LONG-TERM CONSEQUENCES OF ANTIRETROVIRAL THERAPY

The advent of antiretroviral therapy (ART) has revolutionised the treatment of HIV/AIDS in the way that insulin changed the face of diabetes management decades ago.

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Correctly used combinations of antiretrovirals from different classes successfully and sustainably control the virus for years and perhaps decades, allowing for immune recovery. People on ART, it seems, can live decades of fully functional life if side-effects or unforeseen consequences due to HIV infection do not arise. Combinations of these drugs allow the immune system, even with CD4 counts associated with severe opportunistic illnesses, to improve or normalise over the years on treatment.[1] Multiple studies, including several from Africa, show that even people with CD4 counts below 50 cells/µl have 5-year survival rates of over 70%, if they take their medication correctly. The majority of the mortality in this group occurs in the first 6 months, and then the incidence of illness and death declines.[2] South Africa has the world's most ambitious public ART programme in the world, with over a million people anticipated to be on treatment by 2007.[3,4]

The analogy with diabetic treatment is strong. HIV, like diabetes, is a chronic, treatable illness demanding good adherence from the HIV-infected patient and a team approach from all health care workers involved. If successful, family units will remain cohesive, people will return to work and have fully active lives, and HIV will assume the mantle of another chronic disease.

As the immediate mortality and morbidity from opportunistic infections and neoplasms disappear, the focus has shifted to concerns about the long-term consequences of ART. This review does not cover the short-term side-effects of ART – but rather the side-effects in adults on stable, long-term therapy (beyond 3 months).

ART in its current form has only been available since 1995, and was soon thereafter recognised to have profound metabolic effects. By 1998, several warnings regarding lipodystrophy had been posted by regulating authorities, and by 2000, the level at which commencement of ART was recommended had been reduced to 200 - 350 CD4 cells/mm^3, due to the recognition that there was minimal clinical benefit and unnecessary exposure to side-effects if starting earlier.

There are currently 3 commonly used classes of drugs – the nucleoside reverse transcriptase inhibitors (NRTIs) (AZT, 3TC, ddI, d4T, and abacavir are commonly used in South Africa, all of which have alternate generic and commercial names), the protease inhibitors (PIs) (lopinavir, indinavir, saquinavir, usually in combination with ritonavir, nelfinavir), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine and efavirenz).

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Generics are increasingly being used in southern Africa, and the Medicines Control Council maintains strict control over bioequivalence, which is critical when using ART.

The long-tem consequences can be narrowed down to only a few known syndromes, many of which overlap:

- 'lipodystrophy'
- peripheral neuropathy
- lactic acidosis
- osteopenia and osteoporosis.

LIPODYSTROPHY

This is a complex constellation of symptoms, signs and laboratory abnormalities, bundled together under the term 'lipodystrophy', a term that still has defied clear definition. Future research may show multiple overlapping syndromes.

Lipodystrophy includes changes in body fat distribution and metabolic abnormalities, including insulin resistance, hyperglycaemia and hyperlipidaemia (Table I). Patients rarely have the entire constellation, and each may declare itself to a different degree. The pathogenesis appears to be a complex interaction between HIV, ART, weight gain and immune recovery. Gender, race, stage of disease and age all seem to play a part in how the syndrome presents. Patients with more advanced disease on starting ART tend to develop the syndrome more severely. The syndrome, in full form, is remarkably similar to 'syndrome X', the well-described complex of clinical signs and laboratory metabolic abnormalities strongly associated with cardiovascular disease.

PIs have been most firmly linked to lipodystrophy, but other ART classes are also implicated. However, as PIs appear the most potent and predictable cause of the syndrome at present, many clinicians avoid using them unless resistance or side-effects with the other classes force their hand.

The evidence that ART-induced atherogenic profile translates into clinical events is very weak at present, possibly because ART has not been used for long enough for the documented endothelial dysfunction to translate into strokes and myocardial infarction.[5,6] According to the Adult AIDS Clinical Trial Group (AACTG) Cardiovascular Disease Focus Group, 'On the basis of precedent in other disease states, there is reason to believe that HIV treatment-associated changes in lipid levels are likely to result in some degree of increased cardiovascular risk. It appears likely that the chronic presence of traditional cardiovascular risk factors increases risk regardless of the aetiology, and this same potential certainly exists during the long-term management of HIV-infected subjects.'

