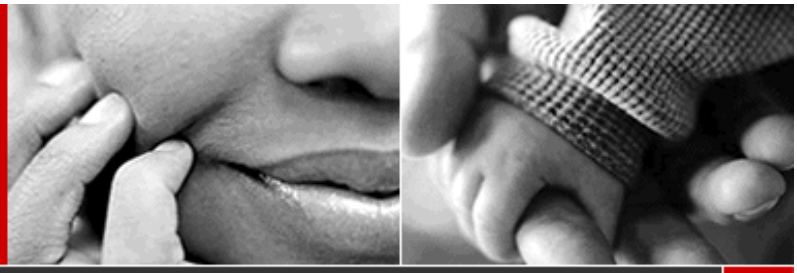

www.aidforaids.co.za

P.O. Box 38597, Pinelands, Cape Town, South Africa, 7430
Email: afa@afadm.co.za
Tel: 0800 227 700 or +27 (0)21 466 1700
Fax: 0800 600 773 or +27 (0)21 466 1744

Healthcare Professional Newsletter

June 2012 – Issue 32

National Department of Health Guidelines on the Management of Drug-resistant TB

Between 2004 and 2010, 45 196 cases of multidrug resistant (MDR) TB and 3 128 cases of extensively drug-resistant (XDR) TB were diagnosed in South Africa. MDR TB is defined as MTB resistant to both rifampicin and INH. XDR TB is MDR TB that has in addition acquired resistance to a fluoroquinolone and one of the second-line injectable drugs (kanamycin, amikacin or capreomycin). The majority of drug-resistant TB cases diagnosed in South Africa occur in people who are co-infected with HIV. It is now recognised that a substantial proportion of patients diagnosed with drug-resistant TB have not been treated for TB previously and have likely been infected or re-infected with a drug-resistant strain. The new Xpert-MTB/RIF assay for TB diagnosis is being rolled out in laboratories across South Africa. This assay is being used for TB diagnosis in first time treatment and retreatment cases. It also provides a reliable diagnosis of rifampicin resistance meaning that more patients are getting earlier access to rifampicin susceptibility testing. It is likely that this will lead to a greater proportion of MDR TB cases being detected than in the past.

Drug-resistant TB is more complex and costly to treat with more side effects and poorer outcomes than first line TB treatment. The NDoH has recently published updated drug-resistant TB management guidelines. A few key features of the guidelines for MDR treatment are:

- The intensive phase consists of 5 drugs (amikacin or kanamycin, moxifloxacin, ethionamide, cycloserine or terizidone, and PZA). Moxifloxacin has replaced ofloxacin in the MDR regimen. Moxifloxacin has been associated with better drug-resistant TB outcomes in observational studies.

- The intensive phase should be continued for 4 months after the date of collection of the first sputum that showed culture conversion (and a minimum of 6 months).

- The continuation phase should be started after completion of the intensive phase and continued for 18 months after the date of sputum culture conversion. It consists of 4 drugs (moxifloxacin, ethionamide, cycloserine or terizidone, and PZA).

- Treatment should be given at least 6 days a week.

- All patients with MDR and XDR who are HIV co-infected should be started on ART regardless of CD4 count.

Contributors:
Prof. Graeme Meintjes
Prof. Gary Maartens
Dr. Leon Regensberg
Dr. Helena Rabie
Prof. Mark Cotton
Dr. Leon Levin

This newsletter has been edited by:
Dr. Leon Regensberg
Liezl Dunn

medscheme

An XDR treatment regimen needs to be designed with expert consultation taking into account treatment history and drug-susceptibility results. Drugs that are included in XDR regimens include capreomycin, PAS and clofazamine, in addition to certain of the MDR drugs. XDR treatment outcomes are very poor. It is hoped that with new TB drugs soon to become available (such as delaminid and bedaquiline) the outcomes of patients with drug-resistant TB could be substantially improved in the future.

