of 38 infants in one study) *[64, 65]*. The elevations were generally not accompanied by clinical manifestations, and serum lactate normalized by age 6 months. In a prospective study conducted during 2000–2002, among 127 perinatally HIV-exposed uninfected infants, 50% developed hyperlactatemia, with 70% of these elevations resolving within the first year of life. Three girls presented a slight and self-limited delay in psychomotor development, with peak lactate concentrations of 7.3, 4.0, and 4.6 mmol/L. Only the gestational use of ddI was associated with a higher risk of hyperlactatemia *[66]*.
A study conducted in the Ivory Coast during 2002–2005 evaluated serum lactate concentrations in infants with ≥2 measurements by type of prenatal ARV regimen (started in the 3rd trimester): ZDV (n=112) (cohort 1) or ZDV plus 3TC (n=110) (cohort 2). Both cohorts received ZDV and nevirapine (NVP) in the intrapartum and postnatal periods. The regimen for the control group (n=70), included NVP in the intrapartum and postnatal periods. The prevalence of hyperlactatemia was 11.6% in cohort 1, 14.5% in cohort 2, and 14.3% in the control group. The relatively low prevalence may be related to the short-course ARV regimens. All elevated lactate levels normalized and no case of symptomatic hyperlactatemia was detected *[67]*.

While routine monitoring of lactate levels in asymptomatic neonates with ARV exposure is not recommended, children with *in utero* ARV exposure should have long-term follow-up with careful clinical evaluations for potential late toxicities as part of routine care. In uninfected children with perinatal ARV exposure who present with severe clinical findings of uncertain etiology, 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.

Table 1: Recommendations for Evaluation and Management of Lactic Acidosis Associated with Antiretroviral Therapy in Symptomatic Patients*

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 • Hepatic transaminases, serum albumin • Amylase • Lipase • Arterial blood gas • Imaging studies, such as, abdominal ultrasound or CT scan, as indicated (to evaluate for hepatic steatosis and/or 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 but consider replacing ddI and d4T components of ARV therapy by other medications. • Alternatively, temporarily discontinue therapy while conducting additional diagnostic work-up *Lactate >5.0 mmol/L (confirm with second test) or if lactate >10.0 mmol/L,* • 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 & Laboratory 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 (recommend monthly monitoring of lactate for at least 3 months)

* Routine monitoring of serum lactate is not recommended in asymptomatic patients.

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HEPATIC TOXICITY

Background

ARV-related hepatic toxicity events include elevations in transaminases (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) with or without clinical symptoms of hepatitis and elevated bilirubin with or without jaundice. Elevations in hepatic transaminases may also herald the rare, but serious, events of hepatic steatosis associated with lactic acidosis or fulminant hepatic necrosis that is associated with hypersensitivity reactions. The majority of our understanding of hepatotoxic events related to ARV use comes from studies of adults. 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, coinfection with hepatotropic viruses (e.g., hepatitis B or C viruses), use of concomitant hepatotoxic medications, thrombocytopenia, renal insufficiency, and use of alcohol *[1-8]*.

In general, children are thought to have fewer hepatic adverse effects with antiretroviral drug treatment compared to adults but this may be related to the reduced prevalence of underlying chronic viral hepatitis associated with hepatitis B and C. Knowledge of the presentations of hepatic toxicity and the potentially associated drugs will help the clinician effectively manage these events.

Clinical Manifestations

Elevations of Hepatic Transaminases

Elevations in hepatic enzymes with or without clinical hepatitis have been reported in 14%–20% of HIV-infected adults receiving HAART *[1, 9-12]*. 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. Elevated AST and ALT levels have been reported with all of the available NRTI, NNRTI, and PI drugs as well as the fusion inhibitor, enfuvirtide. A summary of the known drug-related toxicities is shown in Table 1.

NRTI-associated hepatotoxicity is thought to be primarily due to mitochondrial toxicity *[10]*. 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).

In pediatric patients, elevation of transaminases while receiving only NRTI therapy is well documented. Unfortunately, there are no studies to determine pediatric risk factors 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 were a relatively common event. In an early study of ZDV monotherapy, 12.8% of patients developed ALT >5 times the upper limit of normal [ULN] *[13]***.** In a study of combination NRTI therapies, 4% of the children developed ALT >10 times ULN *[14]*.

Additionally, patients who are coinfected with hepatitis B and are receiving NRTIs for HIV infection which are also active against hepatitis B virus (i.e., 3TC, FTC, or tenofovir) may experience a flare in hepatic enzymes if these agents are discontinued *[15]*. An increase in hepatic enzymes can occur even if the drugs are not stopped if the hepatitis B virus develops resistance to the agents.

NNRTIs are associated with several types of hepatic toxicity, including asymptomatic elevation in transaminases (which can occur early during therapy or, less frequently, with a later onset) and hypersensitivity reaction with hepatitis *[9]*. 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**) *[9, 12, 16, 17]*.

Among NNRTIs, nevirapine (NVP) is reported to be associated with more hepatotoxicity than efavirenz (EFV) or delavirdine (DLV) *[9, 16-18]*. In adults, asymptomatic transaminase elevations have been

reported in 6%–13% of patients receiving NVP, while symptomatic hepatitis has been reported in approximately 4%–5% of patients *[2, 12, 16, 17, 19]*. 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 *[12]*. In adults, this type of reaction has been observed more frequently in females than males and in patients with higher CD4 cell counts (i.e., >250/mm^3 in women, >400/mm^3 in men) *[12, 17]*. Patients coinfected with hepatitis B or C may also be at higher risk *[19]*.

Symptomatic hepatic toxicity appears to be less frequent in children than adults. In a review of 783 HIV-infected children receiving NVP as a component of therapy identified from scientific literature and the FDA Adverse Event Reporting System database, hepatic toxicity was reported in 2.7%, primarily elevated liver enzymes *[20]*. There was only one case of fulminant hepatitis, which occurred in a 17 year old adolescent; there was no evidence of a serious clinical hepatic event associated with NVP in children prior to adolescence *[20]*. However, although rare, this syndrome can progress rapidly to hepatic failure and death within days, and progression can occur even after NVP is discontinued *[3, 21, 22]*. NVP should be permanently discontinued in children who develop severe NVP-associated symptomatic hepatotoxicity.

PI-associated hepatic 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 *[11]*. The overall incidence of hepatic enzyme elevations 5–10 times ULN in adult patients receiving PIs ranged from 3%–18%, but the incidence of symptomatic liver toxicity is lower (1%–5%). Coinfection with hepatitis B or C viruses has been consistently associated with a greater risk of severe liver injury in adult patients receiving PIs. Tipranavir (TPV) with low-dose ritonavir (RTV) has been associated with clinical hepatitis and hepatic decompensation in infected adults, including some fatalities. This toxicity has generally occurred in adults with advanced HIV disease receiving multiple medications. Patients with chronic hepatitis B or C virus coinfection have an increased risk of TPV-associated hepatotoxicity *[23]*. It has also been suggested that TPV/RTV coadministered with enfuvurtide may result in higher levels of TPV and RTV that may increase risk of hepatitis *[24]*. 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 *[3-5, 11, 19]*.

Although it is important to know the contributions of each drug class to hepatoxicity, most patients are treated with a minimum of two drug classes. In pediatric patients, studies with HAART regimens have not demonstrated an increased risk of hepatitis with use of two class combination therapies. 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 moderate to severe hepatic toxicity (defined as >5 times ULN), compared to 10% of the children who received only NRTIs *[25]*. 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%–18% in the NVP-containing arms *[26]*. 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 *[27-32]*.

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 (e.g., immune reconstitution inflammatory syndrome [IRIS]). Patients with chronic hepatitis B or C may experience a rise in transaminase levels after starting HAART therapy. This has been reported in adults and attributed to immune reactivation, with a rapid increase in cytotoxic T cells leading to immune-mediated destruction of HBV- or HCV-infected hepatocytes *[11, 33, 34]*.

Elevations of Indirect Bilirubin

Elevation in indirect (unconjugated) bilirubin levels without increases in transaminases have also been reported with indinavir and atazanavir use in adults *[4, 35-37]*. In children and adolescents, aged 2–21 years, bilirubin levels >5 times ULN occurred in 9% of 130 atazanavir recipients. Of these, only 3 patients developed clinical jaundice *[38]*. In a smaller study of 23 children and adolescents from France, marked elevations of bilirubin (greater than 4.7 mg/dL) leading to discontinuation of atazanavir occurred in 2 children *[39]*. The increase is due to competitive inhibition of UDP-glucuronosyltransferase 1A1 leading to the development of a reversible, asymptomatic, indirect hyperbilirubinemia that clinically resembles Gilbert's disease and is not associated with hepatic injury *[36]*. Although it is a common adverse event with atazanavir usage (22%–47% of patients), only a small number of patients, fewer than 2%, discontinue therapy because of elevated levels *[36]*. In addition, underlying hepatitis B or C infections do not increase the risk of developing indirect hyperbilirubinemia associated with atazanavir *[35]*. Although less common, increased bilirubin levels have been reported in up to 31% of subjects receiving indinavir *[37]*. There are sparse data on the incidence of increased bilirubin levels associated with atazanavir or indinavir in pediatric patients.

Evaluation

Obtaining hepatic 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 *[16, 40]*. However, liver function abnormalities can occur at any time while on treatment. In addition to toxicity from antiretrovirals, other etiologies, including other drugs, drug interactions, and infectious causes of hepatitis, should be considered. Patients with early increases in hepatic enzymes (i.e., within the first 6 weeks) should be monitored more closely to exclude the possibility of hypersensitivity to the drug (e.g., in patients receiving NVP or abacavir [ABC]). Early increases in hepatic enzymes can also herald IRIS in children coinfected with hepatitis B or C virus. In contrast, if hepatic enzymes become elevated months after initiation of therapy, lactic acidosis or liver steatosis should be considered. Children who are coinfected 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 *[1, 3, 34]* 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 or cytomegalovirus) 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 should 3TC be discontinued *[3]*. NVP-containing regimens should be permanently 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 *[34, 41]*. Reintroduction of the potential offending agent after the resolution of severe clinical hepatitis should be done cautiously, as it may result in a relapse of liver toxicity *[34]*. Rechallenge with NVP or ABC after any episode of acute clinical hepatitis, regardless of severity, should not occur as rapid hepatic deterioration and death can occur.

