Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection (SCAS, CHP, DH Nov 2020)

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CME / CNE / PEM point accreditation *(please refer to the attached test paper for the number of credit points awarded)*

Background

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and the leading cause from a single infectious agent. It is also the leading cause of death among people living with HIV (PLHIV), accounting for 30% of AIDS-related deaths. In 2018, TB caused an estimated 1.2 million deaths among HIV-negative people and an additional of 251,000 deaths among HIV-positive people. Among the 10.0 million (best estimate) new TB infections in 2018, 8.6% were PLHIV, with the heaviest burden in South-east Asian region and Africa. Twenty-three percent of the world's population (i.e. 1.7 billion) are estimated to have latent TB infection, and are thus at risk of developing active TB disease during their lifetime[1].

The emergence of multidrug-resistant TB (MDR-TB), including extensively drug resistant TB (XDR-TB), has also been linked to the HIV epidemic. Either biologically or clinically, HIV and TB reinforce each other. For instance, HIV increases the risk of TB disease by up to 100-fold, and this risk increases as immune deficiency worsens. Conversely, active TB is associated with an increased risk of opportunistic infections and rise in HIV viral load. TB disease in the presence of HIV may also produce atypical clinical features greatly complicating management.

In Hong Kong, extrapulmonary TB and, at CD4 count <200/μL, pulmonary TB and TB of cervical lymph node are AIDS-defining conditions. From 1985 to 2019, 504 (23.8%) of reported AIDS were defined primarily by TB. The incidence of TB has remained <100 per 100 000 populations since 2002 and Hong Kong is regarded to have a low TB disease incidence according to the World Health Organization (WHO) definition[2]. It is estimated that 1% of all TB disease in Hong Kong is associated with HIV, representing a relatively low incidence of HIV-TB coinfection. From 1996 to 2017, 9 (1.9%) cases with positive culture result had MDR-TB, a figure that is slightly higher than the MDR-TB rate of around 1% in general population. There is no XDR-TB cases detected among the reported TB-HIV cases so far[3].

Management of HIV-TB coinfection presents substantial challenges including its atypical presentation and diagnostic difficulties, shared toxicities of medications, timing of antiretroviral treatment (ART) initiation, treatment of concurrent opportunistic infections, drug-drug interactions, and immune reconstitution inflammatory syndrome (IRIS). Since 1995, this Committee and its predecessor, the Scientific Committee on AIDS of the Advisory Council on AIDS, have published on the prevention and treatment of TB in HIV disease[4]. This new update of its recommendations has been made necessary by new insights and findings in recent years, with adaptation to the local epidemiology of TB and HIV, particularly with regard to testing strategies and treatment options of latent TB infection (LTBI), diagnostic modalities, regimen and duration of treatment of TB disease, choice of antiretroviral regimen, drug-drug interactions and management of IRIS.

Testing strategies of latent TB infection

Successful management of LTBI, which serves as a reservoir for new tuberculosis cases, is an important component to achieving the goal of WHO's End Tuberculosis strategy. In high-income countries with a low incidence of tuberculosis, management of LTBI can reduce the risk of disease reactivation by 60% to 90%, and can contribute to elimination of the disease[5-6].

Based on the latest international recommendations and local study results, the following updated recommendations on testing strategies of latent TB infection are made[6-10]:

- All PLHIV should be tested for latent TB infection at baseline using either tuberculin skin test (TST) (with 5 mm of induration as the cut-off) or interferon-γ release assay (IGRA).
- Dual testing using both TST and IGRA can enhance detection of LTBI for those with CD4 count <100/μL.
- Testing should be repeated among those upon achieving immune reconstitution and virological suppression with antiretroviral treatment and then repeated as and when necessary, e.g. subsequent to virologic failure.
- While repeated testing might be excessive because of the generally low risk of TB reactivation and infection, re-screen should be offered to those with potential exposure, and regular screening be offered to those with potential ongoing exposure, e.g. among healthcare providers, and those whose household members have active pulmonary tuberculosis with suboptimal response to treatment.
- Those who are tested positive should be treated for LTBI after ruling out active TB disease.
- Treatment is indicated for PLHIV who have significant recent exposure to an infectious source of TB regardless of LTBI test results.

