Adverse effects of antiretroviral therapy for HIV infection

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Abstract

LONG-TERM REMISSION OF HIV-1 DISEASE CAN BE READILY ACHIEVED by combinations of antiretroviral agents. The suppression of plasma viral loads to less than the limit of quantification of the most sensitive commercially available assays (i.e., less than 50 copies/mL) and the coincident improvement in CD4 T cell counts is associated with resolution of established opportunistic infections and a decrease in the risk of new opportunistic infections. However, prolonged treatment with combination regimens can be difficult to sustain because of problems with adherence and toxic effects. All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient. A better understanding of the adverse effects of antiretroviral agents is of interest not only for HIV specialists as they try to optimize therapy, but also for other physicians who care for HIV-positive patients.

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The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality.[1–3] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/mL), toxic effects or noncompliance within the first 8 months of therapy.[4,5] Several strategies have been implemented to improve treatment duration. While development of new antiretroviral agents continues, efforts to maximize the effectiveness of currently available treatments include attempts to better understand and manage adverse effects. Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly, class-specific adverse effects may occur. One of the drug classes used in HAART is the nucleoside reverse transcriptase inhibitors (NRTIs), which commonly form the "backbone" of the antiretroviral cocktail; this class includes zidovudine (AZT), lamivudine, didanosine (ddI), stavudine (d4T), abacavir (ABC) and the newly released nucleotide analogue tenofovir. Two NRTIs are often combined with 1 medication from either of the 2 remaining classes, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs). The NNRTI class comprises nevirapine (NVP), delavirdine (DLV) and efavirenz (EFV). The dosages and adverse effects of all 3 classes of medications are listed in Table 1.

In this article we review the adverse effects of HAART therapy, with specific attention to the metabolic abnormalities associated with HIV treatment, including dyslipidemias, diabetes mellitus, insulin resistance, and the lipodystrophy syndrome and lactic acidosis associated with NRTI mitochondrial toxicity. Our aim is to help physicians gain a working knowledge of these adverse effects, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, promoting the early recognition and reversal of potentially serious adverse effects, and reducing the potential for adverse drug interactions.

Significant antiretroviral adverse effects

Antiretroviral therapy can have a wide range of adverse effects on the human body (Fig. 1). Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy.[6] Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV. Several uncommon but more serious adverse effects associated with antiretroviral therapy, including AZT-associated anemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity (exemplified by pruritus and ingrown toenails) and NNRTI-associated hypersensitivity reactions, are treated according to accepted therapy for these conditions in patients not receiving HAART. However, the subtle and serious nature of other adverse effects — lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash — warrant more detailed discussion.

Lactic acidosis, hepatic steatosis and hyperlactatemia

NRTIs are nucleoside analogues that prevent DNA elongation and viral reproduction. These drugs are triphosphorylated intracellularly to become nucleotides and are then incorporated into the viral DNA chain by the viral reverse transcription enzyme; their presence in the DNA

halts transcription. Unfortunately, these drugs can theoretically also function as substrates for other enzymes capable of DNA formation, including human DNA polymerase γ,[7] the only enzyme involved in the replication of mitochondrial DNA. Recent work has described disruption of mitochondrial function through NRTI-mediated inhibition of human DNA polymerase γ, with subsequent adverse events ranging from nucleoside-associated lactic acidosis to hepatic steatosis.[8–13]

Lactic acidosis has been associated with AZT, ddI and d4T therapy.[6–14] Fortgang and associates[15] estimated that the incidence of NRTI-associated lactic acidosis was 1.3 per 1000 person-years. However, these researchers reviewed patients who had each been treated with a single antiretroviral agent, and their results may underestimate the incidence of NRTI-associated lactic acidosis in the current era of triple therapy. Given its potential lethality, awareness of the signs and symptoms of NRTI-associated lactic acidosis (Box 1) is important in the management of HIV-infected patients. The clinical course is characterized by often vague complaints of malaise, nausea and vomiting, fatigue and tachypnea,[16] followed by liver failure, cardiac dysrhythmias and death.

