Scientific Committee on AIDS and STI

Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

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].

2. 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.

3.	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].

4.	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.

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Testing strategies of latent TB infection

5.   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 which aims to substantially reduce tuberculosis incidence by 90% and mortality by 95% by 2035 compared with the 2015 baselines.   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.   WHO, in its updated guidelines on management of LTBI, suggested a wide array of factors to be considered when developing local guidelines for LTBI management, including the probability of progression to active TB disease in specific population risk groups, the local epidemiology and burden of TB, the availability of resources, the health infrastructure and the likelihood of a broad public health impact etc[2,6].   With regard to the testing modalities, either a tuberculin skin test (TST) or interferon-γ release assay (IGRA) can be used in the HIV infected population.   Both tests are known to have poor concordance of results when used among PLHIV[7].   The same findings had been demonstrated in a local cohort study which showed low agreement between the two diagnostic tests and high within-subject test variability[8].

7.   While LTBI testing has been offered annually to PLHIV in some services, no clear role of its effectiveness and cost-effectiveness have been demonstrated, especially for those with good immunological responses on ART and in places where the risk of TB infection is low.   A local longitudinal study on LTBI screening and its association with TB incidence in PLHIV found significant association between active TB disease development and baseline, rather than subsequent, positive LTBI testing results[9].   Repeated testing might, therefore, be excessive because of the generally low risk of TB reactivation and infection.   The same cohort study used a decision analytical model to evaluate the LTBI testing strategies for HIV-positive individuals in Hong Kong and suggested a less intense subsequent LTBI testing strategy, with either risk-based testing or a limited number of yearly tests to lower cost and increase QALYG. The study also recommended optimising the coverage of baseline LTBI testing and treatment to achieve the best health outcomes with maximum cost-

effectiveness[10].

8.   Based on the latest international recommendations and local study results, the following updated recommendations on testing strategies of latent TB infection are made:

- Baseline testing of LTBI using either tuberculin skin test (TST) (with 5 mm of induration as the cutoff) or interferon-γ release assay (IGRA) are recommended for all PLHIV.
- Dual testing using both TST and IGRA, if employed, can enhance case finding for those with CD4 count <100/μL. As such, blood should be drawn for IGRA before or on the same day as the TST to avoid potential interference of result.
- Testing should be repeated among those without additional risk factors for TB upon achieving immune reconstitution and virological suppression with antiretroviral treatment and then repeated as and when necessary, e.g. subsequent to virologic failure.
- Re-screen should be offered to those with potential exposure, while regular screening should 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 for LTBI should be screened for active TB disease according to a clinical algorithm. They should be treated for LTBI after ruling out active TB disease to achieve the best health outcomes.
- 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

9.　　Recommendations by WHO, The US Centers for Disease Control and Prevention (CDC), British HIV Association (BHIVA) and European AIDS Clinical Society (EACS) are summarised in **Table 1**. The use of twelve doses of once-weekly isoniazid and rifapentine for three months (3HP regimen) by directly observed therapy (DOT) for treatment of LTBI in adults was first recommended by the US CDC in 2011[11]. The recommendation was extended to cover PLHIV who are on ART with acceptable drug-drug interactions with rifapentine in 2018[12]. In 2020, CDC issued its updated LTBI treatment guidelines to include three rifamycin-based preferred regimens and two alternative monotherapy regimens with daily isoniazid[13]. An ultra-short treatment option using 1 month of daily isoniazid and rifapentine (1HP) has been evaluated in the BRIEF-TB ACTG study and found that 1HP was non-inferior to 9 months of isoniazid monotherapy among adolescents and adults living with HIV[14]. This short-course regimen has recently been recommended by the WHO as an alternative TB preventive treatment option subject to specific conditions[6]. It has not yet been addressed, on the other hand, in the latest CDC guideline and further studies evaluating its efficacy are under way. 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

	[Ψ]WHO[6]	CDC[12,13]	BHIVA[15]	EACS[16]
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

[Ψ]Included 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

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10.   Based on the latest international guidelines and information on drug-drug interactions with newer ARVs, the following 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. 3HP, when given under DOT, has been shown to be as effective as isoniazid monotherapy, but with lower risk of adverse events and higher completion rates. Administration of rifapentine is safe and well-tolerated with efavirenz-based or raltegravir-based antiretroviral regimen, contraindicated with protease inhibitors, nevirapine, rilpivirine, doravirine, elvitegravir- and bictegravir-based regimen, while more information is required to recommend its use with dolutegravir-based regimen.

