

FOREWORD

Advances in antiretroviral therapy (ART) in the past few years have transformed HIV/AIDS from a death sentence to a chronic manageable disease. However, like therapy for most chronic conditions, ART can be associated with side effects.

This may have both acute and long-term implications for the health of HIV-infected patients. Intolerance or fear of side effects can lead to non-adherence that may favour emergence of resistance and treatment failure.

In order to optimise and ensure the success of therapy, it is critical to recognise and manage these adverse events. Further, there are important drug interactions between antiretrovirals and drugs used to manage certain adverse effects. These need to be taken into account when drawing up a management plan for the patient.

The aim of this booklet is to serve physicians as a practical guide:

- To understand the management of metabolic abnormalities associated with HIV treatment, including dyslipidaemias, insulin resistance and diabetes mellitus, lipodystrophy syndrome, bone disease and lactic acidosis
- To gain a working knowledge of these adverse effects, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment
- To recognise early and attempt to reverse potentially serious adverse effects, and reduce the potential for adverse drug interactions

Over a decade, Cipla has not only spearheaded the therapeutic revolution in HIV/AIDS but also worked for the cause of updating physicians on more effective methods to manage the disease. This concise booklet is yet another endeavour in this direction.

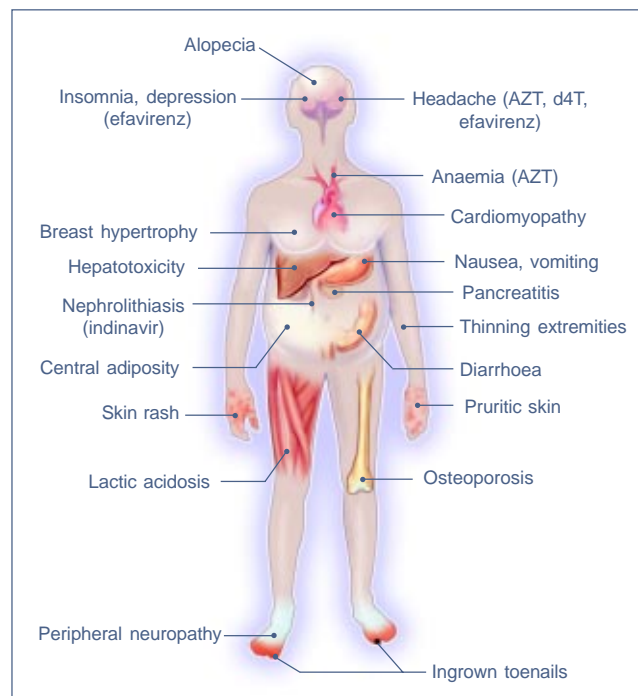
Chapter 1

ADVERSE EFFECTS OF ANTIRETROVIRAL THERAPY: AN OVERVIEW

Introduction

Long-term remission of HIV-1 disease can be readily achieved by combinations of antiretroviral agents. Suppression of plasma viral load to undetectable levels and 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 (Table 1). The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient. The incidence of many toxicities appears to be higher when therapy is initiated at more advanced stages of disease.

Figure 1: Sites of possible adverse effects of antiretroviral therapy



The range of adverse effects

Antiretroviral therapy can have a wide range of adverse effects on the human body (Figure 1). Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhoea, which may be transient or may persist throughout therapy. Other common nuisance adverse effects are fatigue and headache caused by zidovudine and nightmares associated with efavirenz. Several uncommon but more serious adverse effects associated with antiretroviral therapy, including zidovudine-associated anaemia, stavudine-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 antiretroviral therapy. However, the subtle and serious nature of other adverse effects – lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycaemia, fat maldistribution, hyperlipidaemia, bleeding disorders, osteoporosis and skin rash – warrant more detailed discussion.

Table 1: Specific short-term and long-term adverse events associated with antiretroviral therapy

| | |
|--------|--|
| PIs | Diarrhoea (ritonavir, nelfinavir, lopinavir/ritonavir) Kidney stones (indinavir) LFT abnormalities Metabolic complications (fat redistribution, hyperlipidaemia, insulin resistance) (ritonavir, indinavir, others) Nausea (saquinavir, ritonavir, indinavir, amprenavir) |
| NRTIs | Hepatic steatosis Metabolic complications (d4T, possibly other thymidine analogues associated with lipoatrophy) Mitochondrial dysfunction (lactic acidosis) (d4T, AZT, ddl) Myopathy Nausea and diarrhoea (AZT) Neuropathy (d4T, ddl) Pancreatitis (ddl) Skin rash and hypersensitivity (ABC) |
| NNRTIs | Central nervous system (efavirenz) Hypercholesterolaemia (efavirenz) LFT abnormalities (nevirapine, efavirenz) Rash (nevirapine, efavirenz) Teratogenicity (efavirenz) |

Major versus minor toxicities

While considering antiretroviral toxicity, the tendency is often to be more concerned about major toxicities, such as liver damage, without realising that the relatively more minor adverse reactions (e.g. rash, nausea, diarrhoea) can have greater impact on patient acceptance. Gastrointestinal intolerance is a major stumbling block, particularly with the PIs. This is often underestimated in clinical trials because it may not reach the level of severity of Grade 3 or 4 toxicity (Appendix 1). However, these GI problems are sufficiently disturbing to patients that they will either stop their regimens or take them inappropriately in an attempt to avoid the toxicities. In addition to GI problems and rash, well-recognised and more severe treatment-limiting adverse reactions include hypersensitivity, neuropathy, mitochondrial dysfunction and pancreatitis.

