

# Approaches to the management of antiretroviral therapy toxicity

# 9

**Andrew Carr**  
**Olga Vujovic**

Immunology/HIV/Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, NSW  
Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC

Although the introduction of combination antiretroviral therapy (cART) was a watershed event in the management of people with HIV infection, concern about treatment complications has arisen over the past decade. These conditions include lipodystrophy, cardiovascular disease, drug hypersensitivity, hepatic and renal toxicity, peripheral neuropathy, lactic acidosis and bone abnormalities, most of which appear to be multifactorial.

## 9.1 Lipodystrophy

### 9.1.1 Clinical features

HIV lipodystrophy is characterised by peripheral, subcutaneous lipoatrophy and relative central fat accumulation. It affects about 50% of adults receiving cART.<sup>1,2</sup> Central fat accumulation occurs within the abdomen as well as in the breasts, dorso-cervical spine and upper trunk. One or more of several metabolic abnormalities are typically associated with lipodystrophy: elevated total cholesterol, elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, hyperlactataemia, insulin resistance and type 2 diabetes mellitus.

Whether lipoatrophy and fat accumulation represent one or a number of syndromes is unknown, however lipoatrophy is the dominant feature. Lipoatrophy is a diminishing problem in patients commencing contemporary antiretroviral regimens. There remains a large number of patients, however, with persistent lipoatrophy in whom antiretroviral strategies have resulted in very limited recovery. These findings suggest that prevention is paramount and that new interventions are required to accelerate recovery.

### 9.1.2 Risk factors

#### Choice of cART

The two drugs most implicated in the development of lipoatrophy are the thymidine nucleoside analogue reverse transcriptase inhibitors (NRTI), stavudine and zidovudine. In prospective studies of adults initiating therapy, a gradual increase in limb and trunk fat over the first six months, probably representing recovery from HIV wasting was observed.<sup>3</sup> After that time, limb fat loss was seen in those receiving stavudine and zidovudine, but not in those receiving abacavir or tenofovir.<sup>4,5</sup> Fat loss with stavudine and zidovudine appears to progress over three years. Any impact of didanosine and emtricitabine is not well quantified. In patients receiving stavudine or zidovudine, a switch to abacavir or tenofovir improved limb fat by about 0.4kg limb fat over 12 months, which suggests that lipoatrophy may take over five years to resolve without additional intervention.<sup>6,7</sup> As with any inception or switch strategy, choice of cART with the aim of preventing or reversing lipoatrophy should be kept in context of other potential side-effects of new drugs chosen. Few thymidine nucleoside switch studies evaluated central adiposity and have not found any significant benefit with this strategy.

Protease inhibitors probably play a lesser role in the development of lipoatrophy than nucleoside analogues and effects may vary between protease inhibitors. Indeed, low-dose ritonavir reduced the risk of lipoatrophy when used to boost atazanavir, and ritonavir-boosted lopinavir caused less lipoatrophy than efavirenz. The effect of different protease inhibitors on central fat accumulation is uncertain.

### 9.1.3 Assessment

Most clinicians assess lipodystrophy clinically, which may be appropriate for diagnosis, particularly for a condition of mostly cosmetic concern. Subjective evaluation is poor when assessing incident lipodystrophy as well as responses to therapy. Dual-energy X-ray absorptiometry (DEXA) is an inexpensive tool for reliably measuring peripheral fat over time.

### 9.1.4 Treatment

#### Lifestyle interventions

It is commonly recommended that the metabolic associations of lipodystrophy and cART should be treated first with lifestyle interventions, namely a low-lipid, low-calorie diet and increased aerobic exercise. The impact of these interventions on lipoatrophy and fat accumulation is not well known, although they can lower triglycerides, total cholesterol, weight, blood pressure and insulin resistance (Table 9.1). A calorie-restrictive diet and aerobic exercise can reduce both peripheral and central fat.

#### Medical interventions

Several medical interventions have been evaluated in randomised trials: thiazolidinediones, uridine and pravastatin for lipoatrophy; and metformin, growth hormone and growth hormone analogues for visceral fat accumulation.

Thiazolidinediones are agonists of the peroxisome proliferator-activated receptor (PPAR)-gamma and are insulin-sensitising drugs used for the treatment of type 2 diabetes mellitus. PPAR-gamma agonists stimulate both the differentiation and growth of adipocytes and promote their storage of circulating lipid, and increase limb fat in young adults with congenital lipodystrophy. Randomised trials evaluating rosiglitazone have found a possible short-term benefit but no sustained effect of rosiglitazone over a 48-week period, along with improvements in insulin resistance and deterioration in lipids.<sup>8</sup> Pioglitazone increased limb fat modestly without adverse metabolic effect, but only in those not receiving stavudine and, therefore, would only be a candidate for lipoatrophy in conjunction with stavudine and zidovudine withdrawal.<sup>9</sup>

Lipoatrophy caused by nucleoside analogues has been proposed to result from inhibition of mitochondrial DNA polymerase gamma within subcutaneous adipocytes. Not all