Because HIV infection itself can result in elevations of hepatic transaminases, patients naïve to antiretrovirals may have abnormal findings. There are no specific guidelines about initiating HAART in these patients. Alternate etiologies for the elevated hepatic enzymes, including infectious hepatitis and tuberculosis, should be evaluated. Many experts would recommend initiation of HAART therapy with cautious monitoring of liver function. If hepatic enzymes are increased >10 times ULN, most experts would choose not to initiate NVP as a component of HAART.

Table 1. Hepatic Toxicities

Hepatic Toxicity	Associated ARV's	Onset, Clinical Findings, and Management
Elevated AST and/or ALT, including clinical hepatitis	All NRTIs, NNRTIs, PIs, enfuvutide	**Onset and Clinical Findings** • Onset depends on the drug class. With NNRTIs and PI therapy, the majority of events occur during the first 12 weeks of therapy. With NRTI therapy, findings usually occur after months to years of usage. Any HAART regimen can result in early elevation due to immune reconstitution inflammatory syndrome. • Most elevations are asymptomatic but may be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice. • If NRTIs are being administered, care should be taken to rule out lactic acidosis and hepatic steatosis. If NNRTIs are being administered, careful monitoring is necessary to be sure that the elevations are not associated with a hypersensitivity reaction. **Management** • HAART regimens usually do not need to be stopped for elevations in transaminases <10 times ULN. • If clinical hepatitis develops in patients receiving nevirapine and/or abacavir, the nevirapine and/or abacavir should be permanently discontinued. • Investigation for other etiologies of hepatic disease such as hepatitis A, B, and C and cytomegalovirus should be performed. • Rechallenge with an agent suspected to be associated with clinical hepatitis should be done with caution. Rechallenge with nevirapine or abacavir should NOT occur. • Caution should be used when discontinuing NRTI known to be effective in treatment of hepatitis B (lamivudine, emtricitabine, tenofovir) in patients with active hepatitis B disease to avoid flares of hepatic transaminases. • Initiation of HAART recommended if elevation thought related to HIV infection. If hepatic enzymes elevated >10 times ULN, nevirapine should be avoided.
Elevated indirect bilirubin	Indinaivr, atazanavir, fosamprenavir, darunavir	**Onset and Clinical Findings** • Elevations in indirect bilirubin levels are not associated with increases in hepatic transaminases. • Elevations can be asymptomatic or result in jaundice. **Management** • Discontinuation of the offending agent is not necessary except for cosmetic reasons.

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FAT MALDISTRIBUTION AND BODY HABITUS CHANGES

Background

Changes in body fat distribution (lipodystrophy) have been reported to occur in 1%–33% of children with HIV infection in clinic-based case series *[1-10]*, and has been found more commonly in adolescents than in prepubertal children *[4-7]*. In adults, body habitus changes have been reported to occur in 2%–84% of patients *[11-14]*, with prevalence associated with older age at ARV initiation, lower CD4 cell counts, and longer duration of HIV infection *[15]*. These changes of "lipodystrophy" 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. After initiating ARV therapy there is an early increase in both trunk and limb fat noted within a few months (giving an appearance of lipohypertrophy), which may be followed by a relatively faster loss of peripheral fat (giving an appearance of lipoatrophy) in 26% of patients *[16]*.

While biochemical abnormalities may occur in children with body habitus changes, changes in lipid, glucose, and bone metabolism need to be considered separately from those of change in physiognomy since the pathogenesis of each may be different. Hyperlipidemia (elevated cholesterol and triglycerides; see **Hyperlipidemia** section) has been noted more commonly in children with body habitus changes in most, but not all, of the case series reported in children *[2-6, 8-10, 17]*. Insulin resistance may be found along with the body habitus changes, but hyperglycemia is rare (see **Hyperglycemia** section). These biochemical changes frequently occur in the absence of changes in body habitus *[18]*. Bone mineral loss, another HIV-associated metabolic abnormality, may be more common in children with lipodystrophy, but can occur in the absence of body habitus change as well *[19]* (see **Osteopenia** section).

Lipohypertrophy

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 *[20, 21]*. The lipohypertrophy syndrome has been referred to as "pseudo-Cushing's syndrome" *[22]*. In children, this syndrome is defined by physical examination showing increased abdominal girth, dorso-cervical fat accumulation, and/or breast enlargement *[5, 6, 8]*, by trunk/arm skinfold ratio >2 standard deviations from the mean *[10]*, or by dual energy x-ray absorptiometry (DEXA)-identified increase in the trunk/total fat or trunk/limb fat ratio *[9, 23]*. Increased intra-abdominal adipose tissue (IAT) can be measured with MRI *[23, 24]*, or computed tomography (CT) *[25]*. Cross-sectional measurements allow calculation of total, visceral, and subcutaneous adipose tissue (TAT, VAT, and SAT, respectively) and whole-body MRI allows comparison of SAT in trunk and extremities *[24, 26, 27]*.

Genetic and developmental characteristics, interacting with diet *[28]*, activity, and ARV exposure and duration *[29]*, may be important in development of the metabolic and body habitus changes of the lipohypertrophy syndrome *[30]*. 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 *[17]*. 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 *[17]*. 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 *[31]*. Cross-sectional data comparing prevalence of lipohypertrophy in adults with and without HIV infection *[26]* showed no association of HIV with increase in body fat measured by patient report, physical exam, or MRI measurement of VAT and SAT in both men *[24, 27]* and women *[27]*.

While use of PIs, especially indinavir *[32]*, has been implicated in the pathogenesis of lipohypertrophy, hypercholesterolemia, hypertriglyceridemia, and insulin resistance *[33-36]*, central fat accumulation has been found in PI-naïve patients *[15, 37]*. While a complete understanding of the relationship of lipohypertrophy, HIV, and ARVs is still evolving, it seems that the body habitus changes of lipohypertrophy are related to patient genetic and lifestyle factors (diet and exercise) as well as to HIV and its therapy. The biochemical changes associated with PI use in patients with HIV are also associated with morphologic changes similar to lipohypertrophy (even in the absence of HIV), and this association has been an important confounder in case series which may have been performed without appropriate controls who do not have HIV infection. The initial increase in trunk and limb fat observed in adult patients with HIV following initiation of ARVs may add further complexity to evaluation of data from short-term case series *[16]*.

Lipoatrophy

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 on DEXA scan *[23]*, by triceps and biceps skinfold thickness below the third percentile for gender and age *[10]*, changes in SAT on whole-body MRI *[26]*, or based on clinical evaluation *[5, 6, 8]*. The preservation of lean body mass in lipoatrophy helps distinguish it from HIV wasting syndrome, in which there is loss of both SAT and lean body mass *[15]*.

Compared to lipohypertrophy, lipoatrophy is more specific to HIV and its therapy. Lipoatrophy is most closely associated with use of NRTIs, especially stavudine (d4T) and didanosine (ddI) *[38-43]*. It is postulated to occur from alterations in mitochondrial function caused by NRTIs, especially the dideoxynucleosides d4T, ddI, and zalcitabine (ddC) *[44-48]*, although older age, lower pretherapy body mass index, and other host factors may be important risks *[49, 50]*, and there are other theories that may explain the syndrome, making this an area of continued active research *[51, 52]*.

Assessment and Monitoring

Lipohypertrophy and the associated risk of metabolic syndrome in adults are best identified by measurement of waist circumference. In adults, waist circumference >102 cm for men or >88 cm for women is considered abnormally increased and is associated with increased risk of metabolic syndrome *[15]*, so these measurements may reasonably apply to older adolescents. For children and adolescents, both waist circumference, waist to height ratio, and BMI are associated with the presence of the metabolic syndrome *[53-57]*. Waist circumference above the 75% percentile for age has been associated with an increased risk of metabolic syndrome in children without HIV *[58]*. Waist circumference reference charts for children and adolescents can be found at http://www.cdc.gov/nchs/data/nhanes/t47.pdf.

Patient self-report and physicial examination by an experienced clinician are the most appropriate methods for routine diagnosis of lipoatrophy *[15, 26, 59]*. Anthropometric measurements of limb circumference and triceps skinfold thickness are of limited use because results are so examiner-dependent.

Although different technologies may document the presence of lipohypertrophy or lipoatrophy, these modalities add little to the history and physical exam, and are more appropriately used in a research setting. 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 disadvantage of radiation exposure. Bioelectrical impedance analysis 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

Metabolic abnormalities of hypercholesterolemia, hypertriglyceridemia, and insulin resistance (see sections on **Hyperlipidemia** and **Hyperglycemia**) can be partially reversed by switching patients from PIs to NVP or EFV *[60]*, although such a switch may not reverse the body habitus changes of lipohypertrophy *[61]*, and may be associated with breakthrough viremia *[62, 63]*.

Diet and exercise are perhaps the most effective approach to reversing the fat maldistribution and body habitus abnormalities of lipohypertrophy *[64, 65]*. Thiazolinidinediones should not be used for lipohypertrophy *[15]*. Metformin may improve metabolic abnormalities, and produce loss of VAT and SAT, but also causes loss of lean body mass, which may not be beneficial *[66-68]*. There are no data on the use of metformin for treatment of lipohypertrophy in children. Since impaired growth hormone secretion has been found in adolescents and adults with HIV-associated lipohypertrophy *[69-71]*, treatment with growth hormone *[72]* and growth hormone releasing factor (hormone) *[73, 74]* have been tried with some success, but lack of clear dosing guidelines, potential for side effects, and cost limit the use of these therapies, which are not recommended outside of a clinical trial setting. Because of the association of lipoatrophy with the use of certain NRTIs, avoidance of d4T and especially the combination of d4T and ddI is the most effective approach to lipoatrophy prevention. Discontinuation of PI therapy does not lead to improvement in lipoatrophy *[75]*. Substitution of abacavir or tenofovir for d4T or zidovudine leads to an improvement in limb fat *[76, 77]*, but if the change is delayed the improvement in peripheral fat may be slower and less complete *[78]*.

