

## Nutrition and HIV infection

J. Salomon\*, P. De Truchis and J.-C. Melchior

Department of Infectious Diseases and Internal Medicine, Raymond Poincaré University Hospital,  
104 Boulevard Raymond Poincaré, 92 380 Garches, France

Infection by the human immunodeficiency virus (HIV) is characterized by progressive destruction of the immune system, which leads to recurrent opportunistic infections and malignancies, progressive debilitation and death. Malnutrition is one major complication of HIV infection and is recognized as a significant prognostic factor in advanced disease. Malnutrition is multifactorial and poorly treated during the course of HIV. Even if a standardized approach to the management of active weight loss has not been well established, early nutritional intervention is important in HIV infected patients to maximize gain of lean body mass. From early in the era of highly active antiretroviral therapy (HAART), an initial decreased incidence of malnutrition was noted only in western countries while a variety of changes in the distribution of body fat and associated metabolic abnormalities have been recognized under the banner of lipodystrophy.

### HIV wasting syndrome: Lipodystrophy: Insulin resistance: Lactic acidosis

#### Wasting syndrome and malnutrition

Malnutrition is one major complication of HIV infection (Nahlen *et al.* 1993) and has been recognized under the banner of 'wasting syndrome' as a significant prognostic factor in advanced disease (Kotler *et al.* 1989; Guenter *et al.* 1993; Süttmann *et al.* 1995). Wasting syndrome is defined by a body weight loss of more than 10% of the usual body weight and associated with chronic diarrhoea and/or fever and/or asthenia with a lack of other detectable cause of wasting other than the HIV infection itself (CDC, 1987). Malnutrition is not only the result of HIV infection itself but also of the numerous associated complications (Macallan *et al.* 1993). Hence the wide variability in its clinical manifestations. Even if malnutrition is more frequent at the end stage of the disease, it can also occur at the onset of the chronic infection process, before severe immunodepression (Ott *et al.* 1993). However, loss of body weight has been reported to be relatively independent of the level of immunodepression during the course of HIV disease (Guenter *et al.* 1993). Nutritional status (characterized by classes of body weight loss, absolute and/or relative lean body mass, body cell mass, albumin, prealbumin and C Reactive Protein) has been shown to be a significant predictor of survival rate in adults with HIV after adjusting for CD4 count and history of secondary events (Melchior *et al.* 1999). Malnutrition may affect the length

of survival through a number of mechanisms including compromising host-immune function, causing organ damage, diminishing response to therapies and progressive debilitation (Kotler *et al.* 1989).

During HIV infection, malnutrition is multifactorial (Macallan *et al.* 1993). Decreased caloric intake (Grinfeld *et al.* 1992a), malabsorption of nutrients, elevated energy expenditure during secondary bacterial and/or systemic opportunistic infections (Melchior *et al.* 1993) contribute to malnutrition in these patients. Further, a number of metabolic abnormalities has been reported during HIV infection: increased *de novo* hepatic lipogenesis (Hellerstein *et al.* 1993), increased insulin sensitivity (Hommes *et al.* 1991), and increased protein turnover, which probably leads to the predominant loss of lean body mass in the case of decreased energy intake (Macallan *et al.* 1995). Decreased caloric intake, increased resting energy expenditure, chronic diarrhoea and opportunistic infections are the main factors associated with malnutrition (Melchior *et al.* 1999). Malnutrition may be in part a direct consequence of HIV infection itself, digestive secondary effects of drugs, and secondary events of the disease (Perlenicek *et al.* 1996; Wheeler *et al.* 1998).

Between 1987 and 1993, wasting syndrome was reported in 20% of the patients at the time of AIDS diagnosis in USA (Nahlen *et al.* 1993) and reached 70% of the patients at the time of death. Wasting syndrome has also been considered to be present in one third of intravenous drug user patients

---

**Abbreviations:** HAART, highly active antiretroviral therapy; PI, protease inhibitor; nNRTI, non-nucleoside reverse transcriptase inhibitor; IR, insulin resistance; rhGH, recombinant human growth hormone.

\* **Corresponding author:** Dr J. Salomon, fax +33 1 47 10 77 67, email jerome.salomon@rpc.ap-hop-paris

before the diagnosis of AIDS. During the same era, wasting syndrome was considered, in western countries, as the second AIDS-definition case, after pulmonary pneumocystosis (CDC, 1993). In the highly active antiretroviral therapy era (HAART era), after an initial decrease of the incidence of wasting syndrome in western countries, this incidence of strict wasting syndrome and other forms of malnutrition increased (Fig. 1) and reached 33.6% of the patients in a recent study (Wanke *et al.* 2000).

HIV related malnutrition differs notably from simple starvation. Starvation results in predominant loss of body fat and to a lesser degree of lean body mass even though protein synthesis remains unchanged over a long period of time. In contrast, during HIV infection, the loss of lean body mass is predominant (Kotler *et al.* 1985). Anthropometry, consisting of body dimension and weight measurements as well as subcutaneous fat measures, is a non-invasive method of evaluation used to characterize body composition or changes related to nutritional status (Gibson *et al.* 1990; Niyongabo *et al.* 1999). In HIV disease, anthropometric measurements provide an inexpensive and non-invasive means to monitor long-term nutritional status, characterize body fat deposition and assist in screening for nutritional risk (Batterham *et al.* 1999). Lean body mass changes measured by anthropometry have been shown to agree well with lean body mass changes measured by dual X-ray absorptiometry in patients with HIV infection and therefore, may be regarded as a valid tool for prospectively following patients in clinical practice (Paton & Castello 1997). Single frequency (50 kHz) bioelectrical impedance analysis has been evaluated for its ability to estimate lean body mass, total body water fluid and body cell mass (Lukaski *et al.* 1986; Baumgartner *et al.* 1989; Ellis & Bell, 1999). It is a quick, non-invasive and relatively inexpensive way to assess body composition, even if multifrequencies bioelectric impedance (Melchior *et al.* 1993; Niyongabo *et al.* 1999) could be better to assess malnutrition in HIV patients.