Table 9.1 Interventions for HIV lipodystrophy			
Intervention	Lipoatrophy	Central fat accumulation	Comments
Diet and aerobic exercise	May worsen	Improves	<ul style="list-style-type: none"> <li>Reduce systolic blood pressure and weight in adults with metabolic syndrome, but do not alter lipid levels</li> <li>Diet must not affect meals necessary for absorption of antiretroviral therapy</li> </ul>
Thymidine nucleoside analogue switch	Improves (about 0.4 kg limb fat at 12 months)	No change	<ul style="list-style-type: none"> <li>High risk of virological failure without substitution</li> <li>Lipids may improve with switch to tenofovir</li> <li>No effect on insulin resistance demonstrated</li> <li>No excess risk of virological failure with abacavir or tenofovir substitution</li> </ul>
Protease inhibitor switch	No change	Reduction	<ul style="list-style-type: none"> <li>Inception studies show more lipoatrophy with nelfinavir and less lipoatrophy with ritonavir-boosted lopinavir/r, both relative to efavirenz</li> <li>Hyperlipidaemia improves</li> <li>Variable effects on insulin resistance</li> <li>No change in HDL cholesterol</li> </ul>
Uridine	Improved (+0.7 kg limb fat at 12 weeks)	Increased	<ul style="list-style-type: none"> <li>HDL cholesterol decreased</li> <li>Unlicensed dietary supplement</li> <li>Expensive – about US\$250 per month</li> </ul>
Statin	Improved with pravastatin (+0.5 kg limb fat at 12 weeks)	No change	<ul style="list-style-type: none"> <li>Total and LDL cholesterol fall by about 25%</li> <li>No change in insulin resistance or triglycerides</li> <li>Pravastatin preferred as cholesterol-lowering agent, as has no significant cytochrome P450-mediated interaction with antiretroviral therapy</li> <li>Effects of other statins on lipoatrophy are unknown</li> </ul>
Fibrate	No change	No change	<ul style="list-style-type: none"> <li>Triglycerides fall by 20 to 25%, possibly greater effect with fenofibrate than with gemfibrozil</li> <li>Improves HDL cholesterol</li> <li>Minimal effect on insulin resistance, and total and LDL cholesterol</li> <li>May be less effective in people with HIV infection</li> </ul>
Thiazolidinediones	Possibly improves with pioglitazone	No change	<ul style="list-style-type: none"> <li>Improves insulin resistance</li> <li>Rosiglitazone increases triglycerides and LDL cholesterol</li> <li>Reduces liver fat</li> </ul>
Metformin	Worsens	Slight improvement	<ul style="list-style-type: none"> <li>Improves insulin resistance, blood pressure and possibly hypertriglyceridaemia</li> </ul>
Growth hormone	Worsens	Improves	<ul style="list-style-type: none"> <li>Overall reduction in VAT:SAT ratio</li> <li>No effect on triglyceride levels</li> <li>Improves total and LDL cholesterol</li> <li>Transient deterioration in insulin resistance</li> <li>Risks of fluid retention, arthralgias</li> <li>Maintenance therapy required to sustain effect on intra-abdominal fat</li> </ul>
Growth hormone-releasing hormone and analogue	Worsens	Improves (reduced VAT by 20%)	<ul style="list-style-type: none"> <li>Overall reduction in VAT:SAT ratio</li> <li>Minimal safety risk with achievement of physiologic GH levels</li> <li>Modest increase in HDL cholesterol</li> <li>Need for maintenance therapy not known</li> </ul>

LDL = low-density lipoprotein; HDL = high-density lipoprotein; GH = growth hormone; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

Source: modified from Carr A. New treatments for HIV lipodystrophy. *Curr Opin HIV AIDS* 2007;2: 332-38. Used with permission

observed data, however, can be explained by this hypothesis. An alternative hypothesis is intracellular depletion of pyrimidine precursors, rather than depletion of mitochondrial DNA. Uridine is a pyrimidine precursor and so might replenish intracellular pyrimidine pools. *In vitro*, uridine abrogates the mitochondrial toxicity of stavudine and zidovudine, but not of didanosine.<sup>10</sup>

The nutritional supplement, NucleomaxX, a supplement rich in uridine, a nucleoside used in the synthesis of DNA, at a dose of 36 gm (1 sachet) three times a day for 10 consecutive days each month, increased limb fat by approximately 0.9 kg over three months (as well as plasma uridine levels), an effect far greater than the 0.4 kg for nucleoside analogue switching. No significant adverse effect was noted, although the study was small.<sup>11</sup> Furthermore, the supplement is expensive – the current regimen costs about US\$250 per month. Larger randomised trials are underway. One important question to answer from these studies is whether uridine will have benefit in the increasing number of patients no longer receiving stavudine or zidovudine.

Lastly, pravastatin increased limb fat (about 0.5kg) and subcutaneous fat over three months in protease inhibitor-treated men with HIV on cART and was not associated with any significant change of visceral adiposity.<sup>12</sup>

Metformin is an insulin-sensitising agent that has long been used for the treatment of type 2 diabetes. Metformin typically induces weight loss at least in part because of its anorexic effect. Randomised trials of metformin in lipodystrophic patients with significant central adiposity showed a reduction in visceral fat over 24 weeks without development of significant toxicity although lipoatrophy deteriorated.<sup>2</sup> Furthermore, not only did visceral adiposity improve, but insulin resistance and systolic blood pressure also improved significantly. However, no lipid component improved. The effects of metformin and diet have been shown to be additive.<sup>13</sup>

Growth hormone (GH) deficiency is a well-recognised cause of central adiposity. Some adults with HIV-lipodystrophy appear to have a relative growth hormone deficiency, the mechanism of which is unknown. Growth hormone caused a dose-dependent reduction in visceral adiposity. The higher doses initially used were associated with substantial toxicity, in particular loss of peripheral fat mass, fluid retention, joint pain, and worsening insulin resistance and lipoatrophy.<sup>14</sup> Lower doses of growth hormone, as well as growth hormone-releasing hormone (GHRH) and the GHRH analogue tesamorelin, also reduce visceral adipose tissue area but are better tolerated; permanent dosing of all the above may be necessary to maintain the beneficial effect on visceral fat.<sup>15,16</sup> GH and its analogues are unlikely to be used in Australia because of cost. Metformin seems most appropriate for the treatment of type 2 diabetes in patients without lipoatrophy.

## Cosmetic surgery

Facial cosmetic surgery to minimise facial lipoatrophy has been widely used. The most extensively studied agent is poly-L-lactic acid (PLA), which may stimulate collagen synthesis. The first uncontrolled study suggested a rapid and sustained improvement in facial lipoatrophy.<sup>17</sup> Smaller, randomised trials without objective endpoint data were also positive.<sup>18</sup> A randomised trial of PLA every two weeks on four occasions that included volumetric, computerised tomography found PLA

was safe, but increased facial soft tissue volume by only 3%, although there were significant increases around the sites of injection that correlated with patient-perceived improvements in facial lipoatrophy severity.<sup>11</sup> These modest improvements suggest that the amount of PLA generally recommended (four vials per cheek) is inadequate. Increasing the dose to achieve a substantial volumetric effect would make an already expensive treatment even more expensive.

