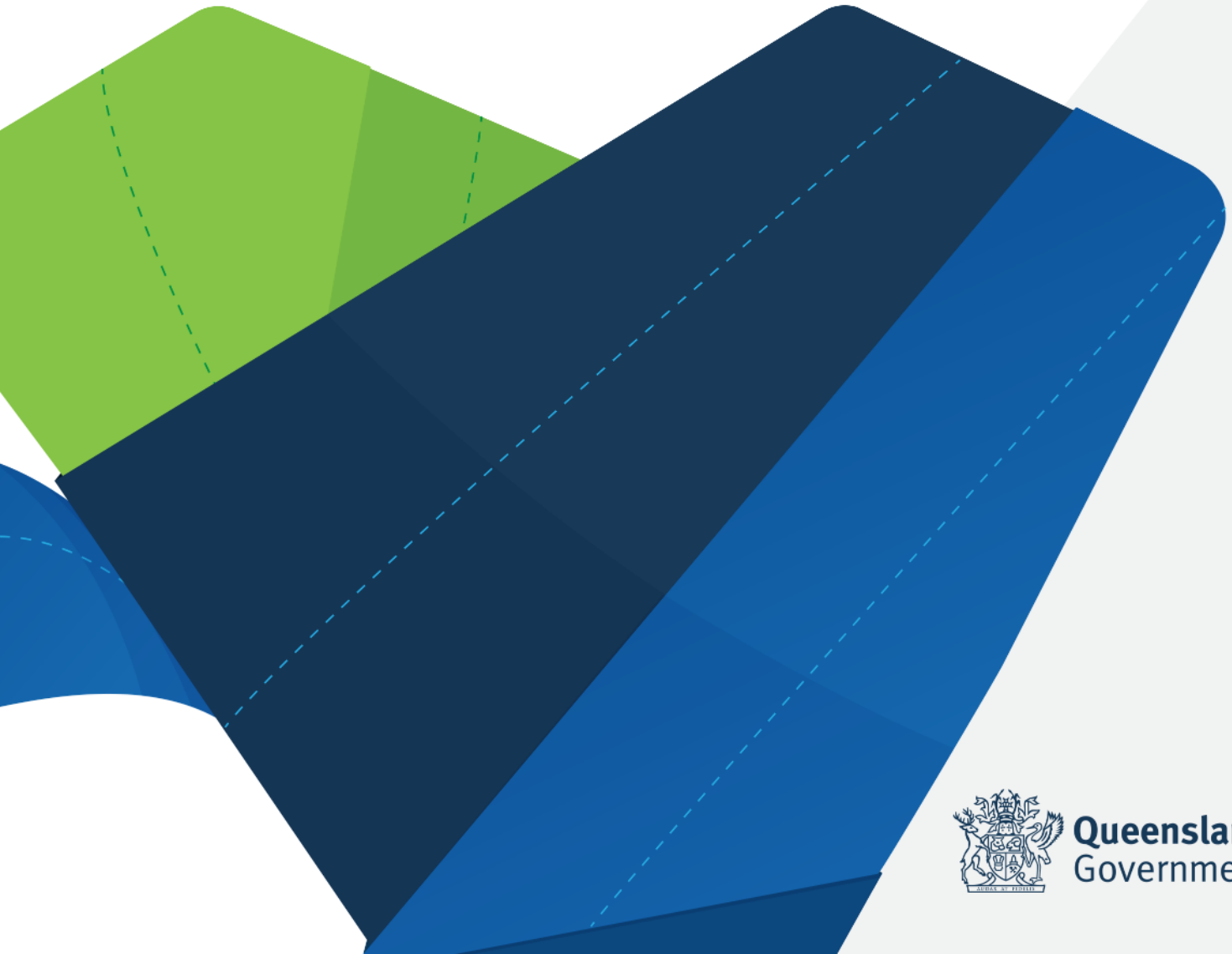
Treatment of tuberculosis in patients with HIV co-infection

Guideline, Version 4.0 July 2021



Queensland Government

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For more information contact:

Communicable Diseases Branch, Department of Health, Queensland Health, GPO Box 48, Brisbane QLD 4001,
email cdu@health.qld.gov.au, phone (07) 3328 9718.

