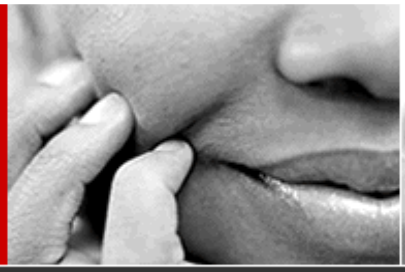

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Managing fat gain in patients on antiretroviral therapy

Lipodystrophy or changes in fat distribution occur very commonly in patients on antiretroviral therapy (ART). Some patients experience fat loss (lipoatrophy), others fat gain (lipohypertrophy), and many experience both forms of lipodystrophy. Subcutaneous fat loss is caused by the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs), stavudine and zidovudine, particularly stavudine. Clinical trials have shown improvement on switching to either tenofovir or abacavir. Fat accumulation occurs intra-abdominally, in the breasts and as the unsightly "buffalo hump". Visceral fat is associated with insulin resistance, dyslipidaemia and an increased risk of vascular disease as occurs in HIV-uninfected people.

It was initially thought that protease inhibitors caused fat gain. However, randomised controlled trials show similar rates of fat gain with ART regimens consisting of dual NRTIs with either protease inhibitors, non- nucleoside reverse transcriptase inhibitors (NNRTIs), or integrase inhibitors, as well as with NRTI-sparing regimens of NNRTI plus PI. Therefore fat gain is not linked to any antiretroviral drug class.

Switching to antiretrovirals with a better metabolic profile is widely practiced for patients experiencing fat gain, but the few trials that have been conducted of switching antiretrovirals have failed to show a benefit. A recent review article on the pathogenesis and treatment of lipohypertrophy concluded "we do not recommend switching antiretrovirals to combat lipohypertrophy". Switching is not only ineffective but also increases the risk of virologic failure.

There are three measures that have been shown to be effective for fat gain. Diet and exercise works, but the effects are modest. Growth hormone (or growth hormone-releasing factor) is more effective but is prohibitively expensive. Finally metformin has a modest effect on body mass index and waist to hip ratio, but should probably be reserved for patients with abnormal glucose tolerance. Thus, as with obesity and the metabolic syndrome in the general population, there are no quick fixes for antiretroviral-associated fat gain. Cosmetic surgery is an option for breast enlargement or "buffalo humps", but recurrences are not uncommon and medical aid schemes will usually not fund this.

Counselling patients with fat gain is crucial. Telling patients that their fat gain is due to a specific antiretroviral is factually incorrect and is likely to have a negative impact on adherence. It is important to screen for hypertension, diabetes and dyslipidaemia and treat these when they are present.

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TB treatment in patients on second-line ART

In patients on second-line ART needing treatment for active TB, a complicating factor is the very significant drug interactions between rifampicin and the protease inhibitors. Rifampicin is a potent inducer of cytochrome P450 and the drug transporter P-glycoprotein, thereby reducing protease inhibitor levels by 80-90%. If no adjustment to ART is made, ART is not suppressive and protease inhibitor resistance mutations accumulate. Neither atazanavir nor darunavir can be used with rifampicin. The protease inhibitor that we advise in patients on rifampicin-based TB treatment is lopinavir/ritonavir (Aluvia) with a doubling of the dose of the Aluvia from 2 tablets bd to 4 tablets bd – this should be done gradually with a dose increase to 3 tablets bd for a week, then 4 tablets bd. This strategy of doubling the Aluvia dose with rifampicin has been shown to provide adequate levels of lopinavir in adults (1, 2). However, in young children this strategy does not adequately compensate for the inducing effect of rifampicin (3), rather additional ritonavir to be given with Lopinavir/ritonavir (see AfA guidelines).

The double dose Aluvia given with TB treatment may be complicated by hepatitis (ALT monitoring is advised) and may be poorly tolerated due to gastro-intestinal side effects (vomiting and/or diarrhea). The GI side effects should be treated symptomatically with anti-emetics or antidiarrhoeals. In patients who absolutely cannot tolerate this strategy the options are few and operationally complex. One option is to switch rifampicin to rifabutin. Lopinavir/ritonavir, atazanavir/ritonavir and darunavir/ritonavir can all be used with rifabutin without the need for dose adjustment of the protease inhibitor dose. However several complexities arise:

1. Rifabutin is not available in public sector TB clinics.
2. This means that these patients have their TB treated outside of the public sector clinics. TB treatment in the public sector clinics follows a systematic approach with adherence support, regular follow-up and sputum monitoring. Without this approach successful outcome of TB treatment may be compromised.
3. It means that all TB drugs need to be taken individually (rifabutin, INH, PZA and ethambutol) rather than as fixed dose combination adding to pill burden and complexity, that may compromise adherence. Separate TB drugs are also often unavailable.
4. The metabolism of rifabutin itself is inhibited by the protease inhibitors, meaning that the rifabutin dose needs to be reduced in order to prevent toxicities (ocular, bone marrow and hepatic).
5. The optimal dosing of rifabutin for TB when given with lopinavir/ritonavir has not been clearly defined. Many reference texts suggest rifabutin 150mg three times per week, but recent data suggest this dose may result in rifabutin levels below the recommended target range (4, 5). Currently we advise alternate day rifabutin 150mg when taken with a boosted PI, but further data is needed.