## 9.2 Cardiovascular disease, dyslipidaemia and insulin resistance

### 9.2.1 Epidemiology

Most protease inhibitors (except unboosted atazanavir, but including low-dose ritonavir), efavirenz, stavudine and zidovudine increase total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels.<sup>2,19</sup> The change in risk of cardiovascular disease with cART (estimated by the Framingham equation, which is useful for estimating cardiovascular risk in this population) is generally not substantial unless other cardiovascular risk factors are present, perhaps in part because most potent cART also increases HDL cholesterol levels.

Diabetes mellitus occurs in 6-10% of those receiving cART.<sup>2</sup> Risk factors for diabetes include increasing age, obesity, family history, lipoatrophy and fat accumulation (and the antiretroviral therapy that cause them), metabolic syndrome and hepatitis C infection.<sup>20,21</sup> Stavudine, as well as indinavir, ritonavir (even at the low boosting dose) and lopinavir, but not atazanavir or amprenavir, induce insulin resistance acutely, but any long-term effect is unknown.

There is strong epidemiological evidence relating the risk of cardiovascular disease with the duration of cART, and in particular, cART including a protease inhibitor (Table 9.2).<sup>22</sup> About half this association can be explained by hypercholesterolaemia, hypertriglyceridaemia and low HDL cholesterol levels, but the other half remains unexplained. Nevertheless, traditional risk factors (greater age, male sex, smoking, hypertension, diabetes, pre-antiretroviral therapy dyslipidaemia) are collectively more important than antiretroviral therapy. The overall cardiovascular risk associated with antiretroviral therapy is declining. Reasons proposed to explain this decreasing risk include the increasing use of lipid-lowering drugs, less smoking, and use of more lipid-neutral antiretroviral therapy.

Nevertheless, intermittent cART is also associated with an increased risk of cardiovascular disease.<sup>23</sup> The causes of this increased risk are not known. Two possible risks are currently being explored: the reduction in HDL cholesterol levels<sup>24,25</sup> and the increases in inflammatory markers associated with viral replication.

These data collectively suggest that cardiovascular risk will best be addressed by suppressing HIV with antiretroviral drugs that cause the least amount of metabolic disturbance. Most recently, however, abacavir and didanosine have been associated, in a lipid-independent manner, with an increased risk of myocardial infarction.<sup>26</sup>

### 9.2.2 Assessment

Cardiovascular risk in HIV disease appears to be reasonably estimated using the Framingham equation although this may

	HIV	Nucleoside reverse transcriptase inhibitors	Protease inhibitors	Other
<b>Increased total and LDL cholesterol</b>	Decreased levels with moderate to advanced disease	<ul style="list-style-type: none"> <li>Recovery from HIV wasting</li> <li>Probably other unidentified mechanism(s)</li> </ul>	<ul style="list-style-type: none"> <li>Recovery from HIV wasting</li> <li>Increased hepatic VLDL synthesis</li> </ul>	Obesity
<b>Low HDL cholesterol</b>	Nef-mediated decreased HDL production with early HIV disease	Lipoatrophy – adipocyte apoptosis and inability to store circulating triglyceride	Mechanism unknown	<ul style="list-style-type: none"> <li>Smoking</li> <li>Physical inactivity</li> <li>Diabetes mellitus</li> </ul>
<b>Increased triglycerides</b>	Increase with advanced disease	Lipoatrophy – adipocyte apoptosis and inability to store circulating triglyceride	Increased hepatic VLDL production	<ul style="list-style-type: none"> <li>Obesity</li> <li>Sensitivity to alcohol</li> <li>Diabetes mellitus</li> </ul>
<b>Glucose metabolism</b>	No change known	Lipoatrophy with reduced leptin and adiponectin secretion	<ul style="list-style-type: none"> <li>Increased hepatic glucose output</li> <li>Hypertriglyceridaemia</li> </ul>	<ul style="list-style-type: none"> <li>Obesity</li> <li>Diabetes mellitus</li> </ul>
<b>Other</b>	Increased inflammation and thrombosis?		<ul style="list-style-type: none"> <li>About 50% of lipid association with CVD not explained by lipid effects</li> <li>Increased foam cell formation?</li> </ul>	<ul style="list-style-type: none"> <li>Age</li> <li>Male sex</li> <li>Smoking</li> <li>Hypertension</li> <li>Family history</li> <li>Cocaine use</li> </ul>

VLDL = very low density lipoprotein ; CVD = cardiovascular disease; LDL = low density lipoprotein.  
 Source: Carr A. Pathogenesis of HIV cardiovascular disease. Curr Opin HIV AIDS, 2008; 3: 234-39. Used with permission.

underestimate risk. This equation can also be used to estimate the change in risk with various interventions. Asymptomatic myocardial ischaemia was detected in about 10% of a large cohort of adults with no history of cardiovascular disease, emphasising the need for universal cardiovascular risk assessment of people with HIV infection prior to the initiation of therapy and then perhaps every year or so thereafter.<sup>27</sup>

