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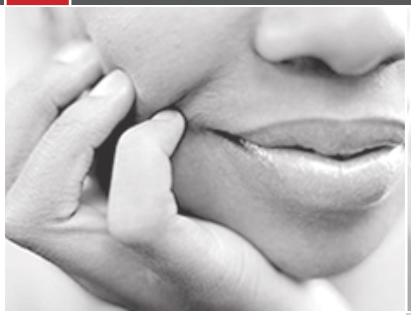

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ANTIRETROVIRALS AND THE LIVER

An important side effect of antiretroviral therapy (ART) is hepatotoxicity. Nucleoside Reverse Transcriptase Inhibitors (NRTIs),Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and protease inhibitors may all cause hepatotoxicity by different mechanisms. In a patient on ART who develops liver dysfunction it is also important to consider other causes for this apart from the ART.

Nevirapine causes symptomatic hepatitis in approximately 2% of patients. Asymptomatic elevations of LFTs are more common. This hepatitis is allergic hypersensitivity reaction and typically occurs within the first 3 months of starting the drug. It may be associated with a drug rash, fever and other systemic symptoms. Rarely, it may result in liver failure (0.1% of those on nevirapine). LFT derangement is predominantly a transaminitis. AfA recommends ALT monitoring at 2, 4, 8, 12 weeks then 3 monthly in patients started on nevirapine. Rash-associated hepatitis is more common in patients starting ART containing nevirapine with less advanced disease (CD4 > 250 in women and > 400 in men). Nevirapine should be avoided if the patient's baseline CD4 prior to ART is above these levels.

Efavirenz may also cause hepatitis, but is less common with clinical hepatitis occurring in about 0.5%. Hepatitis from efavirenz is not associated with rash.

The NRTIs, particularly stavudine and didanosine, may cause fatty liver. This results from mitochondrial toxicity which leads to triglyceride build up in the liver. The onset is insidious and seldom occurs before 6 months on ART. Longer exposure to NRTIs is associated with an increased risk of fatty liver. Clinically there is firm hepatomegaly and LFT derangement may be cholestatic, transaminitis or mixed. Fatty liver may cause fibrosis and cirrhosis, which has been best documented with didanosine. Fibrosis may partially reverse upon withdrawal of the drug.

Protease inhibitors may also result in hepatotoxicity. Ritonavir is the most hepatotoxic protease inhibitor High rates of hepatitis have been reported in patients on rifampicin who require additional ritonavir boosting (to 400mg bd) with lopinavir 400mg bd or saquinavir 400mg bd. These patients should have their ALT monitored at 2 weeks, 4 weeks then monthly while on such a combination. The pattern of LFT derangement is typically a transaminitis.

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The protease inhibitors atazanavir and indinavir may cause a drug-induced unconjugated hyperbilirubinaemaia, which is not associated with liver injury or elevation of liver enzymes. Only if the jaundice is cosmetically unacceptable does the drug need to be switched.

Other causes of liver dysfunction to consider are: acute viral hepatitis, flares of chronic hepatitis B or C, other drugs (especially co-trimoxazole, fluconazole and TB treatment), alcohol abuse, alternative remedies, TB granulomatous hepatitis and HIV cholangiopathy.

Between 5-20% of HIV-infected people in South Africa are co-infected with hepatitis B. There are several considerations in such patients when on ART. They may experience immune flares of hepatitis after starting ART due to IRIS. The NRTIs 3TC (or FTC) plus tenofovir should be part of their ART regimen (as these ART drugs also have anti-hepatitis B activity). It is very important NOT to stop these NRTIs with anti-hepatitis B activity as this may result in life threatening flares of hepatitis B. If they fail first line ART containing these NRTIs they should be continued in a second line ART regimen. AfA should be consulted about which drugs to include in a second line regimen in patients co-infected with hepatitis B – a resistance test would help decision-making in this setting.

In patients who develop hepatitis on ART, AfA recommends the following approach:

1) Consider and investigate for other causes listed above
2) If patient is asymptomatic and ALT < 200 continue ART and repeat within a week
3) If patient asymptomatic and ALT > 200, interrupt ART and other hepatotoxins until derangement resolves then re-introduce safer drugs
4) Any patient with symptoms of hepatitis (right upper quadrant pain, jaundice, nausea and vomiting) and ALT elevation even if less than 200 should have ART and other hepatotoxins interrupted.