Significant advances have been made in the management of HIV infection (antiretroviral drugs, prophylaxis and treatment of opportunistic infections and global medico-psycho-social care of the patients) but despite this progress, malnutrition which was poorly treated during the course of HIV infection remained an important prognostic factor. Weight loss and muscle wasting were unique identifying characteristics of HIV infection early in the epidemic (Serwadda *et al.* 1985; Mhiri *et al.* 1992) and remain significant clinical problems even in the modern era of potent antiretroviral therapy (Wanke *et al.* 2000). Wasting, particularly loss of lean tissue and muscle protein mass (Yarasheski *et al.* 1998), has been associated with increased mortality (Kotler *et al.* 1989; Wheeler *et al.* 1998; Melchior *et al.* 1999), accelerated disease progression (Wheeler *et al.* 1998), and impairment of strength and functional status (Grinspoon *et al.* 1999) in patients with HIV infection. Micronutrient deficiencies are common in HIV infection. Deficiencies in serum vitamin A, vitamin B12, selenium and zinc in particular have been associated with progression of HIV infection (Baum *et al.* 1997, 1998). Measurements of serum proteins and micronutrients can predict outcome and may identify correctable deficiencies. Specific laboratory tests most frequently used include albumin, prealbumin, haemoglobin, serum iron, total iron binding capacity, magnesium, vitamin levels, cholesterol, triglycerides, fasting glucose, CD4, CD8, viral load of HIV, measurements of renal function and liver enzymes. Although the CDC case definition of wasting as an AIDS defining event requires a net weight loss of at least 10%, a weight loss of as little 5% has been associated with increased mortality and morbidity (Wheeler *et al.* 1998). These observations make it critically important to identify and characterize early risk factors for wasting in HIV infected patients and to monitor wasting with a standardized set of strategies for diagnosis, surveillance and appropriate treatment. Unfortunately, appropriate emphasis is often not placed on the nutritional

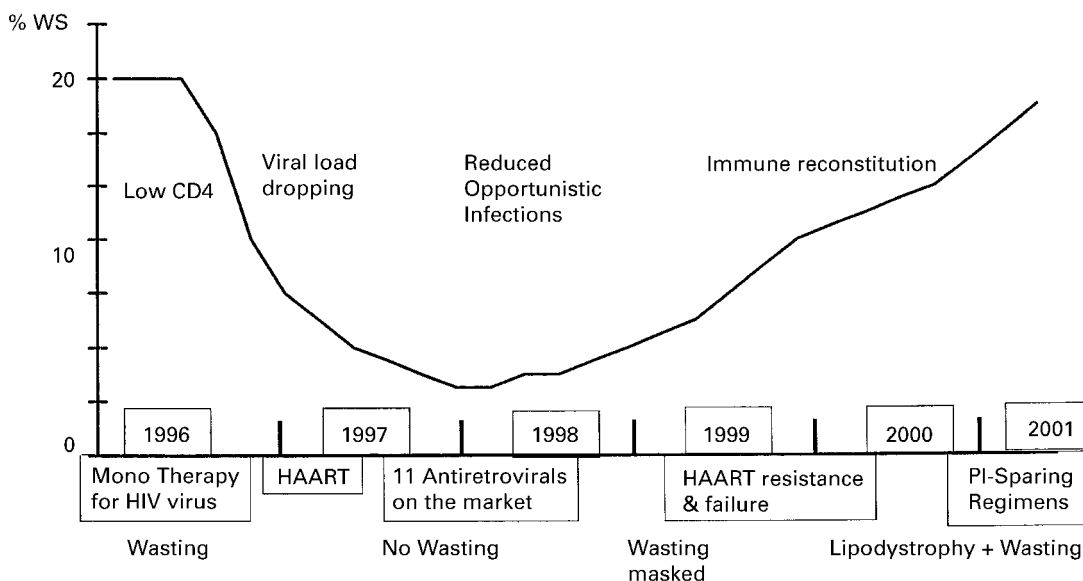


Fig. 1. Evolution of AIDS-wasting in western countries adapted from references Nahlen *et al.* 1993 and Wanke *et al.* 2000.

evaluation of such patients, and it is assumed that treatment with potent antiretroviral therapy will ameliorate nutritional deficiencies and increase lean body mass (Carbonnel *et al.* 1998). This is consistently not the case (Silva *et al.* 1998) and nutritional management during the transition to improved immune function is critical.

Among the factors that have been demonstrated or hypothesized to contribute to wasting are inadequate intake, malabsorptive disorders, metabolic alterations, hypogonadism and excessive cytokine production. Because wasting is a multifactorial phenomenon, strategies for its prevention, interruption or reversal are complex. Although weight loss in HIV infection features depletion of both lean and fat tissues (Kotler *et al.* 1985; Ott *et al.* 1993; Grinspoon *et al.* 1997), it is the lean compartment that is an independent predictive factor of survival. To date, however, standardized recommendations on the appropriate use of weight and body composition for defining wasting have not been made. The significant impact of wasting on survival, disease progression, and functional status highlights the need to prevent muscle wasting and weight loss in HIV infected patients. However, evaluation of weight and nutritional status are most often not part of the initial or subsequent evaluation of the HIV infected patient. Weight history is often not recorded and potential risk factors for wasting are too often not evaluated prior to weight loss. Weight, evaluation of reduced caloric intake due to anorexia or multiple factors leading to inaccessibility of food (opportunistic infections, gastrointestinal disease, malignancies, endocrine conditions) should be monitored with the goal of avoiding reliance on pharmacological interventions to reverse wasting. Education of appropriate nutritional practices, exercise and the importance of maintaining energy balance should be emphasized.

In contrast to the treatment of other HIV-related complications, a standardized approach to the management of active weight loss has not been established. This approach to the assessment of comorbidities is critical in patients with active weight loss. Studies have shown a significant mismatch between reduced energy intake and expenditure during opportunistic infection (Grunfeld *et al.* 1992a; Macallan *et al.* 1995). These data underscore the

need to assess the adequacy of energy and nutrient intake and to treat opportunistic infections or related conditions that increase resting energy expenditure and may exacerbate acute weight loss. Fat redistribution, dyslipidemia and hyperinsulinemia can occur under HAART even in patients with weight loss and wasting syndrome (Hadigan *et al.* 2000a) driving the importance of counselling on appropriate carbohydrate, lipid, protein and vitamins intake. Early nutritional intervention is important in such patients to maximize gain of lean body mass and minimize gain of visceral fat.