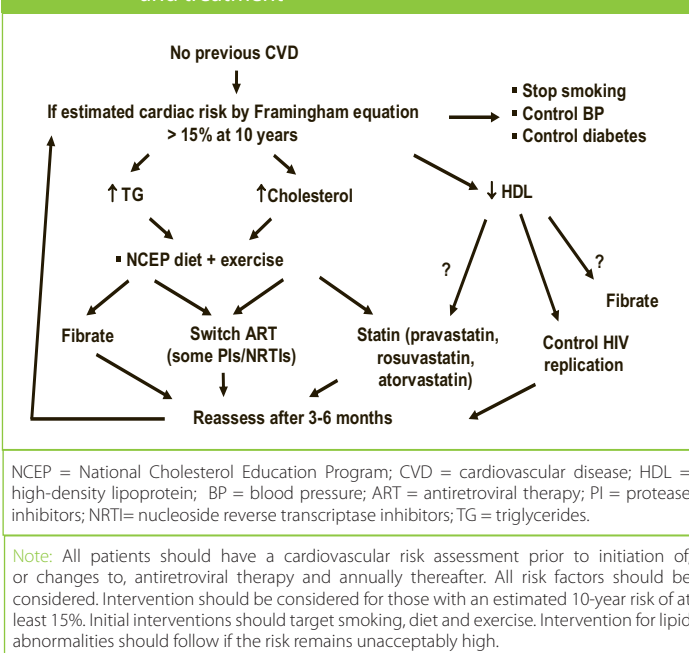
Fasting blood glucose is a poor measure of insulin resistance and diagnoses less than half of all diabetes in people with HIV infection. When other cardiovascular or diabetic risk factors are present, an oral glucose tolerance test should be considered.<sup>2,40</sup>

### 9.2.3 Treatment

Lifestyle factors to address at all times include smoking cessation, the control of blood pressure, diabetes and appropriate exercise and diet (Figure 9.1).<sup>2</sup> Dyslipidaemia would be addressed for those patients in whom the above measures were ineffective in reducing their estimated 10-year risk to <15%-20%. Cessation of smoking is likely to be the single most effective intervention. The potential efficacy of any intervention should be assessed three to six months afterwards as multiple interventions may be required to maximally reduce cardiovascular risk.

In general, elevated total cholesterol is addressed first by changes to antiretroviral therapy or by the initiation of statins that are thought not to interact with antiretroviral therapy. For hypercholesterolaemia, pravastatin is most used as its metabolism is unaffected by antiretroviral therapy, although

Figure 9.1 Algorithm for cardiovascular disease risk assessment and treatment



its effectiveness may be less in people with HIV infection.<sup>12</sup> Plasma levels of more potent statins such as rosuvastatin and atorvastatin can be increased by protease inhibitors, increasing risk of statin toxicity so, if used these statins should be initiated at lower-than-normal doses. Ezetimide also is effective at lowering LDL cholesterol. Fibrates and fish oils are probably more appropriate for those with elevated triglycerides. The best approach to a low HDL cholesterol level would either be

control of HIV replication, a fibrate or drugs that allowed for improvement of HIV lipotrophy, which is strongly linked to low levels of HDL cholesterol.

The other option for dyslipidaemia is switching boosted protease inhibitors, efavirenz and some nucleoside analogues to other virologically-active, more lipid-neutral antiretroviral therapy.<sup>2</sup> As cART is generally permanent, switching is an attractive option as it avoids permanently treating drug toxicity with another drug.

Metformin improves insulin sensitivity and systolic blood pressure, and may reduce visceral fat.<sup>13</sup> Thiazolidinediones also improve insulin sensitivity; rosiglitazone, but not pioglitazone, aggravates dyslipidaemia.<sup>8,9</sup>

## 9.3 Lactic acidosis

### 9.3.1 Clinical features

Lactic acidosis is a rare syndrome, usually of subacute onset, manifest by initial gastrointestinal symptoms (especially nausea, vomiting, weight loss and progressive lipotrophy) followed by dyspnoea, cardiac arrhythmias and multi-organ failure. Severe lactic acidosis (defined as arterial lactate concentrations of  $\geq 5$  mmol/L and pH of  $< 7.35$ ) is often associated with steatohepatitis and pancreatitis, whereas milder increases in plasma lactate without acidosis are mainly associated with milder constitutional symptoms and weight loss. In addition to elevated lactate levels, investigation may reveal elevated liver enzymes, fatty liver on imaging, and microvesicular steatosis (fatty accumulation in hepatocytes due to abnormal mitochondrial oxidation of free fatty acids) on liver biopsy.

### 9.3.2 Risk factors

The syndrome mainly occurs in the first year of therapy with one or more of the NRTIs didanosine, zidovudine and stavudine, and more particularly regimens containing both stavudine and didanosine.<sup>28</sup> In resource-limited settings (where use of these drugs is greatest), the risk appears greater in black women weighing more than 70kg, suggesting the illness may be more likely in those with pre-existing hepatic steatosis rather than being more likely with lower weight and higher NRTI blood levels. Other illnesses that can precipitate lactic acidosis in the setting of HIV infection include malignancy, liver failure, cardiovascular disease, diabetes mellitus (and its treatment with metformin), pregnancy, co-infection with viral hepatitis (and its treatment with ribavirin), and advanced HIV infection.

### 9.3.3 Assessment

To assess a patient with symptoms of lactic acidosis, venous lactate levels should be measured. Blood should be taken without the use of a tourniquet and the person should not have exercised in the preceding two hours. Laboratories differ in the requirement to place the blood sample on ice. Venous and arterial lactate levels differ, with consistently higher levels observed in arterial samples compared with venous samples. Consideration should be given to measuring arterial pH in patients with dyspnoea, substantial weight loss or with clinical evidence of hepatic failure or pancreatitis.

### 9.3.4 Treatment

For symptomatic hyperlactataemia, apart from immediate discontinuation of antiretroviral therapy and general

supportive measures, therapeutic strategies are controversial. Efforts to restore normal blood pH via bicarbonate infusions or administration of dichloroacetate have had conflicting results. Others have anecdotally reported use of haemodialysis, thiamine, riboflavin, vitamin C, L-carnitine, and co-enzyme Q10. It is unlikely these interventions will ever be formally assessed in clinical trials. After resolution of the illness, institution of alternative NRTIs such as abacavir, tenofovir, lamivudine and emtricitabine are thought to be safe in this respect.

