

Body composition in women with HIV/AIDS: The relevance of exercise

Body composition can provide valuable information in the management of women with HIV.

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Untreated infection with the human immunodeficiency virus (HIV) leads to severe physical debilitation, culminating in the acquired immune deficiency syndrome (AIDS). Multiple infections, body mass loss, physical weakness and wasting are characteristic manifestations of each of the four stages of HIV/AIDS, respectively (Table I). The latter two impact especially on the affected person's ability to function, as well as on social and economic levels. However, even though antiretroviral treatment (ART) is now available at many selected public clinics in South Africa, it only complicates the issues surrounding body composition and physical function.

The information gained could lead the medical practitioner to recommend lifestyle changes, including exercise, which will further benefit the patient over and above the use of ART.

Table I. The WHO classification system for HIV infection (rewritten from Weatherall DJ, Ledingham JGG, Warrell DA. *Oxford Textbook of Medicine*. 3rd ed. Oxford, UK: Oxford University Press, 1996)

Group A - C based on laboratory variables		
	Lymphocyte count (x10 ⁶ /l)	
	CD4 ⁺ count (x10 ⁶ /l)	
A	>2 000	>500
B	1 000 - 2 000	200 - 500
C	<1 000	<200
Group 1 - 4 based on clinical variables		
Clinical group 1	HIV infected: Asymptomatic or with only persistent generalised lymphadenopathy Exercise: Can participate in normal physical activities	
Clinical group 2	Early-stage disease: Symptomatic with body mass loss of <10% Symptoms: recurrent upper respiratory tract infections and herpes zoster (shingles) infection occurring within 5 years Exercise: Can still maintain normal physical activity	
Clinical group 3	Intermediate-stage disease: Body mass loss >10%, unexplained chronic diarrhoea for >1 month, unexplained prolonged fever for >1 month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within previous 12 months, severe bacterial infections Physical ability: Frequently bedridden, but <50% of the day/s during the previous month	
Clinical group 4	Late stage disease: Diagnosed with any of the AIDS-defining illnesses Physical ability: Bedridden >50% of the day/s during the previous month	

HIV/AIDS and exercise

AIDS-related wasting and ART-related lipodystrophy are physical conditions affecting the patient and can be monitored on a regular basis. The physical assessments should be practical, i.e. cost and time efficient, objective, accurate and relevant. With proper training, determination of body composition using anthropometry (measurement of skinfold thickness and various circumference measurements) fulfils these criteria. The information gained could lead the medical practitioner to recommend lifestyle changes, including exercise, which will further benefit the patient over and above the use of ART.

Finally, according to UNAIDS and the WHO, 57% of people living with HIV in sub-Saharan Africa are women. Therefore, this review focuses (where possible) on the physical effects of HIV on infected women and the impact of ART on this population.

The AIDS wasting syndrome (AWS)

Wasting is directly associated with HIV/AIDS disease progression. A body mass loss greater than 10% before AIDS is associated with an increased risk of death.¹ Even a body mass loss of between 5% and 10% has been associated with an increased risk of opportunistic complications. However, although measurement of body mass is practical, it may be too insensitive, as patients with a small body mass loss may actually be losing a greater amount of essential lean body mass (LBM).

- Melchior *et al.*² found that LBM index (LBM (kg)/height² (m²)) was an independent predictor of survival in patients with HIV/AIDS, irrespective of body mass.
- Interventions that restore muscle mass are therefore critical for patients suffering from the wasting syndrome, or for those who suffered from it before being on ART.

A drawback of many published studies on HIV/AIDS is that most of the study participants were men. In contrast to men, women lose proportionately more fat during HIV infection;^{3,4} therefore, in comparison, they preserve more lean tissue. A higher initial body fat content may predispose women to lose relatively more fat than LBM during wasting. However, conclusions drawn from women living in a Western society will not necessarily reflect those found in sub-Saharan Africa where socio-economic factors and ethnicity could influence body composition changes.