Impact on treatment options

There is increasing recognition that toxicity can impose major limitations on the options available to physicians. In spite of the development of newer agents, the number of effective regimens is not infinite. Each drug has its own set of toxicities, but side effects shared across classes also limit choices if toxicity occurs. Also, previous toxicities may limit choices of antiretrovirals. For example, neuropathy resulting from one drug in a class restricts the use of other potentially neuropathy-inducing drugs of that same class. Furthermore, newly diagnosed patients typically are placed on simpler regimens to try to improve adherence. Subsequent therapy usually requires using a more complex regimen. Thus, as patients develop side effects or become non-adherent, they progressively have fewer treatment options.

Monitoring patients receiving ART

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 dyslipidaemia, 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 for and examined for changes in fat distribution.

Drug interactions

NRTIs have few interactions with other medications. Clinically significant interactions usually involve additive toxicity (e.g. bone marrow suppression or neuropathy). PIs and NNRTIs are metabolised by the cytochrome P450 enzyme system and can also be inducers or inhibitors of this system. Levels of antiretrovirals and certain medications (used to treat toxicities) that are metabolised by this system can be dramatically altered if these agents are given together. This can result in toxic effects or ineffectiveness of therapy. Thus, the potential for possible drug interactions need to be taken into account.

Patient education

Clinicians should inform patients considering ART what complications they may experience and how to recognise and report these side effects (Appendix 2). This proactive approach is likely to lead to improved adherence.

Chapter 2

DISORDERS OF GLUCOSE METABOLISM

Definitions

Insulin resistance occurs when higher concentrations of insulin are needed to exert its normal physiologic effects, which include inhibiting hepatic glucose production and increasing muscle and fat cell uptake of glucose. In order to maintain normal blood sugar levels, the pancreas will normally compensate by increasing the amount of insulin secreted. Thus, elevated fasting insulin levels are one marker of insulin resistance.

AMERICAN DIABETES ASSOCIATION (ADA) GUIDELINES

| Prediabetes | Diabetes mellitus (DM) |
|--|---|
| <i>Impaired fasting glucose (IFG)</i> Fasting glucose 100-125 mg/dL | Fasting plasma glucose (FPG) > 126 mg/dL |
| <i>Impaired glucose tolerance (IGT)</i> 2 hour post load glucose 140-199 mg/dL during OGTT | OR 2 hour post load glucose 200 mg/dL OR Symptoms of diabetes with random glucose > 200 mg/dL |

Insulin resistance (IR) is usually present when adult-onset, or type II, diabetes mellitus is diagnosed. The fasting blood sugar is elevated when the pancreas is no longer able to secrete sufficient insulin in order to overcome the insulin resistance.

Background

Disorders of glucose metabolism were one of the first metabolic complications of antiretroviral therapy that were identified. Initial reports of new-onset hyperglycaemia, including episodes of diabetic ketoacidosis, were linked to the use of protease inhibitors. Up to 40% of patients on a protease inhibitor-containing regimen will have impaired glucose tolerance due to significant insulin resistance.

Insulin resistance, even without hyperglycaemia, is a concern. This is because in non-HIV-infected individuals, insulin resistance is associated with an increased risk of cardiovascular complications. Whether a similar risk is associated with drug-induced or lipodystrophy-induced insulin resistance

in HIV-1-infected individuals remains to be established. Patients with traditional risk factors for type 2 diabetes mellitus and who are taking protease inhibitors may be at particularly high risk. Insulin resistance is characterised by the reduced ability of insulin to inhibit hepatic gluconeogenesis and to increase muscle uptake of glucose. The pathophysiologic basis of insulin resistance in patients on potent antiretroviral therapy is unknown. Potential mechanisms include direct effects of antiretroviral drugs that impair cellular glucose uptake, or indirect mechanisms related to body fat changes, including central obesity and/or peripheral lipoatrophy. Protease inhibitors may have an early direct effect.

Table 2: Aetiology of insulin resistance

| Usual risk factors | Antiretrovirals | Others |
|---------------------|---------------------|-----------------|
| Genetic | Indinavir | Lipodystrophy |
| Physical inactivity | Lopinavir/ritonavir | HCV coinfection |
| Obesity | | |

Assessment and monitoring

Initiating PI therapy may induce a new or accelerate preexisting abnormalities in glucose tolerance. Fasting glucose should be assessed prior to and during treatment (3-6 months after starting and annually thereafter) with potent antiretroviral therapy that includes a protease inhibitor. Oral glucose tolerance testing is an optional clinical test that may be most appropriate for patients with pre-existing risk factors for type 2 diabetes mellitus or who have developed severe body fat changes.

Treatment

Studies identifying optimal treatment of fasting hyperglycaemia associated with insulin resistance or glucose intolerance in HIV-1-infected patients have not been completed. Hence, established guidelines for treating diabetes mellitus in the general population should be followed.

1. *Avoid a PI-based regimen*

Consideration should be given to avoiding use of a protease inhibitor-based regimen as initial therapy, or to substituting alternatives to protease inhibitors if possible in patients with pre-existing abnormalities of glucose metabolism or with first-degree relatives with diabetes mellitus. Substitution of the PI with nevirapine or efavirenz has been associated with short-term improvements in insulin resistance, and may be considered where virologically appropriate.

2. Diet and exercise

A healthy, balanced diet and regular exercise are recommended for all patients, particularly for those with IGT. Weight loss is recommended for overweight patients with IGT or insulin resistance, or who are at higher risk for development of diabetes mellitus.

3. Drug therapy

When drug therapy is required, consideration should be given to using insulin-sensitising agents. Studies in small numbers of HIV-1-infected patients using metformin suggest potential benefits in reducing insulin levels, waist circumference, blood pressure and cardiovascular risk. The thiazolidinediones increase insulin sensitivity in HIV-1-infected patients with insulin resistance and evidence of lipodystrophy. Oral hypoglycaemic agents and insulin may also be appropriate for patients with more severe degrees of fasting hyperglycaemia, although these may be of less benefit in HIV-1 infected patients with insulin resistance and may induce hypoglycaemia.

