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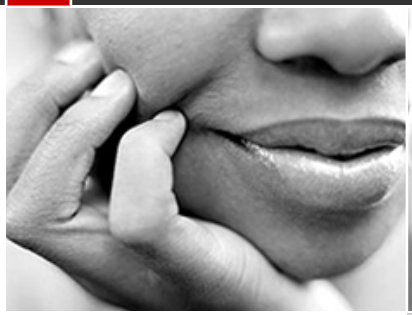

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Double-boosted protease inhibitor therapy for salvage ART: lack of evidence of benefit

Boosting protease inhibitors (PIs) with low doses of ritonavir, which inhibits metabolism and efflux of other protease inhibitors, has become the standard of care for PI therapy. The boosting of PI concentrations allows less frequent dosing intervals, and the high concentrations achieved are associated with better virological outcomes and a lower risk for developing PI mutations when virologic failure occurs. Several cohort studies (reviewed in Temesgen et al) indicate that increasing the concentration of PIs by integrating the trough concentrations with the degree of resistance is able to overcome partial PI resistance. An alternative approach is to use a dual PI combination, both boosted with low dose ritonavir, as part of an ART salvage regimen. The rationale is that both boosted PIs will act synergistically. A number of pharmacokinetic studies and pilot studies have been conducted (reviewed in Temesgen et al). However, the key question is does synergy occur?

Two studies (see table) have compared the efficacy of salvage ART regimens containing double-boosted PIs with single-boosted PIs. Neither study showed any benefit for double-boosted PI regimens. Both were non-randomised observational studies. Loutfy et al, who used boosted amprenavir and lopinavir, argued that their negative finding could be due to an interaction that results in lower concentrations of both PIs. However, Petersen et al used a variety of double-boosted PIs and were unable to show a difference between those on amprenavir and lopinavir compared with other combinations.

Study	No. on single-boosted PI	No. on double-boosted PI	Comparison for virological suppression
Loutfy et al	154	100	Adjusted HR 0.75; P=0.12
Petersen et al	805	183	Adjusted OR 1.29; P=0.26

In view of this negative evidence, AfA does not support the use of double-boosted PIs, pending further evidence (hopefully from an adequately powered randomised controlled trial).

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Important: Addendum to 2006 WHO guidelines on antiretroviral therapy for HIV infection in adults and adolescents.

Stavudine (d4T) is now recommended at the dose of 30 mg twice daily for all adult and adolescent patients regardless of body weight.

The WHO Guidelines Development Group has reviewed evidence for the use of stavudine (d4T) at reduced doses. They have concluded that d4T containing regimens maintain clinical and virologic efficacy when d4T is dosed at 30mg bd and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy.

looked after by
medscheme

Diagnosing and treating smear negative and extrapulmonary Tuberculosis in HIV-infected patients

HIV infection makes patients highly susceptible to reactivation of TB as well as progression to active disease following infection or re-infection with TB. TB in HIV-infected people, particularly those with low CD4 counts, is characterized by the following:

1. The sputum smear is more frequently negative despite the patient having sputum culture proven TB. The poor immune response to TB in the lung results in less cavity formation and thus less expectoration of acid fast bacilli.
2. The chest radiograph is frequently atypical, showing non-cavitating lower zone infiltrates and lymphadenopathy rather than the more typical upper lobe fibrocavitatory pattern.
3. Extrapulmonary forms of TB are more common.
4. The clinical deterioration of untreated TB is more rapid.

The sputum smear has traditionally been used by TB programmes to facilitate an early diagnosis of pulmonary TB. The reduction in sensitivity of this test in HIV-infected patients leads to diagnostic delay. However, it should be noted that the sputum smear still has a reasonably good diagnostic yield in HIV infection, and is often the only affordable rapid diagnostic test. Therefore two sputum smears should be requested as the initial investigation in all TB suspects with a cough. Sputum cultures are a more sensitive diagnostic method, but the result is often available only after several weeks. An HIV-infected patient's condition invariably deteriorates during this interval. Extrapulmonary TB is also problematic to diagnose because of difficulties in obtaining an appropriate clinical specimen.