Asymptomatic hyperlactataemia (venous lactate less than 5 mmol/l) is managed by observation and continuation of cART. The limited clinical data indicate that isolated asymptomatic elevations in lactate are not predictive of future lactic acidosis, although they may be associated with neuropathy and osteopenia. Based on the available evidence, routine monitoring of lactate in asymptomatic individuals on cART is not generally recommended. However, a low threshold for testing of lactate levels is suggested in NRTI treated individuals who develop symptoms, particularly in those at risk.

## 9.4 Peripheral neuropathy

### 9.4.1 Clinical features

HIV- and NRTI-associated peripheral neuropathy is a symmetrical, predominantly sensory distal neuropathy. Initially the peripheral neuropathy is relatively asymptomatic with diminished temperature perception and loss of ankle jerks. With progression, there is numbness or tingling distally. A small percentage of individuals experience severe pain. Drug-induced and HIV-related neuropathy may be clinically indistinguishable. NRTI-associated peripheral neuropathy generally occurs in the setting of suppressed HIV replication, has a more abrupt onset and rapid progression, is more painful, and resolves (at least partially) after NRTI cessation (Chapter 18.2).

### 9.4.2 Risk factors

Sensory neuropathy is a known adverse effect of zalcitabine and stavudine. Rates of neuropathy with didanosine therapy have been variably reported as increased or unchanged from the background rate. Increased susceptibility to peripheral neuropathy has been reported with regimens containing both didanosine and stavudine, with a further increase when these two agents are used in combination with hydroxyurea. Further risk factors for neuropathy in individuals treated with stavudine, didanosine and/or zalcitabine include low CD4 cell count, AIDS, a history of peripheral neuropathy, diabetes, prior cytotoxic chemotherapy, high alcohol intake, vitamin B12 deficiency and possibly hepatitis C co-infection.

### 9.4.3 Assessment

Evaluation of the individual with symptoms suggestive of neuropathy in the setting of cART includes careful neurological examination and nerve conduction studies to confirm the clinical diagnosis. The presence of predisposing factors listed above should be investigated, particularly those which are potentially reversible, such as medications, vitamin B12 or other vitamin deficiencies and alcohol use.

### 9.4.4 Treatment

Treatment includes discontinuation of the NRTIs likely to be contributing to the neuropathy, and substitution with agents such as zidovudine, lamivudine, tenofovir and abacavir. The likelihood of maintaining viral suppression with the new

## 9 Managing the patient on antiretroviral therapy

regimen needs to be considered. Symptomatic measures for pain include topical agents (capsaicin cream and lignocaine), tricyclic antidepressants (amitriptyline or desipramine), sodium valproate and gabapentin. Individuals with severe pain may require narcotic analgesia. In addition, factors such as depression, which may exacerbate chronic pain syndromes, should be sought and treated. Small studies have also suggested possible clinical benefits of lamotrigine, L-carnitine and topical aspirin in diethyl ether.

### 9.5 Hepatotoxicity

Mechanisms of antiretroviral hepatotoxicity include direct antiretroviral toxicity, hypersensitivity, immune reconstitution in those with chronic viral hepatitis, and steatohepatitis secondary to NRTI mitochondrial toxicity. Their features, risk factors, diagnosis and management differ (Table 9.3). In particular, steatohepatitis can be relatively late in onset, and is not usually accompanied by jaundice or with significant increases in hepatic transaminases. Liver toxicity is generally more frequent among subjects with chronic viral hepatitis or elevated baseline hepatic transaminases and in those with excessive alcohol use.<sup>29</sup>

Five percent of nevirapine-exposed patients develop hepatitis in the first three months of therapy, and in 50% of these a rash and fever also occurs. Because immunocompetence is a significant risk factor, guidelines recommend that nevirapine be initiated only in antiretroviral therapy-naïve men and women with CD4 cell counts less than 400 and 250 cells/ $\mu$ L, respectively, with particular caution for those with chronic viral hepatitis.

Recent data suggest that patients already receiving antiretroviral therapy who switch to nevirapine above these CD4 cell count thresholds may not have this greater risk of hepatitis.<sup>30</sup> Whether this is due to the initiation of a single drug in a patient switching or due to the suppression of viral load is not clear.

Immune reactivation is most common in those with low CD4 cell counts and an underlying untreated infection at the time of antiretroviral initiation. The flare of hepatitis B is associated with known chronic active hepatitis B infection that has been successfully treated, followed by interruption of one or more of tenofovir, lamivudine or emtricitabine. Clinicians should bear in mind that more than one of these causes may apply in any individual patient (Chapter 21.1).

Idiopathic hepatic fibrosis has been found in a small proportion (2%) of people with HIV infection and is related to cumulative didanosine exposure. Moreover, long-term didanosine therapy is rarely linked to nodular regenerative hyperplasia of the liver.<sup>31</sup>

### 9.6 Hypersensitivity

HIV is associated with significant risk of hypersensitivity to multiple drugs. The first drugs implicated in the early years of the epidemic were sulphonamide antibiotics, anti-tuberculous drugs, and anti-convulsants. More recently the focus has been on antiretrovirals of which nevirapine, other non-nucleosides, amprenavir, darunavir and abacavir are the most common. There are some differences between each

Table 9.3 Types of liver disease relating to antiretroviral therapy

Cause	Hyperlactataemia	Hypersensitivity	Isolated hepatitis	Immune reactivation	Hepatitis B flare
<b>Antiretrovirals</b>	ddl, d4T, AZT Nucleoside analogues	nevirapine	nevirapine	Any	Stopping 3TC, FTC and/or TDF
<b>Risk factors</b>	Nucleoside analogue duration of exposure Female sex Obesity Ribavirin Pregnancy	Higher CD4 cell count	HCV RNA positive Elevated ALT	CD4 cell count <100 cells/mL Chronic viral hepatitis MAC bacteraemia CMV viraemia Recent TB	HBV DNA positive pre-pregnancy
<b>Clinical features</b>					
Onset	Late	Early	Early/late	Early	Early
Fever	No	Common	Occasional	Yes	Yes
Rash	No	Common	No	No	No
Jaundice	No	Occasional	Occasional	Common	Common
Dyspnoea	Yes	No	No	No	No
Liver failure	Occasional	?1%	?1%	Common	Common
<b>Laboratory features</b>					
ALT >10 x ULN	No	Common	Common	Common	Common
Lactate >2 mmol/L	Yes	No	No	No	No
<b>Therapy</b>	Cease nucleoside analogues	Cease cART	Cease cART Treat HCV or HBV	Cease all cART Treat OI	Restart HBV therapy