Careful monitoring for potential adverse effects, such as hepatic dysfunction (thiazolidinediones) and lactic acidemia (metformin), is recommended after initiation of these drugs. Liver enzymes must be monitored every 2 months for the first 12 months of thiazolidinedione treatment. Patients with significant pre-existing liver disease (SGOT or SGPT > 2.5 times ULN) should not take thiazolidinediones. Patients with serum creatinine above the ULN for their age or lactic acidemia (venous lactate levels > 2.0 times the ULN) should not take metformin.

PRACTICE POINTS

- 1. Prevention of development of IR and DM**
 - Identify those at greatest risk
 - Obtain fasting blood sample for glucose estimation
 - Regular FPG during treatment with PI (3-6 monthly and then annually) or OGTT
 - Diet, regular aerobic exercise
 - Avoid initial regimens using PIs
- 2. Role of metformin**
 - Causes weight loss
 - Improves insulin sensitivity
 - Improves other risk factors
 - Watch for:
 - Lactic acidemia
 - Excessive weight loss
- 3. Role of rosiglitazone**
 - Decreases insulin resistance
 - Improves fat redistribution
 - Increases triglycerides
 - Watch for liver dysfunction
- 4. Sulfonylureas, meglitinides and insulin reserved for severe cases in which insulin sensitisers are contraindicated.**

Chapter 3

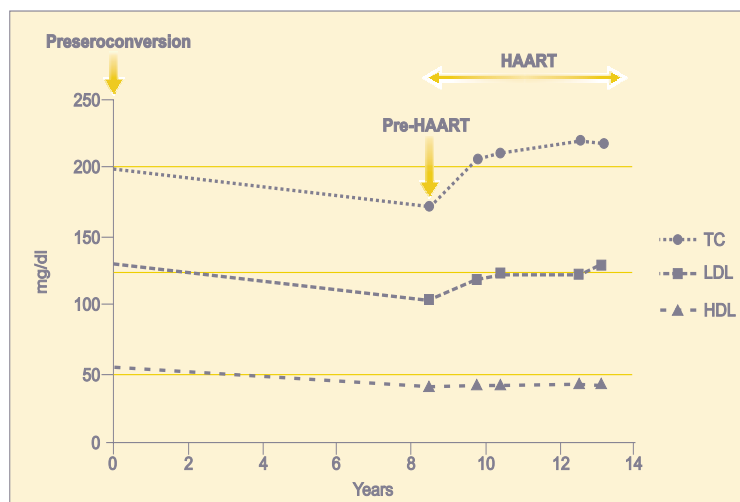
DYSLIPIDAEMIA

Background

Abnormal serum lipids have been noted since the beginning of the HIV epidemic. The HAART era has been associated with a dyslipidaemic profile consisting of high total and LDL cholesterol, elevated triglycerides and a low HDL cholesterol. Although some patients may exhibit all three of these abnormalities in either the cholesterol or triglyceride fractions, the fraction most affected usually depends on the antiretroviral agent(s) used (for example, ritonavir predominantly affects triglycerides). The effect on lipids is most pronounced with PIs, followed by NNRTIs and then NRTIs.

Dyslipidaemia is only one part of the array of factors that increase cardiovascular risk. At present, it is unknown whether the lipid elevations associated with HIV-1 infection and antiretroviral therapy carry the same cardiovascular risk as in HIV-1-uninfected populations. However, these abnormalities are reason for serious concern among patients with improved life expectancy as a result of potent antiretroviral therapy. Identification and management of individuals with dyslipidaemia is now an essential part of HIV care.

Figure 2: Mean lipid values (TC, LDL and HDL) in HIV-infected patients before and after HAART



The mechanisms that induce lipid abnormalities associated with potent antiretroviral therapies remain elusive. Genetic susceptibility may greatly influence the risk for development of drug-, HIV-1-, or fat distribution-induced changes in lipid or lipoprotein levels.

Evaluation of patients

a. Risk stratification

The NCEP ATP III guidelines provide a starting point for the evaluation of HIV-infected patients.

1. First, the number of risk factors for CHD that modify LDL cholesterol goals (Table 3) are counted.

Table 3: Categorical coronary heart disease risk factors that modify low-density lipoprotein (LDL) cholesterol goals

| Risk factor | Definition |
|---|--|
| Cigarette smoking | — |
| Hypertension | Blood pressure of ≥ 140 mmHg or receipt of antihypertensive medication |
| Low high-density lipoprotein cholesterol level ^a | Level, < 40 mg/dL |
| Family history of premature CHD | Male first-degree relative < 55 years old or female first-degree relative < 65 years old |
| Age | > 45 years for men and > 55 years for women |

NOTE: Note that a diagnosis of diabetes mellitus is now considered an equivalent to a known diagnosis of coronary heart disease.

^aAn elevated high-density lipoprotein cholesterol level (≥ 60 mg/dL) is considered a 'negative' risk factor. If this is present, subtract 1 factor from the above risk factor total.

2. For patients who have ≥ 2 risk factors for CHD, a risk assessment tool (available at <http://hin.nhlbi.nih.gov/atpiii/calculator.asp>) based on the Framingham Heart Study is then used to estimate 10-year risk of myocardial infarction or cardiac death.

Managing Metabolic Complications of Antiretroviral Therapy

After determining the appropriate risk category, LDL cholesterol goals are identified (Table 4).

