Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

(Adopted from Scientific Committee on AIDS and STI (SCAS), Centre for Health Protection, Department of Health, July 2008)

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Background

Worldwide, tuberculosis (TB) infects one third of the population. One of its main drivers has been the epidemic of human immunodeficiency virus (HIV) infection. On a biological and clinical level, it has been shown that HIV and TB reinforce each other. HIV increases the risk of TB disease by up to 100-fold. On the other hand, active TB is associated with an increased risk of opportunistic infections and rise in HIV viral load.[1, 2] Their coexistence in an individual also produces atypical features of TB complicating management.

The prognosis has dramatically improved for HIV infected patients with or without TB,[3] following the availability of highly active antiretroviral therapy (HAART). Nevertheless, its concurrent use with anti-tuberculosis treatment may be complicated by immune reconstitution inflammatory syndrome (IRIS) and complex drug-drug interactions.

In 1995, the Scientific Committee on AIDS published an information paper on the prevention and treatment of TB in HIV disease.[4] This was prior to the HAART era. Since then, significant gains have been made in the understanding of drug interactions, clinical presentations, and IRIS involving TB. Both new diagnostic methods and new antiretrovirals have also been developed.

The emergence of multidrug-resistant TB (MDR-TB), including extensively drug-resistant TB (XDR-TB), has been linked with though not explained by the HIV epidemic.[5] Evidence supports the pivotal role of a well funded public health infrastructure and appropriate clinical management in preventing resistance.

In this context, the Scientific Committee on AIDS and STI set out to provide recommendations for management of HIV-TB coinfection, in order to achieve a standard of care in Hong Kong that will translate into clinical benefit and public health control.

Screening

Given the close association and mutual aggravation between HIV and TB, as well as the treatable nature of both diseases, it is important that screening be done for a patient with either diagnosis, regardless of symptoms, signs and risk factors.

In Hong Kong, extrapulmonary TB and, at CD4 count <200/μL, pulmonary TB and TB of cervical lymph node, are AIDS-defining conditions. In recent years, TB incidence in HIV infected patients has steadily increased, despite a gradually declining notification rate in the general population. Among 855 cases of AIDS reported up to the end of 2006, 214 (25%) had been primarily defined by TB. In 2007, it overtook *Pneumocystis jiroveci* pneumonia as the most common primary AIDS-defining condition (41 vs 35%).[6]

It is therefore important to screen for TB in HIV-infected subjects by performing annual tuberculin skin tests (TST) using 2 units of PPD-RT23 and using 5 mm of induration as the cutoff as previously recommended.[7] Newer blood tests based on the detection of interferon-gamma released by T cells in response to *Mycobacterium tuberculosis* specific antigens may be useful alternatives to TST[8] and is being evaluated in Hong Kong. If a patient tests positive and active TB disease has been ruled out, treatment of latent infection is recommended. Of note, the standard therapy is isoniazid of 9 months. The two-month regimen of pyrazinamide and rifampicin is no longer recommended in HIV-uninfected persons because of hepatotoxicity.[9] It may be considered in HIV coinfected patients if no alternative exists and if benefits outweigh the risks.

It is equally important that all patients newly diagnosed with TB are screened for HIV. Diagnosis of coinfection should prompt the involvement of the HIV physician so that assessment can be made of

- the patient's immune and virologic status
- the need to provide prophylactic treatment against other opportunistic infections
- the timing of appropriate antiretroviral therapy and necessary adjustments in anti-TB treatment

Clinical diagnosis

In HIV disease, TB may present atypically, especially in those with a low CD4 count. As of end of 2006, there had been 129 HIV-infected patients seen at the Government HIV and Chest Clinics with TB as the AIDS-defining illness. Among them, 48 (37.2%) had extrapulmonary disease, most of whom had a CD4 count <200/uL.[6] Extrapulmonary TB commonly takes the form of lymphadenitis (other than cervical), bacteraemia, disseminated disease, pleural or pericardial disease, meningitis and tuberculomas. Chest radiography may show more frequent involvement of the lower lobes, or appear normal. Not uncommonly, sputum acid-fast bacilli (AFB) smear examination is negative. On the other hand, TB in those with higher CD4 cell counts present with more typical findings, similar to those in HIV-negative patients.

