Metabolic and Hepatobiliary Side Effects of Antiretroviral Therapy (ART)

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KEYWORDS

• HAART • Hepatobiliary • Metabolic
• Adverse drug events • Side effects

Highly active antiretroviral therapy (HAART), introduced in 1996, refers to the combination of 3 to 4 antiretroviral drugs used to prevent the progression of disease in patients infected by human immunodeficiency virus (HIV). Previously used monotherapy to treat HIV led to a high level of resistance, and was inferior to regimens that include 3 or more drugs.[1] Several different classes of drugs are used in HAART; the earliest included nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). Recently, additional classes have emerged which include fusion inhibitors, chemokine receptor inhibitors, and integrase inhibitors. It was initially perceived that this combination of antiretroviral therapy (ART) would be a cure for HIV, as it often produced remarkable recovery, and arrested the progression of the disease. However, these findings were spurious and HIV is now considered a chronic disease that can be managed medically. A plethora of literature shows that ART has considerably decreased morbidity and mortality from infectious complications of HIV.[2,3] Life expectancy of young patients infected with HIV was 9.1 years in the pre-HAART era of the early 1990s, but now has increased to 23 to 35 years.[1]

Although the prevalence of opportunistic infections, AIDS-related illnesses, and complications have declined dramatically, it seems that patients infected with HIV on ART are now suffering from more HIV-related chronic illnesses including hepatic,

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Emerg Med Clin N Am 28 (2010) 409–419
doi:10.1016/j.emc.2010.01.011 **emed.theclinics.com**
0733-8627/10/$ – see front matter

cardiovascular, and pulmonary diseases.[4–6] The increased use of ART has been associated with the development of these chronic illnesses and adverse drug events.[3,5] It is important for the emergency physician to appreciate this phenomenon, as it has changed the traditional diagnoses of patients with HIV presenting to the emergency department (ED).[5] In 1 study the most prevalent diagnosis of patients with HIV discharged from the ED was ill-defined symptoms/signs.[7] There was no follow-up in this study, but some of these patients may have had unrecognized complications from ART.[4,8]

Although ART for HIV has been in use since 1987, the initiation of HAART has produced an increase in adverse drug reactions.[2,3] This is a new challenge as many of the adverse drug reactions attributable to ART may be indistinguishable from non–drug-related illnesses.[9] The emergency physician must be aware of the potential complications of ART as affected patients may present with nonspecific symptoms. The focus of this article is the metabolic and hepatobiliary adverse effects of ART. Complications are presented based on clinical effects rather than drug class. This is more practical for several reasons; first there are almost 30 different medications within the category of ART today and many medications have several names or abbreviations.[8] Several ART drugs have been combined into single pill regimens, creating another potential area of confusion. Patients on ART may not always know, remember, or be able to communicate their exact regimen. Several adverse effects overlap drug classes and it is more important to recognize and manage potential complications than to focus narrowly on adverse events known to occur from a given class. **Table 1** provides a quick reference to the drugs found in each class of ART and associated metabolic and hepatobiliary complications.

PHARMACOLOGY OF ART

The abbreviation NRTI refers to either nucleoside reverse transcriptase inhibitors or nucleotide reverse transcriptase inhibitors. Both have essentially the same mechanism of action; they are analogues of native deoxynucleotides, such as thymidine, guanosine, or uridine. The only difference between these 2 classes is that nucleosides need to be phosphorylated once they enter the cell. Their structure allows them to be incorporated into the growing viral DNA strand in place of their analogous nucleotide, acting as a competitive inhibitor of HIV-1 reverse transcriptase. This incorporation results in the premature termination of the growing viral DNA strand because they lack an essential hydroxyl group needed to create the proper bond linking the next nucleotide. NRTIs are the cornerstone of ART. NNRTIs are noncompetitive inhibitors of HIV-1 reverse transcriptase, binding to a different site than NRTIs. This mechanism allows them to be used synergistically with NRTIs to decrease viral DNA reverse transcription. Protease inhibitors (PIs) prevent posttranslational enzyme activity in the final steps of HIV viral protein processing rendering them immature and noninfectious.

Newer drugs have emerged and have become incorporated into ART. Entry (fusion) inhibitors interfere with the complex binding and fusion of the HIV virus into the host cell. Chemokine coreceptor antagonists, considered by some to be a subclass of entry inhibitors, specifically arrest the entry of the HIV into the host cell by blocking receptors on the surface that are required for binding. Integrase inhibitors are able to block the action of the viral enzyme integrase that is responsible for the critical step of inserting the viral DNA into the host genome. These medications are relatively new and, although hepatotoxicity is a recognized adverse drug reaction (ADR), there is less known about the other possible adverse effects of these medications.