Treatment options of LTBI

Recommendations by WHO[6], The US Centers for Disease Control and Prevention (CDC)[11-13], British HIV Association (BHIVA)[14] and European AIDS Clinical Society (EACS)[15] are summarised in **Table 1**. In general, factors including drug-drug interactions, tolerability and treatment completion rates should be taken into consideration when devising the optimal treatment regimen for PLHIV.

Table 1: Recommendations of LTBI treatment options by different international guidelines

	ΨWHO[6]	CDC[11-13]	BHIVA[14]	EACS[15]
1) Isoniazid monotherapy 300mg daily (max) + pyridoxine	#6 or 9 months	§6 or 9 months	6 months	6-9 months (consider 9-month duration in high-prevalent TB countries)
2) Rifampicin 600mg daily (max)	4 months	4 months (alternative option: rifabutin)	--	4 months (alternative option: rifabutin) (check DDI between ARVs and non-ARVs)
3) Rifampicin 600mg daily + isoniazid 300mg daily + pyridoxine	3 months	3 months	3 months (check DDIs, substitute with rifabutin where effective ART necessitates the use of a PI/r)	3 months (check DDI between ARVs and non-ARVs)
4) Rifampicin 600mg + isoniazid 900mg 2x/week + pyridoxine	--	--	--	3 months (check DDI between ARVs and non-ARVs)
5) Rifapentine 900mg + isoniazid 900mg once weekly	3 months (i.e. 12 doses, under DOT)	3 months (i.e. 12 doses, under DOT or SAT)	--	3 months (check DDIs) *rifapentine not yet a/v in Europe
6) Rifapentine 600mg + isoniazid 300mg daily + pyridoxine	1 month (i.e. 28 doses) (Age ≥ 13 years)	--	--	4 weeks (check DDIs) *rifapentine not yet a/v in Europe

ΨIncluded options recommended for countries with a low TB incidence only
#Nine months in countries with a low TB incidence and a strong health infrastructure; 6 months' isoniazid is preferable to 9 months from the point of view of feasibility, resource requirements and acceptability to patients
§Analysis has found that 9 months of daily isoniazid therapy was perhaps more effective than 6 months but no clinical trial data was available to directly comparing 6 months and 9 months of isoniazid among HIV-positive persons.
DDI: drug-drug interaction; ARV: antiretroviral; PI/r: ritonavir-boosted protease inhibitor;
DOT: directly observed therapy; SAT: self-administered therapy

Based on the latest international guidelines and information on drug-drug interactions with newer ARVs, the following local recommendations on LTBI treatment options are made:

- Nine months of isoniazid 300mg daily (9H) with pyridoxine supplementation at 10-50mg daily remains the standard treatment in view of its minimal drug-drug interactions with most of the recommended antiretroviral regimens.
- Twelve doses of once-weekly isoniazid and rifapentine for three months (3HP), taken under observation, is an alternative option for those requiring shorter course, after checking for potential drug-drug interactions.
- Daily rifampicin for 4 months (4R), after checking for potential drug-drug interactions with antivirals, can be considered as an alternative especially when the source is suspected or confirmed to have isoniazid resistance.
- Fluoroquinolone-based regimen may be used when the source is MDR-TB. Expert opinion should be sought under these circumstances.

Clinical diagnosis

In HIV disease, TB may present atypically especially in those with a low CD4 count. Extra-pulmonary disease and a low bacillary load in respiratory specimen are more common in HIV co-infected patients. Extrapulmonary TB may manifest as lymphadenitis, disseminated disease, pleural or pericardial disease, meningitis and tuberculomas and rarely, with bacteraemia. Chest radiography may show lower lobe involvement or appear normal. TB in those with higher CD4 counts generally presents with more typical findings, similar to those in HIV-negative individuals.

A full medical evaluation for TB begins with history and physical examination. Clinical specimens should be obtained for microscopy, culture and drug-sensitivity testing +/- histology.