Thus, a high index of suspicion is necessary. A full medical evaluation for TB begins with history and physical examination. Subsequent investigations will be guided by the presentation and should usually include sputum examination and chest radiography. There should be a low threshold in proceeding to bronchoscopy. Depending on clinical circumstances, gastric aspiration, blood culture, bone marrow biopsy and lumbar puncture may also be required for a definitive diagnosis.

AFB in the sputum are not necessarily *M. tuberculosis*. In the HIV infected patient, *M. avium* complex (MAC) colonisation of the respiratory and gastrointestinal tracts may occur, especially in those with a very low CD4 count. Nucleic acid amplification tests such as PCR are useful for differentiating *M. tuberculosis* from nontuberculosis mycobacteria in smear-positive samples. Localised MAC disease is distinctly uncommon unless the patient has been newly put on HAART. *M. kansasii* may rarely cause pulmonary disease and should be considered in the differential diagnosis.

Failure to diagnose TB early could be lethal. When TB is suspected, nuclei acid amplification tests should be considered even in smear-negative sputum samples.[10] Where available, fluorescence microscopy is preferred to Kinyoun or Ziehl-Neelsen stain. Similarly, automated liquid culture systems such as BACTEC™ should be used instead of or concurrently with solid media. DNA hybridisation probes also aid in the rapid characterisation of culture isolates. Novel diagnostic approaches may find clinical roles in the near future.[11]

Treatment of tuberculosis

Treatment should be initiated promptly on the basis of clinical grounds before culture and drug sensitivity tests results are available. In disseminated disease, consideration should be given for empiric coverage of MAC as well. For TB, a standard initial phase of treatment comprising four drugs as used for HIV-negative patients is given, followed by a continuation phase with a reduced number of drugs. Rifabutin should generally substitute for rifampicin if protease inhibitors (PI) are contemplated. (Appendix 1 and 2)

Although international guidelines have recommended using a standard six-month regime for pulmonary TB in HIV positive patients,[12,13] there is concern about a higher risk of relapse.[14] Thus, extending the treatment duration to a total of nine months is preferred and especially recommended for those who have previously been treated for TB or have a delayed clinical or microbiologic response (e.g. persistence of positive culture by two months of treatment). For those who are put on a non-rifamycin regimen, or have TB of the CNS, bone and joint diseases, even longer durations of treatment are necessary.

'Directly observed treatment' (DOT) should be employed for the treatment of all TB patients, including those who are HIV coinfected. This is the standard practice in the TB and Chest Services of the Centre for Health Protection, and should be conducted as a comprehensive package incorporating education, enablers, incentives and holistic care which are conducive to treatment adherence.

Highly intermittent therapy as with twice or once weekly regimens is associated with a high risk of acquired rifamycin resistance and relapse among TB-HIV coinfected patients and cannot be recommended. For those patients with severe immune deficiency, e.g. CD4 <100/μL, drugs should preferably be given daily in the initial phase.[15]

Susceptibility tests against all first line anti-TB drugs should be performed routinely to guide treatment, as drug-resistant TB adversely impacts on prognosis and survival. Treatment of drug-resistant TB, especially MDR-TB and XDR-TB is complex[16] and should be undertaken in consultation with experts in the field.

The concomitant use of anti-TB and highly active antiretroviral therapy

If an HIV-positive patient has already been put on HAART, it should be continued even if incident TB is diagnosed and anti-TB treatment is to be initiated. However, adjustments may be needed to prevent adverse drug-drug interactions. Timely initiation of HAART should also be considered if HIV is diagnosed in a patient with TB, as the occurrence of TB is indicative of significant immune deficiency. Although the optimal timing of combined therapy is uncertain, anti-TB treatment should not be delayed whenever TB is diagnosed.