An electronic version of this document is available at https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/diseases-infection/diseases/tuberculosis/guidance/guidelines

Note, updates after May 2021 are amended in the online version of Treatment of tuberculosis in adults and children ONLY — printed copies may not be current

Contents

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 the other disease. Patients with HIV have an estimated 30 times the risk of developing active TB than those without HIV infection.[1]
- All people diagnosed with HIV infection 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

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 TB 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)

ART should be commenced in all TB patients with HIV, regardless of their CD4 count.[1] The potential benefits of early ART (less than 4 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 adherence
- immune reconstitution inflammatory syndrome (IRIS).

A number of trials have sought to address the question of optimal timing of ART commencement in those with TB/HIV co-infection.[2,3] In general, early commencement of

ART, less than 2 weeks into TB treatment, is advised if CD4 + T cell count is < 50 cells/mm[3]. Early commencement of ART was associated with a reduced all-cause mortality in this group.[4] For those with CD4 counts > 50 cells/mm, there is less evidence that introducing ART within 8 weeks of commencing TB treatment changes mortality. Nevertheless, it is reasonable to introduce ART within 4 to 8 weeks, once the clinician is satisfied that the TB regimen is being well tolerated and that adherence 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 2 to 4 weeks. For those TB/HIV co-infected patients with relatively preserved CD4 counts (> 200 cells/mm), ART is still recommended and should not be delayed until completion of TB treatment.[5]

Immune reconstitution inflammatory syndrome (IRIS) in patients with TB involving the CNS may have serious clinical consequences. Deferral of commencement of ART two to eight weeks beyond commencement of anti-tuberculous therapy (and corticosteroid) is recommended, with a preference for just two weeks deferral for patients with CD4 T cell count < 50x10 cells/µl.[5]

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.[4]

TB patients with concurrent HIV/AIDS may have lower plasma levels of TB drugs requiring dose adjustment. Therapeutic drug monitoring for all first line and many second line TB drugs is available through Pathology Queensland and should be considered in those with failure to respond to therapy or severe disease.

TB infection involving the central nervous system

Consideration of adjunctive corticosteroids in treatment of TB infection involving the CNS for people living with HIV is important. The risk of death is reduced with co-administration of dexamethasone (dose 0.3 to 0.4 mg/kg/day for 2 to 4 weeks, then taper by 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg per week; total duration 12 weeks).[5]

Duration of TB treatment

The principles of treating TB are the same for HIV infected and uninfected patients. Patients should receive at least 6 months of rifamycin based treatment. Some studies have shown a benefit in 9 months of rifamycin based treatment over the standard 6 months.[3] In these studies, however, ART was not usually given concurrently with TB treatment which is now the standard of care. Intermittent regimens (for example, 3 times a week) have 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 9 months in total of rifamycin based

treatment although in the Australian setting the benefits for this, over 6 months with concurrent ART, are likely to be modest.[5]

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 drug susceptible pulmonary infection, who has a satisfactory clinical response to therapy, with smear and culture conversion at 2 months, it would be reasonable to aim for a shorter 6-month duration. Alternatively, significant cavitary disease, failure to smear and/or culture convert within the initial 2 months of therapy, a suboptimal clinical response, significant extrapulmonary involvement or multiple organ involvement/miliary infection, may prompt a longer duration of 9 to 12 months therapy.

Immune reconstitution inflammatory syndrome (IRIS)

IRIS occurs as ART restores immune competence, causing increased immune response to tuberculosis bacilli or antigens. It may lead to unmasking of previously unrecognized 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 of 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. IRIS can occur early (i.e. within weeks) with a rapid decline in viral load even before there is a substantive increase in CD4 + count. 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.[3]

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

ART selection in the setting of concomitant TB therapy can be guided by the U.S. Department of Health and Human Services (DHHS) guidelines. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/table-3-dosing-recommendations-anti-tb

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.

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Definition of terms

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

Revision history

Version number	Date of issue	Date of next revision	Approval date
1.0	June 2006	Rescinded	26 June 2006
2.0	February 2013	February 2015	03 April 2013
3.0	February 2015	February 2017	20 February 2015
4.0	May 2021	May 2023	?

Document custodian

Executive Director, Communicable Diseases Branch

Chief Health Officer and Deputy Director-General Prevention Division Queensland Health

Approving group

Tuberculosis Expert Advisory Group