Thus in patients who require rifabutin-based TB treatment in this situation we advise that clinicians be aware of these complexities, make a written TB treatment plan that includes the dosing of each of the TB drugs to be used over the 6-8 months of TB treatment as well as the sputum monitoring plan and repeatedly counsel the patient about the TB treatment and evaluate adherence. Where possible efforts should be made to integrate the TB treatment into the local TB clinic providing the clinic with the rifabutin and other TB medications and seeking their support with adherence, sputum monitoring, follow-up and TB notification.

Where the rifabutin option is not feasible, another approach is to use triple NRTI antiretroviral therapy for the duration of TB treatment. In a patient on second line ART this is unlikely to suppress viral load but may offer a degree of viral suppression until TB treatment is completed and a more effective ART regimen can be re-introduced.

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Lopinavir/ritonavir and Congenital Adrenal Hyperplasia in exposed infants?

A recent French publication reported unexpected adrenal hypofunction in neonates exposed in utero and postnatally to Lopinavir/ritonavir (LPV/r). In France, LPV/'r is often used antenatally and also postnatally where antenatal antiretroviral exposure has been sub-optimal.

The researchers used data from their national screening program for congenital adrenal hypoplasia (CAH), whereby dried blood spots, collected on day 3 are assayed for 17-hydroxyprogesterone (17OH), which is elevated in CAH. Forty-two neonates exposed to post-natal LPV/r were compared with 93 unexposed infants. Antenatal LPV/r exposure occurred in both groups, but was more common in the post-natal LPV/r exposed neonates (83.3 versus 62.4%: p = 0.01) 17OH levels were higher in postnatally LPV/r-exposed neonates. Three premature infants exposed both in utero and postnatally presented with signs and symptoms of CAH. All 3 had evidence of salt loss with high serum potassium and one had cardiac failure. [1]

Management of CAH requires early recognition, corticosteroids (the mineralocorticoid component is important), volume and salt replenishment. Input from a paediatric endocrinologist is advised.

Although not noted in this publication, CAH may present with ambiguous genitalia in females and an enlarged penis in males.

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Pathology Results

Please remember to mark you pathology request forms "copy to AfA". If this is done,

1. The lab will forward the result to AfA electonically (provided that the patient is registered on the AfA programme).
2. You do not have to fax the result to AfA.
3. Response times from AfA will be improved.
4. This will enable us to assist you in monitoring your patients.

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Aid for AIDS staff will guide you through the process.

Developments in HIV renal transplantation

HIV-associated nephropathy (HIV-AN) is the leading cause of end-stage renal disease (ESRD) in HIV-infected patients in South Africa. Prior to 2008, access of HIV-infected patients with ESRD requiring renal replacement therapy (RRT) in the state sector was prohibited due to the supposition that the outcome of HIV patients undergoing RRT was worse than that of the HIV uninfected population. However, experience from the USA of transplanting HIV-infected patients showed that outcome was comparable to that of HIV-uninfected patients.[1] A larger multicenter study has subsequently confirmed these findings.[2] Another argument against offering RRT to HIV-infected patients was that the expected surge in the new recipient pool as a result of opening up transplants to HIV-infected patients would negatively impact on HIV-uninfected patients with ESRD. Up until 2008, potential donor organs from HIV-infected persons were discarded, whilst the percentage of brain-dead potential donors who were HIV-infected grew.

It was against this backdrop that in September 2008, a team of doctors at Groote Schuur Hospital, Cape Town, led by Dr Elmi Muller embarked on the first kidney transplants of HIV-infected donor kidneys into HIV-infected recipients (HIV-positive-to-positive transplantation). The excellent 1-year outcomes of the first 4 patients have been published.[3] Notably, all patients are dialysis-free and all have undetectable viral loads on ART. The 3-year outcome of these patients and 10 more that have subsequently been transplanted is due for publication in the near future.