Molecular testing, Xpert MTB/RIF has been approved as initial diagnostic test for pulmonary TB, and on selected specimens for the diagnosis of extrapulmonary TB[16-17]. In smear-positive samples, the use of Xpert MTB/RIF can allow rapid confirmation of M. tuberculosis vs. non-tuberculous Mycobacterium species and identify rifampicin resistance, thus allowing earlier initiation of effective treatment and implementation of relevant infection control measures.

Treatment of TB disease

WHO has updated its guidelines for treatment of drug-susceptible tuberculosis in 2017 and the use of rifampicin-based regimen (2HRZE/4HR) for at least 6 months remains the recommended regimen for TB patients with HIV co-infection, while the 4-month fluoroquinolone-containing regimens should not be used[18].

Extending the treatment duration to a total of nine months of rifamycin-based regimen (2HRZE/7HR) is preferred as there has been debate on whether PLHIV are more prone to relapse than HIV-negative people. TB with CNS involvement should receive more prolonged therapy of up to 12 months.

In HIV co-infected patients, the use of intermittent therapy is not recommended as it is associated with a higher risk of treatment failure, disease relapse and acquired drug resistance[19]. Daily dosing remains the recommended dosing frequency. 'Directly observed treatment' (DOT) is recommended for the treatment of all TB patients, including those who are HIV co-infected[20-21].

Drug susceptibility tests against first line anti-TB drugs should be performed routinely to guide treatment, as drug resistance adversely impacts on prognosis and survival. Treatment of drug-resistant TB, especially MDR-TB is complex and should be undertaken in consultation with experts in the field[22].

Antiretroviral therapy for patients with HIV and active tuberculosis

Active TB disease requires prompt initiation of TB treatment. In PLHIV who are already receiving ART when TB is diagnosed, ART should be continued with attention to potential drug-drug interactions. The ARVs may need to be modified to permit use of the optimal TB treatment regimen (see **Table 2** for major drug-drug interactions). Close monitoring of tolerance and adherence are warranted given the additive toxicities associated with concomitant antiretroviral and anti-TB drug use.

Timing of ART initiation

Large randomised clinical trials have convincingly showed that early ART in those with CD4 count of <50 cells/μL significantly reduced AIDS events or deaths. Despite that adverse effects and IRIS were more common in patients initiating ART earlier than those whose treatment was deferred, these were infrequently associated with mortality[23-25]. It is recommended that the optimal timing of ART initiation relative to TB treatment is based on the CD4 count.

- for CD4 count < 50 cells/μL, ART should be started as soon as TB treatment is tolerated and whenever possible within 2 weeks, except in the case of TB meningitis where early initiation of ART does not confer survival benefit and is associated with more severe adverse events associated with central nervous system IRIS[26]. As such, close monitoring and consultation with experts are recommended when considering the timing of ART initiation for TB meningitis at CD4 count <50 cells/μL;
- for CD4 count ≥ 50 cells/μL, ART should be initiated as soon as possible, but can be deferred up to 8 weeks, especially when there are difficulties with drug interactions, adherence and toxicities.

Choice of antiretroviral regimen

The choice of antiretroviral regimen for patients requiring concomitant anti-TB treatment is made based on several factors including hepatitis B, pre-treatment HIV viral load, and most importantly, drug-drug interactions between ARVs, anti-TB drugs and other commonly used drugs for management of concurrent opportunistic infections, e.g. azoles and macrolides.

Antiretroviral therapy consisting of at least three drugs from two classes is recommended. Efavirenz (EFV)-based regimen with either TDF/FTC or TDF/3TC or ABC/3TC (ABC/3TC for those with viral load <100,000 copies/ml only and contraindicated if HLA-B*57:01 positive) as backbone in combination with rifampicin-containing TB treatment is preferred.

When EFV is not chosen due to resistance or intolerance, integrase inhibitor (INSTI)-based ART with raltegravir (RAL) or dolutegravir (DTG) can be considered as an alternative option. The dosage of RAL or DTG should be doubled to compensate for their drug-drug interaction with rifampicin. It is important to note that the dose of RAL 1200mg is not recommended for patients requiring TB treatment. Standard dose of DTG is required with rifabutin.