Nutritional counselling and support (Berger *et al.* 1993; Dowling *et al.* 1990) appetite stimulants and anabolic hormones can reverse weight loss and increase lean body mass in HIV infected patients. Few studies have looked at enteral or parenteral feeding in HIV-infected patients. In general, those patients with poor intake benefit from enteral feeding while those who have gastrointestinal disease including malabsorption and diarrhoea benefit from parenteral feeding and have commonly been reported to gain weight and in some cases body cell mass (Kotler *et al.* 1991; Ockenga *et al.* 1996; Melchior *et al.* 1996; Ireton-Jones *et al.* 1998; Shabert *et al.* 1999). Enteral nutrition as well as parenteral nutrition have been demonstrated to increase life expectancy and quality of life in severe malnourished and immunodepressed patients (Ockenga *et al.* 1996; Melchior *et al.* 1998). Resistance exercise can increase lean tissue in HIV infected patients with or without wasting (Roubenoff *et al.* 1999; Bhasin *et al.* 2000). Placebo-controlled trials have demonstrated the efficacy of a variety of pharmacological agents promoting weight and or lean tissue gain. Megestrol acetate, a synthetic progestational agent is a potent appetite stimulant and effectively increases weight although the weight gain is predominantly or exclusively fat (Von Roenn *et al.* 1994; Oster *et al.* 1994). Use of testosterone has been shown to increase lean body mass among hypogonadal men with AIDS wasting (Grinspoon *et al.* 1998; Bhasin *et al.* 1998). Pharmacological use of growth hormone has been shown to improve nitrogen balance and increase lean body mass in HIV infected patients with wasting (Mulligan *et al.* 1993; Schambelan *et al.* 1996) and to promote lean tissue retention in those with secondary infections (Paton *et al.* 1999). These studies suggest that use of synthetic anabolic agents can increase weight and lean body mass in patients with wasting (Berger *et al.* 1996; Strawford *et al.* 1999).

**Table 1.** Clinical aspects of lipodystrophy syndromes

---

<i>Fat accumulation</i>
● Abdominal obesity
● Dorsocervical pad
● Cervical hypertrophy
● Lipomas
● Adipomasty
<i>Fat loss</i>
● Face wasting
● Loss of subcutaneous fat of extremities
● Loss of buttocks
<i>Mixed symptoms</i> +++
<i>Biological abnormalities</i>
● Glucose intolerance, diabetes, hyperinsulinemia and increased insulin-resistance
● Hypertriglyceridemia
● Hypercholesterolemia: ↑ LDL Cholesterol; ↓ HDL Cholesterol

---

### Fat redistribution syndrome and lipodystrophy

From early in the era of highly active antiretroviral therapy (HAART), changes in the distribution of body fat and a variety of metabolic abnormalities have been recognized. Abdominal obesity, abnormal serum lipids and insulin resistance simulate features of the dysmetabolic syndrome (Syndrome X) which increase the risk of diabetes and accelerated arteriosclerosis (Carr *et al.* 1998; Henry *et al.* 1998). Lactic acidosis is another serious metabolic complication with potential to result in hepatic failure and death.

### Body changes

Depletion of body fat stores and accumulation of excess adipose tissue may occur in various anatomic sites in persons infected with HIV (Table 1). Regional fat loss (lipoatrophy) has been reported in 1–64% of HIV infected subjects, regional fat gain (lipohypertrophy) in 1–68%, and both together in 2–84% (Carr *et al.* 1999). One clinical presentation may involve the accumulation of adipose tissue in the dorso cervical region of the neck, supra clavicular area, abdomen, breasts or subcutaneous tissue as unencapsulated lipomas (Madelung's syndrome). By contrast, lipoatrophy may be the predominant clinical presentation involving primarily the loss of adipose tissue in the buccal fat and other structural fat depots of the face (Bichat's pad fat loss syndrome), subcutaneous region of the extremities and sub gluteal area of the buttock. Most of the patients present with a mixed syndrome with abdominotrocular obesity and peripheral atrophy.

Age, gender, ethnicity, prior type and duration of antiretroviral therapy have been associated with these abnormalities. The fat redistribution syndrome or lipodystrophy has been associated with HAART and therefore is presumed to be related to the use of protease inhibitors (PI). Lipid and lipoprotein abnormalities have been more common in HIV infected patients receiving PI than in subjects receiving other classes of drugs (Carr *et al.* 1998*a,b*; Miller *et al.* 1998). In fact a number of reports describe a sizable portion of patients developing lipoatrophy and/or lipohypertrophy who never received a PI (Madge *et al.* 1999). Mulligan *et al.* (2000) have described abnormalities of lipid and insulin/carbohydrate metabolism occurring on average 3–4 months after initiating therapy with PI. Preliminary results of switch studies in which PI have been changed to non-nucleoside reverse transcriptase inhibitors (nNRTI) have not demonstrated objective improvement in fat redistribution 6–12 months after discontinuing PI (Martinez *et al.* 1999; Ruiz *et al.* 2000). A definitive causal linkage between PI related changes in lipid and carbohydrate metabolism and changes in regional distribution of body fat remains to be established. Results of several cross-sectional studies suggest that the NRTI may also be causally related to anthropometric changes (Carr *et al.* 1999; Saint-Marc *et al.* 1999). In the LIPOCO cohort, those receiving stavudine had less body fat than those receiving zidovudine, by anthropometry and CT scanning (Goujard *et al.* 2000). Patients switched from stavudine to abacavir or zidovudine had significant improvement in fat stores assessed by CT imaging suggesting that stavudine contributed to the lipoatrophy but there was no control group (Saint-Marc *et al.* 1999).