For a patient on HAART newly diagnosed with TB

Anti-TB treatment should be initiated as soon as possible. However, care must be exercised in the choice of drugs and their dosage. For example, rifampicin and, to a lesser extent, rifabutin induce the cytochrome P450 enzyme system. This may reduce plasma concentrations of protease inhibitors (PI) to subtherapeutic levels, resulting in the emergence of drug-resistant HIV. On the other hand, by inhibiting the cytochrome P450 enzyme, PI may increase the toxicity of rifamycins. Of note, other mechanisms are at play and some commonly used drugs may also inhibit the cytochrome system, such as the azoles and macrolides.

The interactions between antiretrovirals and rifamycins are complex but better understood now, so that fairly standard recommendations can be made (Appendix 3). As such, past approaches of interrupting

antiretrovirals or changing to double nucleoside therapy are no longer acceptable. Rifamycins should be included in the anti-TB regimen as far as possible because of their potency. If the decision is made to omit rifamycins, then the treatment duration should be appropriately prolonged. Nevertheless, the recommended dosage adjustments are approximate and based on normal liver function. In cases of doubt, therapeutic drug monitoring is recommended.

It cannot be overemphasised that good communication with the HIV physician is key to arrive at the optimal combination of drugs. In the uncommon event that a PI were to be discontinued so that rifampicin could be used, 2-3 days of washout are advisable. Rifampicin is then started at half dose and increased to full dose after a week.

For a patient diagnosed with TB who is not on HAART

As manifestation of immune deficiency, the occurrence of TB is a clinical indication of HAART. Studies have shown improved mortality and morbidity when HAART is added to TB treatment particularly in those with advanced immune deficiency. Nevertheless, there was also increased risk of adverse events and IRIS during the initial phase of anti-TB treatment which might require interruption of HAART and TB treatment.[17,18,19]

Simultaneous initiation of TB and HIV treatment is not recommended because of the sudden burden of polypharmacy and the difficulty in identifying the culprits in the event of hypersensitivity and other adverse reactions. There is no consensus on a CD4 threshold for initiating HAART, although a count below 100/μL should indicate urgency.

In principle, HAART should be initiated after the following issues are addressed:

- The patient has shown tolerance to the anti-TB regimen,
- There is reliable GI absorption,
- The patient understands and accepts this life-long treatment, and
- A potent and durable antiretroviral regimen is constructed given the patient's treatment history, known or suspected antiretroviral resistance, and potential interactions with the anti-TB drugs.

As aforementioned, the risk of adverse events is particularly high if HAART is added in the initial phase of TB treatment. Even with standard dose adjustment, the risk of hepatotoxicity is significant, especially with nevirapine-containing regimens and with hepatitis B and C coinfection.[20,21] HAART interruption may result in resistance that can be difficult to manage. Similarly, re-initiation of TB treatment is cumbersome and may also result in resistance.

If PI-based HAART were to be interrupted, all components should be stopped together. If not, mono or dual therapy will effectively be given which can easily lead to viral resistance. Of note, rifabutin should be increased to full dose accordingly in a few days' time. Interruption of therapy based on efavirenz or nevirapine is more complex. These non-nucleosides have long half lives and therefore should theoretically be stopped three to seven days prior to the other components. The HIV physician should be involved in the process.

Combination therapy is the standard in anti-TB treatment, as drug resistance emerges when there are inadequate effective drugs. Reintroduction or desensitisation of anti-TB drugs should therefore be done carefully to avoid any unduly prolonged period of suboptimal therapy which may induce resistance.

It is important to monitor adherence as well as adverse events. The dose adjustments necessary in combined treatment means that even if a patient is selectively non-adherent to the antiretrovirals, the dosages of his prescribed anti-TB drugs like the rifamycins may also become inadequate.