Table 4 : ATP III Goals for LDL cholesterol levels

| Risk Category | LDL-C Goal | Initiate TLC | Consider Drug Therapy** |
|--|--|--------------------------|---|
| High risk: CHD* or equivalents† (10-year risk > 20%) | < 100 mg/dL (optional goal: < 70 mg/dL) [¶] | ≥ 100 mg/dL [#] | ≥ 100 mg/dL ^{††} (<100 mg/dL; consider drug options)** |
| <i>Moderately high risk:</i> 2 + risk factors† (10-year risk 10% to 20%) ^{§§} | < 130 mg/dL ^{¶¶} | ≥ 130 mg/dL [#] | ≥ 130 mg/dL (100-129 mg/dL; consider drug options) [‡] |
| <i>Moderate risk:</i> 2 + risk factors† (10-year risk < 10%) ^{§§} | < 130 mg/dL | ≥ 130 mg/dL | ≥ 160 mg/dL |
| <i>Lower risk:</i> 0-1 risk factors [§] | < 160 mg/dL | > 160 mg/dL | > 190 mg/dL (160-189 mg/dL; LDL lowering drug optional) |

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischaemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischaemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP >140/90 mmHg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men >45 years; women >55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

¶ Very high risk favours the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

¶¶Optional LDL-C goal <100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

The highest-risk patients—those with established coronary artery disease – are treated most aggressively, with a target LDL level of <100 mg/dL. In addition, patients without established CHD but with a similar 10-year risk estimate (>20%) are considered to have a “CHD risk equivalent” and are treated equally aggressively. Patients with CHD risk equivalents include those with type 2 diabetes mellitus, other forms of atherosclerotic disease, or a calculated 10-year CHD risk estimate of >20%.

Severe hypertriglyceridemia (>500 mg/dL) may be present in a considerable proportion of HIV-infected patients. Reduction of the triglyceride level becomes a primary target for these individuals. If moderate elevations are present (200-500 mg/dL), then non-HDL cholesterol (total cholesterol level minus HDL level) becomes a secondary target for therapy if LDL goals have been achieved. The target non-HDL level for each risk category is 30 mg/dl higher than the corresponding LDL target.

b. *Metabolic syndrome*

The NCEP ATP III has identified the metabolic syndrome as a secondary target for intervention. Several features of the metabolic syndrome overlap with common features of HIV treatment-associated lipodystrophy, such as hyperinsulinemia, glucose intolerance, an atherogenic lipoprotein phenotype, a prothrombotic state and central obesity. Patients with the metabolic syndrome are encouraged to lose weight, using dietary modification and increased physical activity. Patients who also have moderate to severe lipodystrophy should be encouraged to increase physical activity, but excessive weight loss has the potential to exacerbate lipodystrophy.

c. *Measurement of lipid values*

Evaluation of serum lipid levels should be performed after fasting for a minimum of 8 hours, and preferably for 12 hours. These levels should be determined before initiating (or switching) antiretroviral therapy. This should be repeated within 3-6 months after the initiation of HAART, and subsequently yearly, unless abnormalities are detected or therapeutic interventions are initiated. For individuals with an elevated triglyceride level (>200 mg/dL) at baseline, it may be preferable to repeat a lipid profile sooner (e.g. within 1-2 months after initiating HAART).

d. *Non lipid risk factors*

Intervention should be routinely offered for other modifiable cardiovascular risk factors, such as smoking, hypertension, physical inactivity, obesity and diabetes mellitus. Additionally, the clinician should be alert for potential exacerbating conditions, such as excessive alcohol use, hypothyroidism, renal disease, liver disease and hypogonadism.

Treatment

a. Non-drug therapies

i. For hypercholesterolaemia

Non-drug therapies should be given a thorough trial before instituting drug therapies. Dietary and exercise intervention have been shown to significantly decrease cholesterol and triglyceride levels. Attention must be given to other modifiable risk factors for CHD, such as cigarette smoking, diabetes mellitus and hypertension. Drug therapies should be instituted first only when there is an urgent need to intervene (e.g. individuals with CHD or when LDL cholesterol level > 220 mg/dL).

ii. For hypertriglyceridaemia

Dietary and exercise advice have resulted in decreases in triglyceride levels among HIV-infected patients. Smoking cessation and regular aerobic exercise are general health measures that will reduce the triglyceride level and improve the overall cardiovascular risk profile. Weight reduction should be strongly encouraged if obesity is present. Hyperglycaemia due to diabetes mellitus must be managed aggressively. Fat intake should be decreased. Fish oils variably decrease triglyceride synthesis and may be tried. When extreme elevations are present (>2000 mg/dL, or >1000 mg/dL in persons with a history of pancreatitis), it is reasonable to institute both drug and non-drug therapies simultaneously.

b. Modification of antiretroviral therapy

For patients with preexisting cardiovascular risk factors, hyperlipidaemia, or a family history of a lipid disorder, consideration should be given to initiating or switching to a protease inhibitor-sparing antiretroviral regimen, when appropriate. However, when options are limited, antiretroviral drugs that may lead to lipid elevations should not be withheld for fear of further exacerbating lipid disorders.

c. Drug treatment for hyperlipidaemia

Recommendations for choice of initial drug therapy for dyslipidaemia in HIV-infected individuals receiving antiretroviral therapy are given in Table 5. Due to potent drug-drug interactions, the use of lovastatin and simvastatin is contraindicated in patients receiving protease inhibitors.

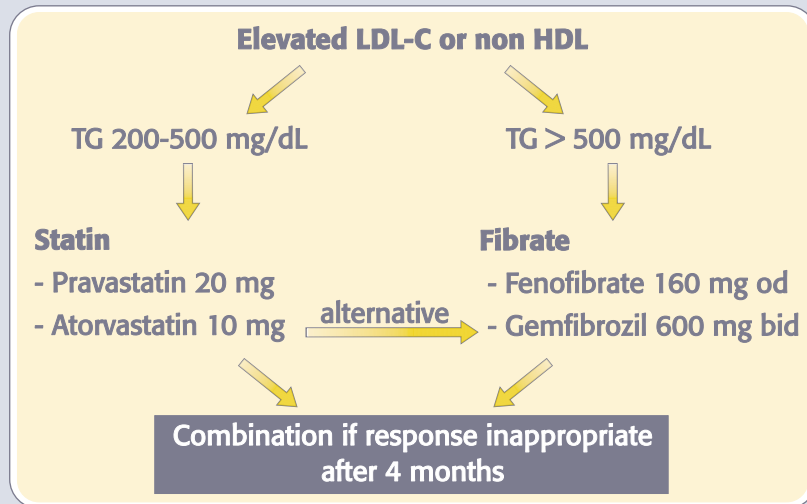
Table 5 : Recommendations for choice of initial drug therapy for dyslipidemia in HIV-infected individuals receiving antiretroviral therapy