Several diagnostic strategies can be used to make an early diagnosis of TB in someone who is HIV-infected and smear negative. These include:

1. Use of an ultrasonic nebuliser to obtain a sputum sample. This improves the sputum smear yield by about 25%.
2. Wide needle aspiration biopsy of any lymphadenopathy > 2cm in size in a patient with suspected TB[1].
3. Bronchoscopy, where available, to obtain a lavage and biopsy specimen for TB microscopy and culture.
4. Radiology (such as abdominal ultrasound or chest x-ray / CT scan) can strongly support but not confirm a diagnosis of TB. The finding of nodes or splenic microabscesses on abdominal ultrasound suggests abdominal TB. Rarely systemic fungal infections or lymphoma can also give rise to these features. Nodes on chest x-ray, and particularly nodes with central hypodensity on CT or ultrasound (due to caseous necrosis), are strongly suggestive of TB.

However, in certain instances an HIV-infected patient with clear symptoms of TB who is deteriorating rapidly in terms of weight loss and decline in functional status, may need to be started on TB treatment empirically prior to microbiological confirmation of the diagnosis. The WHO has recently issued recommendations for diagnosing and treating smear negative and extrapulmonary TB in HIV-infected people **(***Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Stop TB Department, Department of HIV/AIDS, World Health Organisation, 2006,* http://www.who.int/tb/publications/2006/tbhiv_recommendations.pdf**).**

Similar clinical algorithms have been validated locally[2,3]. Before initiating empiric TB treatment in such patients it is important to consider alternative diagnoses and treat with a broad spectrum antibiotic if a bacterial chest infection could be the cause of the symptoms and first assess the response to the antibiotic. TB cultures (preferably two) should always be sent prior to initiating empiric TB treatment so that the diagnosis can be confirmed. TB cultures can be performed on sputum, induced sputum or other clinical specimens such as aspirates from effusions, an early morning urine sample or blood taken into a special mycobacterial blood culture bottle. Urine and blood TB cultures have a yield of about 40% in patients with HIV and disseminated TB. All patients commenced on empiric TB treatment should be followed up by the clinician who has made the decision to start TB treatment in order to assess clinical response and get the results of the cultures. If the patient does not respond, further investigation for alternative diagnoses should take place. Diagnoses such as lymphoma, visceral Kaposi's sarcoma, non-tuberculous mycobacterial infections, systemic fungal infections or MDR TB should be considered in HIV-infected patients with TB symptoms who do not improve on empiric TB treatment.

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Atazanavir in pregnancy

Atazanavir is a protease inhibitor that has recently become available in South Africa (see newsletter 18). It is almost always recommended to be taken combined with ritonavir, as with other protease inhibitors. It has the advantages of once daily dosage and has minimal risk of causing dyslipidaemia. The main adverse effect is raised unconjugated hyperbilirubinaemia, without raised transaminases. Atazanavir is now one of the preferred PIs for adults in the USA[1].

The Food and Drug Administration (FDA) has placed Atazanavir in the pregnancy risk category B, where animal studies fail to demonstrate a risk to the foetus, but adequate well-controlled human studies have not yet been done. The predictive value of animal studies is unknown as only 30 of 1200 compounds with teratogenic potential in animals cause defects in humans[2].

There are limited data on Atazanavir in pregnant women. These data suggest that standard dosing in non-pregnant women is adequate[3,4]. Mild neonatal jaundice requiring phototherapy occurred in 3 infants. There is concern about increased unconjugated bilirubin levels that could exacerbate neonatal jaundice.

In summary, although there are few data, it is reasonable to use Atazanavir in pregnancy if a protease inhibitor-based regimen is indicated.

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Fluconazole and pregnancy

The recently published SA HIV Clinicians Society cryptococcal meningitis guidelines[1] state: “Fluconazole may be teratogenic: Women of child-bearing potential should be advised regarding the need for effective contraception while on the drug”. This is an important issue for clinicians and patients to be aware of.

Teratogenicity and embryotoxicity related to fluconazole have been demonstrated at high doses in rats. Teratogenicity in humans appears to be related to the dose and duration of therapy, and use in the first trimester. Congenital abnormalities that have been described following exposure to fluconazole include skeletal anomalies (craniofacial and limb), heart defects, cleft palate and dysmorphic facial features.

