Guideline

Treatment of tuberculosis in patients with HIV co-infection

Version 3.0

Queensland Government

Key critical points

- Co-infection with Tuberculosis (TB) and HIV is common in many parts of the world, especially sub-Saharan Africa, but uncommon in Australia.
- TB and HIV infection exacerbate the course of each other. Patients with HIV have an estimated 30 times the risk of developing active TB than those without HIV infection[1].
- All HIV patients should be assessed for the presence of active and latent TB.
- All TB patients should be screened for HIV.
- The main challenges related to management of TB/HIV co-infection are immune reconstitution, timing of initiation of antiretroviral treatment (ART) and drug interactions.

Background

One of the reasons for the increased prevalence of TB since the 1990's has been the emergence of the HIV pandemic. In sub-Saharan Africa, up to 80 per cent of TB patients are co-infected with HIV. Globally, an estimated 13 per cent of TB patients are co-infected with HIV[2]. In Papua New Guinea national TB/HIV co-infection rates are 9 per cent, while in Port Moresby they are significantly higher at 23 per cent[3].

Although TB /HIV co-infection is uncommon in Australia it is important that all TB patients are tested for HIV and that all newly diagnosed HIV patients are assessed for the presence of active and latent TB.

A patient with TB/HIV co-infection is ideally managed by a physician with experience in managing both conditions. Otherwise, close co-operation between the physicians managing the tuberculosis and HIV is essential. The Queensland TB Expert Advisory Group (TEAG) exists to offer advice to clinicians on the management of difficult TB cases, including those with TB/HIV co-infection.

Management

Timing of introduction of antiretroviral treatment

ART should be commenced in all TB patients with HIV, regardless of their CD4 count[1]. The potential benefits of early ART (less than four weeks after commencement of TB treatment) relate to the decreased likelihood of AIDS related morbidity and mortality through restoration of cell mediated immune function. The potential risks of early ART relate to:

- drug interactions
- drug toxicity with confusion as to culpable agents
- increased pill burden with diminished tolerability and compliance
- immune reconstitution inflammatory syndrome (IRIS).

A number of trials have sought to address the question of optimal timing of ART commencement in those with HIV/TB co-infection[4]. In general early commencement of ART, less than two weeks into TB treatment, is advised if CD4 + T cell count is < 50 cells/mm3. Early commencement of ART was associated with a reduced all-cause mortality in this group[5]. For those with CD4 counts > 50 cells/mm3, there is less evidence that introducing ART within eight weeks of commencing TB treatment changes mortality. Nevertheless, it is reasonable to introduce ART within four to eight weeks, once the clinician is satisfied that the TB regimen is being well tolerated and that compliance with HIV drugs is likely.

For patients with a CD4 count ≥50, and clinical disease of major severity (low albumin, low haemoglobin, low Karnofsky score, widespread disease, low BMI, or organ dysfunction), ART should commence within two to four weeks. For those HIV/TB co-infected patients with relatively preserved CD4 counts (> 200 cells/mm), ART is still recommended although commencement is less urgent and timing will be weighed against the risk and benefits.

All pregnant women should receive ART as soon as feasible regardless of CD4 + T cell count for the prevention of mother to child transmission, as well as for maternal health[5].

Duration of TB treatment

The principles of treating TB are the same for HIV infected and uninfected patients. Patients should receive at least six months of rifamycin based treatment. Some studies have shown a benefit in nine months of rifamycin based treatment over the standard six months[4]. In these studies, however, ART was not usually given concurrently with TB treatment which is now the standard of care. Interrupted treatment (for example, three times a week) has been associated with increased failure rates in those with HIV and should be avoided, particularly in the intensive phase. Increased rates of acquired rifamycin resistance occur in HIV-positive patients being treated for TB with weekly rifapentine-based regimens, or twice-weekly rifampicin or rifabutin-based regimens.

In summary, the TB regimen chosen will not be altered by HIV status unless drug interactions are anticipated. Some guidelines favour nine months in total of rifamycin based treatment although the benefits for this, over six months with concurrent ART, are likely to be modest.