Table 1
Antiretroviral drugs used in ART, and associated metabolic and hepatobiliary adverse effects

Medication Class	Associated Adverse Effects
NRTI (nucleoside/nucleotide reverse transcriptase inhibitors)	
Abacavir (Ziagen, ABC) Didanosine (Videx, ddI) Emtricitabine (Emtriva, FTC) Lamivudine (Epivir, 3TC) Stavudine (Zerit, d4T) Tenofovir (Viread, TDF) Zalcitabine (Hivid, ddC) Zidovudine (Retrovir, AZT, ZDV)	Hepatotoxicity Hepatic steatosis Pancreatitis Hypersensitivity syndrome Lactic acidosis
NNRTI (non-nucleoside reverse transcriptase inhibitors)	
Delavirdine (Rescriptor, DLV) Efavirenz (Sustiva, Stocrin, EFV) Etravirine (Intelence, TMC 125) Nevirapine (Viramune, NVP)	Hepatotoxicity Hepatic necrosis Hypersensitivity syndrome
Protease inhibitors	
Amprenavir (Agenerase, APV) Atazanavir (Reyataz, ATV) Darunavir (Prezista, DRV, TMC 114) Fosamprenavir (Lexiva, Telzir, FPV) Indinavir (Crixivan, IDV) Lopinavir/ritonavir (Kaletra) Nelfinavir (Viracept, NFV) Ritonavir (Norvir, RTV) Saquinavir (Invirase, SQV) Tipranavir (Aptivus, TPV)	Hepatotoxicity Hyperbilirubinemia Pancreatitis Dyslipidemia Hyperglycemia/insulin resistance Lipodystrophy
Entry (fusion) inhibitors	
Enfuvirtide (Fuzeon, ENF, T-20)	Hepatotoxicity Hypertriglyceridemia Hypersensitivity syndrome
Chemokine coreceptor antagonists	
Maraviroc (Selzentry, Celsentri, MVC)	Hepatotoxicity Lipodystrophy Hypersensitivity syndrome
Chemokine coreceptor antagonists	
Raltegravir (Isentress, RAL)	Hepatotoxicity Hypersensitivity syndrome

The latest recommended starting HAART regimens for patients who are naive to antiretroviral treatment are 1 of the following 2 combinations: 1 NNRTI + 2 NRTIs, or 2 NRTIs + 1 PI.[4] Each class has many different options and practitioners take several factors into consideration when choosing specific drugs in each class such as toxicities, pill burden, dosing frequency, and drug-drug interactions.

HEPATOBILIARY COMPLICATIONS

It is often difficult to determine whether hepatic injury is a direct medication side effect, drug-drug interaction, or unrelated to medications. Hepatic injury from ART may result in long-term liver damage with jaundice, cirrhosis, and fulminant hepatic failure.[10] Liver toxicity in HIV-infected patients increases health care costs as a result of prolonged

hospital stays from ART associated toxicity.[9] Life-threatening events related to hepatic damage occur in about 2.6 per 100 person-years on ART.[8] Most effects are not life threatening but some patients who initially have benign presentations can progress to severe complications. Most hepatobiliary complications resolve with cessation of the inciting drug. Meticulous care must be taken to assess whether stopping part or all of the ART is needed. Patients who miss only a few doses of 1 or more of their medications even for a short period of time may develop viral resistance.[4,11]

Almost all antiretroviral drugs have been associated with hepatotoxicity as most of them are metabolized by the liver and the cytochrome P450 enzyme system.[4,8,10,11] Drug-induced hepatic injury may fall into 3 categories: hepatocellular, cholestatic, and a combination of the 2. Hepatocellular injury is direct hepatocyte damage that is often reflected by an elevation in transaminases.[8] Cholestatic injury occurs from blockage or damage to the biliary tree and is often reflected by elevations in bilirubin, γ-glutamyl transferase, and alkaline phosphatase.[8]

Once hepatic injury is suspected, the first step in the ED is to establish that the patient does not have signs or laboratory abnormalities consistent with hepatic compromise, such as ascites, hyperbilirubinemia, coagulopathy, or encephalopathy.[11] When evaluating a patient in the ED it is probably safe to hold their ART while determining their disposition. Ultrasound and computed tomography (CT) may show signs of hepatic abnormalities, but do not differentiate drug-related from non–drug-related injury.[11] Even a liver biopsy may be not be sufficient to distinguish a drug reaction from another medical cause.[8] Although there is no clear evidence or consensus to date on which patients require admission, those who are symptomatic warrant observation or close follow-up within 12 to 24 hours to prevent the progression of 1 of the adverse events reviewed later in this article.