ISONIAZID (INH) PROPHYLAXIS FOR HIV-INFECTED CHILDREN

Infants and children need repeated and careful evaluation for tuberculosis (TB) and TB exposure (i.e. contact with a source case) at each visit.

There are a number of difficulties in confirming TB in children:
- Infants and young children are unable to cough on demand
- They often have paucibacillary disease, so the smear is often negative
- The Tuberculin skin test is often negative either due to HIV-related immunosuppression or anergy to TB
- Chronic lung disease and abnormal chest radiographs occur commonly

INH prophylaxis was shown to be beneficial in South African HIV-infected children with a median age of 24 months without access to ARVs and in whom TB had been excluded.[1] Subsequently, INH prophylaxis was shown to be ineffective in both HIV-infected and HIV-exposed but HIV-uninfected South African infants when commenced between 3 and 4 months of age in a study where any TB exposure at baseline was excluded and where there was access to ART.[2, 3] Therefore routine INH prophylaxis for all HIV-infected children is not recommended by AfA.

INH prophylaxis is recommended for children who have been exposed to adults with infectious TB, usually sputum smear-positive pulmonary TB. Before giving INH prophylaxis it is extremely important to exclude active TB disease.[4] INH alone can cause resistance if used for TB disease. With the rising prevalence of drug resistance, INH will be ineffective if the source case has INH resistant disease. Under these circumstances, it is best to consult an expert.

INH shares hepatotoxicity with many ARVs and could impact negatively on adherence to ARVs. A pilot study is addressing the tolerability and safety of INH prophylaxis in children on ART is currently underway in Cape Town.

1. Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. Bmj 2007;334(7585):136.
2. Madhi SA, McSherry G, Violari A, et al. Lack of Efficacy of Primary Isoniazid (INH) Prophylaxis in Reducing Tuberculosis (TB) Free Survival in HIV-infected (HIV+) African Children. In: Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington DC: IDSA / ASM; 2008.
3. Mitchell C, McSherry G, Violari A, et al. Primary Isoniazid prophylaxis did not protect against tuberculosis or latent TB in HIV-exposed uninfected infants in South Africa. In: Congress of Retroviruses and Opportunistic Infection. Montreal; 2009.
4. World Health Organization. Guidance for national tuberculosis programs on the management of tuberculosis in children. Geneva; 2006.

ISONIAZID PREVENTIVE THERAPY FOR HIV-INFECTED HEALTHCARE WORKERS

HIV-infected healthcare workers in our region are at very high risk of developing tuberculosis. The best-studied regimen for tuberculosis preventive therapy is isoniazid (INH) for 6 months. It is essential to first exclude active tuberculosis before starting INH – a sputum culture for tuberculosis is recommended. Meta-analyses have shown that only patients with evidence of latent tuberculosis benefit from preventive therapy (in HIV infection this is defined as a Mantoux induration of 5 mm or more). However, there is no need to do a Mantoux test in HIV-infected healthcare workers before offering preventive therapy as it is reasonable to assume that all have been exposed to tuberculosis. Therefore all HIV-infected healthcare workers should be offered INH for 6 months, which should be given together with pyridoxine to reduce the risk of peripheral neuropathy. Retrospective studies suggest that INH preventive therapy provides additional benefit in preventing tuberculosis when taken before or together with antiretroviral therapy (ART), but there is no controlled data. Therefore INH should be commenced before ART is initiated.

What about healthcare workers who are continually exposed to tuberculosis? In some instances it may be possible to deploy them in areas where tuberculosis exposure is very unlikely. If this is not possible then INH is likely only to provide protection whilst it is being taken. A recent randomized controlled trial conducted by Neil Martinson & colleagues in Johannesburg evaluated several different regimens, including long term INH, for preventing tuberculosis in HIV infection. They found that long term INH was no more effective than INH for 6 months, but caused more serious toxicity. However, there was a benefit when they assessed outcomes in those patients who stayed on long term INH. Long term INH is a logical option for healthcare workers who have to remain in settings where tuberculosis exposure risk is high, provided they are counseled about toxicity and carefully followed up.