Immune reconstitution inflammatory syndrome

TB-associated IRIS is similar to the paradoxical reaction in HIV-uninfected patients. IRIS may be defined as 'presentation or clinical deterioration of opportunistic infections in HIV-infected patients as a direct result of the enhancement of immune responses to these pathogens during HAART'.[22] It occurs usually within 6 months, and occasionally as early as 10 days after the initiation of HAART.[23]

It is manifested as aggravation of original disease, constitutional deterioration with weight loss and fever, or occurrence of disease in a new site. IRIS may also present as unmasking of subclinical TB after HAART is started.[24] The clinical challenge is to differentiate IRIS from treatment failure and non-adherence, as the principles of management are very different (Box 1).

In general, HAART should be continued in the face of IRIS. There is no proven treatment but for mild to moderate disease, non-steroidal inflammatory drugs are used. In more severe disease, a short course of prednisolone up to 1mg/kg may be tried.[25] Interruption of HAART is a last resort in life-threatening situations.

Box 1. Clues suggestive of IRIS

- Temporal association between HAART and clinical phenomena (usually within 3 months)
- Unusual clinical manifestations
- Unexpected clinical course
- Exclusion of alternative explanations, e.g. drug resistance and non-compliance
- Evidence of immune restoration - e.g. rise in CD4 count, restoration of a positive PPD reaction, etc
- Histopathological appearance of florid cell-mediated response
- Preceding fall in viral load

Adapted from Lawn SD. Lancet Infect Dis 2005;5:361-73

Infection Control

M. tuberculosis is spread by the airborne route. Effective infection control follows the hierarchy of administrative, engineering and personal controls and, in the context of TB, begins with early suspicion and prompt respiratory isolation. Each institution should continually evaluate its facilities and isolation protocols to ensure effectiveness. In particular, the following should be in place for the management of TB disease, irrespective of the patient's HIV status: a practical and effective set of criteria for single and cohort isolation, adequate air change in the isolation room, availability of appropriate personal protective equipment, and continual education of front line health care staff regarding procedures and requirements of airborne isolation.

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 h apart).[26]

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.[27] All TB patients should preferably be screened for HIV infection before discharge. As a statutorily notifiable disease, TB should be promptly reported to the Centre for Health Protection.

Outlook

The incidence of TB in HIV infection is on an increasing trend and it is necessary that physicians who treat either disease be up to date with new developments in the field. In this regard, the evolution of MDR-TB, including XDR-TB, should be closely monitored.

It is also likely that new drugs and diagnostic methods will be developed and the optimal timing of adding HAART to anti-TB therapy will be better determined. This document is based on the best available knowledgebase as it is today. As with most other areas of medicine, management should be individualised according to the unique circumstances of each and every patient.

Appendix 1. First line anti-TB drugs

Standard dosage

Drug	Daily dose, mg/kg (maximum dose)	tiw dose
Isoniazid (INH)	5 (300 mg)	15 (900 mg)
Rifampicin (RIF)	10-12 (600 mg)	10 (600 mg)
Rifabutin (RFB)	5 (300 mg)	Not applicable
Pyrazinamide (PZA)	<50 kg: 1-1.5 g ≥50 kg: 1.5-2 g	<50 kg: 1.5-2 g ≥50 kg: 2-2.5 g
Ethambutol (EMB)	15-20 (1200 mg)	25-30 (2000 mg)
Streptomycin (SM)	15 (750 mg, 5 times per week)	15-20 (1000 mg)