ARTs are believed to cause hepatotoxicity via 4 mechanisms: direct drug toxicity, hypersensitivity reactions, mitochondrial toxicity, and immune reconstitution.[8,10] The discussion in this article concentrates on the first 3 mechanisms and how each pertains to the hepatobiliary adverse effects. The fourth, immune reconstitution, is a response to dormant infections, including hepatitis, with the initiation of ART and is covered in another article.

Hepatitis and Increased Transaminase Levels

Hepatotoxicity resulting in hepatocellular damage may occur as a direct effect of the parent drug or via accumulation of toxic metabolites created via the cytochrome P450 system in the liver. Various genetic changes, drug interactions, and gene polymorphisms in the P450 system may significantly alter a patient's susceptibility to damage from a drug.[10] The most commonly used markers to screen for hepatocellular injury are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Both of these markers are sensitive for injury but have poor specificity and prognostic value. Hepatic injury is often defined as increases in AST/ALT levels that are 3 to 5 times more than the upper limits of normal or the patient's baseline values before initiation of ART. About 5% to 10% of patients have increased liver enzyme levels after the initiation of ART, with 6% to 18% progressing to severe hepatotoxicity.[8,11] Most patients have mild increases in their AST/ALT levels within the first few months of ART, which may occur with or without symptoms.[12] All drug classes of ART have the potential to cause severe liver injury progressing to fulminant hepatic failure.[12] Although the injury may be caused by ART, the differential diagnosis of such increases is vast, including acute or chronic viral hepatitis (hepatitis A, B, C or D, cytomegalovirus, Epstein-Barr virus), ethanol or substance abuse, systemic or opportunistic infections, nonalcoholic steatosis, and malignancies.[11,13]

In the ED, patients with hepatocellular damage warrant evaluation for drug-induced, viral-associated, or other causes of hepatotoxicity.[11] It is sensible to obtain a serum acetaminophen concentration given that this is one of the most common causes of fulminant hepatic failure worldwide. Patients infected with HIV with clinical signs of hepatitis, such as fatigue, nausea, vomiting, and right upper quadrant abdominal pain and tenderness should be admitted for further evaluation and treatment. Consideration must given to stopping 1 or more of the drugs in the patient's ART drug regimen if the symptoms are significant.[8] There are no clear guidelines on how to manage isolated transaminase increases that are mild and do not concurrently exist with signs of other organ dysfunction or hepatic compromise. These patients should have close follow-up and clear instructions to return to the ED if symptoms worsen.

Increase in Bilirubin Level

The PIs have been associated with hyperbilirubinemia. Atazanavir and indinivir cause isolated hyperbilirubinemia without increase in transaminase levels. About 40% of individuals receiving atazanavir develop a significant increase in their total bilirubin level, 5% of patients develop jaundice, although none of them develop clinically significant hepatotoxicity.[14] This increase in total bilirubin level may be caused by a similar mechanism as Gilbert syndrome involving inhibition of UGT1A1 (UDP glucuronosyl transferase), an enzyme required for conjugation of bilirubin.[15] Indinivir causes unconjugated hyperbilirubinemia in 10% of patients, also without any other evidence of hepatotoxicity. Similar to atazanivir, the mechanism of indinavir-related hyperbilirubinemia is also analogous to Gilbert syndrome and related to specific haplotypes of UDP glucuronosyl transferase.[16,17] Jaundice may occur without actual hepatic damage and is reversible if the drug is discontinued, but this may not be needed if the patient is asymptomatic.[8] Hyperbilirubinemia from PIs are not associated with hepatotoxicity and should not be confused with posthepatic cholestasis, which presents as a delayed increase in bilirubin level seen after hepatocellular injury caused by regeneration of hepatocytes reconnecting with the biliary tree.[12]