Reference:
Martinson N, Barnes G, Msandiwa R, et al. Novel Regimens for Treating Latent TB in HIV-infected Adults in South Africa: A Randomized Clinical Trial. Abstract #36bLB. 16th Conference on Retroviruses and Opportunistic Infections, Montreal, February 8-11, 2009

RISK FACTORS FOR NEPHROTOXICITY IN PATIENTS ON TENOFOVIR

Tenofovir has been associated with the development of renal dysfunction in 0-4% of patients on the drug, in cohort studies. This issue has been covered in a previous newsletter (June 2008).

A number of risk factors for tenofovir nephrotoxicity have been identified. The most important is baseline renal dysfunction. Hence AfA advises that a serum creatinine is checked in all patients considered for tenofovir and a creatinine clearance is calculated using either the Cockgraft-Gault or MDRD formula (many laboratories report this as the "e-GFR"). Patients with a calculated creatinine clearance less than 50 ml/min should not be started on tenofovir and an alternative drug should be used. We stress the importance of actually calculating the creatinine clearance, because many patients with a serum creatinine in the normal range actually do have impaired renal function that only becomes apparent when the creatinine clearance is calculated.

Other important risk factors that have been identified are:
- Concomitant or recent use of other nephrotoxic drugs (eg. NSAIDS, aminoglycosides, amphotericin B)
- Hypertension
- Medical co-morbidities

We advise against chronic NSAID use in patients on tenofovir. Renal function should be monitored closely in patients on tenofovir and amphotericin B. If patients require an aminoglycoside as part of their TB treatment (Regimen 2 or MDR treatment), tenofovir should preferably be avoided while they are receiving the aminoglycoside. Because of the association with medical co-morbidities, we suggest checking serum creatinine in any patient on tenofovir who develops an acute severe illness requiring hospital admission.

Furthermore a moderate association between tenofovir nephrotoxicity and use of protease inhibitors (PIs) has been found. This is likely due to the fact that PIs increase the plasma concentrations of tenofovir. We do not advise against using PIs with tenofovir, but clinicians should be aware of the higher risk of nephrotoxicity in these patients.

In patients on tenofovir, serum creatinine should be checked 1, 2, 3 and 6 months after starting and then 6 monthly.

Reference:
Clinical predictors of Tenofovir-associated nephrotoxicity in HIV-1-infected patients. Castellano, et al. Abstract WEAB0104, International AIDS Conference 2008.

ZIDOVUDINE (AZT) DOSE ADJUSTMENT FOR INFANTS

The recommended dose of AZT suspension for infants as part of prevention of mother to child transmission (PMTCT) is 4mg/kg/dose 12 hourly for 6 weeks.

We have been made aware that some healthcare providers are calculating the dose of AZT based on the birth weight and then giving the same dose for the full 6 weeks. The infant's weight at 6 weeks is of course very different from the birth weight and the child therefore may be under-dosed for much of the 6 week period.

For example, if a child weighs 2.8kg at birth and 4.6kg at 6 weeks the dose of AZT calculated at birth would be 1.1ml bd and by 6 weeks it should be 1.8ml bd.

Healthcare providers are therefore reminded that the dose of AZT should be increased during the 6 week period according to current weight, not birth weight. AfA recommends that the dose is adjusted for the infant's weight at 2 weeks and 4 weeks to ensure that the most effective PMTCT is provided.

PNEUMONIA IN PATIENTS WITH HIV INFECTION

Most medical schemes have noticed a steep increase in the incidence of pneumonia resulting in hospitalization, which has been attributed to the HIV epidemic. Bacterial pneumonia occurs more commonly in HIV-infected patients and becomes progressively more common with declining CD4 counts. Early diagnosis of HIV, together with co-trimoxazole prophylaxis and antiretroviral therapy, will reduce the incidence of pneumonia.

The attention of healthcare providers is drawn to the following statement by the Working Group of the South African Thoracic Society:

"Pneumonia, including infections with the common bacterial pathogens, is a common presenting symptom and is the AIDS-defining infection in a significant proportion of HIV seropositive patients. It is therefore recommended that HIV testing be offered to all patients with pneumonia"

S Afr Med J 2007; 97:1295

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