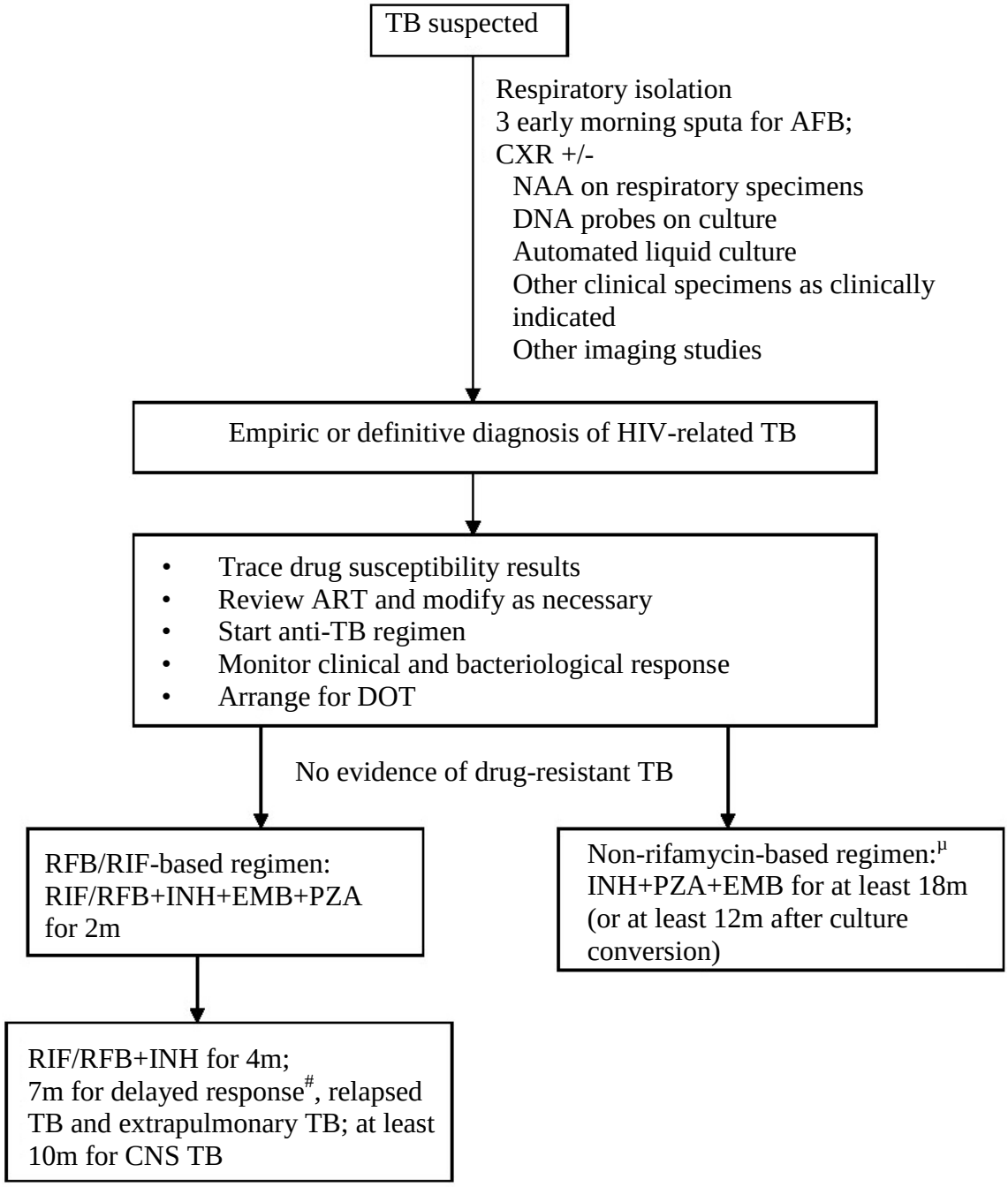
tiw, three times per week

Important adverse reactions

INH*	Hepatitis, cutaneous hypersensitivity, peripheral neuropathy [Rare: optic neuritis, convulsion, mental symptoms, aplastic anaemia, lupoid reactions, gynecomastia, arthralgia]
RIF	Hepatitis, cutaneous hypersensitivity, gastrointestinal reactions, thrombocytopaenic purpura, febrile reactions, 'flu' syndrome [Rare: shock, shortness of breath, haemolytic anaemia, acute renal failure]
RFB	Skin discoloration, uveitis, arthralgia, leukopaenia
PZA	Anorexia, nausea, flushing, photosensitisation, hepatitis, arthralgia, cutaneous reactions, hyperuricaemia, gout [Rare: sideroblastic anaemia]
EMB	Retrobulbar neuritis, arthralgia [Rare: hepatitis, cutaneous reactions, peripheral neuropathy]

*Co-administer pyridoxine 10-25 mg qd to prevent peripheral neuropathy; increase to 50-100 mg qd for 1-2 weeks for treatment.