Improvements of lesser degree have been shown when zidovudine is substituted for d4T *[79]*. These improvements after NRTI switch were associated with increase in mitochondrial DNA *[80]*, consistent with the hypothesis that it is the mitochondrial toxicity of d4T that is responsible for lipoatrophy. Antioxidants and mitochondrial cofactors have been used in small studies, and while uridine supplementation may attenuate decreases in mitochondrial DNA, more studies are needed before these agents can be recommended *[81]*. The insulin-sensitizing agents (thiazolidinediones) rosiglitazone and pioglitazone may be beneficial in some patients with lipoatrophy and associated insulin resistance, but the effect is small and cannot overcome the effects of continuing d4T *[15, 82-84]*. Poly-L lactic acid is approved by the FDA for surgical implantation into areas of severe lipoatrophy, but use is limited by expense of this intervention, need for experience in its application, and potential complications *[85]*. Other than switching from d4T, none of these therapies have been studied in children.

The presence of lipoatrophy is often psychologically difficult for patients, families, and providers, and may lead to non-adherence with antiretrovirals *[86]*. Changes in appearance may be slow to resolve even after changes in NRTI therapy. The choice between loss of viral control and change in appearance may be difficult to make, especially for adolescents. Support of the patient and family is an important aspect of care.

Table: Risk factors, diagnosis, and therapy of body habitus changes in children with HIV

Disorder	**Major Risk Factors**	**Assessment and Monitoring**	**Treatment**
Lipohypertrophy	Obesity prior to therapy	BMI, waist circumference, waist/height ratio	Diet and exercise
Lipoatrophy	Thymidine analogue use, especially stavudine > zidovudine	Self-report and clinical examination	Switch from stavudine or zidovudine (e.g., to abacavir or tenofovir)

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HYPERLIPIDEMIA

Background

HIV infection itself is associated with dyslipidemia characterized by low levels of high density lipoprotein cholesterol (HDL-C) and increased levels of total cholesterol (TC), triglycerides (TG), and low density lipoprotein cholesterol (LDL-C) *[1]*. Although not well understood, proposed mechanisms for HIV-associated dyslipidemia include abnormalities of retinoic acid metabolism, impaired lipid clearance, impaired adipogenesis, apolipoprotein abnormalities, cytokine abnormalities, and increased hepatic TG, fatty acid, and sterol synthesis *[2]*. Changes in lipid parameters are associated with the use of antiretrovirals, particularly the protease inhibitors (PIs), but also with the non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the nucleoside analogue reverse transcriptase inhibitors (NRTIs) in adult patients *[3-12]*. While in general, the PIs may be associated with increases in TG and TC levels, atazanavir (ATV) has the least effect on lipid parameters *[13, 14]*. ATV alone is associated with little or no change in TG but the addition of RTV to ATV may result in significant increases in TG and TC *[15]*. The NNRTIs nevirapine (NVP) and efavirenz (EFV) produce favorable increases in HDL-C; the effect is greater with NVP *[16-18]*. Of the NRTIs, stavudine has the largest adverse effect on TC while tenofovir (TDF) may have little or no effect on lipid parameters *[19-21]*.

There are several published reports on the effects of PIs and NNRTIs on lipid levels in children and adolescents *[22-24]*. PI-containing regimens were associated with increases in TC and TG when compared to dual NRTI therapy *[22, 23]*. The prevalence of hypercholesterolemia (defined as >95% TC standards for age and gender) among 1,812 perinatally HIV-infected children 4–19 years of age in PACTG 219C was 13% compared to 5% in the uninfected control group *[25]*. The prevalence of hypercholesteremia was 5 times higher than among those patients currently receiving a PI *[25]*. A strong association with adherence was found. Those patients with HIV RNA <400 copies/mL had the highest hypercholesterolemia prevalence at 24% *[25]*. An additional 10.9% of patients developed hypercholesterolemia (TC >220 mg/dL) during follow-up in PACTG 219C *[26]*. It is estimated that 20%–50% of children receiving HAART will have lipoprotein abnormalities, particularly elevations in total cholesterol and LDL-C *[27]*. The European Paediatric Lipodystrophy Group evaluated 280 children from 18 European centers for metabolic abnormalities: 27% of children had hypercholesterolemia and 21% had hypertriglyceridemia with an overall prevalence of dyslipidemia of 38% *[28]*.

The cardiovascular risk in HIV-infected adults who are untreated compared to HAART-treated patients is difficult to assess. An increased risk of myocardial infarction was found to be associated with increasing exposure to the PIs in a large cohort study of adults *[29, 30]*. However, it is likely that cardiovascular disease (CVD) risk factors such as family history, poor diet, lack of exercise, obesity, cigarette smoking, hypertension, hyperglycemia, hyperlipidemia, and metabolic syndrome are more important than the contribution of HIV infection or HAART therapy. In both the D:A:D and SMART cohort studies in adults, immunosuppression increased the risk of non-HIV related death, including heart disease, and uncontrolled HIV replication increased the risk of CVD *[29-32]*. These studies strongly suggest that suppression of viral replication and restoration of immune function have protective effects on CVD *[33]*. While the risks associated with hyperlipidemia in adults are well documented, there are no studies documenting a relationship between elevated cholesterol levels in children and an increased risk of premature death, as in adults *[23, 30, 34-41]*. 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) *[23, 40]*. The metabolic syndrome (the combination of obesity particularly central adiposity, hyperinsulinemia/insulin resistance, hypertension, and hyperlipidemia) is likely to significantly increase the risk for cardiovascular disease for children with HIV receiving antiretroviral (ARV) therapy *[27]*.

The National Cholesterol Education Program (NCEP) classification of fasting cholesterol levels in children and adolescents is listed in **Table 1** *[36, 37]*.

Table 1: NCEP Classification of Fasting Cholesterol Levels in Children and Adolescents *[36, 37, 42]*

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 <200 mg/dL are considered acceptable.		

Original recommendations of the NCEP expert panel target those children with extremely high lipid abnormalities and apply mostly to those children with familial hypercholesterolemia. The primary focus of the NCEP guidelines is on elevated LDL-C levels and does not address the more prevalent lipid abnormalities associated with obesity and metabolic syndrome: decreased HDL-C and hypertriglyceridemia *[27, 43, 44]*.

Monitoring

For HIV-infected adolescents and adults, guidelines have been offered for evaluating and monitoring patients who are initiating HAART or who are currently receiving ARV medications *[45]*. A fasting (12 hour) lipid profile, including TC, HDL-C, and TG, with calculation of LDL-C, is recommended before initiating ARV therapy and at 3 to 6 month intervals thereafter *[45, 46]*. TC and HDL-C can be determined with a non-fasting sample while accurate measurement of LDL-C and TG require a fasting specimen. Many laboratories now offer direct LDL-C measurements that permit assessment in non-fasting samples. For pediatric patients on stable therapy without lipid abnormalities or other risk factors, screening of non-fasting lipid profiles every 6 months is recommended. If non-fasting TG or LDL-C are elevated, then fasting levels should be performed. In those patients with lipid abnormalities or other risk factors, fasting lipid profiles should be determined on a schedule similar to that outlined above for adolescents and adults (**Table 2**).

Table 2: Screening and Monitoring of Lipid Parameters and Lipid Therapy During Antiretroviral Therapy

AGE/RISK CATEGORY	LIPID PROFILES/LABS	FREQUENCY
Adolescents and Adults*	Fasting (12 hour) TC, HDL-C, TG, LDL-C	Prior to initiating ARV therapy or changing ARV therapy and every 3–6 months
Pediatric Patients without lipid abnormalities or risk factors	Non-fasting screening lipid profiles. If TG or LDL-C is elevated, obtain fasting labs.	Prior to initiating ARV therapy or changing ARV therapy and every 6–12 months if stable.
Pediatric patients with lipid abnormalities or risk factors	Fasting (12 hour) TC, HDL-C, TG, LDL-C	Every 3–6 months.
Pediatric patients receiving lipid therapy with statins or fibrates	Fasting (12 hour) lipid profiles. LFT's and creatine kinase (CK).	Prior to initiating lipid therapy, and at 4 weeks and 8 weeks after starting lipid therapy. If minimal alterations in AST, ALT, and CK then every 3 months. Whenever doses of antihyperlipidemic agents are increased repeat at 4 weeks *[27]*.

*Adult HIV Guidelines

Management

The Adult ACTG Cardiovascular Disease Focus Group developed preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving ARV agents *[45]*. For children, less is known about the use of the available agents used to treat dyslipidemia and the long-term risks associated with lipid abnormalities in children with HIV infection. The previous NCEP guidelines recommended the consideration of drug therapy in children ≥10 years of age and after a 6 to 12 month trial of dietary management in those children with LDL-C ≥190 mg/dL or ≥160 mg/dL in whom there is a positive family history of CVD or ≥2 risk factors *[37]*. Additional guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood and cardiovascular risk reduction in high-risk pediatric patients have recently been published *[47, 48]*. Although HIV infection is not specifically addressed in these guidelines, risk stratification and a treatment algorithm for high-risk patients are proposed and adapted from those of Kavey, et al (**Table 3**). Recently, NCEP guidelines have been proposed which include the screening of overweight children with a fasting lipid profile and possibly further evaluation of other aspects of the metabolic syndrome *[27]*. For children with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions (such as HIV infection) should be considered when deciding when to initiate drug therapy. At this time, there is no consensus as to what LDL-C levels should prompt treatment in children receiving ARVs.