Hypersensitivity Syndrome

Hypersensitivity syndrome is a life-threatening syndrome that is caused by an immune reaction to either the parent drug or a metabolite.[10] The classic and probably most well-recognized cause is abacavir, an NRTI, but it also occurs with agents from other ART classes (see **Table 1**). The presence of the drug evokes an immune-mediated response that can affect the liver as well as other organs, such as the skin, lungs, kidney, and heart. It most often occurs within the first few days of initiating therapy, but may occur as late as 8 weeks. Appearing suddenly, patients reliably note an exacerbation and progression of symptoms with each successive dose. The most common symptoms are fever, rash, nausea, and vomiting. In abacavir hypersensitivity, 80% of patients have a fever, and 70% have a rash.[10] Patients may also exhibit myalgias, headache, diarrhea, pruritis, lymphadenopathy, mucocutaneous involvement, hypotension, and respiratory symptoms such as cough, dyspnea, or pharyngitis.[8,10,18] Hypersensitivity is usually associated with increased transaminase levels in addition to the presence of other laboratory abnormalities such as leukopenia, thrombocytopenia, increased serum creatinine level, increased creatine phosphokinase level, and eosinophilia.[12] It is critical to have a high suspicion for the presence of this syndrome, as it may progress rapidly to multisystem organ failure even with aggressive and appropriate supportive care.[12]

Although it may be difficult to distinguish hypersensitivity from infectious or other underlying disorders, it has been recommended that all ART be held if the patient

has 2 or more of the following symptoms: fever, rash, gastrointestinal symptoms, constitutional symptoms, and respiratory symptoms. In patients with mild symptoms or less than 2 of these symptoms, patients may continue to take their medications with close observation. Consultation with either the admitting physician or the patient's HIV primary care provider is suggested. The vague nature of these symptoms may result in over diagnosis of hypersensitivity, unnecessarily precluding the use of the suspected drug in the future.

Cessation of the offending agent is currently the only effective treatment, with resolution of most symptoms within 48 to 72 hours. Corticosteroids have failed to show a benefit in prophylaxis and therapy. Communication with the patient and any physician who cares for a patient with a suspected hypersensitivity reaction is critical.[12] Be aware that several medications combine abacavir with other drugs under completely different names and patients may not appreciate this potential hazard of unintended rechallenge.

Genetics may play a role in the occurrence and severity of adverse drug events. In the case of abacavir, there has been an association between developing hypersensitivity and several alleles including a strong link with HLA-B*5701. Currently genetic prescreening for HLA-B*5701 is recommended before initiation of abacavir for all patients.[10,19]

Hepatic Steatosis

Mitochondrial damage is believed to be a prominent cause of hepatic steatosis. The NRTIs can reduce the replication of mitochondrial DNA (mtDNA) in a manner similar to their effects on the HIV DNA replication.[13,20] mtDNA produces several of the subunits that form the electron transport chain found on the inner membranes of mitochondria. Without efficient functioning of this pathway, oxidative phosphorylation is impaired, which leads to an accumulation of fatty acids and other precursors in the cell. This results in hepatic steatosis, also known as nonalcoholic fatty liver disease.[20] It has also been associated with several metabolic and endocrine disorders, including diabetes, cirrhosis, metabolic syndrome, and cardiovascular disease. Hepatic steatosis may have a relatively benign or even asymptomatic presentation and may also mimic other diseases such as alcohol-induced liver injury, pregnancy steatosis, and Reye syndrome.[11] Patients may present with mild symptoms suggestive of hepatitis, such as abdominal pain, nausea, and vomiting. Hepatic steatosis rarely progresses to cause hepatic compromise.[21]

Lactic Acidosis

One of the most severe complications recognized as a risk of ART is the development of symptomatic hyperlactatemia with metabolic acidosis.[22] Lactate, under aerobic conditions, is oxidized to pyruvate using NAD+ and the enzymatic activity of lactate dehydrogenase. The mitochondrial toxicity responsible for causing hepatic steatosis may also cause this disorder, which seems to be exclusive to NRTIs.[20] Disruption of oxidative phosphorylation prevents aerobic energy production and eliminates lactate clearance.[13,23]

