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Fixed dose combination antiretrovirals containing TDF, FTC/3TC and efavirenz

A fixed dose combination (FDC) antiretroviral (ARV) is a combination of two or more active drugs in a single pill. This means that instead of taking two or three different pills, a patient who is starting antiretroviral therapy can conveniently take one pill a day which contains several ARVs.

Making it easier to take ARVs means that there is a better chance of keeping a patient's viral load undetectable. This is associated with improved clinical outcomes, less chance of developing opportunistic infections and a near-normal lifespan.

Fixed dose combinations containing tenofovir (TDF), FTC or 3TC and efavirenz (a commonly used first line regimen) have been available in the private sector for a number of years. Apart from the branded product (Atripla®), there are now several generic formulations (Atroiza®, Citenvir®, Odimune®, Tribuss® and Eflaten®, Tenarenz®) and there is little doubt that they are effective and associated with a high degree of patient acceptance and improved treatment adherence.

The "combination pill" is now being made available in the Public Sector, which is a welcome development.

It is important to point out, however, that the tenofovir/FTC or 3TC/efavirenz FDC is not a "new" antiretroviral, and cannot be used in patients who have already failed first line therapy containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) - either efavirenz or nevirapine - in an attempt to simplify therapy. Patients who have failed first line therapy and have therefore developed viral resistance to one of the NNRTIs need to change to a second line regimen containing a protease inhibitor. Patients already on a second line regimen because of treatment failure cannot go back to a first line regimen as it will be ineffective.

The side-effect profile of the combination product is exactly the same as when the component drugs are taken separately.

Doctors are encouraged to initiate antiretroviral therapy with one of FDC products, but should not attempt to use one to try and simplify therapy if a patient is known to have already failed a first line regimen. However patients who are currently on a first line regimen using separate components and have a fully suppressed viral load can be safely changed to the combination product.

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Combination induction therapy for cryptococcal meningitis

Guidelines for the treatment of cryptococcal meningitis (CM) in the United States have for many years advised induction treatment with the combination of amphotericin B (AmB) plus flucytosine for 2 weeks. Until recently there was not robust evidence from a large clinical trial to support this recommendation. However, a recently published clinical trial conducted in Vietnam[1] demonstrated a statistically significant 39% reduction in 10-week mortality in those who received AmB + flucytosine for 2 weeks compared to those who received AmB monotherapy for 4 weeks (HR = 0.61, 95%CI = 0.39-0.97). Unfortunately, flucytosine is unavailable in SA currently although there are international advocacy efforts underway to increase accesses to this drug in developing countries[2].

In the absence of flucytosine, the recent Southern African HIV Clinicians Society cryptococcal meningitis guidelines[3] have recommended the following induction therapy for CM: AmB deoxycholate (1 mg/kg/day IV) plus fluconazole (800 mg PO daily) for the first two weeks. This advice on adding fluconazole during the induction phase (when flucytosine is unavailable) is in line with the 2011 WHO guidelines. Although the evidence for this combination is not as strong as for that with AmB + flucytosine, in the same Vietnam trial[1] there was a non-significant 29% reduction in 10-week mortality (HR = 0.71, 95%CI = 0.45 - 1.11) with AmB + fluconazole 800mg/day for 2 weeks versus AmB monotherapy for 4 weeks. The failure to demonstrate a significant survival benefit may have been related to the relatively small sample size of this trial (n=100 in each of these arms). Another trial in Thailand also showed a trend towards improved outcome with AmB + fluconazole 800mg/day induction treatment versus AmB alone[4].

In the absence of flucytosine, in line with WHO and SA HIV Clinicians Society guidelines, AfA recommends the induction treatment of CM should be AmB 1mg/kg/day plus fluconazole 800mg daily for 2 weeks.