If a ritonavir-boosted protease inhibitor is included in the ART regimen, rifabutin should be used instead of rifampicin.

Tenofovir alafenamide (TAF), bictegravir (BIC) and doravarine (DOR) are contraindicated with rifampicin since their AUC have been shown to be significantly decreased if co-administered with rifampicin.

Drug-drug interactions

Drug-drug interactions (DDIs) between antiretroviral agents and anti-tuberculous drugs can result in detrimental clinical outcome and should be evaluated with care. The complexity of DDIs highlights the importance of taking a detailed drug history including treatment for other comorbidities, concurrent opportunistic infections and sometimes, cancer treatment, prior to treatment initiation for either TB or HIV. Consultations with HIV physicians, respiratory physicians and infectious disease physicians are required when encountering cases where resistance to first-line regimens for either infection is likely.

Physicians are recommended to use reliable prescribing resources, e.g. the section on drug-drug interactions of the DHHS guidelines for the use of antiretroviral agents in adults and adolescents with HIV, available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview; the Liverpool University HIV drug interactions website, available at www.hiv-druginteractions.org; and the Toronto General Hospital website, available at https://hivclinic.ca/drug-information/drug-interaction-tables/, which constantly update their database to screen for DDIs in all individuals with TB/HIV co-infection.

Table 2 highlights some of the major DDIs between ART and rifampicin/rifabutin that are of clinical importance.

Table 2. Major DDIs between ART and rifampicin/rifabutin (adapted from BHIV, DHHS and EACS guidelines[14,27,15])

ARV drug class	Specific ARVs	DDIs and recommended adjustment of dose of either or both drugs
NRTIs	TDF/FTC/3TC/ABC/AZT	RIF: standard dose of all drugs
		RFB: standard dose of all drugs
	TAF	RIF: not recommended
		RFB: not recommended
PI/r	ATV/r, DRV/r	RIF: contraindicated
		RFB: 150mg daily or 300mg thrice weekly; PI/r at standard dose
	LPV/r	RIF: not recommended, if needed, doubling the dose of LPV/r (i.e. 800mg/200mg BD)
		RFB: 150mg daily; LPV/r at standard dose (i.e. 400mg/100mg BD)
PI/c	DRV/c	RIF: contraindicated
		RFB: not recommended, if needed, rifabutin: 150mg daily; DRV/c at standard dose
NNRTIs	EFV	RIF: standard dose; EFV: 600mg daily
		RFB: 450mg daily; EFV: 600mg daily
	NVP	RIF: not recommended in ART naïve individuals; NVP: maintain at 200mg BD in stable patients
		RFB: 300mg daily; NVP: 200mg BD (use with caution)
	RPV	RIF: contraindicated
		RFB: contraindicated
	DOR	RIF: contraindicated
		RFB: 300mg daily; DOR: 100mg BD (use with caution)
INSTI	RAL	RIF: standard dose; RAL: 800mg BD (*use with caution in patients initiating ART with high initial viral loads due to risk of development of resistance)
		RFB: standard dose; RAL: 400mg BD
	DTG	RIF: standard dose; DTG: 50mg BD
		RFB: standard dose; DTG: 50mg daily
	EVG/c	RIF: contraindicated
		RFB: not recommended
	BIC	RIF: not recommended
		RFB: not recommended (no data available)
Others	MVC	RIF: standard dose; MVC: 600mg BD
		RFB: standard dose; MVC: 300mg BD in absence of a PI, 150mg BD in presence of a PI

*Standard dose of RIF refers to 600mg daily; standard dose of rifabutin refers to 300mg daily.

Immune reconstitution inflammatory syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is a clinical condition caused by the recovering immune system in response to ART driving an inflammatory reaction directed at the pathogen. It is further categorized into paradoxical IRIS and unmasking IRIS. In paradoxical IRIS, the symptoms paradoxically worsened during the course of a treated infection whereas in unmasking IRIS, there is a new presentation of a previously subclinical infection[26].