Table II. Antiretroviral medications and side-effects that could impact on body composition and willingness or ability to exercise (adapted from Baylor College of Medicine, 2003. HIV curriculum for the health professional (www.bcm.edu))*

Class	Antiretroviral drug	Possible side-effects	
NRTI	Didanosine (ddI) (Videx)	Common: nausea, vomiting, diarrhoea Severe: peripheral neuropathy, electrolyte abnormalities, lactic acidosis	
	Lamivudine (3TC)(EpiVir)	Common: nausea, diarrhoea, headache, fatigue Severe: lactic acidosis	
	Zalcitabine (ddC) (Hivid)	Common: headache, malaise Severe: peripheral neuropathy, haematological toxicity	
	Zidovudine (AZT) (Retrovir; Zidovir)	Common: haematological toxicity, headache Less common: myopathy, myositis	
	Stavudine (d4T) (Stavir; Zerit)	Common: headache, nausea, vomiting, diarrhoea Severe: peripheral neuropathy, lactic acidosis	
	Abacavir (in Trizivar; Ziagen)	Common: nausea, vomiting, diarrhoea, loss of appetite, malaise, headache	
	Tenofovir (Disoproxil, Fumarate, Viread)	Common: headache, nausea, lactic acidosis	
	Zidovudine/lamivudine (Combivir or Duovir; in Trizivar)	Common: lactic acidosis	
	NNRTI	Delavirdine (Rescriptor)	Common: headache, fatigue, nausea, vomiting, diarrhoea
		Nevirapine (Nevimune; Viramune)	Common: sedative effects, headache, nausea, diarrhoea
Efavirenz (Stocrin)		Common: central nervous system (dizziness, etc.)	
PI	Indinavir (Crixivan)	Common: nausea, headache, hyperbilirubinaemia Less common: hyperglycaemia	
	Nelfinavir (Viracept)	Common: nausea, vomiting, diarrhoea, headache Less common: abdominal pain, hyperglycaemia	
	Saquinavir (Invi-Rase)	Common: nausea, vomiting, diarrhoea, headache Less common: hyperglycaemia	
	Saquinavir (Fortovase)	Common: nausea, vomiting, diarrhoea, headache Less common: hyperglycaemia	
	Ritonavir (Norvir)	Common: nausea, vomiting, diarrhoea, anorexia Less common: increased serum triglyceride and cholesterol, hyperglycaemia	
	Lopinavir/ritonavir (Kaletra)	Common: nausea, vomiting, diarrhoea, headache Less common: hyperglycaemia	
	Amprenavir (Agenerase)	Common: headache, nausea, vomiting, diarrhoea	

* Some of the abovementioned trade names are used internationally and are included for reference when accessing international literature.

Mechanisms of wasting in patients with HIV/AIDS

There are often multiple underlying causes of the wasting process. Opportunistic

infections, chronic diarrhoea, decreased dietary energy intake and increased resting energy expenditure (hypermetabolism) are correlated with body mass loss.² Primary

muscle disease has been implicated as another possible underlying mechanism of the wasting syndrome.^{5,6}

- Hypermetabolism is related to endocrine abnormalities or elevated cytokines, or both:
- HIV-positive patients may have elevated resting cortisol concentrations (which can lead to increased tissue catabolism) and decreased dihydro-epiandrosterone sulphate (DHEAS)(which is anti-catabolic).⁷
- Cytokines cause anorexia (cachexia in extreme cases), but also stimulate muscle proteolysis by activating the ubiquitin-proteasome pathway.⁵
- Deltoid muscle biopsy samples of 30 patients (of whom 26 were male) with the wasting syndrome, revealed that 11 patients had HIV-related myopathy.⁶

Disturbances in lipid metabolism leading to lipodystrophy, hyperlipidaemia, insulin resistance and hyperglycaemia are strongly associated with PI-based ART.

The lipodystrophy syndrome

Currently, there are three classes of ART medications: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Many of the typical side-effects can affect functional capacity (Table II). In general, in South Africa, stavudine, lamivudine and efavirenz (Stocrin) are used as the first line of treatment, whereas didanosine, zidovudine and lamivudine/zidovudine (Combivir) are used in cases of treatment failure (insufficient viral suppression despite compliance) or if there are other reasons to alter treatment (e.g. lactic acidosis).