- Daily rifampicin for 4 months offers potential advantage of shorter duration and can be considered as an alternative, after checking for potential drug-drug interactions with specific antiretrovirals. It can be considered when the source is suspected or confirmed to have isoniazid resistance.

- Rifampicin can be substituted with rifabutin where effective ART necessitates the use of ritonavir-boosted protease inhibitors.

- Select drugs according to the drug sensitivity profile of the source case for drug-resistant TB contacts. Fluoroquinolone-based regimen may be used when the source is MDR-TB without additional bacillary resistance to fluoroquinolones. Expert opinion should be sought under these circumstances.

Clinical diagnosis

11.   In HIV disease, TB may present atypically, especially in those with a low CD4 count. The more common presentation of extra-pulmonary disease and low bacillary load in respiratory specimen has posed diagnostic challenges in HIV co-infected patients. Extrapulmonary TB takes the form of lymphadenitis, disseminated disease, pleural or pericardial disease, meningitis and tuberculomas and rarely, with bacteraemia. Chest radiography may show more frequent involvement of the lower lobes, or appear normal. On the other hand, TB in those with higher CD4 counts generally presents with more typical findings, similar to those in HIV-negative individuals.

12.   A full medical evaluation for TB begins with history and physical examination. Subsequent investigations will be guided by the presentation and should include obtaining clinical specimens for microbiological and histological investigations and performing relevant radiological workup. In 2010, WHO has endorsed the Xpert MTB/RIF assay for initial diagnostic testing of individuals suspected of multidrug-resistant tuberculosis or HIV-associated tuberculosis[17]. And in 2013, the recommendation was expanded to include the use of Xpert MTB/RIF as the initial diagnostic test in all individuals presumed to have pulmonary TB, and on selected specimens for the diagnosis of extrapulmonary TB[18]. The diagnostic accuracy of Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance has been assessed in Cochrane systematic reviews with a pooled sensitivity of 81% in HIV-positive patients independent of sputum smear status, and pooled specificity of 98%. Performance characteristics for rifampicin resistance were of 96% sensitivity and 98% specificity[19].

13.   Thus, molecular testing, e.g. Xpert MTB/RIF, on respiratory samples (sputum, induced sputum or bronchoalveolar lavage) and other non-respiratory specimen in case of extra-pulmonary TB can be used in conjunction with microscopy, culture and drug-sensitivity testing +/- histology as appropriate to improve the diagnostic yield and for identification of rifampicin resistance. In smear-positive samples, its use can allow rapid confirmation of M. tuberculosis vs. non-tuberculous Mycobacterium species, thus allowing earlier initiation of effective treatment and implementation of relevant infection control measures.

Regimen and duration of treatment of TB disease

14.   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[20]. It is recommended that where effective ART necessitates the use of a boosted protease inhibitor, rifampicin is substituted with rifabutin.

15.   Although international guidelines mostly recommended six months of tuberculosis treatment, debate exists as to whether PLHIV are more prone to relapse than HIV-negative people. Thus, extending the treatment duration to a total of nine months of rifamycin-based regimen is preferred (2HRZE/7HR). TB with CNS involvement should receive more prolonged therapy of up to 12 months. Recommendations on treatment duration of TB in PLHIV by different international guidelines are summarised in **Table 2**.

16.   Twice and thrice-weekly dosing is associated with a higher risk of treatment failure, disease relapse and acquired drug resistance in both drug-susceptible disease and when the strain susceptibility was unknown[21]. Thus, in HIV co-infected patients, the use of intermittent therapy is not recommended in both intensive and continuation phases and daily dosing remains the recommended dosing frequency[22,23].

17.   'Directly observed treatment' (DOT) should be recommended for the treatment of all TB patients, including those who are HIV co-infected. This is also the standard practice of the TB and Chest Service of the Centre for Health Protection. It is conducted as a comprehensive package incorporating education, enablers, and holistic care which is conducive to treatment adherence.

18.   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[24].