HBV = hepatitis B virus; HCV = hepatitis C virus; RNA = ribonucleic acid; ALT = alanine transaminase; ddl = didanosine; d4T = stavudine; AZT = zidovudine; 3TC = lamivudine; FTC = emtricitabine; TDF = tenofovir; DNA = deoxyribonucleic acid; MAC = *Mycobacterium avium complex*; CMV = cytomegalovirus; TB = tuberculosis; cART = combination antiretroviral therapy; OI = opportunistic infection; ULN = Upper limit of normal.

of these drugs that can sometimes be detected clinically. In particular, nevirapine hypersensitivity appears to occur later than hypersensitivity to abacavir.

Abacavir causes a hypersensitivity reaction including fever, rash, fatigue and gastro-intestinal symptoms after a mean 10 days in 8% of unselected, Caucasian adults, but less commonly in black Americans and Africans. Fatalities have ensued after unsupervised rechallenge, which is contraindicated.

Adults with the HLA-B\*5701 major histocompatibility ancestral haplotype have about a 60% risk of abacavir hypersensitivity. Molecular screening for HLA-B\*5701 has positive and negative predictive values of about 80% and 96%, respectively. Prospective screening decreased hypersensitivity from 9% to 2% and also lowered the cessation rate in those with uncertain symptoms. A randomised trial recently found that excluding patients with this haplotype on the basis of simple and cheap genetic testing could virtually eliminate immunologically confirmed hypersensitivity and more than half the risk of clinically suspected hypersensitivity.<sup>32</sup>

## 9.7 Bone disease

### 9.7.1 Epidemiology

Numerous cross-sectional studies have found that people with HIV infection have a higher prevalence of low bone mineral density (BMD) ranging from 40-83%, rates higher than in the general population. A meta-analysis of cross-sectional studies established that people with HIV infection had a 6.4-fold increased odds ratio of reduction in BMD and a 3.7-fold increased odds ratio of osteoporosis compared with uninfected controls.<sup>33</sup> How much of this is due to HIV, to antiretroviral therapy, or to other factors is unclear. Factors associated with low mineral density in one or more of these studies include the traditional risk factors for osteoporosis (increasing age, low body mass index, female sex, low testosterone levels, menopause, current or prior use of corticosteroids), as well as HIV-related factors (duration of HIV infection, elevated plasma HIV viral load, use of antiretroviral therapy, use of thymidine nucleoside analogues with elevated plasma lactate levels, and use of protease inhibitor therapy). In contrast, many studies found no effect of antiretroviral therapy, nor protease inhibitor-based therapy. Not all studies have evaluated all risk factors and the dominant risk factor is unclear. The above-mentioned meta-analysis found an association with increasing age, low body mass index and protease inhibitor therapy.

Prospective studies are less numerous and have not resolved the above uncertainties. There are no published large prospective studies of BMD in untreated people with HIV infection, although a small, short-term study found no significant change. The Gilead 903 study found a significant decline in BMD with both tenofovir and stavudine therapy when either drug was co-administered with lamivudine and efavirenz. The effect was more pronounced with tenofovir particularly in the lumbar spine, although there was no excess risk of fractures. The significant decline was mainly observed in the first year of therapy with levels appearing to be relatively stable thereafter.<sup>34</sup> Bone is one of the main sites of toxicity for tenofovir and reductions in BMD were observed in rats and dogs receiving doses of tenofovir that resulted in a six-fold higher plasma concentration than in humans receiving tenofovir 300 mg daily.

## 9.7.2 Assessment and treatment

Management should be the same as in people without HIV infection. BMD screening is not recommended as routine but should be considered in those with multiple known risk factors. Alendronate for 48 weeks significantly increased BMD in osteopenic adults on cART.<sup>35</sup>

## 9.8 Renal disease

In Australia, traditional risk factors and tenofovir therapy are likely to be the two most common causes of renal disease in people with HIV infection. Tenofovir, in phase 3 trials, was associated with about a 10% decline in renal function over the first year, after which time renal function appeared to stabilise. This was not associated with any severe renal dysfunction.<sup>5,34</sup> In cohort studies, approximately 2-3% of adults initiating tenofovir will develop moderate or severe renal dysfunction requiring tenofovir discontinuation over about 12 months. Risk factors in these cohorts were advanced HIV-disease, anaemia, diabetes, hypertension, use of tenofovir and use of low-dose ritonavir, which increases plasma tenofovir levels by about 30%.<sup>35,36</sup>

Renal function should be assessed in all patients receiving tenofovir approximately every three months by use of the Modification of Diet in Renal Disease equation, which is a more accurate measure than plasma serum creatinine level. Clinicians should be alert to the signs of Fanconi's syndrome (fatigue, nausea, weight loss) which can develop anytime in patients receiving tenofovir, particularly in those with other renal risk factors.<sup>36</sup>

## 9.9 Newer classes of antiretroviral drug

The CCR5 antagonist maraviroc was less toxic than efavirenz over 48 weeks in antiretroviral-naïve adults.<sup>37</sup> Preliminary reports of maraviroc-associated hepatotoxicity and cancer have not been substantiated with greater use, although another CCR5 antagonist, aplaviroc, was withdrawn because of hepatotoxicity in early stage trials. Maraviroc does have alpha adrenoreceptor activity and can cause hypotension at doses higher than used in clinical practice as well as sinus congestion in a small proportion of patients. Although this class of drug raises the theoretical risk of interference with cardiac potassium conduction, no evidence of abnormal cardiac conduction or arrhythmias has been evident in extensive pre-licensing investigation.