Table 3: Treatment Goals Stratified by Risk
(Modified from Kavey 2006)

Risk Category*	Goal of Treatment
For all risk categories:	BMI ≤85th percentile for age/gender, BP ≤90th percentile for age/gender, and fasting glucose <100 mg/dL
High Risk Patients:	LDL-C ≤100 mg/dL
Moderate Risk Patients:	LDL-C ≤130 mg/dL
At Risk Patients:	LDL-C ≤160 mg/dL

*HIV infection is considered a high risk condition. Other risk factors include a positive family history of premature CVD, being overweight, having an elevated BP, having an elevated glucose, poor diet, sedentary lifestyle, and smoking. All risk factors should be considered in evaluating the risk category of the patient.

Lifestyle Changes

Dietary changes and exercise are considered the cornerstones in the management of dyslipidemia in children *[37, 45]*. All patients should be given a trial with American Heart Association Step II diet prior to considering initiation of drug therapy. Lifestyle changes may be difficult to achieve in some pediatric patients with HIV *[49]*. 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 ≥500 mg/dL), in which prompt intervention may be required *[50-52]*. If these efforts fail to produce the desired response, drug therapy for dyslipidemia should be considered. Persistence of elevated LDL-C levels after an adequate trial of lifestyle changes, especially in patients with a positive family history of premature CVD or ≥2 positive risk factors (including smoking), merits drug therapy, although present experience is limited to children over 6 years of age *[3, 37, 53]*. It is often difficult to obtain a good family history for children with HIV, especially those not living with their biologic families. Education about the health risks associated with smoking should be emphasized and children and adolescents with HIV should be strongly encouraged not to smoke.

Drug Therapy-General

There are few prospective studies of lipid-lowering therapy in adults with HIV infection and no published studies in pediatric patients with HIV infection *[9, 15, 49, 54-58]*. 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) (**Table 4**). Advantages and disadvantages are summarized in **Table 4**.

The statins are the most widely prescribed lipid-lowering agents for adults with HIV infection and the drugs of choice for children with HIV infection. The effectiveness of the statins in decreasing cholesterol and TG in adults has ranged from 25%–60% and 10%–15%, respectively *[9, 55-57, 61]*. There are multiple drug interactions between the statins and the PIs and NNRTIs. Lovastatin and simvastatin coadministation with PIs is contraindicated because PIs inhibit CYP3A4 isoenzyme activity, resulting in significantly increased serum concentrations of these agents and a

higher likelihood of toxicity *[45, 62, 63]*. The pharmacokinetics of pravastatin are minimally affected by CYP3A inhibition; this statin is preferred for use in patients receiving PIs *[62]*. 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. In contrast, NVP and EFV are CYP3A inducers and may decrease statin concentrations significantly. Higher statin doses may be required to achieve the desired effect *[45, 64, 65]*. Modest responses have been observed with the use of pravastatin with or without ezetimibe and extended-release niacin in trials involving adults with HIV infection *[15, 58, 66]*. However, results observed in trials with patients with high LDL-C (>130mg/dL) and TG (>400 mg/dL) levels have been disappointing with high failure rates with single agent therapy and the need for combination therapy (pravastatin + fenofibrate or fenofibrate + fish oil) to achieve better responses *[67, 68]*.

Statins-Pediatric Use

Several studies have evaluated the safety and efficacy of the statins in pediatric patients, primarily for the treatment of familial hypercholesterolemia *[59, 69-78]*. Statins have been shown to decrease LDL-C levels in children with familial hypercholesterolemia by 30%–50% *[53, 59, 70-72, 78]*. In addition, they also improve endothelial function and reduce the progressive thickening of the intima media complex of the carotid arteries *[73, 77]*. These data support the use of statins early in therapy when the atherosclerotic process is still reversible *[69, 77]*. The goal of therapy in at-risk children is to prevent atherosclerotic plaque development. There are currently 2 statins that can be recommended for use in pediatric patients taking ARV agents: pravastatin (preferred) and atorvastatin (alternative) *[53, 69-71, 75, 76, 78-82]*. (See **Table 5** for dosing information.) 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. Short-term toxicities in children and adolescents include elevations in alanine aminotransferase and or aspartate aminotransferase without clinical hepatotoxicity in 1%–5% of children treated with atorvastatin, and less common with pravastatin. The elevations observed are mild, asymptomatic, and reversible *[59]*. (See **Table 2** for monitoring guidelines.) Patients should be instructed to recognize symptoms of idiosyncratic hepatotoxicty and rhabdomyolysis. 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. However, statins can be used in women of child-bearing age but only with adequate counseling regarding teratogenicity and effective contraception in those patients who are sexually active.

Table 4: Classes of Drugs Used to Treat Hyperlipidemias

Drug Class	Effects	Agents	Pharmacologic Considerations	Side Effects	Additional Comments
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 EFV and NVP are CYP3A inducers and may decrease statin levels significantly	Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Teratogenic and should not be used in female patients who may become pregnant.	Drugs of choice in pediatric patients with HIV *[59]*. Multiple drug interactions with PIs and NNRTIs. Careful review of potential drug interactions is required before initiating therapy.
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 *[45]*	Unpalatable gastrointestinal side effects such as bloating and constipation	Only decrease LDL-C modest 12% and adherence is poor *[59]*.
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 *[45]*	Cutaneous flushing and pruritus (less with extended-release preparations); hepatotoxicity	Toxicity may limit usefulness in children.
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. Combination of simvastatin, ezetimibe, and gemfibrozil is contraindicated.	Serious toxicities include bone marrow suppression and myositis. Gastrointestinal upset and increased risk of cholelithiasis.	Not approved for use in children. Limited experience in pediatric patients. Alternative agents useful in patients with elevated TG levels in which other treatments have failed.
Cholesterol absorption inhibitor	LDL↓ HDL same TG↓	Ezetimibe (Zetia)*	Additional benefit to patients on statins with primary hypercholesterolemia (not studied with PIs)	Well tolerated	Safe and effective when combined with dietary interventions and statins in children ≥10 yrs of age *[60]*.
Stanol ester margarines	LDL↓	Benecol*	Dietary adjunct	Well tolerated	
Psyllium	LDL↓	Metamucil*	Dietary adjunct	Well tolerated	
Fish Oil	TG↓	Generic	Dietary supplement	Well tolerated	Favorable safety profile offers attractive alternative for patients in which diet alone does not significantly reduce TG levels.

*FDA approved for use in children.

Table 5: Recommended Lipid-Lowering Medications in Pediatric Patients with HIV Infection

Drug Name	Dose	Comments
Pravastatin (Pravachol)	Age 8–13 years: 20 mg once daily Age 14–18 years: 40 mg once daily (manufacturer's prescribing information)	Not approved for use under the age of 8 years. Initiate therapy at 10 mg once daily and titrate to response every 4 weeks or longer.
Atovastatin (Lipitor)	Age >6 years: 10–20 mg once daily (manufacturer's prescribing information)	Not approved for use under the age of 6 years.
Gemfibrozil (Lopid, generic)	Has been dosed 150–300 mg twice daily in older children/adolescents but is only available as a 600 mg tablet *[83-85]*. Adult dose is 600 mg twice daily.	Not approved for use in children.
Ezetimibe (Zetia)	Age >10 years: 10 mg once daily	Best used in combination with statins.

Other Treatments/Interventions

The fibric acid derivatives or fibrates, which include gemfibrozil and fenofibrate, are alternative agents useful in adult patients with elevated TG levels. These agents lower TG levels by 30%–55%, but have only a modest effect on HDL-C and mild effects on LDL-C *[9, 38, 61]*. 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 *[45, 49, 61]*. Gemfibrozil is not approved for use in children, and very limited dosing information is available. (See **Table 5**)

There has been considerable interest in the use of N-3 polyunsaturated fatty acids (PUFAs) derived from marine sources (fish oils) to reduce elevated triglyceride levels in patients receiving ARVs. In one recent study of adult patients receiving ARVs, there was a significant reduction in median TG levels in those receiving PUFA supplementation compared to placebo (25% vs. 1%) *[86]*. Docosahexaenoic acid has been studied in a small trial of children with hyperlipidemia in which favorable changes in lipoprotein subclasses were found *[87]*. Further investigations into the role of PUFAs for the treatment of elevated levels of triglycerides are warranted. Because of the favorable safety profile of PUFAs, they offer an attractive alternative for patients in which diet alone does not result in a significant decrease in TG levels. Other nonpharmacologic therapies that have been studied in children include the use of dietary fiber, plant sterol and sterol esters (dietary spreads), and garlic preparations. The benefits of these dietary supplements are limited and further investigations with controlled trials are warranted before their use can be routinely recommended *[27]*.

Impact of Changes in Antiretroviral Therapy in Patients with Dyslipidemia

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 EFV, NVP, or abacavir. This strategy has been studied in a number of adult patients with varying success *[18, 39, 46, 88-91]*. However, when substitution of an NNRTI for a PI was compared to lipid therapy in adults with dyslipidemia, treatment with statins or fibrates was significantly more effective than switching ARVs *[91]*. The overall trend in these studies has been no change or modest increases in HDL-C and no change or modest decreases in TG *[89]*. The results of the first pediatric switch study were reported in 2003: 17 children in the study well-maintained on a PI-containing regimen were changed to an EFV-containing regimen *[92]*. The authors were able to show significant improvements in fasting cholesterol, LDL-C, TG, and TC/HDL-C ratio *[92]*. However, in this small study, the mean baseline lipid levels were only modestly elevated (mean cholesterol: 203 mg/dL [+/- 50] mean LDL-C: 124 mg/dL [+/- 42]), and only 2 children had triglyceride levels slightly above 200 mg/dL *[92]*. Whether similar improvements would be seen in pediatric patients with significantly elevated lipid parameters is not known. Vigano, et al., studied 28 HIV-infected children with stable undetectable viral loads receiving stavudine, lamivudine, and a PI. The PI was switched to efavirenz and stavudine was switched to tenofovir. A significant decrease in TC (20%) and TG (57%) was observed in this study *[93]*. Limitations of this strategy include the potential toxicity associated with tenofovir (both renal and bone) and the risk of using efavirenz in females who may become pregnant. Another strategy would be to switch to the PI atazanavir, which has been shown to reverse lipodystrophy in some adult patients and to improve therapy-induced hyperlipidemia *[94, 95]*. Limitations to this approach are that atazanavir is not approved for use in children, there is limited dosing information available for this age group, and that boosting atazanavir with RTV is associated with lipid abnormalities.