Issues for the HIV clinician to be aware of are the potential for nephrotoxicity from the injectables used in the intensive phase. It is advised that patients should be switched from tenofovir to an alternative ART agent while on the injectable and only be switched back to tenofovir after completing the injectable and provided the creatinine clearance is > 50 ml/min. Many of the drug-resistant TB drugs (especially terizidone and cycloserine) have neuropsychiatric side effects that overlap with efavirenz. They can also result in seizures. Peripheral neuropathy is a common side effect and HIV-infected patients are probably at heightened risk. All HIV-infected patients should receive prophylactic pyridoxine 150mg daily. Adherence counseling and psycho-social support are critical aspects of management.

Study of switching to atazanavir for lipodystrophy

Lipodystrophy is associated with the long term use of antiretroviral therapy (ART). Lipodystrophy consists of two separate abnormalities of fat distribution, fat loss (lipoatrophy) or fat accumulation. Some patients develop only one abnormality of fat distribution while others develop both lipoatrophy and fat accumulation. Lipoatrophy is caused by the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs), especially stavudine. Randomised controlled trials of switching to the non-thymidine NRTIs tenofovir and abacavir results in very gradual improvement of lipoatrophy.

There is a widespread belief that fat accumulation, especially visceral fat, is due to protease inhibitors (PIs) and is linked to the metabolic abnormalities associated with many PIs: dyslipidaemia and insulin resistance. Unlike older PIs like indinavir, atazanavir does not cause insulin resistance,[1] and is associated with less dyslipidaemia than lopinavir, even when it is boosted with ritonavir[2]. A randomised controlled trial has just been published evaluating the effect on fat distribution of switching to ritonavir-boosted atazanavir. Patients with suppressed viral loads on ritonavir-boosted PIs (mainly lopinavir) and abdominal adiposity (defined by high waist:hip ratios and increased waist circumference) were randomised to continue their PI or switch to atazanavir[3]. Rates of maintaining viral suppression was similar between the two arms. There were no significant difference by study arm in measures of central adiposity (changes in trunk fat, trunk:limb fat or visceral adipose tissue). Lipid abnormalities improved in the atazanavir arm, but measures of dysglycaemia and insulin resistance were similar by study arm. These results are similar to those of other switching studies, which have failed to show benefit for fat accumulation. There is no evidence to back up the practice of switching ARVs for fat gain, and this can result in harm by undermining patients' confidence or switching to less effective ARVs.

Lifestyle interventions are effective for fat gain on ART, but are difficult to achieve. Metformin has shown modest benefit when there is either dysglycaemia or features of the metabolic syndrome.

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Reporting Adverse Drug Reactions

An adverse drug reaction (ADR) is an unwanted or harmful reaction experienced following the administration of a drug (or combination of drugs), and is suspected to be related to the drug. The reaction may be a known side effect or it may be a new and previously unrecognised reaction.

While many ADRs are well documented, particularly with antiretroviral drugs and TB drugs, it is particularly important that all new suspected adverse reactions are reported, particularly if they are serious. Clinical trials have limited ability to identify unusual or delayed ADRs.

It is also particularly important to report ADRs to newly marketed products and reactions that are not clearly reflected in the relevant package insert.

An ADR Report Form which can be sent to the National Adverse Drug Event Monitoring Centre is attached to this newsletter. Advice can also be obtained from the Medicines Information Centre by calling 021 406 6829.

Healthcare providers should also assist patients to be aware of and record reactions to any medication used to treat HIV (including co-trimoxazole and TB drugs) as well so that they can pass on this information to other doctors. This can be by way of a treatment card or a medic-alert bracelet.

Tenofovir for children and adolescents

Tenofovir, a nucleotide reverse transcriptase inhibitor appropriate for once daily dosing and part of first-line therapy in older adults and adolescents, combined with a nucleoside reverse transcriptase inhibitor plus either a PI or NNRTI. It is preferably combined with emtricitabine, atazanavir or efavirenz that are also given daily. Tenofovir (like lamivudine) has excellent activity against hepatitis B infection.

The Food and Drug Administration (FDA) in the USA approved tenofovir in 2010 for children and adolescents above 12 years of age and 35kg in body weight. Recently, the FDA approved tenofovir for children over 2 years of age and weighing above10kg.
(http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM303009.pdf). Reduced dosage tablets (150 and 200mg) and a powder for children between 2 and 5 years of age were simultaneously approved in the USA. In South Africa, only the adult 300mg unscored tablet is available. Recommended daily dosage is 8mg per kg to a maximum of 300mg. These lower dose formulations are critical for accurate dosing in children and young adolescents.