Several recognized criteria have been used to define this complication. Patients may have a lactic acidemia which refers to any increase in lactate more than normal without laboratory evidence of acidosis. Lactate increases are classified as mild (2–5 mmol/L), moderate (5–10 mmol/L), and severe (>10 mmol/L). A patient is considered to have lactic acidosis if their pH is less than 7.3 and bicarbonate less than 20 mEq/L with any abnormal increase in serum lactate level.[23] Patients may present with nonspecific symptoms such as fatigue, general malaise, nausea, vomiting,

abdominal pain, hepatotoxicity, tender hepatomegaly, peripheral edema, and ascites.[23] Severe cases may progress rapidly to cardiomyopathy, encephalopathy, peripheral neuropathy, pancreatitis, panyctopenia, fulminant hepatic failure, and cardiopulmonary shock.[8,20,23] Severe symptoms occur in up to 25.2 of every 1000 person-years of ART, with a mortality of 30% to 60%.[23]

In patients with no symptoms, a screening lactate is not indicated.[24] Because of the vague nature and poor correlation of symptoms to the degree of increase in lactate or acidosis, patients on ARTs who present to the ED with any systemic complaints should be screened with a venous lactate, pH, bicarbonate level, and hepatic function panel.[24] Lactic acidosis may develop within months to years after the initiation of ART (specifically an NRTI). Factors that increase the risk for this adverse event include NRTI use greater than 6 months, pregnancy, female sex, age greater than 40 years, lower CD4 count, concurrent use of stavudine and didanosine, use of hydroxyurea or ribavirin with didanosine, obesity, and an increased body mass index (calculated as weight in kilograms divided by the square of height in meters).[12,23,25]

Managing these patients in the ED varies based on the serum lactate concentrations, symptoms, and suspicion for other causes of increased lactate. Patients with moderate to severe increases in serum lactate level, with an acidosis, or who are symptomatic should have their NRTI discontinued immediately.[20] Any concurrent condition such as metabolic acidosis, renal failure, or other organ dysfunction should be addressed as usual. No systematic trials or clear consensus exists on how to treat these patients beyond drug discontinuation and supportive care. Adjunctive therapies used in the treatment of other causes of lactic acidosis, such as sodium bicarbonate therapy, mechanical ventilation, and hemodialysis with bicarbonate buffer have been used with some success, but none have proved to be routinely beneficial. Because of the proposed mechanism of mitochondrial dysfunction, several cofactors have also been used with varying success, including thiamine, riboflavin, L-carnitine, and coenzyme Q.[12,23] Although they are all relatively benign therapies, they also have yet to show a clear benefit.

Pancreatitis

Pancreatitis is a common adverse event attributable to ART. Advanced HIV disease alone is associated with an increased incidence of pancreatitis, but NRTI use is independently linked to this complication.[26] Patients present with complaints similar to patients with non-ART causes of pancreatitis, including nausea, abdominal pain, vomiting, and fever.[27,28] The incidence of pancreatitis in patients on didanosine (NRTI) ranges from 1% to 7%, with a 6% mortality if it occurs.[29] This complication occurs most often 2 to 5 months after the initiation of ART. The concurrent use of didanosine (NRTI) with hydroxyurea should be avoided as it dangerously multiplies the risk of pancreatitis 4-fold. Stavudine, an NRTI, seems to incur a greater risk of lactic acidosis compared with other NRTIs.[25] Other known risk factors are a CD4 count less than 200 cells/mm^3, age greater than 37 years old, increased baseline amylase, and female gender.[27,30,31]

The mechanism of pancreatic toxicity may be related to the mitochondrial toxicity of NRTIs, as discussed earlier for lactic acidosis and hepatic steatosis. PIs often induce hyperlipidemia, a known cause of pancreatitis. Patients who have clinical symptoms consistent with pancreatitis while on ART should have serum lipase concentrations measured. Increase in pancreatic enzymes 2 to 3 times more than normal with clinical symptoms confirms this diagnosis. There is no evidence to support the screening of pancreatic enzymes in patients who are asymptomatic.

Patients who develop pancreatitis while on ART are treated by discontinuing the drug, and providing supportive care including bowel rest, analgesics, intravenous fluid therapy, and parental nutrition if needed. In addition, controlling hyperlipidemia in patients on PIs may prevent as well as treat pancreatitis.

METABOLIC COMPLICATIONS

The metabolic complications associated with ARTs may indirectly increase the risk of several acute life-threatening conditions such as diabetic ketoacidosis and myocardial infarction. The treatment of these complications does not differ from the standard therapy provided for patients not infected with HIV, but physicians should recognize ART as a nontraditional risk factor for these medical diseases.