### Insulin and carbohydrate deregulation

Since the late 1990s, multiple reports have described insulin and carbohydrate metabolism abnormalities in HIV patients receiving highly active antiretroviral therapy (Lumpkin, 1997; Safrin & Grunfeld, 1999). The prevalence of diabetes,

glucose intolerance and insulin resistance (IR) is not precisely known. Existing data suggest that patients receiving therapy with PI have a greater incidence of IR (30–90%) than patients on non-PI containing regimens (Walli *et al.* 1998). The incidence of frank hyperglycemia and diabetes mellitus has ranged from 1 to 11% (Dubé *et al.* 1997; Behrens *et al.* 1999; Carr *et al.* 1999). In addition to the 7% prevalence of diabetes among PI recipients, 16% had impaired glucose tolerance. In one large cohort study comparing seventy-five HIV infected women experiencing wasting with thirty healthy controls, significant hyperinsulinemia was present in association with HIV infection unrelated to PI therapy (Hadigan *et al.* 1999). Nonetheless, cross-sectional studies strongly implicate PI therapy as a primary cause of IR in HIV-infected patients (Walli *et al.* 1998).

IR increases the risk of arteriosclerosis and is associated with a dyslipidemia that is also atherogenic (Haffner & Miettinen, 1997). The primary dyslipidemia associated with IR is elevation of serum triglycerides due to reduced activity of lipoprotein lipase (Garg, 1998). High-density lipoprotein (HDL-C) levels are consistently low secondary to decreased production and increased catabolism but levels of low-density lipoproteins (LDL-C) are usually not markedly elevated. HIV infected individuals with IR may also be at risk for abnormalities in body fat. Mulligan *et al.* (2000) suggest that IR precedes changes in body fat in HIV patients initiating PI therapy. Recent studies suggest that IR may be more related to PI use and lipoatrophy more to NRTI use but these abnormalities frequently coexist (Carr *et al.* 1999, 2000).

Patients need to be assessed for risk factors for IR and diabetes mellitus as well as for arteriosclerosis, family history, inactivity, smoking, body mass index, hypertension and dyslipidemia. Correction of risk factors is needed when possible. Diet and exercise, mainstays of therapy for type 2 diabetes mellitus are also appropriate for HIV-related IR. Insulin sensitising drugs, such as thiazolidinediones or biguanides might be highly useful because they improve peripheral insulin sensitivity but have not been studied sufficiently in HIV infected patients to recommend their use. Metformin therapy was associated with significant decreases in weight, fasting levels of glucose, insulin, C peptide and triglycerides for non diabetic HIV infected subjects who were receiving PI therapy and who had abdominal obesity (Saint-Marc *et al.* 1999). Visceral fat measured by CT scanning also decreased. A recent study suggests that a relatively low dosage of metformin reduces insulin resistance and related cardiovascular risk parameters in HIV-infected patients with lipodystrophy (Hadigan *et al.* 2000*b*). Because of the risk of lactic acidosis, the combination of NRTI and metformin should be used with caution in patients with HIV (Bell & Hadden, 1997). IR improved after substituting nevirapine for PI therapy in non-nucleoside reverse transcriptase inhibitor (nNRTI)-naive patients (Martinez *et al.* 1999). Improvement in insulin sensitivity measured by intravenous insulin tolerance testing occurred after the substitution of abacavir for PI (Goebel & Walli, 2000). Clinicians must weigh the potential benefits of reduced IR with the risks of virologic relapse and new drug toxicities.



### Lipid deregulation

Abnormalities of lipid metabolism are common in HIV-infected patients and tend to be accentuated in those receiving antiretroviral therapy. Henry *et al.* (1998a) reported that sixty-two of 133 of PI recipients had lipid abnormalities and intervention criteria. Carr *et al.* (1999) reported that 58 % of PI recipients had total cholesterol of >212 mg/dl compared with 11 % of PI-naive subjects. In a Swiss cohort study, 39 % of subjects had total cholesterol levels of >240 mg/dl after a mean of 16 months of PI therapy, compared to 8 % at baseline (Periard *et al.* 1999).

Abnormalities of lipid metabolism were reported prior to the use of HIV PI and were associated with elevations in serum triglycerides (Grunfeld *et al.* 1991, 1992b). During therapy with PIs, increases in serum triglycerides may be extreme particularly with ritonavir (Danner *et al.* 1995; Sullivan & Nelson, 1997). In HIV-negative volunteers, ritonavir increased total cholesterol by 24 % and triglycerides by 137 % within 2 weeks of initiating therapy providing further evidence that PI directly affect lipids (Purnell *et al.* 2000). Several reports suggest that serious premature vascular events may be related to PI therapy and abnormal lipids (Henry *et al.* 1998a; Behrens *et al.* 1998; Gallet *et al.* 1998; Vittecoq *et al.* 1998).

Evaluation of serum lipids should be performed after fasting for a minimum of 8 h and preferably after 12 h. The standard lipid screening profile should include measurement of total cholesterol, HDL-C and triglycerides with calculation of LDL and very low density lipoprotein (VLDL) cholesterol. All patients should be screened for other cardiovascular risk factors. Dyslipidemia in HIV infected patients should have greater long-term consequences for cardiovascular disease risk as in the general population. For the purposes of initiating therapy for dyslipidemia, international guidelines should be followed. Elevated triglyceride levels also represent an independent risk factor even when the values are only modestly elevated (Hokanson & Austin, 1996). The high frequency of low HDL-C in persons with HIV warrants attention. Management should be directed towards abnormalities of HDL-C and triglycerides as well as LDL-C.

Structured exercise plus diet resulted in a 21 % decrease in triglycerides level in HIV infected patients (Henry *et al.* 1998b). Smoking cessation and weight reduction for obesity are also important for improving the overall cardiovascular risk profile. Existing dietary habits should be assessed before a diet is prescribed. After starting the therapeutic diet, total serum cholesterol should be measured and adherence to the diet assessed. Patients with established coronary artery disease or other atherosclerotic complications need to be managed more aggressively. If lipid levels remain above the target goal after intensive dietary interventions, weight reduction for obesity and intensive exercise for a few months, drug therapy should be considered. Drug therapy should be added to and not substituted for dietary therapy. Lipid lowering therapies for HIV infected patients with dyslipidemia are problematic due to the potential for drug interactions. A number of the HMG-CoA reductase inhibitors are metabolized by cytochrome P450 3A4 as are the PI, raising concern that