Raltegravir is the one licensed HIV integrase inhibitor. The results of two 48-week phase 3 trials in adults with prior antiretroviral failure suggest that it is well tolerated both clinically and biochemically. There is a very small risk of hepatic enzyme increases that generally have not been associated with clinical hepatitis.<sup>38,39</sup> Raltegravir, like maraviroc, has been associated with an increase risk of malignancy in the first few months of treatment. The types of malignancies detected have been quite varied suggesting that the observation may relate more to immune reconstitution than to a carcinogenic risk of the drug. Recent advances in antiretroviral toxicity are summarised in Table 9.4.

9 Managing the patient on antiretroviral therapy

Table 9.4 Recent advances in the understanding of antiretroviral toxicity		
	New learning points	Most promising therapies*
<b>Lipoatrophy</b>	<ul style="list-style-type: none"> <li>Largely preventable by avoidance of stavudine and zidovudine</li> <li>Contribution of current-generation protease inhibitors less certain</li> <li>Consider annual DEXA in those receiving stavudine, zidovudine or a protease inhibitor</li> </ul>	<ul style="list-style-type: none"> <li>Stavudine and zidovudine cessation helpful but improvement very gradual</li> <li>Pioglitazone (in those not receiving stavudine)</li> <li>Uridine</li> <li>Pravastatin</li> </ul>
<b>Central fat accumulation</b>	<ul style="list-style-type: none"> <li>Treatment directions limited by uncertainty as to whether central fat accumulation is a direct drug effect or is secondary to lipoatrophy</li> </ul>	<ul style="list-style-type: none"> <li>Growth hormone</li> <li>Growth hormone-releasing hormone analogue</li> <li>Metformin</li> </ul>
<b>Dyslipidaemia</b>	<ul style="list-style-type: none"> <li>No proven benefit for diet or exercise</li> </ul>	<ul style="list-style-type: none"> <li>Protease inhibitor and/or thymidine analogue cessation</li> <li>Pravastatin, low-dose atorvastatin or rosuvastatin</li> </ul>
<b>Insulin resistance / diabetes</b>	<ul style="list-style-type: none"> <li>Fasting glucose a poor tool for diagnosis of diabetes in people with HIV</li> <li>Consider oral glucose tolerance testing in higher-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>Follow standard diabetic treatment guidelines</li> </ul>
<b>Cardiovascular disease</b>	<ul style="list-style-type: none"> <li>Withdrawal of ART increases risk, perhaps because of declines in HDL cholesterol or more inflammation</li> <li>Traditional risk factors affect risk more than does ART</li> </ul>	<ul style="list-style-type: none"> <li>Address all modifiable risk factors, such as smoking, hypertension and diabetes, not just elevated total cholesterol</li> <li>Suppressing HIV replication reduces cardiovascular risk</li> </ul>
<b>Hepatotoxicity</b>	<ul style="list-style-type: none"> <li>Nevirapine should only be initiated in ART-naïve men and women with CD4 cell counts &lt;400 and 250 cells/μl, respectively</li> <li>Didanosine associated rarely with hepatic fibrosis, nodular regenerative hyperplasia and portal hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Nil</li> </ul>
<b>Hypersensitivity</b>	<ul style="list-style-type: none"> <li>Abacavir hypersensitivity strongly linked to HLAB*5701 ancestral haplotype</li> </ul>	<ul style="list-style-type: none"> <li>Molecular testing for HLAB*5701 prevents almost all, if not all, immunologically-mediated abacavir hypersensitivity</li> </ul>
<b>Osteoporosis</b>	<ul style="list-style-type: none"> <li>Tenofovir associated with small increased risk of osteopenia over 3 years, but not with increased fracture rate</li> <li>Role of routine screening (bone mineral densitometry) unknown</li> </ul>	<ul style="list-style-type: none"> <li>Alendronate</li> </ul>
<b>Nephrotoxicity</b>	<ul style="list-style-type: none"> <li>Tenofovir associated with small increased risk of grade 3-4 nephrotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>Nil</li> </ul>
<b>Enfuvirtide injection site reactions</b>	<ul style="list-style-type: none"> <li>Occur in 98% of patients and do not abate over time</li> <li>Have substantially affected enfuvirtide use</li> </ul>	<ul style="list-style-type: none"> <li>Less severe with use of a needle-free injection device</li> </ul>
* in addition to drug withdrawal and avoidance in higher-risk patients		
HLAB = human leukocyte antigen-B; ART = antiretroviral therapy; HDL = high-density lipoprotein; DEXA = dual-energy X-ray absorptiometry.		
Source: Modified from Calmy A, Hirschel B, Cooper DA, Carr A. Clinical update: adverse effects of antiretroviral therapy. Lancet 2007;370:12-14. Used with permission.		

