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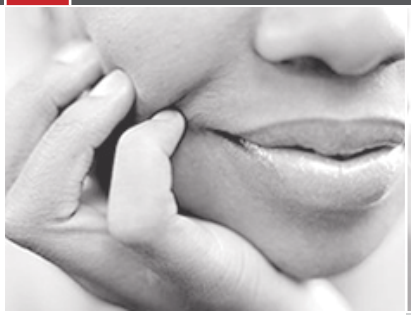

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HIV AND PANDEMIC INFLUENZA; LESSONS LEARNT AND WHAT TO EXPECT?

The 2009 South African influenza season was characterized by an unusual event, a biphasic peak in cases caused by the introduction of pandemic influenza A(H1N1)2009 virus into the population (figure 1). This superseded the seasonal epidemic caused by influenza A(H3N2) virus. Globally, pandemic influenza caused a generally mild upper respiratory tract illness in the majority of those with clinical disease. Moderate-severe disease was particularly prevalent in those with underlying comorbidity or pregnant women in the 3rd trimester of pregnancy. However, about 1/3 of patients admitted to intensive care units were previously healthy individuals. South Africa and the world held its collective breath in anticipation of what could have been a disastrous interaction between HIV and the pandemic influenza virus, as it was feared that HIV-induced immunosuppression would be a risk factor for severe disease with high mortality. Studies prior to 2009, during seasonal influenza epidemics had highlighted higher hospitalisation rates for HIV-infected patients, an increased risk of secondary bacterial infection, prolonged illness and increased mortality[1-3]. However, hospitalisation rates for HIV-infected patients were lower in the post-HAART era[2].

The true number of South African pandemic influenza patients in 2009 who were co-infected with HIV is unknown. Testing for the pandemic virus stopped once we shifted from surveillance of all initial cases, to focusing resources on monitoring and management of severe cases. Despite this, it became clear as the South African epidemic unfolded, that mortality in general was low and that HIV-infected patients were not overly represented in terms of hospitalisation and death. Of the 91 laboratory-confirmed pandemic influenza deaths in South Africa, 36 patients were HIV tested, 18 were found to be infected, 10 of whom were pregnant. Other co-morbidity included obesity, diabetes, active tuberculosis and chronic pulmonary disorders.

We can expect that the 2010 seasonal influenza epidemic will again be dominated by the pandemic influenza A(H1N1) virus. Whether there will be any change in virulence or clinical presentation is unknown, although the '2nd wave' of the epidemic during the northern hemisphere winter has not been characterised by a dramatic change. The current South African guidelines for the management of pandemic influenza include HIV-infected persons as a high risk group[4]. The guideline stresses the importance of early presentation for treatment, as neuraminidase inhibitors (NAIs), oseltamivir and zanamivir used to treat influenza have maximal effect if started within 48hours of symptoms.

HIV AND PANDEMIC INFLUENZA; LESSONS LEARNT AND WHAT TO EXPECT?

It is doubtful whether HIV patients with asymptomatic disease and CD4 counts > 200 cells/mL presenting with a mild influenza-like illness (ILI) after 48 hours would benefit from NAIs, although if they develop any clinical deterioration, treatment should be started as soon as possible. In contrast, although there is a lack of evidence, HIV-infected patients with advanced immunosuppression presenting with respiratory tract infection are advised that they should receive an NAI, independent of the duration of symptoms. This advice may change as more experience of treating co-infected patients accrues. It is also important to consider the differential diagnosis of respiratory symptoms in the HIV-infected patient and be alert for community acquired bacterial infections, Pneumocystis pneumonia and tuberculosis.

Preventing influenza infection centres around immunisation and basic infection control measures. The 2010 Southern hemisphere influenza vaccine will include pandemic influenza A(H1N1) as part of the triple formulation along with influenza A H3N2 and influenza B[5]. It is expected to be available from March 2010 in South Africa. All HIV-infected persons with CD4 counts of >100 cells/mL should receive annual influenza vaccine. Those with lower CD4 counts in whom vaccine response is likely to be sub-optimal, should ideally be vaccinated once the CD4 count improves on antiretroviral therapy. In addition, all HIV-infected pregnant women and children aged 5 months-5 years should be offered vaccination[5].

Good cough etiquette and hand hygiene are the cornerstone of effective infection prevention and control for influenza, should be taught to all patients. Those suspected of having influenza should be isolated at home until 24 hours after the resolution of symptoms, if they do not require hospital admission.

In summary, the 2009 influenza pandemic was characterized in the main by mild clinical disease, without the surge in moderate-severe cases that was predicted in HIV-infected patients. Annual influenza vaccination should be promoted and patients be advised to consult their doctor early, should influenza-like symptoms begin.