Disturbances in lipid metabolism leading to lipodystrophy, hyperlipidaemia, insulin resistance and hyperglycaemia are strongly associated with PI-based ART.^{8,9} However, PI-naïve patients treated with two NRTIs have also been shown to exhibit the same manifestations.¹⁰ Even though ART can reduce generalised body mass loss and improve longevity, the impact on body composition may be negative,^{8,9} e.g.:

- fat loss in the face, arms and legs
- increased waist circumference due to deposition of intra-abdominal visceral fat
- accumulation of adipose tissue in areas such as the dorso-cervical region of the neck and breasts, sometimes in the form of unencapsulated lipomas.

Lipodystrophy is an adverse effect of ART, and not limited to a specific drug or class of drugs.

These ART-associated features (Table III) resemble some characteristics of the

metabolic syndrome, and therefore can be aggravated by high fat intake, chronic psychological stressors and low physical activity, leading to further complications such as fatty liver, hypertension, endothelial dysfunction, renal dysfunction, inflammation, hyper-coagulability and atherosclerosis.¹¹

- The defining physical features of the metabolic syndrome are: body mass index (BMI) >30 kg/m², waist circumference >102 cm (men) or >89 cm (women), or a waist-to-hip ratio >0.90 (men) and >0.85 (women).
- Endurance exercise is frequently promoted as a lifestyle intervention for the metabolic syndrome and should also be implemented in HIV-positive persons on ART.

As fat deposited in the intra-abdominal area could be a result of redistribution of existing fat^{12,13} or the preferential deposition of 'new' fat, it is important to monitor not only a global percentage of body fat but also regional distribution.

Monitoring body composition changes

Portable methods for assessing body composition include bio-electrical impedance analysis (BIA) and skinfold measurements. Different equations used with BIA resulted in highly variable estimations of fat-free mass (FFM) and fat mass (FM) in HIV-infected individuals showing signs of AIDS wasting,¹⁴ and may not be the method of choice for this population. To improve the reliability of skinfold measurements, the same technician should perform measurements repeated on the same patients. Measurement of circumferences at specific sites is also simple to perform and is reliable, provided the specific landmarks are understood. Table IV summarises

Table III. Clinical aspects of the lipodystrophy syndrome

Fat accumulation

- Abdominal obesity
- Dorsocervical pad ('buffalo hump')
- Cervical hypertrophy
- Lipomas
- Breast enlargement

Fat loss

- Face wasting (reduction or absence of subcutaneous tissue on the cheeks with sparing of the facial musculature)
- Loss of subcutaneous fat of extremities
- Loss of gluteal mass

Biological abnormalities

- Glucose intolerance, diabetes, hyperinsulinaemia and increased insulin resistance
- Hypertriglyceridaemia
- Hypercholesterolaemia: increased LDL cholesterol, decreased HDL cholesterol

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SOUTH AFRICAN RENAL SOCIETY RECOMMENDATIONS FOR EARLY DETECTION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

CKD is a major public health problem in South Africa and is associated with significant morbidity, mortality and high medical expenditures. Early detection and optimal management can prevent premature death, and prevent or delay the need for dialysis/transplantation. CKD may be present in more than 10 % of the adult population, particularly in high-risk groups.^{1,2}

Definition:

Glomerular Filtration Rate (GFR) < 60 ml/min or markers of kidney disease present for more than 3 months.

Such markers include:

- Proteinuria
- Haematuria
- Abnormal renal imaging eg. Sonar

NB: Serum creatinine alone may not accurately reflect kidney function and therefore the GFR should be estimated from the serum creatinine using prediction equations. For example this modified **Cockcroft-Gault** formula:

$$\text{GFR} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l)}} \quad (\times 0,85 \text{ if female})$$

Risk factors for Chronic Kidney Disease:

- Diabetes Mellitus
- Hypertension/CVS disease
- Age > 50 years
- Family history of kidney disease
- HIV/AIDS

In children include:

- Glomerulonephritis
- UTI's
- Congenital abnormalities
- Kidney stones

Schwartz Formula for Children

$$\text{GFR} = \frac{K \times \text{height (cm)}}{\text{Serum creatinine } (\mu\text{mol/l})}$$

Where K is:

- Low birth weight infant	30
- Normal infants 0 – 18 months	40
- Girls 2 – 16 yrs	49
- Boys 2 – 13 yrs	49
- Boys 13 – 16 yrs	60

How to screen for CKD:

- Urine dipstix and blood pressure measurement at least on an annual basis
- In diabetics, perform a microalbumin dipstix or a spot urine albumin:creatinine ratio (ACR) at least annually
- Patients with detected abnormalities should have a serum creatinine test performed, urine protein:creatinine ratio and a creatinine clearance calculated as suggested above

Consider referring the following patients for an opinion:

- Proteinuria or persistent haematuria
- GFR < 60 ml/min or creatinine > 150 $\mu\text{mol/l}$ (**lower in children**)
- Familial kidney disease e.g. Polycystic kidney disease
- **All children with renal problems should be referred immediately**

Why investigate or refer patients with kidney disease?