Several large cohort studies of infants of mothers who have been exposed mainly to lower doses (≤ 150mg/day) for shorter durations (usually single dose therapy for vaginal candidiasis) have not demonstrated an increase in congenital anomalies when compared to the infants of unexposed pregnant women.

The FDA has categorized fluconazole as a category C drug, defined as: “Either animal studies have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.”

Cryptococcal meningitis is a severe infection with a high mortality, and there are no good alternatives to fluconazole (apart from initial therapy with amphotericin B). Therefore AfA recommends that all women on fluconazole (especially those on long term secondary prophylaxis after an episode of cryptococcal meningitis) be counselled about these risks and advised to use effective contraception while on the drug. Pregnant women with cryptococcal meningitis may be treated with fluconazole after the risks have been explained to the patients. In the first trimester treatment with amphotericin B should be considered.

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Nutritional Management of the HIV positive patient “facts, fallacies and folk-lore”

Introduction
“What should I eat?” is one of the commonest questions addressed to the clinician by the HIV+ patient. In addition, many patients make use of the myriad of nutritional supplements and “immune boosters” available without prescription in pharmacies and supermarkets, as well as herbal supplements provided from various sources.

The clinician needs a working understanding of the mechanisms resulting in nutritional deficiency in these patients, as well as being able to calculate basic nutritional needs, and offer sound scientifically based advice as regards the use of nutritional supplements.

What constitutes a balanced diet?
“The amount of food substances an individual must consume daily in order to achieve an adequate nutritional status with the aim of ensuring good individual health” (WHO)

– Provide adequate nutrient and energy intake for the regulation of all metabolic processes and the working of the body.
– Supply nutrients with an essential regulatory function (e.g. proteins, iron, calcium and vitamins).
– Ensure a good balance of all nutrients.

Maintaining a balanced diet

– Eat a sufficient variety of food substances.
– Maintain an ideal weight.
– Choose a diet rich in vegetables, fruit and cereals (complex carbohydrate and fibre content).
– Choose a diet low in fat, saturated fat and cholesterol.
– Moderate consumption of sugar, salt, sodium and alcohol.

The aetiology of malnutrition in the HIV infected patient:
It is vital to take a comprehensive history when assessing malnutrition, as the appropriate intervention(s) will differ from patient to patient
Nutrient Deficiency

– Lack of supply – Socioeconomic reasons (poverty).
– Lack of supply – anorexia [This is a multifactorial problem, including psychological problems (depression), medical issues (nausea and vomiting), medication (pill burdens and taste issues), metabolic problems related to opportunistic infections, as well as cytokine imbalances and olfactory disturbance (associated with protease inhibitors)].

Lack of nutrient utilisation – Maldigestion / Malabsorption

– This includes diarrhoeal episodes, opportunistic infections, ileal dysfunction, bacterial overgrowth and autonomic neuropathy.

Energy Balance Alterations

– HIV positive patients have significant changes in energy expenditure, with an increased Resting Energy Expenditure of approximately 10% in asymptomatic patients, increasing to over 30% in symptomatic patients, particularly tuberculosis.
– In addition, hypermetabolism, metabolic alterations (futile cycles) and the shunting of essential amino acids to acute phase protein synthesis decreases somatic muscle synthesis.
– A functional imbalance of anabolic hormones, with associated endocrine system alterations have been well documented in HIV positive patients.

Nutritional interventions in the HIV infected patient
Once a comprehensive history has been taken, and complicating issues addressed, nutritional status should be addressed.

Evaluation of energy needs
35 – 45 Kcal/kg/day regular weight according to clinical situation (e.g. increase energy intake for level of activity, sepsis etc.).

Protein supplementation:

HIV is a protein losing illness

– Protein supplementation –1.0 -1.4g/kg /day.
– In severe wasting increase protein intake to 1.5-2.5g/kg.