statin levels might be higher than needed resulting in an increased risk for myopathy and rhabdomyolysis. Similarly, levels of PI might be reduced through interactions with the statins, increasing the risk for anti-HIV treatment failure. When statin therapy is necessary, it is recommended to use primary pravastatin, which does not interfere with cytochrome P450, rather than atorvastatin or other statins, with careful monitoring of virologic status and creatine kinase values. The fibrates are well tolerated alternative agents when hypercholesterolemia is accompanied by elevated triglycerides: fibrates should be prescribed if drug therapy is necessary for hypertriglyceridemia. Gemfibrozil resulted in a 57 % reduction in triglyceride levels and a 32 % reduction in cholesterol in HIV infected patients receiving PI (Henry *et al.* 1998b). Because niacin may cause insulin resistance, it should be avoided as first-line therapy in patients receiving PI, since they frequently reduce insulin sensitivity, which may increase the risk for visceral abdominal obesity, lipid abnormalities and hypertension (Garg & Grundy, 1990). The effect of substituting an antiviral agent with a lesser tendency to induce dyslipidemia for an existing agent with a greater tendency is being evaluated. Substitution of neftinavir on indinavir or ritonavir resulted in improvement in hyperlipidemia in seven patients (Periard *et al.* 1999). Results of other studies suggest that in non-nucleoside reverse transcriptase inhibitor (nNRTI)-naive patients, substituting nevirapine for a PI can improve serum lipids (Martinez *et al.* 1999). The substitution of efavirenz for a PI has not consistently had a beneficial effect (Tebas *et al.* 2000; Bonnet *et al.* 2000; Gharakanian *et al.* 2000). Improvements in lipid levels have also been reported with the substitution of abacavir for PI (Goebel & Walli, 2000; Opravil *et al.* 2000; Rozenbaum *et al.* 2000).

### Lactic acidosis and mitochondrial dysfunction

Numerous toxicities of nucleoside reverse transcriptase inhibitors (NRTI) and monophosphorylated nucleotide analogue reverse transcriptase inhibitors (NtRTI) have been postulated to have a mitochondrial pathogenesis, although proof is lacking for several of these. These toxicities include skeletal and cardiac myopathy (zidovudine), distal sensory peripheral neuropathy (stavudine, didanosine, zalcitabine), pancreatitis (didanosine), hepatic steatosis and lactic acidosis (didanosine, stavudine, zidovudine), peripheral lipoatrophy (possibly all NRTI) and renal tubular acidosis and weight loss (adefovir). Most manifest gradually after medium to long term NRTI exposure and their capacity to resolve with NRTI cessation varies. The most serious manifestation of mitochondrial toxicity is lactic acidosis, characterized by elevated venous lactate levels (>2 mmol/l) and low arterial pH (<7.30) (Mizock & Falk, 1992). The primary clinical features of lactic acidosis include malaise, weight loss, nausea and dyspnoea. The onset may be acute or subacute. Because NRTI-associated lactic acidosis appears to represent hepatic toxicity, features of hepatic failure may also be present and include fatty hepatomegaly, peripheral oedema, ascitis and encephalopathy. Patients with low-level lactacidemia but with normal arterial pH also present with constitutional features (weight loss, fatigue, and nausea) which are

generally milder in severity and/or peripheral fat loss (Carr *et al.* 2000). This association of lactic acidemia with peripheral lipoatrophy has led to speculation that lipoatrophy in patients receiving HAART might be due to mitochondrial toxicity (Saint-Marc *et al.* 1999; Brinkman *et al.* 1999). Lactic acidosis occurs relatively infrequently in HIV-infected patients with a prevalence of approximately 1:1000 (Blanche *et al.* 1999). In the largest study reported to date, symptoms consistent with mitochondrial toxicity were detected in 5 % of patients receiving at least one NRTI (Carr *et al.* 2000). No patient or treatment characteristic appears to identify those most at risk for lactic acidosis. No preventive strategy against mitochondrial toxicity or lactic acidosis has been developed, although patients should of course be made aware of these potential toxicities at regular intervals. The direct management of mitochondrial toxicity is generally limited to cessation of the responsible NRTI and of other drugs that might exacerbate the condition. In patients with symptomatic, laboratory confirmed lactic acidosis, the implicated NRTI should be discontinued to avoid progression to acute life threatening illness.

#### *Growth hormone and lipodystrophy*

Recombinant human growth hormone (rhGH) has been observed to decrease dorsocervical fat in persons with HIV and has reduced intra-abdominal fat, lipids and diastolic blood pressure in HIV uninfected men with abdominal obesity. rhGH might not be appropriate for subjects who also have peripheral loss of adipose tissue since the lipolytic effects of rhGH may be indiscriminate and might potentiate further loss of peripheral fat in patients who have also lipoatrophy rhGH may worsen insulin resistance in subjects receiving PI, those with glucose intolerance and patients with diabetes. Fear of developing fat redistribution syndrome, with central obesity and loss of cutaneous fat may prevent patients from beginning potent antiretroviral therapies (Lo *et al.* 1998; Walli *et al.* 1998; Babl *et al.* 1999). The appearance of these metabolic changes may induce patients to stop highly active antiretroviral therapy or to change to less effective antiretroviral regimens.

#### **Conclusion**

During the first two decades of the HIV infection story, the wasting syndrome and other forms of malnutrition were on the first line of the complications of the disease. The biggest consequences were on life expectancy and also on the quality of life of the patients. This major complication did not disappear in western countries, mainly in patients with a long past history of HIV infection and those patients under failure of treatments and remains with a very high frequency in developing countries free of active antiviral therapies. For these reasons it is necessary to develop strategies to prevent early weight loss and to actively treat the patients with severe malnutrition.

Fat redistribution syndrome and metabolic abnormalities associated with HAART now occur in numerous patients. As the pathophysiology of these complications is not well known, the therapeutic approach is difficult, but should take into account dietary recommendations including physical

activity, prevention and treatment of all cardiovascular risk factors and also some switch in HIV treatments depending on each individual case. A nutritional and morphological evaluation associated with a determination of metabolic parameters should be done for each patient before and during the initiation of a new HIV treatment. By this way, one can expect that the deaths and the decreased quality of life induced by the HIV infection itself will not be replaced by the morphological and metabolic complications of HAART. The rate of the cardiovascular events has to be prospectively evaluated during the next decade of the HIV story.