- Establish a specific diagnosis and treat reversible diseases
- Identify co-morbid conditions, prevent and manage further complications of CKD
- Optimise management to slow progression of CKD; most effective when instituted early in the disease
- Plan renal replacement therapy well before end-stage kidney disease is reached

Recommendations to preserve renal function in patients with CKD:

- **Lifestyle modification** Weight loss, aerobic exercise and smoking cessation
Healthy balanced diet, lipid control and salt restriction
- **Blood pressure control**³ Blood pressure target < 130/80 mm Hg – **lower in children**, diabetics or proteinuria
ACE inhibitors and ARBs are the first line antihypertensive agents
Combination therapy is often required to achieve targets
- **In Diabetics** BP control is paramount
Optimal glycemic control - HbA1c < 7 %
Reduce proteinuria using ACE inhibitors and/or ARBs – target < 1 g/day
- **Proteinuria** Avoid NSAIDs and COXIBS, aminoglycoside antibiotics and contrast agents
- **Nephrotoxic drugs** Maintain normal calcium and phosphate levels, monitor PTH levels, **especially in children**
- **Calcium and Phosphate** Develops early in CKD and requires therapy to maintain an Hb of 11-12 g/dl
- **Anaemia**⁴

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Table IV. Anthropometric variables that can be considered as indicators of wasting status or manifestations of lipodystrophy, or both

Variables related to	
Wasting	Lipodystrophy
Body mass (BM)	Waist-to-hip ratio (W:H)
Percentage of ideal body mass (%IBW)	
Body mass index (BMI)	
Percentage of ideal arm circumference (%IAC)	
Upper arm fat area (UAFA)*	Upper arm fat area (UAFA)
Upper arm muscle area (UAMA)*	
Thigh skinfold	
Thigh circumference	
Fat mass index (FMI)	
Lean body mass (LBM)	
Fat-free mass index or LBM index (LBMI)	

* Anthropometry calculations for measurements in mm:
 $UAMA = [(upper\ arm\ circumference - (\pi \times triceps\ skinfold))^2] / 4\pi$
 $UAFA = [\pi/4 \times (upper\ arm\ circumference / \pi)^2] - UAMA$

Resistance training is an effective treatment to increase LBM, strength and functional status in patients with HIV/AIDS.

anthropometric variables related to wasting or lipodystrophy.

The only variable in traditional anthropometry related to lipodystrophy is the waist-to-hip ratio, but it does not distinguish between subcutaneous and intra-abdominal fat. It is also affected by gluteal wasting¹² that would exacerbate an already abnormal waist-to-hip ratio. However, the female body tends to store fat more easily in the gluteal area, which could mask gluteal wasting in women.

A longitudinal study conducted by Galli *et al.*¹⁵ found simultaneous fat loss and fat accumulation in HIV-positive women on ART followed up for 12 months, with further progression (especially peripheral lipoatrophy) after 24 months. It is also possible for lipoatrophy to occur without the concomitant increase in waist circumference.¹⁶ Of 14 patients with a clinically abnormal reduction or an absence of subcutaneous fat in the cheeks, 6 did not have an enlarged abdomen, while 5 had abnormally reduced fat in the legs and arms without an enlarged abdomen.

Exercise – effective intervention to reduce wasting and lipodystrophy

Oral nutritional supplementation combined with dietary counselling can diminish whole-body protein catabolism and increase LBM in HIV-positive patients with modest-to-moderate malnutrition. Although positive effects of whey protein supplementation on body mass were found, Agin *et al.*¹⁷ also showed that the combination of supplementation and resistance exercise led to gains in LBM, whereas supplementation alone increased fat mass.