| Lipid abnormality | Therapy | | Comments |
|---|--------------|---------------------|--|
| | First choice | Alternative(s) | |
| Elevated LDL-C level or elevated non-HDL-C level with triglyceride level of 200-500 mg/dL | Statin | Fibrate or niacin | <ul style="list-style-type: none"> - Start with low doses of statins and titrate upward; with CYP3A4 inhibitors (PIs), pravastatin, 20-40 mg o.d. or atorvastatin, 10 mg o.d. initial dose is recommended - fluvastatin 20-40 mg o.d. is an alternative - fibrate may elevate the LDL-C level when the triglyceride level is elevated |
| Triglyceride level >500 mg/dL | Fibrate | Niacin or fish oils | <ul style="list-style-type: none"> - Reduction of triglyceride level becomes a primary target in these individuals - drug interactions with fibrates are unlikely - fenofibrate dosage is 54-160 mg o.d. and gemfibrozil dosage is 600 mg b.i.d. |

Note: Niacin may worsen insulin resistance; combining fibrate and statin increases the risk of rhabdomyolysis (more so with gemfibrozil). Hence, use the combination with caution and monitor for clinical evidence of myopathy.

PRACTICE POINTS

- With continued use of HAART, managing metabolic abnormalities will be important.
- PIs increase TC, LDL, TG and normal HDL. Effect is most with ritonavir and lopinavir/ritonavir and least with indinavir and saquinavir. Switching from PIs to nevirapine improves the lipid profile.
- Stavudine increases triglycerides.
- NNRTIs increase TC and HDL. Efavirenz increases triglycerides.
- Although treatment is similar to that for non-HIV-infected patients, watch out for drug interactions and monitor more closely.
- Monitor statin therapy by LFT and symptoms for myopathy
- Niacin can cause flushing and worsen insulin resistance



Chapter 4

BODY FAT DISTRIBUTION ABNORMALITIES

Definitions

One of the most disconcerting toxicities increasingly recognised is lipodystrophy, a disturbance in the way the body produces, uses and distributes fat. Two patterns have been recognised: lipohypertrophy and lipoatrophy.

Lipoatrophy predominantly involves loss of peripheral subcutaneous fat in the face, arms, legs or buttocks and may be seen independently or in conjunction with visceral fat accumulation and other body shape changes. The peripheral lipoatrophy associated with HIV therapy is distinguished from the traditional wasting syndrome by the preferential loss of fat tissue without substantial loss of lean tissue mass. Additionally, while wasting syndrome most commonly is associated with an absence of virologic suppression and advanced HIV disease, lipoatrophy most frequently occurs among patients who are responding to HIV therapy.

A variety of syndromes of **fat accumulation** (lipohypertrophy) have been documented in patients with HIV infection. These include abdominal obesity, enlarged dorsocervical fat pad (buffalo hump), and less commonly, benign symmetric lipomatosis. In addition, breast enlargement in women and gynaecomastia in men have also been noted. Syndromes of fat accumulation have been noted both in the presence and absence of lipoatrophy.

Risk factors

Although several early studies suggested that fat distribution abnormalities were associated with protease inhibitor use, other studies provided clear evidence that these could occur in protease inhibitor-naïve subjects. Specific roles for each class of drugs have not been defined, but an association between lipoatrophy and NRTIs, possibly accelerated in the presence of a protease inhibitor, has been suggested. Some studies suggest an increased risk of lipoatrophy when stavudine is part of the regimen. Current data do not support a role for NNRTIs in the development of these abnormalities. In addition to type and duration of antiretroviral drug exposure, a number of host factors have been implicated (see Table 6).

Table 6 : Host factors predisposing to risk for fat redistribution abnormalities

- older age
- baseline body mass index or change in body mass index
- duration of HIV-1 infection
- effectiveness of viral suppression
- baseline degree of immunodeficiency and subsequent immune restoration with therapy
- white race
- women more likely to develop fat accumulation and men fat loss.

Aetiology

The underlying mechanisms and specific site(s) of dysregulation accounting for the morphologic abnormalities have not been identified. It has been suggested that NRTI-associated inhibition of DNA polymerase gamma, which is required for mitochondrial DNA replication, may trigger events that result in fat distribution abnormalities. *In vitro* studies of protease inhibitors suggest that they might affect preadipocyte differentiation.

Prognosis

Studies in HIV-infected subjects with central fat accumulation have demonstrated marked accumulation of visceral or intra-abdominal fat tissue (VAT). This observation is of particular concern because studies in HIV-negative populations have demonstrated that excess VAT is associated with increased risk of coronary artery disease, type II diabetes mellitus, cerebrovascular disease, gallstones and breast cancer in women. In addition, visceral adiposity can be a factor in the development of metabolic syndromes that are also associated with increased risk of cardiovascular disease and are characterised by glucose intolerance, hyperinsulinaemia, insulin resistance, dyslipidaemia, and hypertension, each of which has been noted in patients with HIV infection in the current treatment era.

Assessment and Monitoring

Lipoatrophy

The diagnosis of peripheral lipoatrophy is usually made by clinical examination and patient self-report. Anthropometric evaluations of limb circumferences can provide data regarding changes of

the size of the arm and leg. Direct evaluation of fat wasting of the extremities can be obtained using imaging techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DEXA). Although considered the gold standard, the expense and limited availability of these techniques are limitations. There are no widely accepted techniques for assessing facial lipoatrophy.