Table 2. Recommendations on treatment duration of TB in PLHIV by different international guidelines

	WHO[20]	CDC[23]	BHIV[15]	EACS[16]
Pulmonary, drug-susceptible TB	At least 6 months	6 months; 9 months for those who do not receive ART during TB treatment or if positive culture at 8 weeks of TB treatment	6 months	6 months; extend to 9 months if positive culture at 8 weeks of TB treatment
TB with CNS involvement or disseminated TB	--	9-12 months	12 months	9-12 months
Extrapulmonary TB with bone/joint involvement	--	--	--	9 months
Extrapulmonary TB in other sites	--	--	--	6-9 months

Antiretroviral therapy for patients with HIV and active tuberculosis

19.   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 3** 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

20.   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[25-27]. Therefore, when TB is diagnosed in a patient not yet receiving ART, synthesis of these data has led to the recommendation that the optimal timing of ART initiation relative to TB treatment be 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[28]. 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

21.   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.

22.   It is recommended that the antiretroviral therapy should consist of at least three drugs from two classes. Efavirenz (EFV)-based and raltegravir (RAL)-based regimen with two NRTIs are recommended options in all three guidelines published by BHIVA[15], DHHS[29] and EACS[16].

23.   Based on proven clinical effectiveness, and susceptibilities permitting, efavirenz-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.

24.	When EFV is not chosen due to resistance or intolerance, integrase inhibitor (INSTI)-based ART with raltegravir (RAL) or dolutegravir (DTG) has been assessed as an alternative to EFV-based regimen for treatment of patients co-infected with HIV and TB. Pharmacokinetic analyses showed that using a double dose of RAL or DTG compensates for their drug-drug interaction with rifampicin. The Phase 3 REFLAT TB2 trial compared ARV regimens including standard dose of RAL 400mg twice daily or EFV 600mg once daily and showed that RAL 400mg twice daily did not demonstrate non-inferiority to EFV 600mg daily[30]. Thus, when RAL is used, a dosage of 800mg twice daily is preferred over 400mg twice daily with a rifampicin-containing TB regimen. Toxicities and tolerability should be monitored and therapeutic drug monitoring can be considered. It is also important to note that due to scarcity of data, the dose of RAL 1200mg is not recommended for patients requiring TB treatment. If a DTG-based regimen is considered, doubling the dosage from 50mg daily to 50mg twice daily is needed with a rifampicin-containing regimen whereas standard dose is required with rifabutin (see next session on *Drug-drug interactions*).

25.	Where effective ART necessitates the use of ritonavir-boosted protease inhibitors, rifabutin should be used instead of rifampicin. If rifabutin is not available, a double-dose lopinavir/ritonavir-based regimen with rifampicin can be used for those who are virologically suppressed at the time of tuberculosis[23].

26.	Newer ARVs like tenofovir alafenamide (TAF), bictegravir (BIC) and doravarine (DOR) are contraindicated with rifampicin since their AUC is decreased by 55%, 75% and 82% respectively. While TAF and BIC are also not recommended with rifabutin due to reduction in drug level that might potentially affect their treatment efficacy, the dosage of DOR need to be adjusted when rifabutin is used (See **Table 3**).

27.   Drug-drug interactions (DDIs) between antiretroviral agents and anti-tuberculous drugs can result in detrimental clinical outcome and should be evaluated with care. While rifamycin antibiotics (rifampicin, rifabutin and rifapentine) constitute the most crucial component of TB treatment regimens, they are associated with substantial drug-drug interactions with some major drugs that are used to treat patients with HIV co-infection. 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.

28.   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.

29.   **Table 3** highlights some of the major DDIs between ART and rifampicin/rifabutin that are of clinical importance.

Table 3. Major DDIs between ART and rifampicin/rifabutin (adapted from BHIV, DHHS and EACS guidelines[15,29,16])

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.

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30.   Immune reconstitution inflammatory syndrome (IRIS) is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections. It is further categorised into i) paradoxical IRIS when symptoms paradoxically worsened during the course of a treated infection; and ii) unmasking IRIS when there is a new presentation of a previously subclinical infection, both occurring during the ART-induced immune reconstitution period in association with inflammatory signs[31].

31.   TB-associated IRIS has been reported in 8% to >40% of patients starting ART after TB is diagnosed. Predictors of IRIS include a 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[32].