- Resistance training is an effective treatment to increase LBM, strength and functional status in patients with HIV/AIDS.¹⁸
- Progressive resistance training with an aerobic component, undertaken for 16 weeks, reduced trunk fat mass in patients on ART.¹⁹
- Increased LBM lasted up to 8 weeks after a resistance training programme was discontinued.²⁰

Grinspoon *et al.*²¹ showed that androgen administration increases LBM and quality of life (QoL), but testosterone administration in combination with resistance exercise resulted in similar increases in skeletal muscle fibre size compared with testosterone alone, suggesting exercise was not essential. However, Bhasin *et al.*,²² who also found that testosterone and exercise together did not produce greater gains than testosterone alone, showed that exercise alone was sufficient.

- Considering longer-term side-effects of androgen treatment, exercise alone may

be a better long-term strategy to prevent or reverse muscle loss in HIV-infected persons.

Shevitz *et al.*²³ compared the effectiveness of nutritional intervention alone, nutrition with oral androgen (oxandrolone), and nutrition with progressive resistance training. The mid-thigh muscle cross-sectional area increased significantly only when nutrition was administered with oxandrolone or with resistance training, indicating that nutrition alone is not sufficient.

- Self-reported physical functioning improved significantly with resistance training.
- QoL improved more with exercise than with nutrition or nutrition plus androgen interventions.
- Exercise is more cost effective.

Relatively straightforward lifestyle changes (such as eating well, exercising and adequate sleep) can make a difference, even in a complicated context involving HIV, poverty and oppression.

Although strength training and cardiovascular exercise have been suggested as treatment interventions for the AWS, and more recently to address the metabolic

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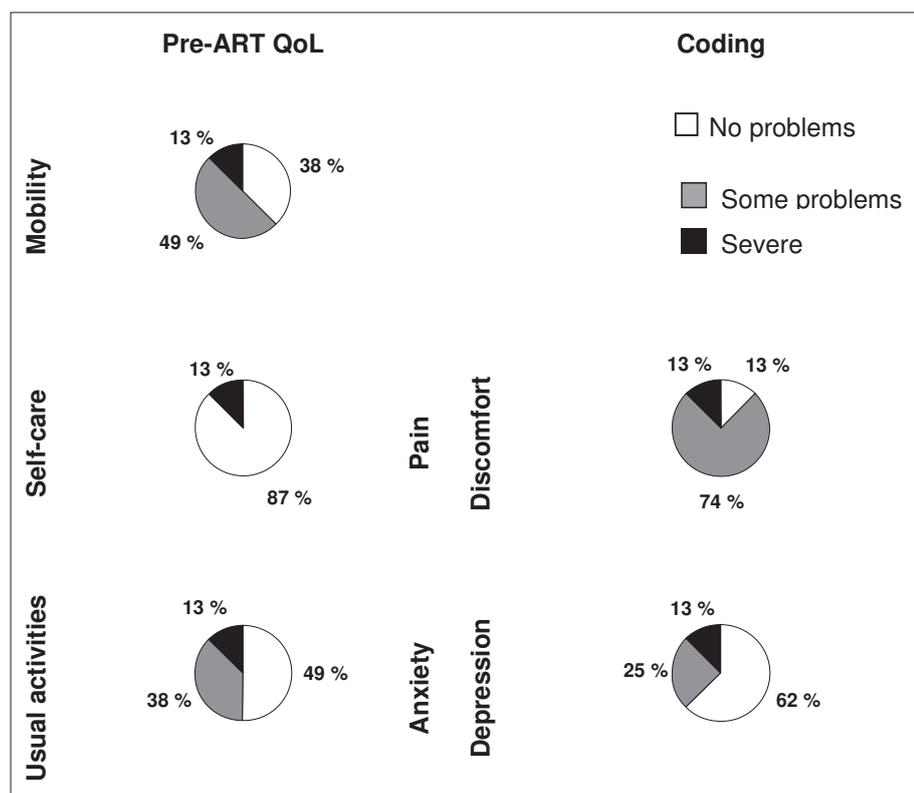


Fig. 1. The proportion of HIV-positive women (N=8, just before initiating ART) who fitted into one of three categories for variables describing quality of life (QoL).

abnormalities associated with ART,^{19,24} there is a distinct lack of data on the longitudinal effects of cardiovascular exercise although it has been shown to be safe.^{25,26}

Quality of life

The number and severity of HIV-related symptoms are associated with a patient's perceived QoL.²⁷ QoL includes multiple aspects of life satisfaction related to physical functioning, mental health status and functioning within social roles.²⁸ Physical functioning includes variables such as self-care, mobility and fatigue.