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. At this time, there is no consensus as to what LDL-C levels should prompt treatment in children receiving ARVs. 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 the use of lipid-lowering agents or changes in ARV regimens. 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. For some patients, the best option may be to try switching to a regimen less likely to cause lipid abnormalities. Alternatively, the use of statin agents such as pravastatin can be initiated in an attempt to decrease elevated LDL-C or TG. 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 *[46]*.

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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 *[1-5]*, especially *[6-8]*, but not exclusively *[9-11]*, with PI-containing regimens. Incidence estimates of 3%–25% are suggested for hyperglycemia in adults, with median onset approximately 60 days following initiation of ARV therapy. Impaired glucose tolerance has been found in as many as 16%–35% of HIV-infected adults taking combination ARV therapy *[12]*. The wide range of these estimates is in part due to varying definitions of impaired glucose tolerance, choice of antiretroviral therapy, and presence of associated fat maldistribution (lipodystrophy).

The mechanism of hyperglycemia and insulin resistance in patients treated with antiretroviral therapy is unknown and likely to be multifactorial *[4, 5, 13]*. Several PIs can have direct effects on insulin resistance through the inhibition of insulin-stimulated glucose transport; NRTIs also may contribute by increasing the visceral-to-subcutaneous

fat ratio, inducing chronic lactic acidosis, and decreasing serum adiponectin *[4, 5, 13]*.

Insulin resistance is associated with increased free fatty acids *[14]* and is a common accompaniment of the lipodystrophy/fat maldistribution syndromes, which may occur in up to 33% of children treated with PIs *[15]* or stavudine *[9]*. New onset clinical type 1 diabetes mellitus occurs only rarely in children or adolescents treated with PIs *[16]*. However, combined type 1 and type 2 diabetes incidence rates (variably defined by self report, medication lists, and fasting blood glucose concentrations) in HIV-infected adults receiving combination ARV therapy range from 1.2–4.7 cases per 100 person-years, about 2–4-fold greater than that of non-HIV-infected adults *[17, 18]*. While insulin and glucose abnormalities may resolve with change from PI therapy, the abnormalities may persist in some patients, and type 2 diabetes is being increasingly recognized in ARV-treated adults *[12]*.

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 *[19]*. Insulin resistance without fasting hyperglycemia has been found to cause growth delay in children with cystic fibrosis *[20]*. However, pubertal children normally display decreased insulin sensitivity (increased insulin resistance) compared with prepubertal children, confounding analyses of cause and effect over time.

Most patients with insulin resistance, with or without fasting hyperglycemia associated with ARV therapy, will remain entirely asymptomatic. In adults, insulin resistance may contribute 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.

Finally, there are marked overall increases in obesity *[21, 22]* and metabolic syndrome *[23]* occurring in the United States and other industrialized nations *[24]* unrelated to HIV infection. Thus, hyperglycemia and insulin resistance may be the end-result of a mixture of the effects of HIV infection, combination ARV therapy, and changes in societal lifestyle and diet.

Assessment and Monitoring

Insulin resistance is mostly commonly discovered in asymptomatic patients who have fasting blood glucose concentrations of ≥126 mg/dL. However, fasting blood glucose measurements may be difficult to arrange in the pediatric outpatient setting, and some degree of insulin resistance is possible without demonstrable fasting hyperglycemia. Even the use of more complex techniques such as the fasting insulin:glucose ratio, homeostatic model assessment insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) did not reliably demonstrate changes in insulin resistance and glucose disposition associated with PI therapy; such changes were revealed only when the children underwent insulin-modified, frequent-sampling intravenous glucose tolerance tests (FSIVGTT) *[25]*.

It is thus difficult to construct reasonable recommendations for ambulatory monitoring of insulin resistance in children receiving combination ARV therapy. Even for non-HIV-infected children, the role of screening tests for insulin resistance and type 2 diabetes mellitus is still rather restricted (**Table 1A**). The Working Group makes the following recommendations based upon expert consensus in the absence of clinical trials data (see below and **Table 1B**).

Screening for signs and symptoms of diabetes. When starting PIs, guardians and patients should be educated about the signs and symptoms of overt insulin-dependent (type 1) diabetes mellitus (days to a few weeks of polyuria, polyphagia, polydipsia, weight loss, blurred vision), as well as insulin resistance, or type 2 diabetes mellitus (increasing change in body habitus, e.g., overweight, obesity, lipodystrophy; acanthosis nigricans; in females, polycystic ovarian syndrome [oligomenorrhea with acanthosis nigricans, hirsutism, or increased acne]).

Preferred laboratory tests for diabetes screening. Measurement of fasting blood glucose, rather than random ("casual") blood glucose, is the screening test preferred by diabetes experts *[26, 27]*. Fasting blood glucose measurements may identify impaired glucose tolerance or diabetes: repeated fasting blood glucose >100 but <126 mg/dL indicates impaired glucose tolerance, and repeated measurements ≥126 mg/dL indicates diabetes.

However, it is recognized by the Working Group that random glucose measurements are generally included in laboratory panels obtained for monitoring hepatic and renal function in patients receiving combination ARV therapy, and fasting measurements may be harder to obtain in the pediatric outpatient setting. Thus, at present the consensus of the Working Group is to measure random blood glucose levels for screening instead of fasting levels. If random blood glucose levels are elevated, arrangements should then be made to measure fasting blood glucose levels (fasting defined as 8 hours without caloric intake—water is acceptable). The Working Group has conservatively chosen the definition of elevated random blood glucose as repeated measurements of >140 mg/dL (Table 1B), based upon the definition of normoglycemia in standardized glucose tolerance tests *[26-28]*.

The Working Group recommends against the routine performance of oral glucose tolerance tests, and the measurement of either insulin or hemoglobin A_{1c} concentrations. However, these tests may be useful in research protocols, in the confirmation of the diagnosis of diabetes, and in monitoring antihyperglycemic therapy in conjunction with an expert in diabetes *[29]*.

Laboratory screening for diabetes (Table 1B).
HIV-infected children and adolescents without signs or symptoms of diabetes. Routine laboratory tests for hyperglycemia or insulin resistance are not indicated for asymptomatic children and adolescents with HIV infection who are not receiving PI-based combination ARV therapy, and who are without any risk factors for type 2 diabetes mellitus (Table 1A).

HIV-infected children and adolescents receiving PI-based combination ARV therapy. For adults receiving PI-based combination ARV therapy, 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 thereafter while on therapy *[30]*. Such monitoring is of unproven benefit in children receiving PI-based combination ARV therapy. Instead, the Working Group suggests monitoring of random blood glucose levels on a similar schedule, with confirmation of repeatedly elevated levels by fasting blood glucose determination (**Table 1B**).

HIV-infected children and adolescents with signs or symptoms of insulin resistance or diabetes. Patients with signs of overt diabetes mellitus of either type, or ketoacidosis (fruity odor to breath, rapid deep respirations, tachycardia, low blood pressure, possibly altered mental status and weight loss) should be evaluated immediately with appropriate laboratory testing, including measurement of random blood sugar, urinalysis, and hemoglobin A_{1c}.

Treatment

All of the following recommendations are based upon adult studies, in the absence of pediatric-specific data (**Table 1B**).

Lifestyle modification (i.e., an exercise program combined with a moderate-fat, low-glycemic-index, high-fiber diet) is indicated for all patients with insulin resistance without overt diabetes, especially those associated with lipodystrophy or metabolic syndrome. Lifestyle modification can reverse several aspects of lipodystrophy, including mild to moderate insulin resistance *[12, 31, 32]*.

Lifestyle modification, as well as institution of oral insulin-sensitizing therapy (or even injectable insulin), is indicated for all patients with diabetes. The consultation of an expert in pediatric diabetes is important for these patients, as the anti-hyperglycemic drug of choice for each patient must be individually assessed *[12, 26-28, 33]*. A change from PI therapy to nevirapine, efavirenz, or abacavir might also be indicated in the setting of diabetes as an adjunctive measure to reduce insulin resistance *[12, 30, 34]*.

Table 1A: Criteria indicative of need for Type 2 diabetes screening in children and adolescents whether or not HIV infection is present.*

- Overweight (BMI >85th percentile for age and sex, or weight for height >85th percentile, or weight >120% of ideal [50th percentile] for height

Plus

- Any 2 of the following risk factors:
  - Family history of type 2 diabetes in first- or second-degree relative
  - Race/ethnicity (Native American, African-American, Hispanic, Asian/Pacific Islander)
  - Signs of insulin resistance or associated conditions (acanthosis nigricans, polycystic ovarian syndrome, hypertension, dyslipidemia)
- Begin testing at age 10 years or onset of puberty (whichever is earlier) for those meeting above criteria, and continue testing every 2 years

Table 1B: Diagnosis and treatment of Type 2 diabetes in children and adolescents with HIV infection.