One of the concerns surrounding this programme has been the possibility that the introduction of a new HIV strain to the already infected HIV-patient via the incoming kidney could result in acceleration of HIV disease, as has been rarely reported during 'superinfection' by other routes.[4] To control replication of incoming virus, all recipients of an HIV-infected kidney that are not already on a PI-based regimen have their ART regimen changed to incorporate a PI. With the resistance rate to PIs in South Africa being exceptionally low at this stage of the epidemic, we are confident that this measure will control HIV replication, particularly as the donor kidneys have come from persons who were diagnosed with HIV during transplant work-up and had therefore not been on ART prior to donation. An added benefit of using a PI-based regimen is that the drug-drug interaction between ritonavir and tacrolimus used as part of the immunosuppressive regimen, means that the amount of tacrolimus that is required to achieve immunosuppression is a fraction of that required in the non-HIV transplant setting. This reduces the cost of transplantation considerably. The success of the programme has brought about a change in the Western Province's entry requirement to RRT, where now, HIV-infected patients with ESRD who have been on stable ART for ≥6 months whose HIV viral load is undetectable are candidates for RRT, which includes both dialysis and transplantation.

In light of the excellent short-term outcomes of the HIV positive-to-positive renal transplantation programme, the interesting ethical question arises as to whether it would be acceptable to transplant an HIV-infected kidney, into an HIV uninfected recipient. The shear demand for RRT in South Africa ensures that patients with ESRD are turned down each day and sent home to die, whether they are HIV-infected or not. The efficacy of ART in occupational post-exposure prophylaxis, the success of PMTCT and of PrEP all suggest that HIV replication could be controlled by ART given to an HIV-uninfected recipient of an HIV-infected donor kidney. As HIV patients are now able to access an HIV-infected or an HIV-uninfected donor kidney through the Western Cape transplantation programme, is it ethical not to offer an HIV-uninfected patient with ESRD the chance of a kidney transplant with an HIV-infected kidney?

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Report back from the Mind, Body, HAART Symposium – Integrating mental health into HIV care

The *Mind, Body and HAART Symposium*, hosted by the Anova Health Institute, was held in Cape Town on 11 and 12 August 2011. One of the key topics addressed was the complicated nature of HIV treatment adherence and the fact that mental health, alcohol and substance abuse are significant barriers to achieving optimal adherence.

The World Health Organization acknowledges that there is 'No Health without Mental Health'. Worldwide, up to 25% of all HIV positive patients are visiting a health service to assist with mental health challenges. With mental health and addictive disorders potentially affecting treatment adherence and overall wellness, it is reported that psychiatric disorders are 2 to 3 times more prevalent in people living with HIV.

Mental illness in people living with HIV was highlighted by Freeman, 2007 and the *South African Stress and Health Survey* (SASH Study), 2009. Findings included:

- 43.7% had some form of mental health disorder
- 11.1% had major depression
- 29.9% had mild depression (i.e. 41% had some form of depression)
- 4.9% had post traumatic stress disorder
- 17.5 % had alcohol and/or other substance dependence

The effects of mental illness are manifested by delayed initiation of antiretroviral therapy (ART), erratic adherence, reduced rates of retention in care and general loss of well being. In addition to this, it appears that depression, substance abuse and domestic violence are the top three reasons for failure of first line therapy due to poor adherence.

This group also reported more side effects, incorrect taking of treatment such as double dosing and delaying 2nd line therapy, and preferring alcohol to ART as other reasons for poor treatment adherence. Fifty percent of the group reported not taking ART as directed due to some sort of psychiatric disorders, with most reporting anxiety disorders, panic attacks, social anxiety (social phobia) and agoraphobia.

Between 30% and 64% of people living with HIV will experience some degree of post traumatic stress disorder (PTSD) during their lifetime. This is as a direct result of traumatic events such as the diagnosis itself, sexual assault or rape, child abuse, intimate partner violence, accidents or natural disasters.

The rate of PTSD among people living with HIV substantially exceeds that found in the general population (between 2.3% and 8% per lifetime). In South Africa 15% of people who were recently diagnosed HIV+ showed PTSD symptoms at 6 months (Stein et al., 2008). It appears that those individuals who have experienced trauma and are HIV positive have poorer treatment adherence. The traumatic event may also be associated with increased drug and alcohol use.

Professor Charles Parry of the Alcohol and Drug Abuse Research Unit at the South African Medical Research Council suggested that heavy alcohol drinkers are less likely to be adherent to ART compared to those who abstain. Biologically alcohol consumption affects the immune system and there is a strong and consistent association between alcohol consumption, HIV infection, re-infection and death for people living with HIV/AIDS as individuals are more likely to make poor choices when under the influence of alcohol.

The symposium highlighted the need to focus on extensive counseling, commencing at diagnosis, with an emphasis on mental health issues. Counseling should include discussion around how such mental health issues can cause barriers to treatment adherence and provide tangible tools to overcome them. Whilst this type of counseling would go a long way to addressing non-adherence as a result of mental health issues, it was acknowledged that because of late presentation, this is often a challenge in itself.

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