32.   In general, ART should be continued without interruption during IRIS unless life-threatening. Systemic steroid has been shown to confer clinical benefit when used to treat and alleviate symptoms associated with IRIS and can be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response[33]. Prophylactic use of systemic steroid has also been shown in a placebo-controlled randomized trial to lower the incidence of tuberculosis-associated IRIS[34]. Thus, preventive treatment with prednisolone, started within 48 hours of ART initiation and given at 40mg per day for 14 days, followed by 20mg per day for 14 days, may be considered for HIV-infected TB patients 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.

Infection Control

33. *M. tuberculosis* is spread by the airborne route. Effective infection control generally follows the hierarchy of administrative, engineering and personal controls. In health care settings, this begins with early suspicion of TB and respiratory isolation including the use of surgical masks by patients and placement in airborne isolation. A room with negative pressure and ventilation of at least 6 air changes per hour is ideal for isolation purpose. Use of air purifiers equipped with HEPA (high efficiency particulate air) filtration units may be an alternative measure. Donning of an N95 mask by health care personnel is recommended when conducting high risk procedures. Aerosolisation procedures such as pentamidine inhalation and sputum induction should be especially undertaken with care with strict observation of airborne precautions.

34. In general, respiratory isolation should not be terminated until after at least two weeks of effective treatment and the patient has clinically improved. For patients with MDR-TB, isolation should last till sputum conversion (three consecutive sputum smears negative for AFB collected 8 – 24 hours apart)[35].

35. The decision to discharge a patient with TB should be individualised, taking into account 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. As a statutorily notifiable disease, TB should be promptly reported to the Centre for Health Protection. (Available at https://www.dh.gov.hk/english/useful/useful_forms/files/dh1a.pdf) All TB patients should also be screened for HIV infection as explained above.

Way forward

36. Against the background of TB endemicity and an enlarging pool of HIV infected patients in Hong Kong, TB/HIV coinfection will continue to be a significant public health and clinical problem in the years to come. With the scale up of ART coverage for prevention in the past few years, and emerging evidence refining the management of TB/HIV coinfection along its cascade of care, we are working towards the goal to end the global tuberculosis epidemic. We should keep in view of the new scientific knowledge and innovations

including new drugs and regimen for both drug-susceptible and multidrug resistant TB, development of TB vaccines and new diagnostics, e.g. Xpert Ultra, Xpert MDR Cartridge and urine lipoarabinomannan etc., that may bring forth dramatic changes in TB prevention and care.

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References

1   World Health Organization. Global tuberculosis report 2019. 2019. Available from https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1. Accessed Aug 2020.

2   World Health Organization. Latent TB infection: updated and consolidated guidelines for programmatic management. Geneva:WHO, 2018. Available from https://apps.who.int/iris/bitstream/handle/10665/260233/9789241550239-eng.pdf?sequence=1. Accessed Aug 2020.

3   Tuberculosis & Chest Service/Special Preventive Programme, Centre for Health Protection, Department of Health. Surveillance report on TB/HIV co-infection in Hong Kong 2017. Available from https://www.info.gov.hk/tb_chest/doc/TB-HIV_Registry_2017.pdf. Accessed Aug 2020.

4   Scientific Committee on AIDS and STI, Centre for Health Protection, Hong Kong. Recommendations on the management of HIV and tuberculosis co-infection. Hong Kong: Department of Health, 2015. Available from https://www.chp.gov.hk/files/pdf/recommendations_on_the_management_of_human_immunodeficiency_virus_and_tuberculosis_coinfection_march_2015.pdf. Accessed Aug 2020.

5   World Health Organization. The end TB strategy. Geneva, WHO, 2015. Available from https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1. Accessed Aug 2020.

6   World Health Organization. WHO consolidated guidelines on tuberculosis Module 1: Prevention: Tuberculosis preventive treatment, 2020. Available from https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment. Accessed Sept 2020.

7   Cattamanchi A, Smith R, Steingart KR, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2011;56:230-8. doi: 10.1097/QAI.0b013e31820b07ab.

8   Leung CC, Chan K, Yam WC, et al. Poor agreement between diagnostic tests for latent tuberculosis infection among HIV-infected persons in Hong Kong. Respirology. 2016;21:1322–9. doi: 10.1111/resp.12805.