Appendix 2. Approach to the management of TB in known HIV disease on treatment*



*Adapted from Lee NLS, Leung ECC, Tam CM. Tuberculosis in HIV/AIDS. In: Lee SS, Wu JCY, Wong KH (eds). *HIV Manual 2007*. CEID, CUHK & CHP, DH 2007 (Available at http://www.info.gov.hk/aids/english/hivmedcare/hivmanual2007.htm)

#response is delayed when assessment at the end of the 2-month initial phase shows (a) lack of culture conversion, or (b) lack of resolution or progression of signs and symptoms of TB

μnot generally recommended because of inferior treatment efficacy. May also consider using fluoroquinolone to construct alternative regimens.

NAA, Nucleic acid amplification; INH, isoniaizid; RIF, rifampicin; RFB, rifabutin; EMB, ethambutol; PZA, pyrazinamide

Appendix 3. Dosage adjustments for concurrent use of rifamycins and antiretrovirals[28]

Dosage adjustment of RIF in combination with some ARV (in mg)

	NVP	EFV	RTV/SQV combination*	LPVr (Kaletra™)	RTV*	MVC	RAL
RIF	***600 qd***	***600 qd***	***600 qd***	***600 qd***	***600 qd***	***600 qd***	***600 qd***
ARV	200 bid	600 qd#	400/400 bid	4 tablets bid or (2 tablets + RTV 300 mg) bid	600 bid	600 bid	400 bid

*High risk of hepatotoxicity; #may consider increasing to EFV 800 mg in those who weigh >60 kg

Dosage adjustment of RFB in combination with ARV (in mg)

	NVP	EFV	ATV	FPV	IDV	NFV	RTV-boosted ATV, FPV, IDV, TPV, DRV, LPV	MVC	RAL
RFB*	***300 qd***	***450-600 qd***	***150 qod or tiw***	***150 qd or 300 tiw***	***150 qd or 300 tiw***	***150 qd or 300 tiw***	***150 qod or tiw***	***300 qd***	***300 qd***
ARV	200 bid	600 qd	400 qd	1400 bid	1000 q8h	1250 bid	No change	No change	400 bid

*If RIF were to be replaced by RFB so that PI could be given, allow 2-3 weeks of full dose substitution (RFB 300 mg qd) before the PI is added.

ARV, antiretroviral
RIF, rifampicin
RFB, rifabutin
NVP, nevirapine
EFV, efavirenz
RTV, ritonavir
SQV, saquinavir
LPVr, lopinavir, coformulated with ritonavir
FPV, fosamprenavir
IDV, indinavir
NFV, nelfinavir
TPV, tipranavir
DRV, darunavir
MVC, maraviroc
RAL, raltegravir

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Test paper - Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

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1. Which of the following statements is incorrect about drug interaction and dosage adjustment with concomitant TB and HIV treatment?
   (a) Rifamycins are the TB drug most implicated with highly active antiretroviral therapy
   (b) Often but not always the dosage of protease inhibitor or non-nucleoside reverse transcriptase inhibitor need not be adjusted when administered together with TB drugs
   (c) Before the addition of protease inhibitor, a washout period of 1 week is recommended for switching rifampicin to rifabutin
   (d) Rifabutin is preferred to rifampicin as a whole when protease inhibitor is to be used
   (e) Kaltera is used at standard dose together with rifabutin 150mg alternate day or twice weekly

2. Which of the following is not true about the presentation of TB in HIV-infected subjects?
   (a) Extrapulmonary involvement is more common in HIV positive than HIV negative subjects
   (b) Disseminated TB disease is associated with a low CD4 count of 200/ul or less
   (c) Chest radiography may reveal more lower lobe shadows
   (d) Meningitis, gastro-intestinal disease and pleural effusion are common presentations of extrapulmonary TB in HIV patients
   (e) None of the above