In addition to this serious but rare syndrome, there is evidence of a persistent mild to moderate elevation of venous lactic acid (hyperlactatemia) in 10% to 20% of patients undergoing long-term treatment with NRTI-containing regimens.[17–22] Patients with hyperlactatemia may have a decreased anaerobic threshold, which is a surrogate for underlying mitochondrial dysfunction.[17] The hyperlactatemia and associated symptoms tend to resolve when NRTIs are discontinued,[18] although resolution may be slow. In a recent case series (20 patients) the mean time to resolution was 62 (range 7 to 176) days.[19] Hyperlactatemia has been independently associated with exposure to d4T and hydroxyurea.[20,21]

The mechanism of NRTI-associated lactic acidosis is shown in Fig. 2. During normal glycolysis, glucose is converted to pyruvate (in the cytosol), which is then transferred into the mitochondria. There, most of the pyruvate is converted into acetylcoenzyme A, which in turn enters the tricarboxylic acid cycle to form NADH (the reduced

Table 1: Antiretroviral medications and their adverse effects

Drug	Abbreviation	Dosage	Most common adverse effects	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)				
Zidovudine	AZT	400–600 mg/d, divided (i.e., administered bid)	Nausea, headache, rash, anemia, leukopenia, elevation of liver enzyme levels, elevation of lactic acid level, elevation of CPK level	Should not be combined with d4T
Lamivudine	3TC	150 mg bid	Neutropenia (rare)	
Didanosine	ddI	Body weight 35–49 kg: 100 mg bid Body weight > 50 kg: 200 mg bid	GI intolerance, pancreatitis, gout, reversible peripheral neuropathy	Should not be combined with ddC. Should be taken separately from food. Full daily dose can be given once daily
Didanosine-EC	ddI-EC	Body weight > 50 kg: 400 mg once daily		
Zalcitabine	ddC	0.75 mg tid	Reversible peripheral neuropathy, mouth ulcers, pancreatitis	Should not be combined with d4T or ddI. Relatively weak risk–benefit ratio limits usefulness
Stavudine	d4T	Body weight 40–60 kg: 30 mg bid Body weight > 60 kg: 40 mg bid	Reversible peripheral neuropathy, lactic acid elevation (rarely fatal)	Should not be combined with AZT
Tenofovir	TDF	300 mg once daily	GI upset, low phosphate levels	
Abacavir	ABC	300 mg bid	Hypersensitivity reaction, which may be characterized by fever, rash, myalgias, arthralgias, malaise	Reaction may be fatal if medication is continued or patient is rechallenged
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine	NVP	200 mg once daily for 2 wk, then increase to 200 mg bid	Rash, elevation of liver enzyme levels	Full daily dose can be given once daily
Delavirdine	DLV	400 mg tid	Rash	
Efavirenz	EFV	600 mg once daily (or 300 mg bid)	Central nervous system toxicity ("hangover," drowsiness), rash	

form of nicotinamide adenine dinucleotide). The mitochondria use the NADH to produce adenosine triphosphate through oxidative phosphorylation. As described above, DNA polymerase γ is inhibited in the presence of NRTIs, which diminishes mitochondrial function, especially oxidative phosphorylation. This allows pyruvate and NADH to accumulate, enhancing the conversion of pyruvate to lactate. Impaired oxidation may also lead to a decrease in fatty acid oxidation. Free fatty acids then accumulate and are metabolized to triglycerides. These excess triglycerides may accumulate in the liver, causing the characteristic hepatic steatosis.

The risk factors for lactic acidosis are currently unknown. Although in vitro studies have suggested that some antiretroviral agents are more likely than others to cause mitochondrial dysfunction, the clinical relevance of these findings is unclear.[23,24] In addition, there is significant polymorphism in the mitochondrial DNA of the general population,[25] and a specific form of the DNA may place certain individuals at higher risk for mitochondrial dysfunction. Furthermore, the number of possible forms of mitochondrial DNA appears to increase with age. Other risk factors may include obesity and nutritional depletion of cofactors and vitamins required for normal mitochondrial function, such as thiamine and riboflavin. Finally, HIV infection itself may be a risk factor. Mitochondrial necrosis is caused by HIV infection in vitro,[26] and HIV-infected patients who have never taken NRTIs have a significantly lower ratio of mitochondrial to nuclear DNA in the peripheral blood cells than control subjects without HIV infection.[27] The depletion of cellular mitochondria caused by HIV infection makes these patients more susceptible to significant problems when the mitochondria are subjected to further damage by NRTIs.

Elevation of the anion gap (see Box 1) is characteristic of severe NRTI-associated lactic acidosis.[28–30] However, metabolic acidosis may also present with a normal anion gap, either as a result of concurrent acid–base disturbances or because of factors such as hypoalbuminemia, which may lead to underestimation of the anion gap.[31] Thus, the anion gap is less attractive as a screening tool for NRTI-associated lactic acidosis, because it can be an indicator of multiple concurrent illnesses or malnutrition.