Advanced nutritional intervention

– Protein / carbohydrate / fat balance is difficult in the HIV wasting syndrome.
– In cases of severe diarrhoea or protein losing enteropathies (e.g. cryptosporidium) – consider enteral nutrition or, in rare instances, total parenteral nutrition.
– Seek specialised dietetic assistance.

Multivitamins

– It is currently advised that all HIV positive patients receive a balanced multivitamin with doses at no greater than recommended daily allowance (RDA) on a daily basis. Evidence for this recommendation is not ideal, but a study in patients without access to HAART in Tanzania demonstrated delayed disease progression and decreased morbidity. A study from Thailand demonstrated a survival benefit of administering multivitamins only in a subset of patients with CD4 counts < 200.
– Dosing of fat soluble vitamins and micronutrients above the RDA must be avoided as this is potentially harmful.

“Immune boosters”

– There are many so-called “immune booster” products available to the HIV positive patient. There is minimal scientific data on these products.
– When advising on the use of these products it is useful to remember that if these products do in fact boost immunity this may cause harm as immune stimulation increases HIV replication.
– Hypoxis products (African Potato) have been associated with drug interactions, as well as with severe bone marrow suppression in a pilot human study.
– Sutherlandia has also been associated with drug interactions.
– Garlic in large doses (>2-3 cloves) is a gastric irritant, which could affect adherence to antiretroviral therapy. In addition, garlic induces hepatic metabolism and has been shown to reduce protease inhibitor concentrations.

In Summary

– In spite of new treatment developments, nutrition remains a cornerstone of HIV management.
– Metabolic, morphologic and cardiovascular disturbance associated with HIV imply a central role for dietary intervention.
– Nutritional intervention should be started early.
– Adverse events that affect the gastro-intestinal tract should be aggressively treated in order not to worsen nutrition deficit(s).
– Multivitamin and micronutrient supplementation should be considered for all patients, but the recommended daily allowance should not be exceeded.
– Herbal products and “immune boosters” should be discouraged as several have been associated with drug interactions, and toxicity.

Monitoring patients on tenofovir – an update

In an earlier newsletter (July 2007), doctors were advised to monitor the serum creatinine and eGFR 3 months after starting tenofovir (TDF) and then 6-monthly.

Since the launch of TDF in South Africa last year, 3093 patients on AfA have either started or been changed to this drug. An early significant increase in serum creatinine was noted in 4 patients. In 3 patients, the increase occurred after a month of therapy and in 1 patient the increase occurred after only 3 weeks. One of the 4 patients required dialysis. The baseline creatinine was normal in 3 patients and slightly increased in one.

Although uncommon, it appears nephrotoxicity may occur soon after starting TDF even in patients with normal renal function. In view of this, AfA now recommends that the serum creatinine is measured at baseline, 1 month, 2 months, 3 months, 6 months and then 6-monthly if the creatinine remains normal.

Completing the AfA application form

The following people are eligible to be registered on the AfA programme:

1. Any beneficiary of a medical scheme option contracted to AfA or
2. Any employee who meets the eligibility rules of a corporate HIV treatment programme contracted to AfA or
3. Any member of a NGO or other public sector based treatment programme for which AfA provides disease management support.

A list of AfA's clients is available on our website - www.aidforaids.co.za (click clinical care and then client list). AfA application forms can be downloaded from the website (clinical care, downloadable forms). Application forms can also be obtained by contacting AfA on 0860 100 646. To maintain confidentiality AfA uses a **separate** application form to the chronic medicine benefit programme – please ensure that the **correct** form is used to register patients with AfA to avoid delays in processing.

Signed consent from the individual applying to join the programme is essential. Corporate programmes mostly have separate detailed consent forms which must be completed and sent with the application form before the application can be processed.

A fee is payable either under the tariff code 0199, or as otherwise specified under the rules of the treatment programme for completing the AfA application form. The amount payable by most medical schemes is R243.20. (This fee can only be paid once and is therefore only paid if the patient has never been registered with AfA before.) It is not necessary for medical providers to submit an account for this purpose – AfA undertakes to ensure that the appropriate payment is made. **NB: This fee can only be paid if the correct form is used, the form is completed in full and the form is signed by both the doctor and patient.**