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For more than 15 years, Aid for AIDS (AfA) was a business division of Medscheme along with other managed healthcare operations. However, over time, AfA was gradually positioned as a stand-alone business due to its strong brand and strong visibility in the healthcare industry and corporate business environment. Aid for AIDS Management (Pty) Ltd ("AfA") was subsequently restructured as a wholly owned separate legal entity within the AfroCentric Health Group. AfroCentric Health is also the holding company of Medscheme (Pty) Ltd. During the course of the current year, we have focused on repositioning AfA as a company that is completely patient-centric and caring. This is in line with our philosophy of ensuring that AfA-registered individuals lead longer and more productive lives. Our patient-centric focus is reflected not only in our value proposition and operational processes, but also in our new, recently launched brand. Our new brand reflects a warmer, more organic design and feel and was launched officially on the 18 August 2013 at the BHF conference in Cape Town. The new branding now appears on our stationary and all communication material, including this newsletter.

Isoniazid preventive therapy for people on ART

Many clinical trials in HIV-infected adults who are ART-naive have shown that isoniazid preventive therapy (IPT) significantly reduces the risk of tuberculosis, but only in people whose tuberculin skin test (TST) is positive (in the context of HIV infection a Mantoux of ≥5 mm induration is considered positive)[1]. A major limitation of IPT is that the duration of benefit with the standard 6 month regimen is lost after 1-2 years[2-4]. A large Botswana study compared the efficacy of 6 months with 36 months IPT. They found that the longer duration was considerably more effective[4]. The benefit was seen in only TST positive participants, which is in keeping with prior IPT studies. There was a dramatic reduction in tuberculosis of 92% among TST positive participants in the 36 month IPT arm. The prolonged IPT regimen was well tolerated, except in patients with negative TSTs who experienced an increased risk of mortality, which is difficult to explain as only one death was ascribed to hepatitis. The Department of Health is now recommending 36 months IPT in TST positives. Patients started on IPT should complete the course if ART is started before the IPT course is complete.

Until recently it was unclear if IPT would be safe and effective in patients on ART. A South African randomised controlled trial evaluating the effect of IPT in patients on ART has reported results at an international conference[5]. IPT for 12 months was compared with placebo. There was a 38% reduction in TB in the IPT arm, and IPT was well tolerated. Curiously, TST status did not predict response to IPT, unlike all the pre-ART IPT studies[6].

AfA's recommendations on IPT are summarised in the table. TST is available at private pathology laboratories. If the patient finds it difficult to return for reading the TST, a blood test for latent TB infection, QuantiFERON-TB Gold, can be done instead.

Tuberculin skin test	Positive	Negative	Not done
Pre-ART	36 months IPT	No IPT	No IPT*
On ART	36 months IPT	12 months IPT	12 months IPT

*WHO recommends 6 months IPT in this setting for resource-poor settings unable to do TST.

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Telephonic and Online Registration

Doctors may register new patients telephonically ***(between 09h00 and 16h00)*** via our toll-free line 0800 227 700
or
online by applying for a username and password via afa@afadm.co.za
Aid for AIDS staff will guide you through the process.

Doctors are also urged to register patients on AfA as early as possible so that they can access ART at the most appropriate time and obtain the maximum benefit from regular monitoring and treatment support.

An approach to weight loss in HIV-infected patients

While HIV itself causes weight loss this is usually gradual over many months or years (typically not more than 1 to 2 kg per month). When weight loss is more rapid then additional causes need to be considered and investigated. It is advisable to weigh patients at each visit as the patient's quantification of weight lost may be inaccurate.

There are several causes to consider:

- **Chronic diarrhoea**. This will be obvious from the history and should be investigated with stool investigations (special stains for *Isospora belli* and *Cryptosporidium*) and if negative then gastro-intestinal biopsies (duodenal biopsy likely has higher yield in this clinical scenario).
- **TB**. Investigations include sputum and extrapulmonary specimens for microscopy, MTB/RIF Xpert and TB culture, as well as chest X-ray and abdominal ultrasound.
- **Oesophageal candida** and other causes of oesophagitis such as CMV. Give empiric course of fluconazole if symptoms are suggestive. If no resolution of symptoms then gastroscopy.
- In patients with low CD4 counts (usually < 100 cells/mm^3) consider other **disseminated opportunistic infections such as MAC and deep fungal infections**. Examine for rash compatible with deep fungal infection and biopsy if present. Serum cryptococcal antigen and Myco-F-lytic blood culture are useful in investigation of such patients.
- **Malignancies**. Both AIDS-related (lymphoma, Kaposi's sarcoma and invasive cervical carcinoma) and non-AIDS related. Lymphoma is investigated using imaging to detect nodal or extranodal masses and biopsy of any suspicious nodes/lesions or bone marrow biopsy if cytopaenia present.
- **Major depression**. This is common in patients with HIV infection. Patients should be asked about mood symptoms, tearfulness, hopelessness and their appetite. Psychiatric referral and antidepressants may be indicated.
- **Lack of food**. Food insecurity with poor nutritional intake may be the cause or a contributor to weight loss.
- Other **non-HIV related causes** such as new onset diabetes and hyperthyroidism.
- **Stimulant abuse** may be an issue in certain risk groups.

In patients on ART there are additional issues to consider:

- **NRTI-related symptomatic hyperlactataemia/lactic acidosis**. This is most frequently due to d4T and ddI, but other NRTIs may cause it. Weight loss may be the first symptom with or without gastro-intestinal symptoms such as nausea, vomiting or abdominal pain. When suspected, serum lactate should be urgently tested.
- **NRTI-related lipoatrophy**. This may occur in association with hyperlactataemia or in isolation. The mechanism is mitochondrial toxicity in adipose tissue. Patients typically lose weight predominantly from the face, buttock and limbs. The drugs most implicated are d4T and AZT.
- Consider **virological failure** (with or without a new OI or TB) and check HIV viral load.
- **GI toxicity** (anorexia, nausea, diarrhoea) from ARVs.

When the patient is first assessed for weight loss laboratory tests to consider are:

1. **C-reactive protein (CRP)** (this is a non-specific test but if it is elevated > 10 mg/L then this suggests that the cause of weight loss is not HIV alone but that TB, an OI or a malignancy is likely the cause)
2. **TB work-up** as described above
3. **Serum lactate** if patient is on NRTI drugs
4. **HIV viral load** if patient on ART (to detect virological failure)
5. **FBC** to detect cytopaenia

Further investigations will be dictated by the individual patient's clinical condition and their CD4 count, and the clinician should consider the above differential diagnoses while investigating the patient.

World Health Organization raises the bar

On June 30th this year, the World Health Organization (WHO) launched the 2013 WHO Consolidated ARV guidelines. In addition to increasing emphasis on community-based testing, consolidation of services and continuity of care, and the use of viral load testing rather than CD4 count for monitoring of therapy, the bar is now raised for starting ART from CD4 counts of <350 cells/mm^3 to <500 cells/mm^3.

Although the priority remains to initiate individuals with CD4 counts <350, stage 3 or 4 disease, the earlier start for all individuals with CD4 counts <500 and HIV-infected individuals in serodiscordant relationships (treatment as prevention), heralds the next step in the management of HIV infection.

Any change in policy must be weighed up in terms of pros and cons. The benefit of starting earlier will be to hopefully impact further on the incidence of tuberculosis, particularly if coupled with isoniazid preventative therapy, to reduce HIV-driven pathology such as HIV-associated nephropathy (HIV-AN) or HIV-associated Neurocognitive Disorder (HAND), and potentially, to impact on the incidence of HIV-associated cancers i.e. lymphoma, cervical cancer and Kaposi's sarcoma. Other potential benefits could be reduction in non-AIDS defining cancers, and non-infectious comorbidities such as cardiovascular disease.

These are all important goals, yet the potential for harm also exists when starting patients on ART earlier. Adherence and the potential emergence of drug resistance, the spectre of adverse drug events and the cost to a middle-income country such as South Africa are all important considerations.

The AFA clinical committee recently debated the WHO guidelines and a decision was made to support the initiation of all patients who are ready to start ART at the higher CD4 count threshold. However, this change must be accompanied by strengthening of adherence counselling and continued support for patients who start ART to ensure good compliance.

World Health Organization 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Accessed on 20th August 2013 at http://www.who.int/hiv/topics/strategic_use_arv/en/