#### **References**

- Babl FE, Regan AM & Pelton SI (1999) Abnormal body-fat distribution in HIV-1 infected children on antiretrovirals. *Lancet* **353**, 1243–1244.
- Batterham MJ, Garsia R & Greenop P (1999) Measurement of body composition in people with HIV/AIDS: a comparison of bioelectrical impedance and skinfold anthropometry with dual-energy x-ray absorptiometry. *Journal of American Dietetic Association* **99**, 1109–1111.
- Baum MK, Shor-Posner G & Lai S (1997) High-risk of HIV-related mortality is associated with selenium deficiency. *Journal of Acquired Immunodeficiency and Human Retrovirology* **5**, 370–374.
- Baum MK *et al.* (1998) Micronutrient status in relationship to mortality in HIV-1 disease. *Nutrition Reviews* **56**, S135–S139.
- Baumgartner RN, Chumlea WC & Roche AF (1989) Estimation of body composition for bioelectric impedance of body segments. *American Journal of Clinical Nutrition* **50**, 221–226.
- Behrens G, Schmidt H & Meyer D (1998) Vascular complications associated with use of HIV protease inhibitors. *Lancet* **351**, 1958.
- Behrens G, Dejam A, Schmidt H, Belks HJ, Brabant G, Korner T, Stoll M & Schmidt RE (1999) Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* **13**, 63–70.
- Bell PM & Hadden DR (1997) Metformin. *Endocrinology and Metabolism Clinics of North America* **26**, 523–537.
- Berger B, Ollenschlager G, Schrappe M, Stute A, Fischer M, Wessel D, Schwenk A & Diehl V (1993) Nutrition behavior of malnourished HIV-infected patients and intensified oral nutritional intervention. *Nutrition* **9**, 43–44.
- Berger J, Pall L, Hall C, Simpson D, Berry P & Dudley R (1996) Oxandrolone in AIDS-wasting myopathy. *AIDS* **10**, 1657–1662.
- Bhasin S, Storer T & Asbel-Sethi N (1998) Effects of testosterone replacement with a nongenital transdermal system, androderm, in human immunodeficiency virus-infected men with low testosterone levels. *Journal of Clinical Endocrinology and Metabolism* **83**, 3155–3162.
- Bhasin S, Storer T & Javanbakht M (2000) Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *Journal of the American Medical Association* **283**, 763–770.
- Blanche S, Tardieu M & Rustin P, Slama A, Barret B, Firtion G, Ciraru-Vigneron N, Lacroix C, Rouzioux N, Mandelbrot L, Desguerre I, Rötig A, Mayaux MJ & Delfraissy JF (1999) Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* **354**, 1084–1089.
- Bonnet E, Lepec R & Bluteau M (2000) A prospective, open-label pilot trial of a maintenance nevirapine-containing regimen in patients with undetectable viral loads on protease inhibitor

- regimens for at least 6 months. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Brinkman K, Smeitink JA, Romijn JA & Reiss P (1999) Mitochondrial toxicity induced by nucleoside analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral therapy related lipodystrophy. *Lancet* **354**, 1112–1115.
- Carbonnel F, Maslo C & Beaugerie L (1998) Effect of indinavir on HIV-related wasting. *AIDS* **12**, 1777–1784.
- Carr A, Samaras K, Chisholm DJ & Cooper DA (1998a) Pathogenesis of HIV-1 protease inhibitor associated peripheral lipodystrophy, hyperlipidemia and insulin resistance. *Lancet* **351**, 1881–1883.
- Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm D & Cooper DA (1998b) A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance due to HIV protease inhibitors. *AIDS* **12**, 51–58.
- Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ & Cooper DA (1999) Diagnosis, prediction and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia and diabetes mellitus: a cohort study. *Lancet* **353**, 2093–2099.
- Carr A, Miller J, Law M & Cooper DA (2000) A syndrome of lipotrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* **14**, 25–32.
- CDC (1987) Revised classification system for HIV infections and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report* **36**, 1–15s.
- CDC (1993) Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report* **41**, 1–19.
- Danner SA, Carr A & Leonard JM (1995) A short-term study of the safety, pharmacokinetics and efficacy of zidovudine, an inhibitor of HIV-1 protease. *The New England Journal of Medicine* **333**, 1528–1533.
- Dowling S, Mulcahy F & Gibney M (1990) Nutrition in the management of HIV antibody positive patients: a longitudinal study of dietetic out-patient advice. *European Journal of Clinical Nutrition* **44**, 823–829.
- Dubé MP, Johnson DL & Currier JS (1997) Protease inhibitor-associated hyperglycemia. *Lancet* **350**, 713–714.
- Ellis KJ & Bell SJ (1999) Bioelectrical impedance methods in clinical research: a follow-up to the NIH Technology Assessment Conference. *Nutrition* **15**, 874–880.
- Gallet B, Pullik M & Genet P (1998) Vascular complications associated with use of HIV protease inhibitors. *Lancet* **351**, 1958–1959.
- Garg A & Grundy SM (1990) Nicotinic acid as therapy for dyslipidemia in non-insulin dependent diabetes mellitus. *Journal of the American Medical Association* **264**, 723–726.
- Garg A (1998) Dyslipoproteinemia and diabetes. *Endocrinology and Metabolism Clinics of North America* **27**, 613–625.
- Gharakanian S, Salhi Y & Adda N (2000). Identification of fat redistribution metabolic anomalies in a cohort treated by 2 NRTIs + 1 PI and absence of significant modification following PI substitution. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Gibson RS *et al.* (1990) *Principles of Nutritional Assessment*, New York, NY: Oxford University Press.
- Goebel F & Walli RK (2000) A novel use of abacavir to simplify therapy in PI experienced patients successfully treated with HAART: CNA30017. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Goujard C, Lascaux AS, Dulioist A, Boué F, Delfraissy JF, Sobel A & Boufassa F. (2000) Lipodystrophy in PI-naive patients treated with RTI combinations: frequency and risk factors. In: *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Grinspoon S, Corcoran C & Miller K (1997) Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *Journal of Clinical Endocrinology and Metabolism* **82**, 1332–1337.
- Grinspoon S, Corcoran C & Askari H (1998) Effects of androgen administration in men with AIDS wasting: a randomized, placebo-controlled trial. *Annals of Internal Medicine* **129**, 18–26.
- Grinspoon S, Corcoran C & Rosenthal D (1999) Quantitative assessment of cross-sectional muscle area, functional status and strength in men with the AIDS wasting syndrome. *Journal of Clinical Endocrinology and Metabolism* **84**, 201–206.
- Grunfeld C, Kotler DP & Shigenaga JK (1991) Circulating interferon-alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. *American Journal of Medicine* **90**, 154–162.
- Grunfeld C, Pang M & Shimizu L (1992a) Resting energy expenditure, caloric intake and weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* **55**, 455.
- Grunfeld C, Pang M & Doerrler W (1992b) Lipids, lipoproteins, triglyceride clearance and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *Journal of Clinical Endocrinology and Metabolism* **74**, 1045–1052.
- Gunter P, Muurahainen N & Simons G (1993) Relationships among nutritional status, disease progression and survival in HIV infection. *Journal of Acquired ImmunoDeficiency Syndrome* **6**, 1130.
- Hadigan C, Corcoran C, Stanley T, Piecuch S, Klibanski A & Grinspoon S (2000a) Fasting hyperinsulinemia in HIV-infected men: relationship to body composition, gonadal function and protease-inhibitor use. *Journal of Clinical Endocrinology and Metabolism* **85**, 35–41.
- Hadigan C, Miller K, Corcoran C, Anderson E, Basgoz N & Grinspoon S (1999) Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. *Journal of Clinical Endocrinology and Metabolism* **84**, 1932–1937.
- Hadigan C, Corcoran C & Basgoz N (2000b) Metformin in the treatment of HIV lipodystrophy syndrome. *Journal of the American Medical Association* **284**, 472–477.
- Haffner SM & Miettinen H (1997) Insulin resistance implications for type II diabetes mellitus and coronary heart disease. *American Journal of Medicine* **103**, 152–162.
- Hellerstein MC, Grunfeld C & Wu F (1993) Increased de novo lipogenesis in human immunodeficiency virus infection. *Journal of Clinical Endocrinology and Metabolism* **7**, 559.
- Henry K, Melroe H & Huebsch J (1998a) Severe premature coronary artery disease with protease inhibitors. *Lancet* **351**, 1328.
- Henry K, Melroe H & Huebsch J (1998b) Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet* **352**, 1031–1032.
- Hokanson JE & Austin MA (1996) Plasma triglyceride level is a risk factor for cardiovascular disease independent of HDL cholesterol level: a meta-analysis of population-based prospective studies. *Journal of Cardiovascular Risk* **3**, 213–219.
- Hommel MJT, Romijn JA, Ender E, Eeftink-Schattenkerker JKM & Sauerwein HP (1991) Insulin sensitivity and insulin clearance in human immunodeficiency virus infected men. *Metabolism* **40**, 651.