TB-associated IRIS has been reported in 8% to >40% of patients starting ART after TB is diagnosed. Predictors of IRIS include low baseline CD4 count of <50 cells/μL; higher on-ART CD4 counts; high pre-treatment and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and <30-day interval between initiation of TB and HIV treatments. Most IRIS in HIV/TB disease occurs ≤ 3 months of ART initiation[29].

In general, ART should be continued without interruption during IRIS unless life-threatening. Systemic steroid can be considered for treatment of symptomatic IRIS[30]. It can also be used as a preventive treatment to lower the incidence of tuberculosis-associated IRIS, especially in those with a CD4 nadir <100 cells/μL who have started TB treatment within 30 days, and who have had hepatitis B and Kaposi's sarcoma excluded[31].

Infection Control

Infection control measures for airborne diseases should be in place to prevent the spread of M. tuberculosis in health care setting. Early suspicion of TB should prompt placement in airborne isolation. Health care personnel should put on N95 mask when conducting high risk procedures. Aerosolization procedures such as pentamidine inhalation and sputum induction should be especially undertaken with care with strict observation of airborne precautions.

In general, respiratory isolation should not be terminated until after at least two weeks of effective treatment and the patient has clinically improved. The decision to discharge a patient with TB should be individualized based on treatment response, the extent of disease, the frequency of cough, circumstances of contact with household members, willingness to adhere to DOT and the likelihood of drug-resistant TB[32].

TB is a notifiable disease and should be promptly reported to the Centre for Health Protection. Besides, all TB patients should be screened for HIV infection.

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Test paper - Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection (SCAS, CHP, DH Nov 2020)

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#

CME point / CNE point: 1 / PEM point: 0 (Midwifery related)

- Please choose the best option.
- Answer these on the answer sheet and make submission by fax to Special Preventive Programme, Department of Health.

 # Please contact respective authorities directly for CME/CPD accreditation if it is not on listed below.

Accreditors	CME Point
Department of Health / HKMA/ HKAM / HKDU *(for practising doctors who are not taking CME programme for specialists)*	1
Anaesthesiologists	1
Community Medicine	1
Dental Surgeons	1
Emergency Medicine	1
Family Physicians	1
Obstetricians and Gynaecologists	Pending
Ophthalmologists	1
Orthopaedic Surgeons	1
Otorhinolaryngologists	1
Paediatricians	1
Pathologists	1
Physicians	1
Psychiatrists	1
Radiologists	1
Surgeons	1

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1. Which of the following is not true regarding clinical diagnosis of TB in HIV patients?

   a. Negative AFB smear or culture is not uncommon in HIV/TB coinfected patients especially in those with a low CD4 count
   b. Xpert MTB/RIF assay can only be used as a diagnostic test on respiratory samples
   c. AFB smear in sputum can be non-tuberculosis Mycobacterium
   d. Antibiotic sensitivity testing has to be done as a routine in culture positive case
   e. None of the above

2. Which of the following is not true regarding treatment in HIV/TB disease?

   a. Use of Biktarvy (BIC) is contraindicated with rifampicin as it has been shown to reduce the AUC of Biktarvy (BIC)
   b. A standard dose of Dolutegravir (DTG) is recommended in rifabutin-based regimen
   c. Efavirenz (EFV) should be doubled from 600mg daily to 1200mg daily when given with rifampicin
   d. The once daily dosing of Raltegravir (RAL) 1200mg daily is not recommended for HIV patients requiring TB treatment
   e. None of the above

3. Which of the following is not true about the drug-drug interaction of anti-TB and antiretroviral treatment?

   a. Rifabutin should be used instead of rifampicin if a ritonavir-boosted protease inhibitor (PI) is considered
   b. Tenofovir alafenamide (TAF) has been shown to have minimal drug-drug interaction with rifampicin and thus is recommended as a first-line option of antiretrovirals for HIV/TB coinfected patients
   c. The dosage of Dolutegravir(DTG) has to be doubled from 50mg daily to 50mg BD with a rifampicin containing regimen
   d. Rifampicin is contraindicated in patients on protease-inhibitor (PI) based regimen as it can significantly decrease the PI concentration
   e. None of the above