HIV-infected Group	Type of Combination ARV Therapy	Diagnostic Screening Indicated	Specific Management Indicated
No symptoms of insulin resistance or diabetes †	None	None beyond those for non-HIV-infected children and adolescents	None
	NNRTI-based	None beyond those for non-HIV-infected children and adolescents	None
	PI-based	• RBG upon initiation of therapy, at 3–6 mos, and yearly thereafter o Obtain FBG if RBG repeatedly ≥140 mg/dL	• RBG <140 mg/dL: none; recheck in 6–12 mos • RBG ≥140 mg/dL: obtain FBG after 8hr fast o FBG <100 mg/dL: none; recheck RBG in 6–12 mos [if multiple risk factors, consider consultation with endocrinologist and lifestyle modification despite normal FBG] o FBG 100–126 mg/dL: suggests insulin resistance, consult endocrinologist; lifestyle modification o FBG ≥126 mg/dL: diagnostic of diabetes; consult endocrinologist; lifestyle modification, possible pharmacologic therapy
Symptoms of insulin resistance or diabetes †	None, NNRTI-based, or PI-based	• RBG, urinalysis, and hemoglobin A_{1c} immediately	• RBG ≥200 mg/dL, or if performed, FBG ≥126 mg/dL diagnostic of diabetes; consult endocrinologist; lifestyle modification & pharmacologic therapy indicated

* BMI = body mass index; RBG = random blood glucose measurement; FBG = fasting blood glucose measurement; criteria of Table 1A adapted from American Diabetes Association *[26]*. See text for details.

† Symptoms of insulin resistance or diabetes include: polydipsia, polyuria, polyphagia, weight loss, blurred vision, acanthosis nigricans, polycystic ovarian syndrome. Symptoms of ketoacidosis include: fruity odor to breath, rapid deep respirations, tachycardia, low blood pressure, possibly altered mental status, and weight loss.

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OSTEOPENIA, OSTEOPOROSIS, AND OSTEONECROSIS

Background

Decreased bone mineral density (BMD) is 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. While dual energy X-ray absorptiometry (DEXA) measurements are used to define osteoporosis in adults, osteoporosis is a clinical diagnosis in children. Osteopenia and osteoporosis are common in HIV-infected adults, occurring in 23%–46% of patients *[4, 5]*.

Epidemiology of low BMD in HIV infected adults: The decreased BMD in HIV-infected patients is multifactorial, related to HIV infection, HIV treatment, and comorbidities as well as HIV-unrelated risk factors. Independent contributors to low BMD in studies of HIV-infected adults, including older age, smoking, steroid use, and low BMI are well established risk factors in HIV-uninfected patients *[4, 6]*. Several studies have demonstrated an increased risk of osteopenia or osteoporosis in HIV-infected patients in the absence of antiretroviral therapy *[7-9]*. The temporal linkage of increased recognition of low BMD in HIV-infected individuals with increased use of HAART has also 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 *[10]*. However, in longitudinal studies of HIV-infected adults, PIs were not associated with increased risk of low BMD and switch from PI-based

to NNRTI-based HAART did not lead to an improvement in BMD, leading most experts to conclude that PIs do not cause osteopenia or osteoporosis *[11-15]*. Tenofovir disoproxil fumarate (TDF) has been associated with a decrease in BMD in adults, but bone mineral loss appears to stabilize within 2 years without discontinuing TDF *[5]*. Stavudine *[6]* and initiation of HAART *[16]* in the setting of low CD4 counts–regardless of specific ARV agents–have also been implicated as risk factors for low BMD in HIV-infected adults.

Epidemiology of low BMD in HIV-Infected Children: Data on BMD in HIV-infected children and youth are more limited but demonstrate a lower BMD than would be expected for healthy people of similar age, weight, and race *[17-20]*. Jacobsen et al. studied 37 HIV-infected children compared to 9 sibling controls *[21]*. When compared with population norms, HIV-infected children had lower than expected age- and sex-adjusted bone mass. Independent predictors of low BMD in HIV-infected children suggested contributions from delays in growth, sexual maturity, duration of HIV infection, ethnicity, and disease severity. Multivitamin use was strongly associated with better bone mineral density, but not with changes in BMD over time. Over time, BMD was stable or increased in only 44% of the HIV-infected children compared to all of the controls *[21]*. 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 *[20]*. Additionally, total body BMD was lower in HAART-treated children who had lipodystrophy than in those without lipodystrophy *[20]*. Use of TDF in heavily ARV-experienced children was associated with significant decreases in BMD, especially in the first year of TDF therapy *[22, 23]*, similar to the finding in adults *[5]*.

Mechanism of BMD loss in HIV infection: 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 *[11, 24]*. Serum markers of bone formation and resorption were also higher in HIV-infected children receiving HAART, indicating increased rates of bone turnover *[20]*. 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, 25]*. However, BMD changes have also been observed in HIV-infected adults receiving antiretroviral regimens without PIs, such as TDF or stavudine in combination with lamivudine and efavirenz; the changes in BMD were associated with increased lactate levels, suggesting possible NRTI-associated mitochondrial toxicity *[26]*. 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, 27, 28]*.

Higher bone resorption rate has also been observed in vertically HIV-infected children and adolescents on long-term PI-based HAART compared to healthy age-matched control children. Increased resorption in these children may be the result of a profound modification of serum factors (osteoprotegerin [OPG], Receptor Activator for Nuclear Factor κ B Ligand [RANKL]) regulating osteoclastogenesis mediated by observed *in vitro* effects of antiretroviral drugs on RANKL production by T cells *[29]*.

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, 9, 11, 19, 29, 30]*. 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 *[31]*. 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, 4]*. HIV-infection also increases resorption-promoting RANKL production by T cells *[29]*. 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, 4, 32, 33]*. 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 *[34]*, although more recent reports have suggested that incidence may be increasing in adults *[1]*. Incidence of symptomatic (0.26 per 100 patient-years) and asymptomatic (0.65 per 100 patient-years) hip osteonecrosis in HIV-infected adults is approximately 100-fold higher than the estimated incidence in the general population *[33]*. Avascular necrosis of the hip (Legg-Calve-Perthes disease) was reported in a small series of HIV-infected children in 2001 *[35]*. Factors associated with osteonecrosis in HIV-infected adults include alcohol abuse, hemoglobinopathies, hyperlipidemia, pancreatitis, osteopenia/osteoporosis, hypercoagulable states and particularly steroid use *[32, 33]*. Ritonavir and other PIs may increase adverse bone effects of steroids through inhibition of CYP450-mediated steroid metabolism. Chronic inflammation may also contribute to development of osteonecrosis. Though osteonecrosis incidence has increased in the HAART era, there is no clear association with a specific antiretroviral regimen *[1, 33]*. Prospective clinical studies will be required to establish whether antiretroviral agents are directly or indirectly linked to risk of osteonecrosis.

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 *[19]*. 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 15 (33%) of evaluable children, higher than has been reported in similar studies in adults *[22, 23]*. This study found that smaller, prepubertal children were most likely to experience substantial loss of bone density on TDF. BMD loss was associated with increased urinary calcium losses, suggesting renally-mediated mechanisms for increased bone resorption. Ongoing bone mineral loss ceased after cessation of TDF.

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 *[4]*. BMD is most commonly measured by DEXA, the standard and validated method for use in adults *[36]*. While DEXA t-scores are used to define osteoporosis in adults, DEXA t-scores should not be used to make a diagnosis of osteoporosis in children; instead, a DEXA z-score <-2.0 is used to identify children with low BMD. The variations in bone and body size and composition in growing children make accurate BMD assessments by DEXA in children more difficult; formulas and factors to correct for these variation have been proposed but no single approach has been accepted as standard. Normative data for DEXA assessment of BMD in children have been established, accounting for differences by gender, age and pubertal stage *[37]*. Quantitative CT scan may be a more accurate assessment of BMD in growing bones but entails significantly more radiation; radiation-free quantitative ultrasound is an appealing alternative that needs further study. The correlation of low BMD with vertebral fracture risk in adults is well established; the correlation between low BMD and fracture (usually at non-vertebral sites) in children is not as clearly established.

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. However, the high rates of vitamin D insufficiency among HIV-infected urban youth and the association of vitamin supplementation with higher BMD in HIV-infected

children may warrant periodic screening for vitamin D deficiency by measurement of plasma 25-OH-vitamin D in this population *[21, 38]*. In addition, until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DEXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with TDF. 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 *[32]*. Radionuclide bone scan and CT may be considered if the earlier tests are negative but the clinical suspicion of disease is high *[32]*. 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 *[32, 39]*.

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 low BMD *[35]*. 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. Vitamin D supplementation is recommended for patients with low levels of 25-OH-vitamin D. At least one study in HIV-infected adults reported no beneficial effect on BMD of withdrawal of PI therapy *[3, 40]*. For children who experience significant loss of BMD associated with TDF treatment, TDF should be discontinued if alternative HIV-suppressive antiretroviral regimens are available; however, the frequent use of TDF in salvage regimens for highly ARV-experienced children may require the goal of achieving or maintaining HIV suppression to be balanced against the potential long-term risk of fractures on an individual basis.

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 drugs such as bisphosphonates might be considered but these drugs are not currently licensed for use in children. Parenteral (clodronate disodium, pamidronate, zoledronic acid) and oral (alendronate) bisphosphonates have been used in clinical trials of children with non-HIV chronic illnesses that are associated with atraumatic fractures, osteonecrosis and/or severe bone pain *[41-48]*. 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. There have been no studies of bisphosphonates in HIV infected children; however, in two studies of HIV-infected adults with osteopenia or osteoporosis, oral alendronate, in addition to vitamin D and calcium supplementation, appeared to be a safe and effective treatment to improve BMD *[49, 50]*.

The early stages of osteonecrosis may be managed conservatively (e.g., decreased weight bearing on the affected joint and use of analgesic as needed) *[32]*. 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 *[51, 52]*. 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, 32, 35]*.

Table: Risk factors, diagnosis, and therapy of bone disorders in children with HIV

Disorder	Major Risk Factors	Assessment and Monitoring	Treatment
Low Bone Mineral Density (BMD)	Growth delay, delayed puberty, longer HIV infection duration, non-black race, greater HIV disease severity, smoking, steroid use, low BMI, TDF	Nutritional intake assessment Serum 25-OH-Vitamin D [(a)] DEXA [(b)]	• Ensure Calcium and vitamin D sufficiency • Exercise (weight bearing) • Reduction in modifiable risk factors (smoking, BMI, steroids, TDF) • Role of bisphosphonates not established
Osteonecrosis	Steroid use, alcohol abuse, hemoglobinopathies, hyperlipidemia, pancreatitis, low BMD, hypercoagulable states	History & Physical (limb or joint pain, tenderness, limited movement) Diagnosis: plain radiograph or MRI	• Analgesics • Early disease: non weight bearing • More advanced disease: surgery

(a) Some experts would periodically measure 25-OH-Vitamin D, especially in HIV-infected urban youth because of high prevalence of vitamin D insufficiency.
(b) Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DEXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with TDF.