Table 1 continued

Drug	Abbreviation	Dosage	Most common adverse effects	Comments
Protease inhibitors (PIs)*				
Saquinavir	SQV			
Brand Invirase	INV	Administer with RTV, with SQV/RTV ratio as follows: 400 mg/400 mg bid *or* 1000 mg/100 mg bid *or* 1600 mg/100 mg once daily	Elevation of liver enzyme levels	Very poor bioavailability unless combined with RTV. Better tolerability (e.g., GI) and similar pharmacokinetics to FTV when used with RTV boosting
Brand Fortovase	FTV	1200 mg tid. Alternatively, administer with RTV, with SQV/RTV ratio as follows: 1000 mg/100 mg bid *or* 1600 mg/100 mg once daily	GI toxic effects, elevation of liver enzyme levels	Better bioavailability than INV in the absence of RTV
Ritonavir	RTV	600 mg bid	GI upset, diarrhea, circumoral paresthesias, elevation of liver enzyme levels, hypertriglyceridemia	Most common use at present is as a PI booster at low doses (e.g., 100–400 mg/d)
Indinavir	IDV	800 mg tid. Can be given with RTV boosting: IDV 800 mg/RTV 100 mg bid	Elevation of liver enzyme levels, nephrolithiasis, hypertension, ingrown toenails, benign hyperbilirubinemia	
Lopinavir/ritonavir	LPV/RTV	3 capsules bid	GI upset	Two drugs combined in a single capsule. Dose should be increased to 4 capsules bid if used with EFZ or NVP and in the presence of moderately to highly PI-resistant HIV virus
Amprenavir	APV	1200 mg bid. Can be given with RTV boosting: APV 600 mg/RTV 100 mg bid	Rash, GI upset	
Nelfinavir	NFV	750 mg tid	GI upset, mostly diarrhea	

Note: bid = twice daily, tid = 3 times daily, CPK = creatine phosphokinase, GI = gastrointestinal, EC = enteric coated.
*PIs have multiple drug interactions and may be associated with various metabolic adverse effects such as diabetes mellitus, hyperlipidemias or lipodystrophy (limb and face wasting and accumulation of abnormal fat deposits).

Peripheral venous lactate levels are currently used as a screening tool in some centres, but they do not reliably distinguish patients at risk for severe lactic acidosis from those with chronic hyperlactatemia.[23] The ratio of mitochondrial DNA to nuclear DNA may provide a more sensitive and specific tool to evaluate the risk of toxic effects due to mitochondrial damage in patients with severe lactic acidosis.[26] Plymale and associates[26] found that mitochondrial DNA levels were lower among patients with symptomatic, nucleoside-related hyperlactatemia than among controls (without HIV infection) and HIV-infected, asymptomatic, treatment-naive patients. The decrease in mitochondrial DNA preceded an increase in venous lactate levels. In addition, mitochondrial DNA levels increased in all patients with symptomatic hyperlactatemia when antiretroviral therapy was discontinued. Measurement of mitochondrial DNA remains a research tool but may eventually become important in the management of patients receiving antiretroviral therapy.

To date, the treatment of NRTI-associated lactic acidosis has been largely supportive. Case reports have suggested a possible role for supplementation with essential cofactors (e.g., thiamine and riboflavin) in the management of severely ill patients,[32–36] but there is an urgent need for formal trials exploring the effectiveness of these and other agents for prophylaxis and treatment of this adverse effect. Because definitive data are lacking, physicians treating a case of severe lactic acidosis should seek expert consultation whenever possible. The antiretroviral therapy should be discontinued immediately. Consideration could be given to twice-daily intravenous (IV) administration of vitamin B complex (e.g., 100 mg thiamine, 20 mg riboflavin, 200 mg nicotinamide, 20 mg pyridoxine, 20 mg depanthenol), as well as coenzyme Q_{10} 50 mg daily and L-carnitine 1000 mg IV twice daily. These agents have been studied in the treatment of other mitochondrial disorders, although with variable success.[35,37–39]