4. Which of the following(s) is/are true about the initiation of antiretrovirals in patients coinfected with TB?

   I. For patients with CD4 count ≥ 50 cells/μL, antiretrovirals should be started as soon as possible but can be deferred up to 8 weeks
   II. For patients with CD4 count ≤ 50 cells/μL and in the presence of TB meningitis, antiretrovirals should be started as soon as possible within 2 weeks
   III. In patients who are already started on antiretrovirals when TB is diagnosed, ART should be continued without the need of modification
   IV. Adverse effects and IRIS were more common in patients with deferred initiation of ART
   V. The optimal timing of ART initiation relative to TB treatment is based on both CD4 count and the HIV viral load.

   a. I only
   b. I and III
   c. II and III
   d. I, III and IV
   e. I, III and V

5. Which of the following is not true about the epidemiology of TB-HIV coinfection?

   a. In Hong Kong, extrapulmonary TB and, at CD4 count <200/μL, pulmonary TB and TB of cervical lymph nodes are AIDS-defining conditions
   b. Hong Kong is regarded to have low TB disease incidence according to the World Health Organization (WHO) definition
   c. It is estimated that 1% of all TB disease in Hong Kong is associated with HIV
   d. Worldwide, TB is a leading cause of death in people living with HIV
   e. None of the above

6. Which of the following is not true about immune reconstitution inflammatory syndrome (IRIS) in TB-HIV coinfection?

   a. Antiretrovirals should be continued without interruption during IRIS unless life-threatening
   b. IRIS in TB-HIV coinfected patients are frequently associated with mortality
   c. Most IRIS in HIV/TB disease occurs within 3 months of ART initiation
   d. IRIS is more commonly seen in patient with low baseline CD4 count that has risen at a fast rate with antiretroviral treatment
   e. Prednisolone has been shown to lower the incidence of tuberculosis-associated IRIS when given to patients with a very low CD4 count

7. Which of the following(s) is/are true about the treatment of TB-HIV coinfection?

   I. More prolonged anti-TB treatment e.g. up to twelve months is recommended for patients with CNS involvement
   II. Rifamycin should be included in the anti-TB regimen as far as possible
   III. 4-months fluoroquinolone- containing regimens is an acceptable treatment option for HIV/TB disease
   IV. Daily dosing remains the recommended dosing frequency in coinfected patients
   V. Directly observed treatment (DOT) is not recommended for the treatment of TB in those who are HIV co-infected

   a. I and II
   b. I and III
   c. I, II and IV
   d. II, IV and V
   e. I, II and IV and V

8. Which of the following(s) is/are true about the screening of latent TB infection (LTBI) in PLWH?

   I. A positive tuberculin skin test result should be confirmed by interferon-ɣ release assay (IGRA)
   II. A baseline LTBI testing should be offered to all PLWH
   III. A cut-off at 10mm of induration is diagnostic of LTBI in PLWH
   IV. Testing should be repeated for those who have achieved immune reconstitution and virological suppression with antiretroviral treatment and be offered again for those with potential ongoing exposure
   V. There is no ground for regular screening of LTBI for PLWH

   a. I and II
   b. II and III
   c. II, III and IV
   d. II and IV
   e. II, IV and V

9. Which of the following is not true about the interaction between HIV and TB in coinfection?

    a. Active TB disease is associated with an increased risk of opportunistic infections in PLWH
    b. In HIV, TB may present atypically
    c. HIV increases the life-time risk of TB disease by up to 100-fold
    d. Globally, the emergence of multi-drug resistant (MDR-TB) and extensively drug resistant TB (XDR-TB) has been linked to HIV epidemics
    e. None of the above

10. Which of the following is not true regarding the treatment of latent TB infection (LTBI) in HIV patients?

    a. Nine months of isoniazid 300mg daily with pyridoxine supplementation remains the standard treatment
    b. Twelve doses of once-weekly isoniazid and rifapentine for three months (3HP) is an alternative option for those requiring shorter course of treatment
    c. Treatment is not required for PLWH with a negative LTBI test result despite a significant recent exposure to an infectious source of TB
    d. Active TB disease should be excluded before initiation of LTBI treatment
    e. None of the above