- Iretton-Jones CS *et al.* (1998) Evaluation of outcomes for patients with AIDS receiving home total parenteral nutrition. *Nutrition* **14**, 731–735.
- Kotler DP, Wang J & Pierson R (1985) Studies of body composition in patients with acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* **42**, 1255–1265.
- Kotler DP, Tierney AR, Wang J & Pierson RE (1989) Magnitude of body cell mass depletion and the timing of death from wasting in AIDS. *American Journal of Clinical Nutrition* **50**, 444–447.
- Kotler D, Tierney AR & Ferraro R (1991) Enteral alimentation and repletion of body cell mass in malnourished patients with acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* **53**, 149.
- Lo JC, Mulligan K, Tai VW, Algren H & Schambelan M (1998) Buffalo hump in men with HIV 1 infection. *Lancet* **351**, 867–870.
- Lukaski HC, Bolonchuk WW, Hall CB & Siders WA (1986) Validation of tetra polar bioelectrical impedance method to assess human body composition. *Journal of Applied Physiology* **60**, 1327–1332.
- Lumpkin MM (1997) Reports of diabetes and hyperglycemia in patients receiving protease inhibitors for the treatment of human immunodeficiency virus (HIV). FDA Public Health Advisory.
- Macallan DC, Noble C & Baldwin C (1993) Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *American Journal of Clinical Nutrition* **58**, 417.
- Macallan DC, Noble C & Baldwin C (1995) Energy expenditure and wasting in human immunodeficiency virus infection. *New England Journal of Medicine* **333**, 83–88.
- Madge S, Kinloch-de-Loes S, Mercey D, Johnson MA & Weller IVD (1999) Lipodystrophy in patients naive to HIV protease inhibitors. *AIDS* **13**, 735–737.
- Martinez E, Conget I & Lozano L (1999) Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS* **13**, 805–810.
- Melchior JC, Raguin G & Boulrier A (1993) Resting energy expenditure in HIV infected patients. Comparison between patients with and without secondary infections. *American Journal of Clinical Nutrition* **57**, 614.
- Melchior JC, Chastang C & Gelas P (1996) Efficacy of 2 month total parenteral nutrition in AIDS patients: a controlled randomized prospective trial. *AIDS* **10**, 379–384.
- Melchior JC, Gelas P, Carbonnel F & Zazzo JF (1998) Improved survival by home total parenteral nutrition in AIDS patients: follow-up of a controlled randomized prospective trial. *AIDS* **12**, 336–337.
- Melchior JC, Niyongabo T & Henzel D (1999) Malnutrition and wasting, immunodepression, and chronic inflammation as independent predictors of survival in HIV-infected patients. *Nutrition* **15**, 865–869.
- Mhiri C, Belec L, DiCostanza B, Georges A & Gherardi R (1992) The slim disease in African patients with AIDS. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 303–306.
- Miller KD, Jones E & Yanovski JA (1998) Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* **351**, 871–875.
- Mizock BA & Falk JL (1992) Lactic acidosis in critical illness. *Critical Care Medicine* **20**, 80–93.
- Mulligan K, Grunfeld C, Hellerstein M, Neese RA & Schambelan M (1993) Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. *Journal of Clinical Endocrinology and Metabolism* **77**, 956–962.
- Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN & Schambelan M (2000) Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *Journal of Acquired Immunodeficiency Syndrome* **23**, 35–43.
- Nahlen BL, Chu SY, Nwanyanwu OC, Berkelman RL, Martinez SA & Rullan JV (1993) HIV wasting syndrome in the United States. *AIDS* **7**, 183.
- Niyongabo T, Melchior JC, Henzel D, Bouchard O & Larouze B (1999) Comparison of methods for assessing nutritional status in HIV-infected adults. *Nutrition* **15**, 740–743.
- Ockenga J, Sittmann U & Selberg O (1996) Percutaneous endoscopic gastrostomy in AIDS and control patients: risks and outcomes. *American Journal Gastroenterology* **91**, 1817–1822.
- Opravil M, Yerly S, Lazzarin A (2000) Protease inhibitor class-sparing maintenance therapy with abacavir + lamivudine + zidovudine in patients with long-term suppression of HIV-1 RNA. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Oster M, Enders S & Samuels S (1994) Megestrol acetate in patients with AIDS and cachexia. *Annals of Internal Medicine* **121**, 400–408.
- Ott M, Lembcke B & Fisher H (1993) Early changes of body composition in human immunodeficiency virus-infected patients: tetrapolar body impedance analysis indicates significant malnutrition. *American Journal of Clinical Nutrition* **57**, 15.
- Paton NI & Castello-Branco LR (1999) Impact of tuberculosis on the body composition of HIV-infected men in Brazil. *Journal of Acquired Immunodeficiency Syndrome* **20**, 265–271.
- Paton N, Newton PJ & Sharpstone D (1999) Short-term growth hormone administration at the time of opportunistic infections in HIV-positive people. *AIDS* **13**, 1995–2002.
- Periard D, Telenti A & Sudre P (1999) Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation* **100**, 700–705.
- Perlenicek JP, Graham NM & He YD (1996) Weight loss prior to clinical AIDS as predictor of survival. Multicenter AIDS cohort Study Investigators. *Journal of Acquired Immunodeficiency Syndrome* **10**, 366.
- Purnell JQ, Zambon A & Knopp H (2000) Effects of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* **14**, 51–57.
- Roubenoff R, McDermott A, Weiss L, Heflin T, Cloutier GJ, Wood M & Gorbach S (1999) Short-term progressive resistance training increases strength and lean body mass in adults infected with human immunodeficiency virus. *AIDS* **13**, 231–239.
- Rozenbaum W, Molina JM & Delfraissy JF (2000) Improvement of lipodystrophy in HIV-1 infected subjects switching from 2 NRTI/PI to 2NRTI/Abacavir (French substudy, CNA30017). In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Ruiz L, Negrodo E & Domingo P (2000) Clinical, virological and immunological benefit of switching the protease inhibitor by nevirapine in HAART-experienced patients suffering lipodystrophy: 36-week follow-up. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Saint-Marc T, Partisani M, Poizot-Martin I, Rouvière O, Bruno F, Avallaneda R, Lang JM, Gastaut JA & Touraine JL (1999) A syndrome of peripheral fat wasting in patients receiving long-term nucleoside analogue therapy. *AIDS* **13**, 1659–1667.
- Safrin S & Grunfeld C (1999) Fat distribution and metabolic changes in patients with HIV infection. *AIDS* **13**, 2493–2505.
- Schambelan M, Mulligan K & Grunfeld C (1996) Recombinant human growth hormone in patients with HIV-associated wasting. *Annals of Internal Medicine* **125**, 873–882.
- Serwadda D, Mugerwa R & Sewanfambo N (1985) Slim disease: a