The MOS-HIV questionnaire (HIV-specific scales adapted from the Medical Outcomes Survey) is a widely used instrument to assess QoL. An European questionnaire (EQ-5D) has been used extensively in various countries (including Japan, Canada and Zimbabwe), and has been translated into Xhosa and validated in a South African population.

Health-promoting behaviours, including exercise, improved mental health, physical functioning and overall QoL in women with HIV who had various socio-economic and educational stratifications.²⁸ The researchers concluded that relatively

straightforward lifestyle changes (such as eating well, exercising and adequate sleep) can make a difference, even in a complicated context involving HIV, poverty and oppression. Resistance training and cycling have also been shown to increase QoL and physical functioning in HIV-infected men and women.^{19,26,29}

Muscle wasting and impaired QoL in a pilot study of 8 women with HIV in a South African semi-rural clinic

Just before initiating ART, the percentage of ideal body mass (%IBW) of the patients ranged from 67 to 153. Therefore, it should be noted that many infected individuals have an initial body mass much greater than 100%. Nonetheless, the upper arm showed signs of wasting of both muscle and fat (low percentage ideal arm circumference (%IAC)) despite the fact that mean %IBW was normal (Table V). Such individuals could be experiencing the wasting syndrome (loss of LBM and regional loss of fat mass) without having a body mass less than 10% of the ideal. For example, one participant was classified with late-stage (WHO stage 4) disease and her calculated upper arm muscle area (UAMA) was below the 5th percentile threshold, but her body mass was only 1% below the ideal prescribed for a female of her height, suggesting muscle wasting but not fat wasting.

Fig. 1 shows the proportion of these women who reported no problems, some problems or severe problems for each of the five QoL dimensions (before ART). Patients had difficulties with mobility and usual activities.

Conclusions

There is a complex interaction between disease and treatment, and body composition, physical activity and QoL in patients with HIV/AIDS. Monitoring of body mass alone is insufficient to understand the dynamic of the patient. Insufficient data are available, particularly in women, but normal body mass and fat deposition in the hip area may mask muscle and fat atrophy in other peripheral sites. The role of exercise in the long-term management strategy is essential for the health and QoL of patients before ART and for those on ART in order to reverse wasting and ameliorate lipodystrophy and the accompanying metabolic abnormalities.

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Table V. South African HIV-positive women: Pilot study of measurements taken just before initiation of ART

Variable	Baseline pre-ART	
	Mean±SD	N
CD4+ count (cells/µl)	118±67	7
CDC immune category	3±0	7
Body mass (kg)	56.1±14.6	8
Body mass index (kg/m ²)	22.4±6.4	7
Percentage of ideal body mass (%)	108±33	7
Arm circumference (cm)	24.7±5.3	8
Waist circumference (cm)	72.0±7.8	8
Percentage of ideal arm circumference (%)	87±17	8
Hip circumference (cm)	94.5±14.4	8
Waist-to-hip ratio	0.77±0.08	8

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In a nutshell

- AIDS-related wasting and ART-related lipodystrophy are physical conditions that should be monitored on a regular basis.
- Body mass loss between 5% and 10% has been associated with an increased risk of opportunistic complications.
- Patients with only a small body mass loss may actually be losing a greater amount of essential lean body mass (LBM).
- Cytokines play a role by causing anorexia (cachexia in extreme cases), but also stimulate muscle proteolysis by activating the ubiquitin-proteasome pathway.
- One-third of patients may have HIV-related myopathy.
- Currently lipodystrophy is an adverse effect of ART, not limited to a specific drug or class of drugs, but more commonly associated with protease inhibitors.
- Intra-abdominal fat deposition and loss of facial and peripheral fat are features of lipodystrophy.
- Assessment of skinfold thickness and circumferences is cost effective, but requires proper training for reliable measurements.
- Lipodystrophy shares many features with the metabolic syndrome, for which endurance exercise is known to be beneficial.
- Interventions that restore muscle mass are critical for patients suffering from the wasting syndrome, or for those who suffered from it before being on ART. Endurance exercise is important for patients on ART.



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