Even if there is a substantial increase in cardiovascular risk in later decades, the benefit of ART far outweighs the risk of these postulated events.

Drug development must increasingly be tailored to minimise metabolic consequences. Newer protease inhibitors tend to have minimal effects on glucose and lipid homeostasis.

Management of the complications of lipodystrophy involves managing the risk profile, and considering substitution of the offending drug (Table I). Guidelines exist for the management of these conditions by the International AIDS Society (IAS) and others, but the recommendations are rarely evidence-based.[7-9] Trials examining different interventions are ongoing.

Morphological changes

These changes can be severe if not recognised early and are highly stigmatising. Clinicians often tend to dismiss complaints of fat redistribution, ignoring the fact that HIV-infected people are being permanently marked by the disease. This may have profound consequences for quality of life, delay initiation of therapy and decrease ART adherence. It should never be ignored. Reversal of the morphological changes is usually marginal with substitution of the offending drugs, and early recognition of the syndrome is therefore essential. Furthermore, it appears that the morphological changes may worsen the metabolic abnormalities seen in the syndrome. The increased abdominal girth is a strong risk factor for cardiovascular disease in studies of non-HIV populations.

Changes are usually slow in onset and rarely completely reversible. Changes include wasting of the face and periphery, altered fat distribution including increased intra-abdominal fat (the 'protease paunch'), enlarged breasts, and even 'buffalo humps' on the back of necks. The wasting aspect is most strongly associated with d4T (stavudine), and the other features with the PIs. Treatment is unrewarding, as the changes are largely irreversible. If significant irreversible change has occurred, reconstructive surgery can be used in some situations. Growth hormone has been used to treat the lipoatrophy wasting syndrome, but is expensive and the effects reverse on cessation of treatment.

Laboratory abnormalities

The HI virus itself is associated with a variety of metabolic abnormalities, many of these associated with atherogenic profiles. These include raised cytokine profiles, raised triglycerides, decreased HDL, raised C-reactive protein, changes in apolipoprotein B, raised fibrinogen, and increased plasminogen-activating

Table I. **Long-term consequences of ARVs**

Side-effect	Prevention	Treatment (always check drug interactions!)	Usual offending drug
Lipodystrophy			
• Fat accumulation (breasts, intra-abdominal, back/buffalo hump)	Early patient identification	Change PI to another class, usually marginally reversible	PIs
• Lipoatrophy (loss of fat pads in cheeks/ thin face, buttocks, arms and legs)	Early patient identification	Change drug to another class, usually marginally reversible	Usually d4T
• Hyperlipidaemia	Avoid PIs	Address other cardiovascular risk factors, diet, exercise; fibrates for raised triglycerdides (TG), pravastatin/low dose atorvastatin for mixed raised TG/cholesterol	Usually PIs, occasionally other ARVs
• Hyperglycaemia	Avoid PIs	Diet, exercise, address other diabetic risk factors; metformin if fat accumulation/overweight, sulphonylureas/insulin as needed; consider stopping PI	PIs
Lactic acidosis	High patient vigilance with all NRTIs, especially if using d4T/ddI	Supportive, discontinue all ARVs, including NRTIs till settled, expert advice subsequently on NRTI choice	D4T, ddI common, but occurs with other NRTIs
Peripheral neuropathy	High patient vigilance, avoid the d-drugs (d4T, ddI, ddC)	Ensure taking pyridoxine; try conventional symptom control (e.g. amitriptyline 25 mg nocte); if symptoms continue/are severe, replace d-drugs	d-drugs (d4T, ddI, ddC)
Osteonecrosis/ osteopenia	Unknown; ensure calcium/vitamin D intake is adequate, discourage smoking, encourage exercise	Conventional	All ARVs

inhibitor activity. In Western populations, the high incidence of smoking in HIV-infected populations means that analysis of cardiovascular disease incidence is very complex.
ART is responsible for a wide array of different metabolic disorders as well.