3. Which of the following is incorrect about diagnosis of TB in HIV-infected patients?
   (a) Sputum for acid fast bacilli (AFB) smear examination is usually positive in pulmonary disease
   (b) AFB in sputum of HIV infected patients could be due to infections other than TB
   (c) Automated liquid culture systems such as BACTEC is preferred to solid culture media
   (d) DNA hybridization probe may aid rapid diagnosis
   (e) *Mycobacterium kanasii* should be considered in the differential diagnosis of pulmonary Mycobacterial diseases

4. Which of the following statements is not true concerning screening and management of TB and HIV?
   (a) HIV should be screened in patients diagnosed with TB and vice versa
   (b) A cutoff of 5mm induration is recommended for a positive tuberculin skin tests using 2 units PPD-RT23 in screening for latent TB in HIV patients
   (c) A course of 9-month isoniazid is the standard for treating latent TB infection
   (d) Blood testing for interferon-gamma against TB antigens is a standard diagnosis tool for latent TB in HIV infected subjects
   (e) None of the above

5. Which of the following is incorrect about HIV and TB interaction?
   (a) TB epidemic can be worsened by HIV infection if prevalence of the latter is high in the population
   (b) HIV increases the risk of TB disease by up to 10 fold
   (c) Multi-drug resistant TB and extensively drug resistant TB have been implicated in HIV patients
   (d) Mortality of TB could be higher in HIV infected than HIV negative patients

(e) Atypical presentation of TB is more common in HIV coinfected patients

6. Which of the following is not true about general principles of TB treatment in HIV patients?
   (a) Absence of microbiologic proof should not preclude TB treatment in clinically compatible setting
   (b) Directly observed treatment should be followed as a rule
   (c) A four-drug regimen of rifamycin, isoniazid, pyrazinamide and ethambutol is the standard first-line treatment
   (d) Six months TB therapy is often adequate
   (e) None of the above

7. Which of the following is incorrect about TB-related immune reconstitution inflammatory syndrome (IRIS) in HIV setting?
   (a) IRIS in TB/HIV coinfected patients is similar to the paradoxical reaction in HIV negative subjects
   (b) Unmasking of subclinical TB after initiation of HAART can occur
   (c) Other conditions such as treatment failure from drug resistance need to be excluded when considering IRIS
   (d) A rise in CD4 supports IRIS
   (e) Occurrence of disease in another site compared with original presentation excludes IRIS

8. Which of the following is incorrect about infection control in TB/HIV coinfection?
   (a) The same principle of infection control for TB in HIV negative subjects applies
   (b) Isolation for multi-drug resistant TB should last till sputum conversion
   (c) Early suspicion of active TB facilitates prompt respiratory isolation
   (d) Adequate air change and appropriate personal protective equipment are important components
   (e) None of the above

9. Which of the following is not true regarding TB treatment in a patient not yet on anti-HIV therapy?
   (a) TB treatment and highly active antiretroviral therapy (HAART) should be started simultaneously
   (b) Advanced immunosuppression calls for earlier initiation of HAART
   (c) Concomitant HAART and TB treatment initiation runs a higher risk of adverse drug events
   (d) Tolerance to TB drugs is one factor to consider on the timing of HAART
   (e) Being a life-long treatment further complicates HAART initiation as compared to TB treatment

10. Which of the following statement is not true concerning treatment of TB/HIV coinfection?
    (a) Anti-TB treatment takes priority over anti-HIV treatment initiation when TB disease is diagnosed
    (b) Reduction of protease inhibitor concentration by rifamycin is a concern that needs attention
    (c) HAART can often be continued but regimen may need to be adjusted when incident TB is diagnosed
    (d) Protease inhibitor may increase the toxicity of rifamycin such as hepatotoxiciy through inhibition of cytochromc P450 enzyme
    (e) None of the above