Clinical and radiological response should be used to help determine the appropriate duration of therapy in a similar fashion to the non-HIV population. In a patient with fully sensitive pulmonary infection, who has a satisfactory clinical response to therapy, with smear and culture conversion at two months, it would be reasonable to aim for a shorter six month duration. On the other hand, significant cavitary disease, failure to smear and/or culture convert within the initial two months of therapy, a suboptimal clinical response, significant extrapulmonary involvement or multiple organ involvement/miliary infection, may prompt a longer duration of nine months therapy.

Immune reconstitution inflammatory syndrome

IRIS occurs as ART restores immune competence, causing increased immune response to tuberculosis bacilli or antigens. It may lead to unmasking of previously unrecognised TB soon after commencement of ART. Paradoxical IRIS involves worsening of TB clinical manifestations after a patient on TB treatment commences ART.

Examples of IRIS would include:

- an increase in the size of TB lymphadenopathy weeks or months into treatment
- the development of a pleural effusion in a patient with known pulmonary TB
- signs on non-communicating hydrocephalus in a patient with TB meningitis.

IRIS usually occurs in the first three months of ART and is associated with a decrease in viral load and an increase in CD4+ T cell count. It may be mild to severe, or even life-threatening. With the exception of IRIS related to TB meningitis, most cases are not serious and treatment is based on steroids with the continuation of TB and HIV drugs[4].

It is important not to attribute a change in condition to IRIS without ruling out other AIDS related infections or malignancies. Cryptococcus, CMV and Pneumocystis jirovecci are other pathogens which frequently co-infect patients with HIV and TB and need to be actively excluded.

Earlier initiation of ART in treatment-naïve patients is associated with a higher chance of IRIS, but this is rarely life-threatening, and earlier HIV treatment can reduce mortality and HIV progression.

Drug interactions in patients on antiretroviral therapy

The increase in the number of retroviral classes available means that clinicians have a greater range of options for selecting an ART regimen with fewer interactions with TB drugs.

The main source of drug interactions in the management of TB/HIV co-infection is through the effects of rifampicin inducing the cytochrome P450 system. There are now up-to-date websites covering all known interactions between FDA approved HIV drugs and other agents including tuberculosis drugs:

- www.hiv-druginteractions.org
- www.hivinsite.org

The most significant reactions between antimycobacterial and antiretroviral drugs occur with rifamycins inducing the metabolism of non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Rifampicin is a more potent inducer of the cytochrome P450 system than rifapentine, which in turn is more potent than rifabutin.

Despite potential drug interactions, rifamycin should be included in TB regimens, with dosage adjustment if necessary. Rifabutin is the preferred rifamycin.

Drug toxicity

Antiretrovirals and TB drugs share toxicities such as skin rashes, gastrointestinal intolerances, hepatotoxicity, peripheral neuropathy, and blood dyscrasias[6]. Treating clinicians should monitor for these side effects. One of the key reasons for delaying the introduction of ART is to allow time to monitor for side effects of TB drugs so as to minimise the uncertainty as to which agent is responsible for a possible adverse reaction.

Definition of terms

Term	Definition / Explanation / Details	Source
AIDS	Acquired Immune Deficiency Syndrome	HIV Foundation Queensland
ART	Antiretroviral	Queensland Health
CMV	Cytomegalovirus infection	Queensland Health
FDA	United States Food and Drug Administration	Food and Drug Administration
HIV	Human Immunodeficiency Virus	HIV foundation Queensland
IRIS	Immune Reconstitution Inflammatory Syndrome	Queensland Health
TB	Tuberculosis	Queensland Health
TEAG	Tuberculosis Expert Advisory Group	Queensland Health

Revision history

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References

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2. Naidoo K, Baxter C, Karim S. When to start antiretroviral therapy during tuberculosis treatment. Current Opinions Infectious Disease. 2013 Feb; 26(1):35-42

3. PEPFAR.Papua New Guinea Operational Plan Report FY 2013 http://www.pepfar.gov/documents/organization/222178.pdf

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