Hyperlipidaemia

ART, especially the PIs but the other classes as well, may also cause or exacerbate raised triglycerides, decreased HDL and variably affect LDL. Patients on PIs should have regular fasting lipid evaluations.

Aggressive dietary and lifestyle interventions should be identified, with conventional risk factor management. Isolated fasting hypertriglyceridaemia should be managed with fibrate therapy. Treatment of hypercholesterolaemia or mixed hyperlipidaemia should be with a statin, with a fibrate added if necessary. Benefits in lipid profiles appear to be comparable with those in HIV-uninfected people. Pravastatin is currently the statin of choice, as it seems to have very little pharmacological interaction with the PIs. Cases of rhabdomyolysis have been reported with simvastatin, and levels of atorvastatin have been shown to be significantly raised, when given with PIs.

Hyperglycaemia

Impaired glucose tolerance and hyperglycaemia due to insulin resistance, even to the degree of causing overt clinical diabetes, is described with use of PIs, especially in individuals with other risk factors. The side-effect can occur rapidly or some years after starting therapy. Many clinicians regard regular glucose monitoring as necessary, and it is essential if the person has other risk factors for cardiovascular disease. If hyperglycaemia occurs, substitution of this class of drug should be considered. If this is not possible, management should involve attention to risk factors (weight reduction, exercise, diet, etc.), and use of hypoglycaemics should follow conventional routes, using sulphonylureas, metformin and insulin as necessary. Newer classes of drugs, such as the glitazones, are being evaluated in trials.

Other components of the lipodystrophy syndrome may include hypertension, decreased bone density and hypogonadism, but the precise place of these is still controversial. Management is conventional.

LACTIC ACIDOSIS

This uncommon (estimated at 1 - 2% a year) but extremely dangerous syndrome is associated exclusively with the use of the NRTI class of drug. The syndrome is most commonly associated with stavudine (d4T), but is seen with all the nucleoside analogues. The syndrome is easily missed in the early stages if clinicians and patients are not vigilant, and we have seen a number of deaths in Johannesburg over the last few years, most of which exhibited early warning signs that were not recognised by patient or clinician.

The NRTIs have inhibitory effects on mitochondrial function. Over time, this may result in an accumulation of lactate. Lactic acidosis and lactic acidaemia are not synonymous, as an elevated lactic acid can be seen with the use of NRTIs with no apparent ill consequences. The definitions of the two syndromes are:

- Hyperlactataemia: venous lactate > 2.5 mmol/l. May be symptomatic or asymptomatic.
- Lactic acidosis: arterial pH < 7.35, venous lactate > 5 mmol/l. May be symptomatic or asymptomatic. It is rare to have normal bicarbonate levels when lactic acidosis is present.

It is important that the blood lactate is taken properly (without torniquet) and sent immediately, on ice, to the laboratory for processing if accurate results are to be obtained. An arterial lactate is more accurate than a venous lactate. Lactate may be increased due to other factors such as alcohol and exercise.

The syndrome has vague but key symptoms that usually evolve and worsen over days and weeks:

- loss of weight
- gastrointestinal symptoms, including nausea, loss of appetite, abdominal pain, painful hepatomegaly and vomiting
- weakness and fatigue
- hyperventilation secondary to the metabolic acidosis.

Patients typically have been on treatment for several months before these symptoms occur.

Routine lactic acid measurement does not seem to provide much help, as the predictive value is very limited. Rather, attention to symptoms and educating the patient about symptoms is a much more effective early warning system (Table II).

If lactic acidosis is suspected or identified, ART must be stopped immediately, and support, including inotropic, respiratory and renal replacement therapy, administered as necessary. In our experience, these patients may have profound metabolic acidosis out of keeping with their clinical assessment, and arterial blood gas measurement should be done on all suspected cases. Patients requiring support interventions have a high mortality. There is very limited evidence for the use of the B-complex vitamins and carnitine, but supportive therapy should remain the priority. Once the patient has been stabilised, future ART options should be discussed with an ARV specialist.