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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 including HIV infection itself, HIV-related conditions, or to ARV or other drug therapy that must be differentiated to direct appropriate management. Children with advanced or untreated HIV infection may develop bone marrow suppression or autoimmune disease, resulting in anemia, neutropenia, and/or thrombocytopenia. These hematologic complications may improve with initiation of effective ARV therapy. AIDS-related conditions, such as disseminated or extrapulmonary *Mycobacterium avium* complex and other atypical mycobacterial species, cytomegalovirus disease, or lymphoma, may contribute to hematologic abnormalities. Hematologic complications resulting from these non-ARV-associated conditions require specific therapeutic strategies; therefore initial efforts should be made to identify the causative factors. 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 may be difficult to identify the individual contribution of newer ARVs to hematologic adverse reactions.

Anemia as a consequence of ARV 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 treatment, 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]*.

Neutropenia (absolute neutrophil count [ANC] <500 cells/mm^3) as a consequence of ARV therapy is common. According to many pediatric HIV experts, the definition of clinically significant severe neutropenia in an HIV-infected child differs markedly from the criteria that apply 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. Infectious complications of neutropenia generally occur when neutropenia is severe (ANC <250 cells/mm^3) and prolonged. Neutropenia as a complication of ARV therapy is most often attributed to the use of ZDV; however, the contribution of other agents is difficult to determine. In PACTG 152, neutropenia (ANC<500 cells/mm^3) 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 (ANC<500 cells/mm^3), occurring in 6.1% of patients *[3]*. PACTG 382, a study evaluating the combination of EFV, NFV, and NRTIs, identified neutropenia (ANC<500 cells/mm^3) in 12% of children *[2]*. Similarly, in PACTG 377, a study enrolling NRTI-experienced children to receive 1 of 4 regimens without ZDV (combinations of d4T, 3TC, NVP, and NFV), neutropenia (ANC<500 cells/mm^3) was reported in 9%–23% of patients in each treatment arm *[4]*. 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 *[5]*. Thrombocytopenia is most likely a complication of HIV infection, and not a complication of ARV therapy. It was reported to occur in up to 30% of untreated children with HIV infection early in the pediatric HIV epidemic. Severe thrombocytopenia (platelet count <20,000 cells/mm^3) 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 *[6]*. Children with undiagnosed and untreated HIV infection may present with thrombocytopenia as the first manifestation of disease. This appears to be much more common than the development of thrombocytopenia secondary to ARV therapy *[7, 8]*. Thrombocytopenia may resolve once ARV therapy is initiated.

Recommendations for Monitoring

Complete blood count (CBC) with differential and platelet count should be performed at regular intervals based on the child's stage of disease and past medical history. This may be monthly for children with more severe disease or who have recently changed ARV 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 hematologic abnormalities should be evaluated for other pathophysiologic processes that might result in or contribute to anemia, neutropenia, or thrombocytopenia. Conditions such as hemoglobinopathies or G6PD enzyme deficiency may contribute to hematologic adverse events. If opportunistic infection, secondary malignancy, nutritional deficiency, or worsening HIV status is unlikely, the 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 possible to switch the presumed culprit drug to another drug of the same class if options for treatment are available, safe, and effective. In a child with limited therapeutic options due to HIV resistance or previous intolerance, a simple switch may not be possible. Furthermore, in a child with an excellent antiviral response with one ARV regimen, a switch may risk a loss of the antiviral effect. 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 <7.0–8.0 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 50–200 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 (ANC >250 cells/mm^3 in children >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 (ANC <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 5–10 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.

Monitoring and management of anemia in HIV-exposed infants

Anemia has also been also documented in HIV-exposed neonates receiving ZDV for 6 weeks as a component of a prophylaxis regimen to prevent perinatal HIV transmission. In PACTG 076, infants in the ZDV group had lower hemoglobin at birth than infants in the placebo group, with the maximal difference (1 gm/dL) occurring at age 3 weeks *[14]*. The lowest mean value for hemoglobin (10 gm/dL) occurred at 6 weeks of age in the ZDV group. By 12 weeks of age, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed.

A CBC with leukocyte differential count should be performed on the HIV-exposed newborn as a baseline evaluation before administration of ZDV. Decisions about timing of subsequent hematologic monitoring of infants following birth will depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the child, receipt of concomitant medications, and maternal antepartum therapy. Some experts recheck hematologic values in healthy infants receiving ZDV prophylaxis only if the child is symptomatic, while others recheck hemoglobin and neutrophil count after 4 weeks of ZDV treatment. For infants exposed to combination antiretroviral therapy *in utero* or during the neonatal period, more intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life is advised.

If hematologic abnormalities are found in the HIV-exposed infant receiving prophylaxis, decisions on whether to continue ARV therapy need to be individualized. Some of the considerations include the extent of the abnormality, whether the child has any symptoms, duration of the infant prophylaxis received, the risk of HIV infection in the infant (as assessed by whether the mother had received antiretroviral prophylaxis and her viral load near delivery), and availability of alternative interventions (e.g., erythropoietin, transfusion). Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Table: Hematologic Complications

Complication	Monitoring	Management
Anemia		
HIV-exposed newborns on prophylaxis	Baseline; with symptoms	If severe and has received ≥4 weeks of ZDV, consider stopping ZDV if low risk for transmission in consultation with an HIV expert
HIV-infected on ARV therapy	Baseline; every 3–4 months	Evaluate for contributing opportunistic infections or malignancy. Change ARVs if acceptable therapeutic options exist. Support with erythropoietin if necessary. In rare cases, transfuse.
Neutropenia	Baseline, every 3–4 months, more frequently if more severe disease	Generally well tolerated. If <250 cells/mm^3 or symptomatic evaluate for contributing factors. Change ARV if acceptable therapeutic options exist. Consider granulocyte colony stimulating factor (G-CSF).
Thrombocytopenia (<100,000 cells/mm^3)	Baseline, every 3–4 months, more frequently if more severe disease	Evaluate for contributing opportunistic infections or malignancy. If severe (<20,000 cells/mm^3) or bleeding occurs treat with IV immunoglobulin (1 gm/kg/day for 2–3 consecutive days). Consider anti-D antibody 50 ug/kg every 4–6 weeks in Rh(D) positive children; if these fail corticosteroids may be tried, followed by splenectomy as a last resort.

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Hypersensitivity Reactions and Skin Rashes

Background

Skin rashes and hypersensitivity reactions are potential concerns following administration of any medication. While skin rash may accompany a hypersensitivity reaction, hypersensitivity reactions may also occur in the absence of a rash. Evaluation requires careful consideration of the type of antiretroviral medication and other medications that the patient is receiving, the timing of the onset of rash or symptoms, and investigation of intercurrent illness as the possible etiology.

Clinical Manifestations

Cutaneous Reactions:
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 non-nucleoside reverse transcriptase inhibitors (NNRTI's) *[1, 2]*.

In both adults and pediatric patients, most cutaneous adverse events occur with the NNRTIs. Rash develops in approximately 17% of adult nevirapine (NVP) recipients; 6%–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]*. In clinical trials of children, a mild, diffuse rash developed in 21%–27% of NVP recipients and a severe (grade 3 or 4) rash developed in 6%–15% *[4-6]*. 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. Rash generally

occurs during the first 2 to 4 weeks of treatment and usually does not occur after 8 weeks of therapy. The rash is usually maculopapular, confluent, and erythematous. It most commonly involves the arms and trunk. Cutaneous reactions may also occur in patients receiving EFV; a mild rash occurred in 4 of 10 children as the most common adverse affect *[7]*. In general, these EFV-associated skin rashes are less severe than those with NVP and resolution of the rash during EFV treatment continuation is common.

Rash has also occurred in children receiving antiretroviral regimens containing nucleoside reverse transcriptase inhibitors (NRTIs) alone, with or without ABC *[8]*, or in combinations with protease inhibitors (PIs) *[9-12]*. A history of sulfonamide allergy may be important in patients receiving PIs that have sulfa moieties such as amprenavir, fosamprenavir, tipranavir, and darunavir. The sulfa moiety may cause cross reaction and risk for hypersensitivity reaction to these antiretroviral medications. Antiretroviral medications more commonly associated with rash are listed in Table 1.

Enfuvirtide, an HIV fusion inhibitor, is administered by subcutaneous injection. Injection site reactions occur in nearly all patients who receive enfuvirtide (up to 98% in published clinical trials) *[13-16]*. The injection site reactions include induration, erythema, and subcutaneous nodules or cysts. Most reactions are reported as mild or moderate in intensity. In adult and pediatric patients, the injection site reactions have resulted in treatment discontinuation in <3% of patients receiving enfuvirtide. Histopathologically, the lesions are interstitial granulomatous drug reactions *[17]*. The lesion usually resolves in <7 days.

Hypersensitivity Syndrome

While rash is common with many hypersensitivity reactions, hypersensitivity to antiretroviral medications can result in numerous other symptoms, with or without rash. Anaphylaxis has rarely been reported as caused by antiretroviral medication *[18, 19]*. However, because antiretroviral medications are not common causes of IgE mediated hypersensitivity, anaphylaxis or anaphylactoid reactions, other causes should be investigated. The hypersensitivity reactions of most concern with antiretroviral drugs include those associated with ABC and NVP. Hypersensitivity reactions to ABC occur in 5% of patients (range 0 to14) *[20, 21]*. ABC hypersensitivity occurs more frequently in treatment-naïve patients and in patients with specific genetic markers (HLA-B*5701, HLA-DR7 and HLA-DQ3) *[20, 21]*. Meta-analysis supports decreased risk in patients of African descent *[22]*. ABC causes a potentially fatal systemic illness characterized by fever, rash, nausea, vomiting, diarrhea, fatigue, flank or abdominal pain, myalgia, and arthralgia *[20]*. 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.
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). Symptoms are acute in onset and worsen after each dose of ABC. If ABC is continued, symptoms may deteriorate to include hypotension, respiratory distress, and vascular collapse.