Toxicity affecting proximal tubular renal function and reduced bone mineralisation are serious concerns. Proximal tubular dysfunction causes a partial or complete Fanconi syndrome with metabolic acidosis and increased phosphate loss, both of which contribute to bone demineralisation (BMD). Tenofovir also reduces calcitriol synthesis in proximal tubular mitochondria, contributing to bone demineralisation. (1) BMD decline begins after 12 to 24 weeks and has been noted up to 144 weeks on therapy. Children and young adolescents grow rapidly. Bone mineralisation should peak with the pubertal growth spurt. Young children, especially Tanner Stage 1 and 2, are at higher risk for decreased bone mineral density. Also, cumulative exposure to tenofovir is associated with increased risk of fractures in adults. (2) Post licensure reports indicate more renal toxicity than reported during the initial clinical studies. Adults with body mass below 60kg are most vulnerable to renal toxicity. (3)

How safe is tenofovir in children?

In utero exposure does not impair bone metabolism in young children. (4) In a prospective multi-centre study of children in Spain with median age 12.5 years and followed for a median of 77 months, a decrease in tubular phosphate absorption was documented in 28 of 38 patients, with 33 of 37 patients having proteinuria. (5) In contrast, Vigano found no renal impairment in 28 children followed for 60 months. (6) Bone toxicity is most common in smaller children. For example, in a series of 6 children receiving off-label tenofovir, 5 had decreased BMD. The smallest child, an 11 year old on the highest dose/m^2, experienced a 27% loss of BMD that fortunately reversed once the drug was removed. (7) A prospective study documented a mild reduction in estimated glomerular filtration in 37 of 38 adolescents on tenofovir. (8) Vigano et al documented good safety in 28 children followed for 60 months with regular monitoring. (6) Most authors agree that increasing the dosing accuracy is extremely important for reducing toxicity.

How effective is tenofovir in children?

A retrospective study of 159 highly experienced older children from the UK showed good efficacy, with 38% attaining virological suppression and 7.5% needing to discontinue due to serious adverse effects. (9) In a randomized study from Brazil, Della Negra and colleagues showed safety but no increased efficacy when tenofovir or placebo was given with optimized background therapy. This was ascribed to background resistance. (10) Note that the data used to license the drug in the youngest children has not yet been placed in the public domain.

What is the role for tenofovir in children and adolescents?

Currently, it is reserved for 2nd or 3rd line therapy in children over 12 years of age where options are limited by ARV resistance. There is also a place for tenofovir together with FTC or 3TC in patients co-infected with Hepatitis B. Although it can be used in first line therapy for older adolescents it requires regular monitoring.

What monitoring is necessary for children?

The following should be done at baseline, after 3 and 6 months & then yearly:

1. Creatinine clearance: (mL/min per 1.73 m^2):

A useful equation is the modified Counahan-Barratt formula: GFR = 40 X Height (cm)/Serum Creatinine (µmol/L) (www.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g4.htm). Alternatively, a web-based calculator can be used (Creatinine must then be converted to mg/dL) (www-users.med.cornell.edu/~spon/picu/calc/crclsch2.htm)

2. Serum phosphate (By extrapolation, a low serum phosphate implies concern for BMD)
3. Urinalysis for proteinuria or glycosuria
4. Dual–energy X-ray absorptiometry (DXA) should be performed at baseline and after a year for children below 12 years of age. The same machine should be used for repeat studies.

Drug Interactions of note: (http://www.gilead.com/pr_1650180)

- Tenofovir increases ddI concentrations. ddI is best avoided in children or adolescents, as there is no guidance if weight below 60kg. This combination has an inferior virological response especially with high viral loads. CD4 recovery is inferior even after viral suppression.
- Tenofovir decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with ritonavir and monitor for tenofovir toxicity.
- Lopinavir/ritonavir increases tenofovir concentrations. Monitor for tenofovir toxicity.

Acknowledgement

We thank Dr Christelle du Buisson, paediatric nephrologist for advice.

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