Fat accumulation

A waist/hip ratio is easily obtained, and values >0.95 in men and >0.85 in women are associated with increased risk of cardiovascular disease and other adverse outcomes. Although accurate quantitative measurements of visceral fat volume can be obtained by CT or MRI, variability in scanning methods and approaches to interpretation makes it difficult to use these techniques as diagnostic tools. DEXA cannot distinguish between visceral and subcutaneous adipose tissue, and thus cannot be used to diagnose visceral obesity. Clinical evaluation is required to diagnose buffalo hump or benign symmetric lipomatosis. Buffalo hump may be accompanied by complaints of increasing shirt neck size. Significant lipomatoses might be identified from self-reports of new regional circumscribed fat accumulation. Lipomatoses are frequently seen around the neck; they have also been noted on the trunk, head and other regions.

In addition to increased risk of cardiovascular disease and other adverse medical outcomes, regional fat accumulation may be associated with the development of headaches, difficulty breathing and interference with exercise and sleep.

Treatment

Although numerous approaches are under investigation, there are no proven or approved therapies for fat distribution abnormalities. It is unlikely that a single therapeutic approach will apply in all cases. Therefore, if the decision is made to intervene, it is crucial to identify the specific objectives of treatment (e.g. general or regional fat loss, or peripheral fat gain) and associated metabolic factors (such as insulin resistance, hyperlipidaemia, lactic acidemia, hypogonadism or liver disease) that may require treatment or contraindicate certain therapeutic approaches.

Lipoatrophy

Currently, there are no proven therapies known to reverse or prevent peripheral lipoatrophy. The following approaches have been considered:

Modification of antiretroviral therapy

Data from preliminary results of randomized studies suggest that withdrawal of stavudine and substitution with abacavir or zidovudine is associated with statistically significant but clinically modest increases in peripheral fat, measured by DEXA, and maintenance of virologic control.

Thiazolidinediones

These insulin sensitisers have been shown to result in partial restoration of subcutaneous fat tissue in diabetic individuals with lipoatrophy.

Antioxidants/cofactors

Use of various cofactors in mitochondrial metabolism and antioxidants to ameliorate oxidative stress have been suggested for the prevention and treatment of diseases known or suspected to be due to mitochondrial dysfunction. These agents include vitamins B₁ (thiamine), B₂ (riboflavin), C and E, carnitine and acetylcarnitine, and coenzyme Q. No prospective studies are currently available on the efficacy of these agents.

Cosmetic surgery

Some patients with facial fat wasting have undergone cosmetic surgery, including cheek implants to minimise the effects of facial fat wasting.

Fat accumulation

Although currently there are no approved treatments for fat accumulation in patients with HIV infection, the following approaches have been used:

Modification of antiretroviral therapy

In most studies in which PIs were removed from the antiretroviral regimen, there is little objective evidence of a reversal of abdominal fat accumulation.

Non-pharmacological approaches

Diet

If overall weight reduction is indicated, a moderate reduction in energy intake, reflecting decreased intake of saturated fat, simple sugars and alcohol is warranted. Patients should be aware that weight reduction is likely to be accompanied by a generalised fat loss (peripheral as well as central fat).

Exercise

Studies in HIV-positive subjects have demonstrated that endurance and resistance exercise can reduce total and abdominal fat. Exercise may also contribute to improvements in insulin sensitivity and lipid profiles, and weight-bearing exercise may protect against bone mineral loss.

Pharmacologic approaches

Metformin

Two randomised studies in HIV-infected patients with syndromes of abnormal fat distribution and evidence of insulin resistance have reported significant improvements in glucose tolerance and insulin and lipid levels, as well as decreases in weight. Metformin has been associated with lactic acidosis, and its use in patients with lactate levels $> 1.5 \times \text{ULN}$ is contraindicated.

Thiazolidinediones

A study with troglitazone in HIV-negative subjects with lipodystrophy showed significant reductions in VAT, improvements in insulin sensitivity, and increases in subcutaneous fat. It is not known whether other drugs in this class will have the same effects. These drugs should not be used in patients with significant liver disease.

Growth hormone

Treatment with pharmacologic doses of recombinant human growth hormone has reduced total and visceral fat in small, open-label studies in subjects with HIV infection and either visceral or dorsocervical fat accumulation. However, many patients developed glucose intolerance during treatment, and fat is regained in the affected areas after therapy is discontinued. Loss of peripheral fat is likely to occur in patients receiving this treatment. Growth hormone is not indicated for patients with impaired glucose tolerance or a history of carpal tunnel syndrome.

Surgery

Liposuction has been performed in some patients. There have been anecdotal reports that fat is regained in the affected areas.

Chapter 5

HYPERLACTATEMIA AND LACTIC ACIDOSIS

Definition

Lactic acidemia is defined as an elevated venous lactate level and normal arterial pH.

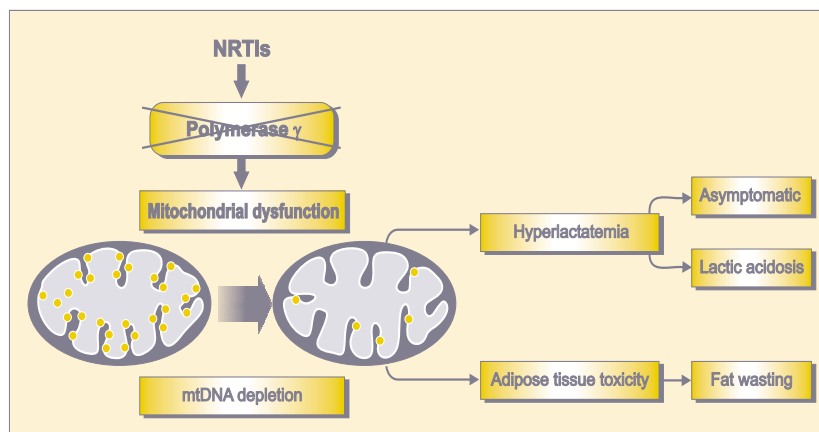
Lactic acidosis is defined as an elevated venous lactate level (> 18 mg/d or 2 mmol/L) and low arterial pH (<7.3).