- new disease in Uganda and its association with HTLV-III infection. *Lancet* **2**, 849–852.
- Shabert J, Winslow C, Lacey J & Wilmore D (1999) Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized double-blind controlled trial. *Nutrition* **15**, 860–864.
- Silva M, Skolnik P & Gorbach S (1998) The effect of protease inhibitors on weight and body composition in HIV-infected patients. *AIDS* **12**, 1645–1651.
- Strawford A, Barbieri T & Neese R (1999) Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss. *Journal of Acquired ImmunoDeficiency Syndrome and Human Retrovirology* **20**, 137–146.
- Sullivan AK & Nelson MR (1997) Marked hyperlipidaemia in ritonavir therapy. *AIDS* **11**, 938–939.
- Süttmann U, Ockenga J & Selberg O (1995) Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus-infected outpatients. *Journal of Acquired ImmunoDeficiency Syndrome* **8**, 239.
- Tebas P, Yarasheski K & Powderly WG (2000) A prospective open-label pilot trial of a maintenance nevirapine-containing regimen in patients with undetectable viral loads on protease inhibitor regimens for at least 6 months. In *Seventh Conference on Retroviruses and Opportunistic Infections*. San Francisco, CA.
- Vittecoq D, Escaut L & Monsuez JJ (1998) Vascular complications associated with use of HIV protease inhibitors. *Lancet* **351**, 1959.
- Von Roenn J, Armstrong D & Kotler D (1994) Megestrol acetate in patients with AIDS-related cachexia. *Annals of Internal Medicine* **121**, 393–399.
- Walli R, Herfort O, Michl GM, Demant T, Jager H, Dieterle C, Bogner, Landgraf R & Goebel FD (1998) Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1 infected patients. *AIDS* **12**, 167–173.
- Wanke C, Silva M, Knox T, Forrester J, Speigelman D & Gorbach S (2000) Weight loss and wasting remain common complications in individuals infected with HIV in the era of highly active antiretroviral therapy. *Clinical Infectious Diseases* **31**, 803–805.
- Wheeler DA, Givert CL & Launer CA (1998) Weight loss as a predictor of survival and disease progression in HIV infection. *Journal of Acquired ImmunoDeficiency Syndrome and Human Retrovirology* **18**, 80–85.
- Yarasheski K, Zachwieja J & Gisher J (1998) Increased plasma Gln and Leu R and inappropriately low muscle protein synthesis rate in AIDS wasting. *American Journal of Physiology* **275**, 577–583.