## References

- 1 Carr A. New treatments for HIV lipodystrophy. *Curr Opin HIV AIDS* 2007;2:332-38.
- 2 Grinspoon SK, Carr A. Cardiovascular risk and body fat abnormalities in HIV-infected adults. *N Engl J Med* 2005;352: 48-62.
- 3 Mallon PWG, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003;17:971-79.
- 4 Podzamczer D, Ferrer E, Sanchez P, Gatell JM, Crespo M, Fisac C, et al. Less lipodystrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. *J Acquir Immune Defic Syndr* 2007; 44:139-47.
- 5 Arribas JR, Pozniak AL, Gallant JE, DeJesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr* 2008; 47:74-8.
- 6 Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: a randomized trial. *J Am Med Assoc* 2002; 288:207-15.
- 7 Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipodystrophy. *AIDS* 2006;20:2043-50.
- 8 Carr A, Workman C, Carey D, Rogers G, Martin A, Baker D, et al. No effect of rosiglitazone for HIV-1 lipodystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2004;363: 429-38.
- 9 Slama L, Lanoy E, Valantin MA, Bastard JP, Chermak A, Boutekatiert, et al. Effect of pioglitazone on HIV-1 related lipodystrophy: a randomized double-blind placebo-controlled trial (ANRS 113). *Antiviral Ther* 2008;13:67-76.
- 10 Walker UA, Auclair M, Lebrecht D, Kornprobst M, Capeau J, Caron M. Uridine abrogates the adverse effects of antiretroviral pyrimidine analogues on adipose cell functions. *Antivir Ther* 2006;11:25-34.
- 11 Sutinen J, Walker UA, Sevastianova K, Klinker H, Häkkinen AM, Ristola M, et al. Uridine supplementation for the treatment of antiretroviral therapy-associated lipodystrophy: a randomized, double-blind, placebo-controlled trial. *Antivir Ther* 2007;12:97-105.
- 12 Mallon PW, Miller J, Kovacic JC, Kent-Hughes J, Norris R, Samaras K, et al. Effect of pravastatin on body composition and markers of cardiovascular disease in HIV-infected men—a randomized, placebo-controlled study. *AIDS* 2006;20:1003-10.
- 13 Driscoll SD, Meininger GE, Lareau MT, Dolan SE, Killilea KM, Hadigan CM, et al. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients. *AIDS* 2004;18:465-73.
- 14 Grunfeld C, Thompson M, Brown SJ, Richmond G, Lee D, Muurahainen N, et al. Recombinant human growth hormone to treat HIV-associated adipose redistribution syndrome: 12-week induction and 24-week maintenance therapy. *J Acquir Immune Defic Syndr* 2007;45:286-97.
- 15 Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. *N Engl J Med* 2007;357:2359-70.
- 16 Bickel M, Zangos S, Jacobi V, Lutz T, Knecht G, Goebel F, et al. A randomized, open-label study to compare the effects of two different doses of recombinant human growth hormone on fat reduction and fasting metabolic parameters in HIV-1-infected patients with lipodystrophy. *HIV Med* 2006;7:397-403.
- 17 Valantin MA, Aubron-Olivier C, Ghosn J, Laglenne E, Pauchard M, Schoen H, et al. Poly(lactic acid) implants (New-Fill) to correct facial lipodystrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS* 2003;17: 2533-5.
- 18 Carey DL, Baker D, Rogers GD, Petoumenos K, Chuah J, Easey N, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipodystrophy. *J Acquir Immune Defic Syndr* 2007;46:581-9.
- 19 Carr A. Pathogenesis of HIV cardiovascular disease. *Curr Opin HIV AIDS* 2008;3:234-39.
- 20 De Wit S, Sabin CA, Weber R, Westring Worm S, Reiss P, Cazanave C et al. Incidence and risk factors for new onset diabetes mellitus in HIV infected patients: the D:A:D study. *Diabetes Care* 2008;31:1224-9.
- 21 Wand H, Calmy A, Carey DL, Samaras K, Carr A, Law MG, et al. Metabolic Syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy. *AIDS* 2007;21:2445-53.
- 22 DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *New Engl J Med* 2007;356:1723-35.
- 23 Strategies for Management of Anti-Retroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283-96.
- 24 Mujawar Z, Rose H, Morrow MP, Pushkarsky T, Dubrovsky L, Mukhamedova N, et al. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol* 2006; 4: e365.
- 25 Phillips AN, Carr A, Neuhaus J, Visnegarwala F, Prineas R, Burman WJ, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antiviral Ther* 2008;13:177-87.
- 26 D:A:D Study Group, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008;371:1417-26.
- 27 Carr A, Grund B, Neuhaus J, El-Sadr WM, Grandits G, Gibert C, et al; SMART study investigators. Asymptomatic myocardial ischaemia in HIV-infected adults. *AIDS* 2008;22:257-67.
- 28 Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1 infected adults exposed to anti-retroviral therapy. *AIDS* 2007;21:2455-64.
- 29 Servoss JC, Kitch DW, Andersen JW, Reisler RB, Chung RT, Robbins GK. Predictors of antiretroviral-related hepatotoxicity in the adult AIDS Clinical Trial Group (1989-1999). *J Acquir Immune Defic Syndr* 2006;43:320-3.
- 30 Mocroft A, Staszewski S, Weber R, Gatell J, Rockstroh J, Gasiorowski J, et al. Risk of discontinuation of nevirapine due to toxicities in antiretroviral-naïve and -experienced HIV-infected patients with high and low CD4+ T-cell counts. *Antivir Ther* 2007;12:325-33.
- 31 Mallet V, Blanchard P, Verkarre V, Vallet-Pichard A, Fontaine H, Lascoux-Combe C, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. *AIDS* 2007;21:187-92.
- 32 Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al; PREDICT-1 Study Team. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358: 568-79.
- 33 Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006;20:2165-74.
- 34 Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *J Am Med Assoc* 2004;292:191-201.
- 35 Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;40:1194-98.

- 36 Gupta SK, Eustace JA, Winston JA, Boydston II, Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;40:1559-85.
- 37 Saag M, Iye P, Heera J, Tawadrous M, DeJesus E, Clumeck N, et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine (ZDV)/lamivudine (3TC)), for the treatment of antiretroviral naive subjects infected with R5 HIV-1: week 48 results of the MERIT study. 4th International Conference on AIDS Pathogenesis, treatment and Prevention, Sydney, July, 2007. 22-25 Abstract WESS104.
- 38 Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet* 2007;369:1261-9.
- 39 Markowitz M, Nguyen BY, Gotuzzo E, Mendo F, Ratanasuwan W, Kovacs C, et al. Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment naive patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007;46:125-33.
- 40 Schambelan M, Benson CA, Carr A, Currier JS, Dubé MP, Gerber JG, Grinspoon SK, Grunfeld C, Kotler DP, Mulligan K, Powderly WG, Saag MS. Management of the metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immun Defic Syndr* 2002; 31: 257-75