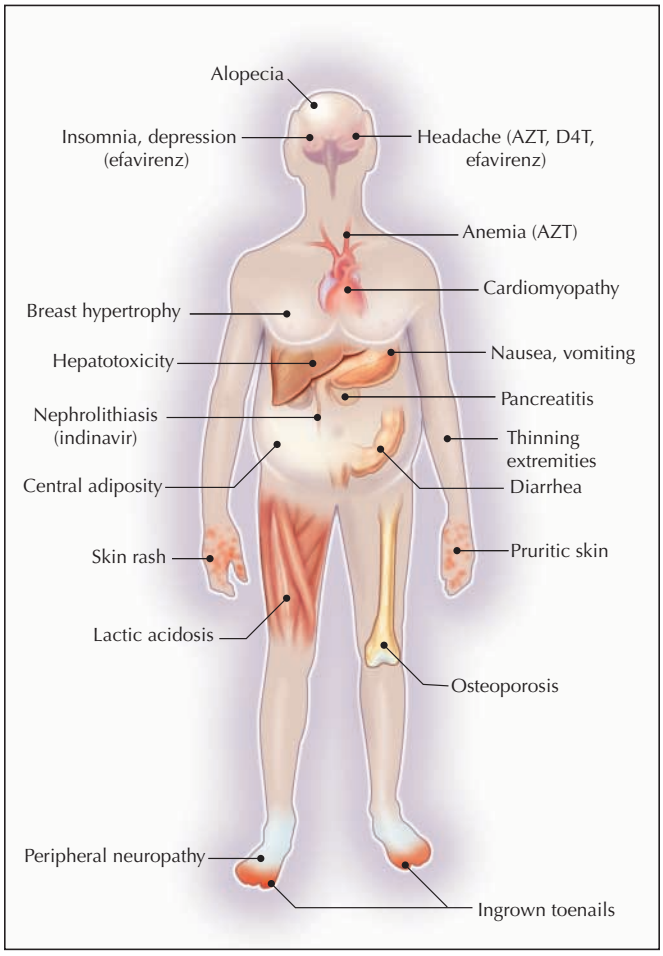

Fig. 1: Adverse effects of antiretroviral therapy. In some cases, only a certain drug causes the effect (drug name in parentheses).

Hepatotoxicity

Transaminitis and hepatotoxicity are associated with most of the antiretroviral agents, although initially most concern focused on the PIs. The hepatotoxicity of this drug class varies with the specific drug: in a prospective cohort study, 30% of patients who initiated treatment with ritonavir (RTV) but only 6% to 7% of those who initiated therapy with saquinavir, nelfinavir (NFV) or indinavir (IDV) experienced severe hepatotoxicity (defined as a grade 3 or 4 change in the serum levels of alanine aminotransferase and aspartate aminotransferase).[40] The rate of severe hepatotoxicity associated with any PI among patients with hepatitis C infection was 12%, twice as high as among patients without hepatitis C infection. Similar findings have been reported by den Brinker and colleagues.[41] The risk of liver enzyme elevation among patients with chronic hepatitis B or C was, respectively, 2.77- or 2.47-fold greater after initiation of a PI-containing regimen than among patients without evidence of viral hepatitis.[41] In this context, it has been suggested that successful treatment of hepatitis C in dually infected patients may facilitate the introduction of PI-containing antiretroviral therapy.[42] Coadministration of low-dose RTV with other PIs is now common; in fact, the newest member of the class represents a coformulation of lopinavir and low-dose RTV (see Table 1). The extent to which such combinations will affect the safety profiles of the individual agents remains to be fully characterized.

In addition, there have been recent attempts to understand the hepatic histologic changes, other than elevation of transaminases, that occur with PI-containing antiretroviral regimens. Benhamou and associates[43] reviewed liver biopsy samples from 182 patients with both HIV and hepatitis C. The liver fibrosis stage was lower among patients receiving PIs than among those who had never received PI therapy. The authors concluded that long-term use of PIs may have a beneficial impact on the progression of liver fibrosis in patients infected with HIV and hepatitis C.

The NNRTIs are also associated with transaminitis and hepatotoxicity. Reisler and colleagues[44] found that the rate of hepatotoxicity was 8.9% (95% confidence interval [CI] 6.6% to 11.2%) and 10.8% (95% CI 3.3% to 18.3%), respec-

Box 1: Signs and symptoms of and laboratory tests for antiretroviral-associated lactic acidosis

Signs and symptoms

Fatigue

Diminished exercise tolerance

Shortness of breath, tachypnea

Nausea, weight loss

Laboratory tests

Elevated anion gap: $[Na] - ([Cl] + [HCO_3]) > 10$

Elevated random serum lactate level: > 3 mmol/L

Decreased ratio of mitochondrial DNA to nuclear DNA*

*Currently a research tool, rather than a common screening method.

tively, among patients receiving NVP and EFV. These 2 drugs were significantly more likely to be associated with grade 3 or 4 elevation of transaminases than DLV (DLV v. NVP: OR 2.7 [95% CI 1.6 to 4.7], $p = 0.003$; DLV v. EFV: OR 2.5 [95% CI 1.2 to 5.5], $p = 0.01$). Others have observed similar rates of hepatotoxicity for NVP and EFV but found that elevation of CD4 cell count of more than 50/μL was most strongly linked to hepatotoxicity, perhaps due to adherence or immune reconstitution.[45]

The hypersensitivity reaction observed with NVP (characterized by rash and fever) can also include severe transaminitis. In one study in which NVP was used for postexposure prophylaxis, 2 patients experienced liver failure, and 1 of them required liver transplantation.[46] Therefore, NVP is no longer used for postexposure prophylaxis and is used with caution in the setting of liver disease.