9   Wong NS, Leung CC, Chan KCW, Chan WK, Lin AWC, Lee SS. A longitudinal study on latent TB infection screening and its association with TB incidence in HIV patients. Sci Rep. 2019;9:10093. doi: 10.1038/s41598-019-46570-5.

10   Wong NS, Chan KCW, Wong BCK, et al. Latent tuberculosis infection testing strategies for HIV-positive individuals in Hong Kong. JAMA Network Open. 2019;2(9):e1910960. doi:10.1001/jamanetworkopen.2019.10960.

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[11] Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2011;60:1650-3.

[12] Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2018;67:723–726. doi: 10.15585/mmwr.mm6725a5.

[13] Sterling TR, Njie GJ, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69:1-11. doi: 10.15585/mmwr.rr6901a1.
Available from https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6901a1-H.pdf. Accessed Aug 2020.

[14] Swindells S, Ramchandani R, Gupta A, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019;380:1001–11. doi: 10.1056/NEJMoa1806808.

[15] Pozniak A, Bracchi M, Awosusi F, et al. British HIV Association guidelines for the management of TB/HIV co-infection in adults 2017. Available from https://www.bhiva.org/file/wciyxvzCuTmjD/BHIVA-TB-HIV-co-infection-guidelines-consultation.pdf. Accessed Aug 2020.

[16] European AIDS Clinical Society. EACS Guidelines version 10.0. November 2019. Available from https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf. Accessed Aug 2020.

[17] World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. Geneva, WHO, 2011.
Available from
http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf. Accessed Aug 2020.

[18] World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extra-pulmonary TB in adults and children. Policy update. Geneva, WHO, 2013.
Available from
https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf?sequence=1. Accessed Aug 2020.

[19] Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019;6:CD009593. doi: 10.1002/14651858.CD009593.pub4.

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[20]   World Health Organization, 2017. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Available from https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf?sequence=1. Accessed Aug 2020.

[21]   Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. Clin Infect Dis. 2014;59:1798-1804. doi: 10.1093/cid/ciu674.

[22]   Gopalan N, Santhanakrishnan RK, Palaniappan AN, et al. Daily vs intermittent antituberculosis therapy for pulmonary tuberculosis in patients with HIV: a randomized clinical trial. JAMA Intern Med. 2018;178:485-93. doi: 10.1001/jamainternmed.2018.0141.

[23]   Nahid P, Dorman SE, Alipanan N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. doi: 10.1093/cid/ciw376.

[24]   World Health Organization, 2019. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Available from https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1. Accessed Aug 2020.

[25]   Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011;365(16):1492-1501. doi: 10.1056/NEJMoa1014181.

[26]   Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011;365(16):1471-1481. doi: 10.1056/NEJMoa1013911.

[27]   Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011;365(16):1482-1491. doi: 10.1056/NEJMoa1013607.

[28]   Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis. 2011;52(11):1374-83. doi: 10.1093/cid/cir230.

[29]   Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed Aug 2020.

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30   De Castro N, Marcy O, Chazallon C, et al. Virologic efficacy of raltegravir vs. efavirenz based antiretroviral treatment in HIV1-infected adults with tuberculosis W48 results of the ANRS 12300 Reflate TB2 trial. Presented at: 10th IAS Conference on HIV Science;2019; Mexico City, Mexico. Available at: http://www.natap.org/2019/IAS/MOAB0101_july22_decastro.pdf. Accessed Aug 2020.

31   Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010;24(1): 103-108. doi: 10.1097/QAD.0b013e32832ec1f4.

32   Haddow LJ, Moosa MY, Mosam A, Moodley P, Parboosing R, Easterbrook PJ. Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. PLoS One. 2012;2(11):e40623. doi: 10.1371/journal.pone.0040623.

33   Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010;24:2381-90. doi: 10.1097/QAD.0b013e32833dfc68.

34   Meintjes G, Stek C, Blumenthal L, et al. PredART Trial Team. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. N Engl J Med. 2018;379:1915-25. doi: 10.1056/NEJMoa1800762.

35   Leung CC, Yew WW, Seto WH. Tuberculosis control measures in the health care setting. In: Tam CM, Leung (eds). TB Manual 2006. Centre for Health Protection, Department of Health 2006.

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