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Figure 1. Epidemic curve showing laboratory-confirmed cases of all pandemic influenza A(H1N1)2009 in South Africa[6]

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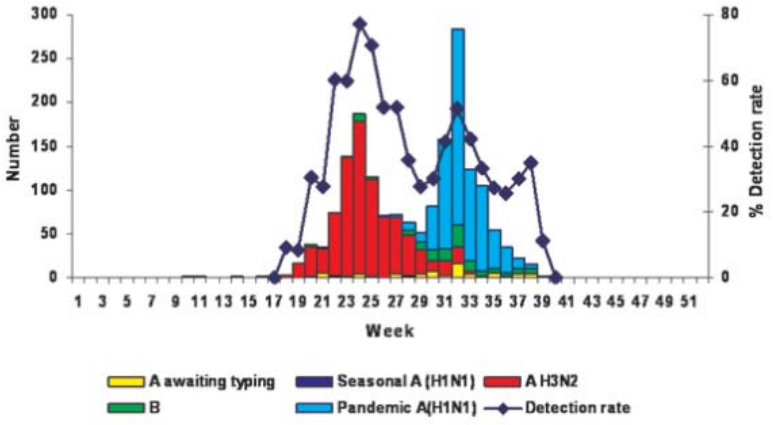

DIFFERENTIAL DIAGNOSES TO CONSIDER IN A PATIENT WITH SUSPECTED TB

In Southern Africa when patients with HIV and low CD4 counts present with one or more of recent weight loss, night sweats, fevers, deterioration in level of daily function and cough, TB is the most frequent diagnosis. The diagnostic work-up and indications for empiric TB treatment have been discussed in a previous newsletter (February 2008). However, in such cases the diagnosis is not always TB.

It is important to consider differentials during the diagnostic process and particularly when a patient who has been started on empiric TB treatment continues to deteriorate.

In patients who present with suspected pulmonary TB (cough, other TB symptoms and pulmonary infiltrate on chest radiograph) the important differential diagnoses to consider are:

- Bacterial pneumonia. If this is a consideration an appropriate broad-spectrum antibiotic should be prescribed.
- Pneumocystis pneumonia (PCP). Patients typically have marked tachypnoea, hypoxia at rest (or desaturate on exertion) and a bilateral groundglass infiltrate on chest radiograph. Investigations include bronchoscopy with lavage or induced sputum for direct fluorescence antigen test or silver stain.
- Pulmonary cryptococcosis. This is investigated with a fungal culture of sputum and serum cryptococcal antigen test.
- Infective exacerbation of bronchiectasis, which is a particular consideration in patients previously treated for TB who have post-TB bronchiectasis.
- Pulmonary Kaposi's sarcoma. Carefully examine the skin and oral cavity for KS lesions.
- Heart failure.

In patients with suspected disseminated TB, differential diagnoses to consider include:

- Disseminated non-tuberculous mycobacterial (NTM) infection. The most common is *Mycobacterium avium* complex (MAC) infection. This is mainly seen when CD4 < 50 and investigations include mycobacterial blood culture or bone marrow biopsy.
- Disseminated Kaposi's sarcoma (as above).
- Systemic fungal infections, particularly cryptococcosis and histoplasmosis. These may closely mimic disseminated TB. Some patients may have suggestive skin lesions and in the case of histoplasmosis oral ulcers. Investigations include fungal blood culture, biopsy of skin lesions and serum antigen test for cryptococcosis.
- If the patient has chronic diarrhoea consider chronic intestinal infections such as isospora, cryptosporidium, microsporidia, CMV or MAC. Submit stool for special stains and consider endoscopy and biopsy. CMV is typically seen in patients with CD4 < 50 and fundoscopy for CMV retinitis is important when the diagnosis is considered.
- If the patient is on D4T, ddI or AZT consider symptomatic hyperlactataemia as a cause for recent weight loss.
- Lymphoma. Diagnosis relies on tissue biopsy.

The differential diagnosis of a pleural effusion in an HIV-infected patient includes TB, bacterial empyema, Kaposi's sarcoma (often bloody) and primary effusion lymphoma.

Another consideration in patients started on empiric TB treatment who do not improve is MDR TB. Diagnosis obviously relies on TB drug susceptibility testing, hence the importance of sending samples for TB culture before a patient is started on empiric TB treatment.

USING NEVIRAPINE-BASED ART IN PATIENTS WITH TB

Rifampicin, which is a key component of TB therapy, is a potent inducer of enzymes involved in drug metabolism. Nevirapine is a substrate of one of these induced enzymes, the cytochrome P450 isoenzyme CYP3A4. Nevirapine plasma concentrations are reduced by about a third when it is used in patients on rifampicin-based TB therapy.[1] By contrast, efavirenz concentrations are little affected.[1] Although a number of small studies in patients with TB suggest that outcomes with nevirapine are as good as with efavirenz,[1] the largest cohort study to date (conducted in the MSF clinics in Khayelitsha, Cape Town) showed inferior outcomes with nevirapine.[2] Interestingly, in the Khayelitsha study patients who developed TB after starting nevirapine-based ART did not experience a higher risk of viral rebound. This suggests that the lead-in dose phase of nevirapine (200 mg daily for the first two weeks) might be the problem. Two pharmacokinetic studies in TB patients reported that the majority of patients had sub-therapeutic nevirapine concentrations during the lead-in dose phase.[3,4]