Hyperglycemia/Insulin Resistance

Before the development of ARTs, there was no recognized association between HIV infection and alterations in glucose metabolism. PIs have been found to cause hyperglycemia caused by peripheral insulin resistance resulting in diabetes mellitus in some patients and worsening diabetes in patients with preexisting disease.[32–35] Patients may develop hyperglycemia or present with diabetic ketoacidosis, generally within 11 weeks of starting a PI.[36] Specifically, indinivir is associated with hyperglycemia and insulin resistance in healthy volunteers without HIV infection, even after only 1 dose.[37] The mechanism of insulin resistance is likely related to the inhibition of the GLUT-4 transporter found in pancreatic, fat, skeletal, and cardiac muscles cells.[20,38] Another possible mechanism may be an increase in pancreatic β-islet cell apoptosis.[39]

Management is the same as that provided to patients without HIV, including the use of oral antidiabetic or hypoglycemic agents, the use of insulin, and close monitoring of serum glucose levels.[40] In the ED, patients on PIs should have their serum glucose levels checked. If increased, screening for diabetic ketoacidosis should include the assessment of serum pH, bicarbonate level, anion gap, and serum and/or urine ketones, as appropriate.

Dyslipidemia

Dyslipidemia, resulting in hypercholesterolemia, hypertriglyceridemia, increased low-density lipoproteins, and reduced high-density lipoproteins is another metabolic complication of ART specifically associated with PIs. These metabolic changes have been seen as early as a few weeks after initiation of ART. Enfuvirtide, a fusion inhibitor, increased triglycerides in 8.9% of patients in clinical trials.[41] Approximately 50% of patients after 1 year on ART have newly diagnosed hyperlipidemia.[20]

There are several mechanisms believed to cause the dyslipidemia associated with ARTs, each mediated by alterations in different receptors and enzymes.[20] Ultimately they result in increased lipoprotein synthesis and impaired lipoprotein clearance.[42]

Initially, patients on ART were not found to have an increased risk of cardiovascular events, but recent studies show that increased lipid panels and the risk of cardiovascular disease increases with each year that a patient takes a PI.[43] Therefore, in addition to traditional risk factors such as smoking and hypertension, it seems that ART use should also be considered a cardiovascular risk factor.

Lipodystrophy/Fat Redistribution Syndrome

For years, generalized wasting was commonly seen as a complication of HIV from a loss of muscle mass.[20] Lipodystrophy, or fat redistribution syndrome, results from a combination of lipohypertrophy and lipoatrophy in patients on PIs and NRTIs.[44]

Increased fat accumulation may result in a buffalo hump, truncal obesity, and breast enlargement. Concurrently, there may be loss of fat in the subcutaneous tissues of the face, arms, and legs, leading to an altered body habitus.[20] The overall result is often an appearance of truncal obesity with peripheral wasting. The prevalence of this ill-defined condition is wide, ranging from 10% to 64% at 1 year and as high as 83% when approaching 2 years on ART.[20]

The mechanism of lipodystrophy is unclear. Patients may be managed with diet and exercise, but this may only exacerbate peripheral wasting. Although many of these changes seem Cushingoid, they have not been associated with changes in cortisol levels. This syndrome does not seem to be an acute concern to emergency physicians, but it may represent an increased risk for the other metabolic adverse effects of ART.

ADVERSE EFFECTS OF ART IN OVERDOSE AND POSTEXPOSURE PROPHYLAXIS

There is limited experience with intentional overdose of ARTs, but it seems that there may be no additional risks associated with an overdose of these medications outside of the already recognized adverse effects. Seizures are reported from zidovudine (NRTI).[45] In patients who are naive to these drugs it would seem extremely unlikely that metabolic complications would occur following a single acute ingestion, but many of the hepatobiliary complications have occurred after only a few doses. Patients who overdose on these medications may be on them chronically, so the same metabolic and hepatobiliary complications discussed earlier should be considered. The most concerning acute ADR would be a hypersensitivity syndrome.

Another population to consider at risk for complications of ARTs is patients with exposures to HIV who require postexposure HIV prophylaxis (PEP). The latest PEP recommendations are to prescribe 2 to 4 agents consisting of combinations of NRTIs and PIs.[12] The duration of therapy is often suggested to be at least 4 weeks. This is a significant exposure given that almost all of the metabolic and hepatobiliary complications have been known to occur within the first 4 weeks of therapy.[8] Lactic acidosis has been documented in patients on PEP therapy.[30] It is recommended that nevirapine not be given for PEP because of cases of hypersensitivity syndrome, fulminant hepatic failure, and severe hepatotoxicity with the use of this drug in several otherwise healthy patients.[12]

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