PERIPHERAL NEUROPATHY

This may be the commonest serious side-effect seen in Southern Africa, predominantly because of the widespread use of d4T (stavudine) and ddI (didanosine). HIV disease is a common cause of neuropathy in itself,

Table II. **Interpreting lactate levels**

Lactate	Symptoms	Action
< 2 mmol/l	No	No intervention
	Yes	Investigate other causes
2 - 5 mmol/l	No	Observe
	Yes	Exclude other causes Consider discontinue
5 - 10 mmol/l	No	Observe
	Yes	Discontinue NRTI Exclude other causes
> 10 mmol/l	Any	Discontinue NRTI Exclude other causes

as is alcoholism and the use of isoniazid (INH), a staple of the anti-TB regimen. Patients, particularly with very low CD4 counts, often have pre-existing peripheral neuropathy when starting ART. The 'd' drugs, d4T, ddI and ddC (very rarely used now) all cause this syndrome. They should be avoided or used with caution if there is existing peripheral neuropathy.

The neuropathy is usually sensory, but may develop a significant motor component if left untreated. Rarely, the motor form is the presenting feature. The neuropathy can occur at any point in treatment, but usually arises in the first few months. If ART is the cause, replacing the offending drug with another NRTI usually reverses the neuropathy. This may take months if the neuropathy is allowed to progress. All patients with symptoms, particularly those previously exposed to INH, may benefit from pyridoxine (25 mg daily) supplementation.

Education of the patient is essential. Patients with HIV often complain of altered sensation in their periphery, especially tingling and pins and needles, and immediate discontinuation of ART may not be appropriate. The treating doctor should document the presence and extent of a sensory peripheral neuropathy at baseline. Symptoms may get slightly worse on initiation of ART, but it is useful to let the patient alert the clinician when the sensory symptoms go beyond mild discomfort, in which case replacement may be appropriate. Until that point symptom control with amitryptiline is useful. There are drug interactions between the NNRTIs and the anti-epileptics used to treat sensory neuropathies, and these should be used with care. Permanent neuropathies can be managed conventionally.

It is important to distinguish between a recovering HIV sensory peripheral neuropathy presenting with dysaesthesias and improving numbness, as opposed to a developing peripheral neuropathy with worsening numbness related to ARVs.

OSTEOPENIA AND OSTEOPOROSIS

Decreases in bone mineral density have been shown in patients receiving HAART, especially in those patients on protease inhibitor-based regimens. These bone abnormalities may be linked to other metabolic abnormalities found in HIV patients.

Initially recommending adequate calcium and vitamin D intake may be appropriate.

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References available on request.

IN A NUTSHELL

Common sense in the management of lipodystrophy seems prudent. Behaviour modification, especially smoking and weight reduction, should be encouraged. Metabolic complications should be treated according to conventional guidelines for HIV-negative populations, but with regard for drug interactions with ART. Avoid PIs with atherogenic profiles in patients with other cardiovascular risk factors.

Identify lactic acidosis and peripheral neuropathy early. The best tool is a switched-on patient, who can let the astute clinician know well before the development of critical illness.

AIDS is a disease with 100% mortality if untreated. ART makes the vast majority of HIV-infected people better. Cardiovascular disease is treatable in most cases, and risk factors easily identified and addressed. Lipodystrophy, lactic acidosis, and peripheral neuropathy are usually identifiable by the informed patient and clinician. Use ART correctly, and deal with the consequences using clinical common sense.

ERRATUM

We apologise for omitting Table III in the following article in the February 2005 edition of *CME* – Diagnosing tuberculosis in adults: opportunities and challenges, by Douglas Wilson and Gary Maartens.

Table III. **WHO guidelines for distinguishing between pulmonary TB and PCP**

	Typical of PCP	Typical of TB
Symptoms	Dry cough Sputum mucoid (if any) Dyspnoea	Productive cough Purulent sputum Pleuritic pain Haemoptysis
Signs	May be normal Fine inspiratory crackles	Signs of consolidation Signs of pleural effusion
Chest X-ray	Bilateral diffuse interstitial shadowing May be normal	Lobar consolidation Cavitation Pleural effusion Intrathoracic lymphadenophathy