Finally, as discussed in the previous section, the NRTIs are associated with risk of mitochondrial toxicity and hepatic steatosis. While these may be particular problems with d4T and ddI, the overall rate of severe hepatotoxicity with NRTI therapy reported by Reisler and colleagues[44] was 12%, which highlights the complexity and difficulty of evaluating and managing hepatotoxicity associated with antiretroviral therapy.

Hyperglycemia

New-onset diabetes mellitus, clinically similar to type 2 diabetes, affects a small proportion (1% to 6%) of HIV-infected patients treated with PI-based antiretroviral regimens. Many more patients receiving PI therapy have evidence of insulin resistance without frank diabetes.[47] However, insulin resistance may also be associated with HIV infection itself in patients not receiving PI therapy, perhaps resulting from the direct effects of the HIV virus on pancreatic β cell function and insulin secretion.[48]

Fat maldistribution

Lipodystrophy is part of a metabolic syndrome that includes dyslipidemias, insulin resistance and accelerated bone loss. Lipodystrophy affecting HIV-positive patients

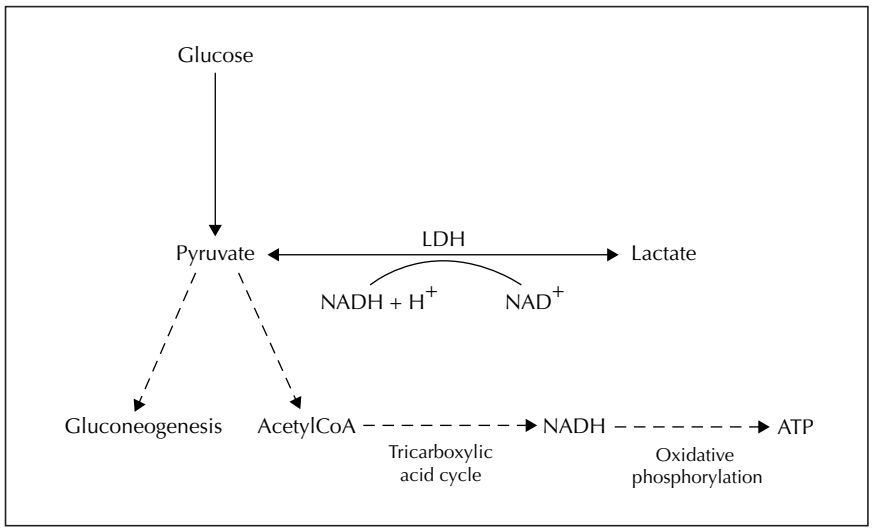

Fig. 2: Postulated mechanism by which nucleoside reverse transcriptase inhibitor (NRTI) therapy interferes with glycolysis, leading to lactic acidosis. Dashed lines indicate steps occurring within the mitochondria, for which normal mitochondrial function is required. These steps are subject to impairment by NRTI therapy. If such impairment occurs, pyruvate and NADH accumulate, enhancing the conversion of pyruvate into lactate, which ultimately leads to lactic acidosis. AcetylCoA = acetylcoenzyme A, ATP = adenosine triphosphate, LDH = lactate dehydrogenase, NAD = nicotinamide adenine dinucleotide, NADH = reduced form of NAD.

was first described in 1998.[49] The main clinical features are peripheral fat loss (lipoatrophy) in the face, limbs and buttocks, accompanied by central fat accumulation in the abdomen and breasts and over the dorsocervical spine (the "buffalo hump") and lipomas (Fig. 3, Table 2).[5] PI therapy has been most strongly linked to the lipodystrophy syndrome, although NRTIs, especially d4T, have also been associated with lipodystrophy.[51,52] The overall prevalence of at least one physical abnormality related to lipodystrophy has been estimated at about 50% after more than a year of antiretroviral therapy.[53]