A hypersensitivity syndrome has also been reported with NVP sometimes preceding or occurring without a skin rash. Systemic symptoms such as fever, myalgia, arthralgia, hepatitis, and eosinophilia may be noted as part of the NVP hypersensitivity reaction. Severe, life threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (less common in children than in adults) have occurred sometimes in association with rash or other signs or symptoms of hypersensitivity reaction (see, "Hepatic Toxicity"). The hypersensitivity reaction is most commonly noted early in therapy; it is unusual after 12 weeks of treatment. Life-threatening hepatic events have been observed with greater frequency in treatment-naïve women with CD4 counts >250/mm^3 and men with pretreatment CD4 counts >400/mm^3 *[23]*. Given these data it is recommended that NVP use in treatment naïve adults is limited to use in women with pretreatment CD4 counts ≤250/mm^3 and men with pretreatment CD4 counts ≤400/mm^3. Symptomatic hepatic events have not been reported in infants or mothers receiving single dose NVP regimens for prevention of perinatal HIV infection. In children, hepatic toxicity due to NVP is less frequent than in adults and has not been associated with pretreatment CD4 values.

Unexplained hypersensitivity reactions have been reported in clinical trials with enfuvirtide *[13-15]*. This syndrome may include fever, rash, and shortness of breath.

Evaluation

Key points to address in evaluating rash or hypersensitivity include: current history of antiretroviral medication administration; prior antiretroviral drug reaction history; temporal relationship between administration of the medication and onset of the symptom(s); listing of all medications with start and stop dates and dose changes; and identification of other possible causes of the signs and symptoms. Table 1 lists the typical timing of the onset of symptoms following the start of the antiretroviral medication. A history of length of time that the patient has been on each medication is informative because often the hypersensitivity reaction or rash is caused by one of the more recently added medications of the overall regimen.

Patients with symptoms suggesting a hypersensitivity reaction should have a complete blood count with differential and platelets, creatinine, and hepatic transaminases performed. Laboratory abnormalities found with ABC hypersensitivity may include atypical lymphocytosis, eosinophilia, thrombocytopenia and elevated creatine phosphokinase, creatinine, and hepatic transaminases. Clinical symptoms and examination may demonstrate the need for further evaluation of these or other organ systems. For example, physical examination findings such as right upper quadrant abdominal tenderness and/or jaundice indicate more severe liver toxicity. Respiratory symptoms and abnormal lung findings such as wheezing or crackles indicate the need for a chest radiograph and evaluation for hypoxemia. Patients should be followed closely as symptoms may worsen even after the medication has been discontinued.

Management of Cutaneous Eruptions and Hypersensitivity Syndrome

Discontinuation is appropriate and rechallenge is contraindicted 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.

Nevirapine

Use of the standard 14-day once daily lead-in period for NVP treatment has been shown to reduce the frequency of rash (see, "Appendix", for specific dosing information). Nevirapine elimination increases up to 2-fold over the first several weeks of therapy because of autoinduction of enzymes involved in its metabolism. The standard lead-in dose used in the first 2 weeks of therapy avoids elevated NVP concentrations thus reducing the risk of rash *[3]*. In addition, NVP may be continued in the presence of mild or moderate non-urticarial rash during the lead-in phase, as spontaneous resolution of the rash can occur. However, since progression of the rash may occur with continued administration of NVP, patients with rash require close monitoring; if the patient has urticaria or increased hepatic transaminases, NVP should be discontinued. The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period

should not have the NVP dose increased until the rash has resolved. The risk of developing resistance with extended lead-in dosing is unknown and of concern and must be weighed against the patient's overall tolerability of the regimen and the current antiviral response. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. NVP should be stopped if the rash is severe or is worsening or progressing.

Children receiving NVP should routinely have hepatic transaminases performed at baseline, prior to dose escalation, 2 weeks post dose escalation, and at 3 month intervals thereafter. Skin rash that develops in children who are receiving NVP therapy is an indication to check and follow hepatic transaminases even more closely.

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 or hepatic toxicity. 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 or antihistamines (cetirizine) *[24, 25]* given during the lead-in phase can prevent NVP-associated rashes or hypersensitivity syndrome *[26]*.

Cross-reactivity among NNRTIs may occur. However, in children with mild or moderate rash without mucosal involvement or systemic symptoms, substitution of a different NNRTI other than NVP, such as efavirenz (EFV), should be done with caution. It is prudent to avoid other currently available NNRTIs, delavirdine and EFV, in children who develop the more severe adverse effects following receipt of NVP. Also, as rash can occur with EFV as well, if EFV-associated rash is severe, or accompanied by mucosal or systemic symptoms, EFV should be permanently discontinued.

NVP should be permanently discontinued for any patient who develops the hypersensitivity syndrome with or without rash, and use of delavirdine and EFV should be avoided. Reactions may worsen temporarily after drug discontinuation. Treatment is supportive. DRESS syndrome and Stevens Johnson syndrome are sometimes treated with corticosteroids; however, use of corticosteroids remains controversial *[27]*.

Abacavir

Reaction to ABC necessitates permanent discontinuation of the medication. Discontinuation of ABC will usually result in improvement in a few days, although symptoms may continue to worsen for 1 to 2 more days after ABC is discontinued. ABC should never be restarted following a hypersensitivity reaction, since anaphylactic-like reactions (some fatal) with hypotension, renal failure, and/or bronchoconstriction and respiratory insufficiency, have occurred within hours of rechallenge *[26]*. Treatment is supportive. Antipruritics and corticosteroids do not appear to help.

Enfuvirtide

Management of local injection site reactions caused by enfuvirtide include rotating injection sites, avoiding existing injection site reactions, and following manufacturer's instructions for injection. 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. Enfuvirtide should be discontinued if the systemic hypersensitivity reaction occurs. Rechallenge is contraindicated as the syndrome has recurred with rechallenge.

Other Considerations

In addition to antiretroviral medications, HIV-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 *[28]*. Concomitant medications may make it difficult to determine which is the offending medication in the HIV-infected child with a drug rash.

Table: Skin Rash and Hypersensitivity* (Page 1 of 2)

Adverse Event	ARVs	Onset, Clinical Findings and Management
Skin Rash	***Common*** (>10% adults and/or children) NVP, EFV, DLV, APV, f-APV, ATV ***Less common*** (5%–10%) ABC, DRV, TPV	**Onset and Clinical Findings** Onset in the first few days to weeks after starting therapy. Most rashes are mild to moderate, diffuse and maculopapular. **Management** •Mild to moderate rash can be managed by use of an antihistamine as needed and the antiretroviral medication can be continued. •The antiretroviral medication should be discontinued if the rash is severe (accompanied by blisters, fever, involvement of the oral/anal mucous membranes, conjunctivitis, edema, arthralgias) or if systemic symptoms occur. Do not restart the medication. •Hepatic transaminases should be measured if rash develops with NVP treatment (see NVP hypersensitivity). If hepatic transaminases are elevated, NVP should be discontinued and not restarted.
	Enfuvirtide (>90%)	**Onset and Clinical Findings** •Local injection site reaction with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. **Management** •Continue the agent as tolerated by the patient and adjust injection technique, rotate injection sites.
Stevens-Johnson Syndrome	***Infrequent:*** NVP (0.3%), EFV (0.1%), DLV (0.1%) ***Case reports:*** APV, f-APV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	**Onset and Clinical Findings** •Onset in the first few days to weeks after initiating therapy. Skin eruption occurs with mucous membrane ulceration; conjunctivitis. Can evolve into blister/bullae formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, and arthralgia. **Management** •Discontinue all ARVs and other possible agents such as cotrimoxazole. •May need intensive care support, intravenous hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, antibiotics in case of superinfection. •Corticosteroids and/or IVIG are sometimes used but use of each is controversial. •Do not reintroduce the offending ARV. In case of NNRTIs, avoid use of currently available NNRTIs (NVP, EFV, or DLV) in the new regimen.

* Skin rash and allergic reaction has been reported for each of the ARV medications. The most common ARVs causing skin rash are listed in the table.

Table: Skin Rash and Hypersensitivity* (Page 2 of 2)

Adverse Event	ARVs	Onset, Clinical Findings and Management
Hypersensitivity Reaction	ABC (3.7%)	**Onset and Clinical Findings** •Onset within the first 6 weeks with first use; within hours with reintroduction. •Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. Symptoms can mimic anaphylaxis with rechallenge. **Management** •Discontinue ARVs and investigate for other causes of the symptoms such as an intercurrent viral illness. Treat symptoms as necessary. •Most symptoms resolve by 48 hours after discontinuation of ABC. •Do not rechallenge with ABC.
	NVP 4% (2.5%–11%)	**Onset and Clinical Findings** •Onset is most frequent in the first few weeks of therapy but can occur through 18 weeks. Flu like symptoms including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice, with or without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been described. **Management** •Discontinue ARVs. •Consider other causes for hepatitis and discontinue all hepatotoxic medications. •Supportive care as indicated and close monitoring •Do not reintroduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
	Enfuvirtide (<1%)	**Onset and Clinical Findings** •Onset any time during therapy. Symptoms may include rash, fever, nausea, vomiting, rigors, hypertension, elevated hepatic transaminases. **Management** •Discontinue ARVs •Rechallenge with enfuvirtide is not recommended.

* Skin rash and allergic reaction has been reported for each of the ARV medications. The most common ARVs causing skin rash are listed in the table.

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