Background

In the presence of adequate oxygen delivery and normal mitochondrial function, the oxidative breakdown of glucose yields energy in the form of ATP. Under conditions of impaired mitochondrial function, ATP production switches to anaerobic glycolysis – which leads to excess production of lactate. This lactate eventually accumulates, diffuses out of cells, and reaches the systemic circulation. Sufficiently elevated levels of lactate in the systemic circulation (hyperlactatemia) may lead to lactic acidosis and a drop in blood pH.

Hyperlactatemia and lactic acidosis represent a spectrum of disease depending on the degree to which blood lactate homeostasis is affected. Evidence suggests that exposure to one or more NRTIs plays a central role through toxic effects on mitochondrial function. This is because NRTIs inhibit mitochondrial DNA polymerase and inhibition of this enzyme depletes mitochondrial DNA and impairs mitochondrial function.

Figure 3 : Effect of NRTIs on mitochondrial dysfunction



Risk factors

Known risk factors for lactic acidosis include the following:

1. Female gender
2. Obesity
3. Prolonged use of NRTIs
4. Use of concomitant stavudine and didanosine in pregnancy

Signs and symptoms

The spectrum of disease ranges from mild to moderate asymptomatic (or sub-clinical) hyperlactatemia to fulminant and life-threatening lactic acidosis. The onset is acute or subacute. Patients generally present with vague constitutional complaints, including fatigue, malaise, abdominal pain, and nausea and vomiting. Over the course of several weeks, these patients can develop tachypnoea, pancreatitis and/or hepatitis in the setting of progressive acidemia. If unrecognised, death may occur.

Features of hepatic dysfunction are common and can include tender hepatomegaly, peripheral oedema, ascites and encephalopathy. Modest elevations in liver enzymes are common. Hepatic steatosis is frequently observed on imaging and biopsy, with necrosis noted in more fulminant cases.

Patients with low-level lactic acidemia (18-45 mg/dL or 2-5 mmol/L) may have milder constitutional and hepatic abnormalities, but are often asymptomatic.

Assessment and Monitoring

The clinician considering this diagnosis early on in the setting of vague complaints should obtain an arterial or venous lactate level.

A confirmed lactate level above 45 mg/dL (5 mmol/L) in the presence of related new symptoms and signs, or above 90 mg/dL (10 mmol/L) regardless of the clinical presentation, should be used to establish the diagnosis of NRTI- associated lactic acidemia. Measurement of arterial pH confirms the presence of acidosis, but this may not be necessary in many instances.

An elevated lactate level should always be confirmed by repeat measurement. Measurement is recommended in those receiving NRTIs who have clinical signs or symptoms suggestive of lactic acidemia, low bicarbonate, chloride or albumin levels, raised anion gap, unexpected increases in liver enzymes, or new onset of clinical liver failure.

Treatment

For symptomatic patients whose levels are less than 45 mg/dL or 5 mmol/L, continuation of NRTIs is reasonable as long as lactate levels are measured regularly. There is no proven intervention for lactic acidemia apart from NRTI cessation. Prognosis of lactic acidemia depends on the level at the time of diagnosis.

Antiretroviral therapy should be discontinued in the following groups of patients if no other cause is evident:

1. In all patients with confirmed lactate levels >90 mg/dL or 10 mmol/L
2. In all patients with confirmed lactate levels greater than 45 mg/dL or 5 mmol/L who are symptomatic

Combination NNRTI and protease inhibitor therapy can be restarted after the lactate level normalises and the associated illness resolves. Reinstitution of alternative NRTIs in patients with prior lactic acidemia may be possible in some individuals, with close monitoring.

Chapter 6

BONE DISORDERS

Definitions

Bone Demineralisation

The World Health Organisation (WHO) has devised four diagnostic categories related to bone demineralisation: Normal, Osteopenia, Osteoporosis and Established Osteoporosis with Fragility Fractures. The classification relies on the use of dual energy x-ray absorptiometry (DEXA) scanning to determine bone density.

Regional DEXA scans of the hip and the spine are used to assess bone density. Total hip (trochanteric, inter-trochanteric and neck) imaging provides assessment of hip fracture risk and is associated with risk of spine fracture and demineralisation. DEXA results are reported in absolute terms, g/m² and relative terms, T-score and Z-score. Absolute levels may differ depending on the DEXA equipment manufacturer.

The T-score is the number of standard deviations (a statistical unit) between the obtained result and the value expected in a young individual (25-30 years old).

The Z-score represents the number of standard deviations between the obtained result and an age-matched average value from healthy individuals.

- ***Osteopenia*** is a T-score between 1 standard deviation and 2.5 standard deviations below the average found in young people
- ***Osteoporosis*** is a T-score lower than 2.5 standard deviations below the average found in young people
- ***Established osteoporosis*** is a T-score lower than 2.5 standard deviations in the presence of fragility fractures.

NOTE: There can be variability of 3%-6% in the reproducibility of DEXA results due to differences in technique, machine reading, and technologist.

Avascular necrosis (AVN)

Avascular necrosis, or osteonecrosis, is characterised by death of bone tissue due to compromised blood flow. The femoral head (hip) is most commonly involved. The femur at the knee and the humeral head (shoulder) are frequently involved.

Background

The use of protease inhibitor antiretroviral therapy has been reported to be associated with increased levels of osteocalcin, indicating increased bone turnover. Reports suggest rates of osteopenia of 22-50% and osteoporosis of 3-21% in patients receiving mainly protease inhibitor-containing antiretroviral therapy (*AIDS 2001;15: 703-9; AIDS 2000; 14: F63-F67; AIDS 2001; 15: 975-82; Abstract 208, 7th CROI, 2000*). Although to date reports of bone fractures are rare, the long-term consequences of osteopenia in HIV-1-seropositive patients are unknown.