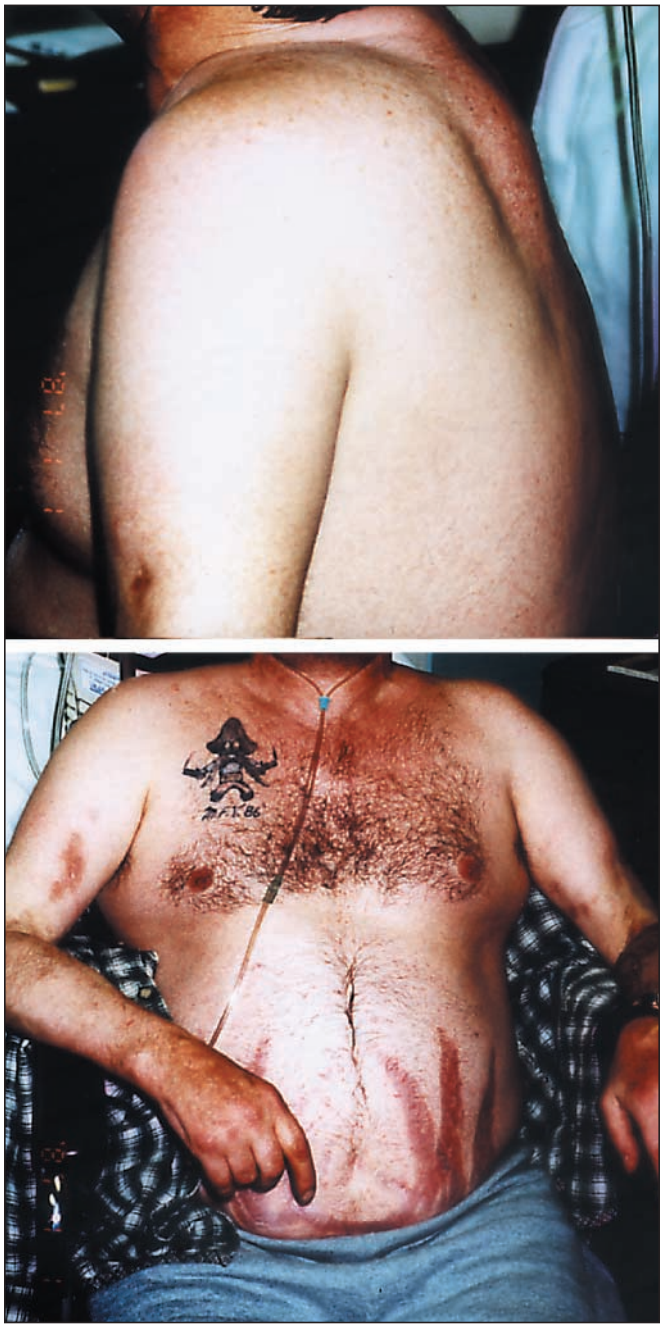

Fig. 3: Clinical features of lipodystrophy. Top: Dorsocervical fat pad. Bottom: Central fat accumulation with abdominal skin striae and thinning of the extremities. Reproduced, with permission, from the *Canadian Respiratory Journal*.[50]

Attempts to identify patients most likely to experience lipodystrophy are in progress. Risk factors may include a longer duration of PI therapy, increasing age and advanced HIV disease.[54,55]

The pathogenesis of lipodystrophy is poorly understood. Most likely, the cause is multifactorial, with combined endocrine and metabolic abnormalities having profound effects on the distribution of body fat.[47] Lipodystrophy is recognized as the source of significant cosmetic concerns and threatens the confidentiality of HIV serostatus: the typical changes of lipodystrophy, particularly in high-risk individuals, essentially result in a visible manifestation of HIV positivity. In addition, an increase in visceral and abdominal fat has been associated with an increased risk for glucose intolerance. Inability to manage lipodystrophy and its associated risks threatens the effectiveness of antiretroviral therapy by discouraging patients from continuing treatment.

Dyslipidemia

Dyslipidemia to levels associated with increased risk of cardiovascular disease occurs in about 70% of HIV-1 infected patients receiving antiretroviral therapy.[5,56] Features of the dyslipidemia in this syndrome include severe hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol and elevation of low-density lipoprotein (LDL) cholesterol. The dyslipidemia is more profound among those receiving PIs and in those with fat redistribution (lipoaccumulation or lipoatrophy).[5]

The dyslipidemia pattern (low HDL cholesterol level, high LDL cholesterol level, high triglyceride level) is extremely atherogenic and, coupled with other factors present in HIV patients such as insulin resistance and vascular inflammation, puts these patients at increased risk for premature cardiovascular disease. Several case reports have de-

Table 2: Features of the antiretroviral-associated metabolic syndrome

Condition	Observation or test
Clinical	
Central fat accumulation	Intra-abdominal, dorsocervical spine, breast hypertrophy, lipomas
Peripheral lipoatrophy	Face, arms, legs, buttocks
Laboratory	
Dyslipidemia	Hypertriglyceridemia, low HDL cholesterol, high LDL cholesterol
Diabetes	High fasting blood sugar and HbA_{1c} levels
Insulin resistance	Increased insulin and C-peptide levels
Osteoporosis	Bone densitometry
Lactic acidosis	