USING NEVIRAPINE-BASED ART IN PATIENTS WITH TB

When patients are switched to nevirapine from efavirenz the recommendation is to omit the lead-in dose phase as efavirenz induces CYP3A4. Omitting the nevirapine lead-in dose phase in this setting was not associated with an increased risk of adverse drug reactions in a large Cambodian cohort study.[5] Rifampicin is a much more potent inducer than efavirenz, therefore it is logical to also omit the lead-in dose when patients are started on nevirapine-based ART when they are already on TB therapy. The nevirapine lead-in dose phase is being omitted in the ongoing ANRS 12146 trial in Mozambique – preliminary safety data from this trial are reassuring.[6]

Efavirenz is the preferred non-nucleoside reverse transcriptase inhibitor to be used with TB therapy. When efavirenz is not tolerated or contraindicated (e.g. in early pregnancy) nevirapine should be used. The lead-in dose phase should be omitted. Some clinicians prefer to use double dose lopinavir/ritonavir when efavirenz is not tolerated or contraindicated in the mistaken view that this is safer than nevirapine. Adjusted dose protease inhibitors have in fact been associated with high risks of hepatotoxicity in healthy volunteers and there is minimal safety data in patients[1]. Patients who develop TB when on nevirapine-based ART should continue with the nevirapine.

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USE OF RITONAVIR (NORVIR®) AS A SINGLE PROTEASE INHIBITOR IN INFANTS AND CHILDREN

It has come to our attention that a number of infants and children are still on ritonavir syrup as a single protease inhibitor (PI) despite evidence that ritonavir-boosted lopinavir (Kaletra®, Aluvia®) has a much higher resistance barrier. Use of ritonavir on its own poses a significant risk of developing major PI mutations which depends on the duration of therapy and time failing while on the drug[1]. These mutations confer resistance to the newer PIs and make it very difficult to construct new ART combinations.

AfA strongly advise starting new paediatric patients who require a PI on ritonavir-boosted lopinavir (Kaletra®, Aluvia®) in preference to ritonavir on its own. Please note that a non-nucleoside reverse transcriptase inhibitor (NNRTI) may also be used as first-line therapy in infants and children provided neither the mother nor the infant received SD nevirapine as part of the PMTCT strategy and the mother has not failed an NNRTI combination. This approach may have benefits over starting with a PI.

Please contact our clinical department (toll-free) on 0800 227 700 to arrange switching any infants or children still on ritonavir syrup to an alternative protease inhibitor.

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DISCONTINUATION NOTICE: KALETRA® SOFT GEL CAPSULES

Aluvia® is a tablet formulation containing lopinavir 200mg and ritonavir 50mg per tablet. This tablet formulation is clinically equivalent to Kaletra® soft gel capsules. The benefits of Aluvia® over Kaletra® capsules include:

1. **Reduced pill burden.** The adult Aluvia® dose is 2 tablets twice a day.
2. **No food effect.** Aluvia® tablets may be taken with or without food.
3. **No refrigeration.** Aluvia® tablets may be stored at room temperature and do not need to be refrigerated before or after dispensing.

Abbott have decided that once current inventories of Kaletra® capsules are depleted, only Aluvia® film coated tablets will be available. Kaletra® oral solution will still be available.

Please note the following recommendations which have been prepared and distributed by the Paediatric Sub-Committee of the SA HIV Clinicians Society:

For paediatric patients it was hoped that Aluvia® Half Dose (HD) (100m g lopinavir / 25mg ritonavir) would take the place of Kaletra® capsules. Unfortunately Aluvia® HD has still not been registered by the Medicines Control Council. In the interim it is necessary to find an alternative to Kaletra® capsules for those children currently able to swallow Kaletra® capsules. The Kaletra® solution (80mg lopinavir/20mg Ritonavir per ml) has a very unpleasant taste and should only be used **as a last resort** in these children as it could lead to adherence problems.

The Paediatric Sub-Committee of the SA HIV Clinicians Society's recommendation is to use Aluvia® full strength tablets (200mg Lopinavir/50mg Ritonavir) according to the following table as an interim measure. Once the Aluvia® HD tablets are available, change to a more accurate dose using the Aluvia® HD tablets.

Body surface Area (m^2)	**Dose of Aluvia® Tablets (200mg lopinavir/50mg ritonavir)**
<0.5 or cannot swallow Aluvia Tablets	Use Kaletra® solution dosed at 300mg/m^2/dose bd
0.5-0.9 and can swallow Aluvia Tablets	1 tab bd
> 0.9 and can swallow Aluvia Tablets	2 tabs bd

Please ensure that you change all patients currently on Kaletra® capsules to Aluvia® tablets as soon as possible and provide them with a new prescription. Please also contact Aid for AIDS on 0800 227 700 so that the authorized treatment can be updated and claims are paid correctly.