Assessment and monitoring

Routine screening of HIV-1-infected patients for the presence of osteoporosis or osteonecrosis is not recommended.

Osteopenia and osteoporosis are typically diagnosed using DEXA scanning. DEXA results correlate to risk for bone fracture in the general population. Severe bone demineralisation may be noted on plain x-rays. If reduced bone mineral density is found, an assessment for additional factors that are associated with osteopenia should be undertaken. All patients should have an adequate dietary intake of calcium and vitamin D.

AVN is often first suspected when acute pain develops in a joint, typically a large joint such as the hip or shoulder. Diagnostic testing depends on the stage of the disease. MRI is the most sensitive and specific technique and should be used for very early diagnosis, when collapse of the femoral head or other bone may be preventable. If duration or disease is not clear, an X-ray or CT scan is often obtained to rule out advanced disease. Bone scanning is more sensitive than X-ray but is non-specific. X-ray findings may not become apparent for months to up to 5 years after symptom onset.

Treatment

Osteoporosis

The safety and efficacy of standard therapies used to treat bone demineralisation have not been studied in HIV-infected persons. The goal of treatment of osteoporosis is to reduce risk of fractures and maintain function.

Lifestyle

Weight loss, malnutrition, physical inactivity and smoking have each been associated with development of osteoporosis. Lifestyle changes that eliminate or reduce these risk factors should be attempted in patients with osteopenia and osteoporosis.

Calcium and vitamin D

Clinical trials have demonstrated a significant reduction in fractures with calcium and vitamin D. For patients with osteoporosis, the total daily calcium intake should be 1500 mg.

Bisphosphonates

These are drugs that slow down or stop bone resorption. In the general population, these agents are typically reserved for patients who have established osteoporosis or high risk of osteoporosis. Alendronate is the most commonly used, and is the only drug approved for treatment of osteoporosis in men.

Hormone Replacement Therapy

In post-menopausal women, osteoporosis can be effectively treated with oestrogen-replacement therapy.

Calcitonin

Intranasal and parenteral calcitonin has been used for osteoporosis, with relatively low tolerability and efficacy compared to bisphosphonate therapy.

Teriparatide

This drug is the first in a new class of drugs that work primarily to stimulate new bone formation by increasing the number and/or activity of the bone-forming osteoblasts.

FURTHER READING

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11. Keeping Perspective: Evaluating the Risks and Benefits of HAART <http://www.clinicaloptions.com/hiv/manage/metabolics/> Accessed 25th August 2004
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APPENDIX 1: FOR CLINICIANS

Grading of side effects

A general indication of grading (based on US NIH Division of AIDS) is shown below together with specific details for some of the most common side effects.

| Side effect | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|-----------------------------------|---|---|---|--|
| Diarrhoea | 3-4 loose stools a day OR mild diarrhoea lasting less than one week | 5-7 loose stool a day OR diarrhoea lasting more than one week | Bloody diarrhoea OR over 7 loose stools a day OR needing IV treatment OR feeling dizzy when standing | Hospitalisation required (possible also for grade 3) |
| Fatigue | Normal activity reduced by less than 25% | Normal activity reduced by 25-50% | Normal activity reduced by over 50%; cannot work | Unable to care for yourself |
| Liver toxicity: AST or ALT levels | 1.25 – 2.5 Upper Limit of Normal (ULN) | > 2.5-5.0 ULN | 5.0-7.5 ULN | > 7.5 ULN |
| Mood disturbance | Mild anxiety, able to continue daily tasks | Moderate anxiety/ disturbance, interfering with ability to work, etc | Severe mood changes requiring medical treatment. Unable to work | Acute psychosis, suicidal thoughts |
| Nausea | Mild OR transient reasonable food intake | Moderate discomfort OR intake decreased for less than 3 days | Severe discomfort OR minimal food intake for more than 3 days | Hospitalisation required |
| Rash | Redness or itchy skin on part or whole body | Rash that breaks skin, hard or soft pimples OR light peeling/ scaling | Blistering, open ulcers, wet peeling, serious rash over large areas | Severe rash, Stevens Johnson syndrome. Severe broken skin, etc |
| Vomiting | 2-3 episodes a day OR mild vomiting for less than one week | 4-5 episodes a day OR mild vomiting for more than one week | Severe vomiting of all food and fluids over 24 hours OR needing IV treatment OR feeling dizzy when standing | Hospitalisation for IV treatment (possibly also for Grade 3) |

APPENDIX 2: INFORMATION THAT MAY BE GIVEN TO PATIENTS

How to report side effects

In order to be able to accurately describe your side effects to your doctor, you may find the following points useful:

Frequency

- How often do you get symptoms?
- Once or twice a week? Once every day, or 5-10 times a day etc?
- Do they occur at night as well as during the day?

Duration

- How long do the symptoms last?
- If you feel sick or get headaches, do they last for 20 minutes or for 3-4 hours, or for different times?
- Is there a pattern to when they occur – i.e. when you take your medications or at a regular time afterwards?

Severity

- How bad are the symptoms?
- Often it helps to rate them on a scale (from 1 for very minor to 10 for very severe).
- Recording how severe side effects are when they occur is better than recording them later.
- Have you noticed anything that helps to reduce or stop them?

Quality of life

If you are feeling more anxious or nervous, are not sleeping properly, have a lower sex drive, have experienced taste changes, or are too nauseous to eat proper meals, it is important that your doctor knows about this.

If side effects are preventing you from taking your treatment regularly, you must tell your doctor about this. The side effects diary given on the next page would help you to note down your symptoms. Take this diary with you when you see your doctor.