Note: HDL = high-density lipoprotein, LDL = low-density lipoprotein, HbA_{1c} = hemoglobin A_{1c} (glycosylated hemoglobin).

scribed premature coronary artery disease in HIV-infected patients with few or no risk factors who were receiving PI therapy.[5] The cardiovascular event rate is difficult to calculate at present because the metabolic syndrome has been defined only recently and patients have been prospectively followed for just a short period of time (approximately 4 to 5 years).[57,58] In at least one cohort, HAART was associated with a 27% relative increase in the rate of myocardial infarction per year of exposure over the first 7 years of use.[59] However, the overall risk of myocardial infarction remains low, and the beneficial effects of antiretroviral therapy in preventing HIV progression outweigh the deleterious cardiovascular effects.

The pathogenesis of dyslipidemia is poorly understood. PIs may bind to or interfere with LDL receptor-related protein and cytoplasmic retinoic acid binding protein type 1, both of which are lipid regulatory proteins involved in fat storage and lipid release. However, the interaction of PIs with these proteins has not been fully elucidated, and other mechanisms may also be involved.[60]

Increased bleeding episodes among patients with hemophilia

Soon after the introduction of PIs, several case reports suggested an association between these drugs and increased frequency and severity of bleeding in patients with hemophilia.[61,62]

In most patients, bleeding increased within the first few weeks of PI therapy, but the onset ranged from a few days to many months after initiation of therapy. Not only did bleeding occur more frequently, but it occurred at unusual sites such as the small joints of the hands and the soft tissues of the palms. Although most PIs have been implicated, RTV in particular is associated with this adverse effect. The mechanism is unknown. However, the patients' coagulation parameters are typically normal, and factor VIII replacement is not efficacious in resolving the bleeding.[63] Hemophiliac patients taking PIs should be monitored for increased bleeding, and PI therapy should be discontinued if it occurs. If undergoing surgery, these patients may benefit from temporary cessation of PI therapy during the perioperative period. When possible, a non-PI regimen should be considered for these patients.

Osteonecrosis, osteopenia and osteoporosis

Osteonecrosis results in cell death of various bone components, including fat marrow and mineralized tissue. It is not a specific entity but a final common pathway of several conditions that may impair blood supply to the bone. The first report of osteonecrosis in association with HIV infection described an HIV-infected woman who presented post partum with avascular necrosis of multiple bones, as well as a similar case in a young HIV-positive man with no other risk factors who was not receiving antiretroviral therapy.[64] After HAART became available, additional cases emerged, some linked to hyperlipidemia and others to alcoholism, pancreatitis, corticosteroid therapy and hypercoagulability, all previously described risk factors for osteonecrosis. There is no apparent difference in the overall use of PIs among HIV-infected patients with and without osteonecrosis.[65]

Osteonecrosis occurs only rarely in HIV patients. For example, in one series 6 cases occurred among 508 HIV patients (of whom 280 were receiving triple therapy).[66] Although unusual, osteonecrosis is a serious bone abnormality that can lead to the need for joint replacement. HIV-infected patients presenting with persistent hip, knee or shoulder pain, especially in the absence of trauma, should undergo MRI to evaluate for possible osteonecrosis.

The diagnosis of osteoporosis is based on measurement of bone mineral density, which can be accomplished by a variety of techniques. However, the current standard of care and the most widely accepted method is dual-energy x-ray absorptiometry (DEXA) at the spine and hip.[67]

Osteoporosis in HIV-infected patients was reported in the pre-HAART era, when it was thought to be secondary to poor nutrition or perhaps increased cytokine levels related to chronic infection.[68] After the introduction of HAART, Tebas and collaborators[69] reported a cross-sectional DEXA analysis of whole body, lumbar spine and proximal femur bone mineral density in 112 male subjects: 50% of the HIV-positive patients receiving PIs, but only 23% of HIV-positive patients not receiving PIs and 29% of healthy seronegative controls, had osteoporosis or osteopenia ($p = 0.02$).

The pathophysiology of osteoporosis in the setting of HIV infection is unclear. In some studies osteoporosis occurred in conjunction with antiretroviral-associated lactic acidosis, a situation in which phosphate may act as a buffer.[70] Others have postulated that PIs may inhibit new bone formation by stimulating osteoclast activity or inhibiting osteoblast activity.[71] The PIs are metabolized by cytochrome P450 enzymes, and inhibition of 2 cytochrome P450 mixed-function oxygenases that mediate vitamin D activation has been suggested as a possible mechanism for development of osteoporosis. Dusso and associates[72] found that the PIs IDV, RTV and NFV all inhibited conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D in vitro.

The need for formal osteoporosis evaluation and therapy in HIV-infected patients remains to be clarified. However, patients with additional risk factors for osteoporosis (e.g., corticosteroid use, postmenopausal) should be considered for evaluation with DEXA scanning.[73] Treatment of osteoporosis in the setting of antiretroviral therapy is evolving, and referral for specialist assessment, when possible, is warranted. Standard therapy, including vitamin D and calcium supplementation and exercise, as well as pharmacologic measures such as hormone replacement and bisphosphonate therapy, may be indicated. Review of the patient's

current antiretroviral combination should also be considered, although the links between specific medications and risk of osteoporosis have yet to be defined.

Skin rash

Rash is a common adverse effect of the NNRTIs, particularly NVP. Approximately 16% of patients taking this agent experience a mild to moderate maculopapular rash, with or without pruritus, on the trunk, face and extremities, within the first 6 weeks on therapy.[74]

If the rash occurs during the initial 2-week dose lead-in period, the dose should be held at 200 mg daily until the rash resolves.[75] Although most rashes are self-limited, NVP should be permanently discontinued if the rash is severe or accompanied by constitutional symptoms.[75] Severe rashes occur in about 6.5% of NVP-treated patients, mainly during the first 4 weeks of treatment, including Stevens-Johnson syndrome and toxic epidermal necrolysis in less than 1% of all patients treated with NVP.[74]

The nucleoside analogue ABC causes a hypersensitivity syndrome in 3% to 5% of patients,[76,77] who present with nonspecific symptoms (including malaise and fever, with or without rash) starting during the first 6 weeks of treatment. The symptoms worsen with continued therapy and resolve gradually after discontinuation of the drug. Rechallenge with ABC after a hypersensitivity reaction should not be attempted, as severe symptoms may occur rapidly, including life-threatening hypotension and death. Risk factors for ABC hypersensitivity have not been identified.

Monitoring of patients who are receiving HAART

Routine laboratory monitoring should be done approximately every 3 months to determine whether the patient has asymptomatic abnormalities. Monitoring laboratory tests include complete and differential blood counts and measurement of electrolyte, creatinine, liver transaminase, bilirubin and amylase levels. Patients should also be monitored at regular intervals (approximately every 3 months) for dyslipidemia, diabetes, and lipoaccumulation or lipoatrophy. This laboratory work should include determination of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and fasting blood glucose levels. Patients should be asked about and examined for changes in fat distribution. Imaging tests, such as abdominal CT to detect visceral fat, are not recommended for routine monitoring.

Patients switching from PI-based therapy to NNRTI or triple-nucleoside regimens have shown improvements in lipodystrophy, dyslipidemia and insulin resistance.[78,79] However, not all switch studies have shown beneficial effects.[78,79] As well, some patients have no alternatives to PI-based regimens because their infection is resistant to other classes of antiretrovirals. In this situation, treatment for dyslipidemia should be the same as for dyslipidemia in the general population, including lifestyle modifications and pharmacotherapy.[80,81] Diabetes and insulin resistance should also be treated in accordance with national guidelines.[82] Lipodystrophy has no easy and proven treatment. Intense exercise can decrease central fat accumulation but may increase peripheral fat wasting. Surgery, such as implants for facial atrophy and liposuction for buffalo humps, is another option but is not widely recommended.[83]

NRTIs have few interactions with other medications. Clinically significant interactions usually involve additive toxicity (e.g., bone marrow suppression or neuropathy) or problems with drug absorption (e.g., ddI buffered tablets when given with fluoroquinolones.)

PIs and NNRTIs are metabolized through the cytochrome P450 enzyme system and can also be inducers or inhibitors of this system. Levels of antiretrovirals and concomitant medications that are metabolized by this system can be dramatically altered if these agents are given together, which can result in toxic effects or ineffectiveness of therapy. RTV is the most potent inhibitor of the cytochrome P450 system and the most likely to interact with other medications. Caution is advised when interpreting drug interaction information. Most such information covers only 2-way interactions, whereas most HIV-infected patients take 3 or more medications. Valuable information about drug interactions, including summaries of important toxic effects, can be found online (e.g., the Toronto General Hospital's Immunodeficiency Clinic at www.tthhivclinic.com or the HIV InSite of the University of California, San Francisco at hivinsite.ucsf.edu).

Conclusions

Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient nonadherence.[4,5] To optimize adherence, and hence efficacy, clinicians must focus on preventing adverse effects, when possible, and distinguishing those that are self-limited from those that are potentially serious. As efforts continue in the development of medications with more favourable adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with antiretroviral use.

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