衞生防護中心
Centre for Health Protection

Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

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

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(a) to advise the Controller of the Centre for Health Protection (CHP) on the scientific basis for the prevention, care and control of HIV/AIDS and STI in Hong Kong;

(b) to develop recommendations and guidance regarding HIV/AIDS and STI in Hong Kong; and

(c) to keep under review local and international development of HIV/AIDS and STI.

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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. 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. 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.

2. In Hong Kong, extrapulmonary TB and, at CD4 count <200/μL, pulmonary TB and TB of cervical lymph node are AIDS-defining conditions. From 1996 to 2012, 358 (26.5%) of reported AIDS were defined primarily by TB. In 2005 and 2007, it briefly overtook *Pneumocystis jiroveci* pneumonia as the most common AIDS-defining condition. It is estimated that 1% of all TB disease in Hong Kong is associated with HIV. The corresponding figure in the US is 8%.

3. Management of TB/HIV coinfection commonly involves physicians other than HIV specialists, who may not be familiar with certain nuances in its management. 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. This new update of its recommendations has been made necessary by new insights and findings in recent years, particularly with regard to diagnosis, Immune Reconstitution Inflammatory Syndrome (IRIS), timing of antiretroviral therapy (ART), and drug-drug interactions.

Screening

4. Given the close association and mutual aggravation between HIV and TB, it is important that screening be done for the other infection in a patient with either diagnosis, regardless of symptoms, signs or risk factors.

5. Thus, it is appropriate to screen for TB in all HIV-infected subjects by performing annual tuberculin skin tests (TST) using 2 units of PPD-RT23 with 5 mm of induration as the cutoff as previously recommended.[1] If a patient tests positive and active TB disease has been ruled out, treatment of latent infection is also recommended as it reduces occurrence of TB disease by 60%.[2] Of note, treatment is indicated for HIV infected patients with significant recent exposure to an infectious source of TB regardless of TST results.

6. Nine months of isoniazid remains the standard treatment of latent TB, given either at 300 mg daily, or 900 mg twice weekly under DOT. Pyridoxine supplementation at 10-50 mg daily is recommended. Twelve doses of once-weekly isoniazid and rifapentine taken under observation are as effective and a useful alternative.[3] Four months of rifampicin may be considered if isoniazid resistance is of concern. On the other hand, the two-month regimen of pyrazinamide and rifampicin, though effective, cannot be recommended because of unacceptable hepatotoxicity.[4] Due caution should be exercised against drug drug interaction were a rifamycin-containing regimen to be used with concomitant antiretroviral therapy. For those patients who are contacts of MDR-TB, expert consultation should be sought to evaluate if treatment is warranted and with what regimen.

Interferon-γ release assay (IGRA)

7. Lately, use of IGRA is gaining acceptance for the diagnosis of latent TB. These tests, the QuantiFERON-TB Gold IN-Tube® and T-SPOT.*TB*®, address several limitations of TST, namely false positives arising from exposure to environmental mycobacteria or BCG vaccination, the need of the patient returning after 48 to 72 hours, and operator-dependent variability in test reading.

8. In low income countries highly endemic of TB, the role of IGRA is limited. The clinical benefit of treating latent TB has been restricted to randomised controlled trials based on TST. There is poor concordance of results between IGRA and TST in the HIV infected. In addition, its cost effectiveness is doubtful since IGRA does not predict active TB better or is more sensitive than TST in these settings.[5, 6]

9. However, in high income countries with incidence of TB<100/100,000, the rationale of using IGRA is stronger.[7] Its predictive utility of active TB is better than TST. It is also more specific. In one local study, CD4 count<100/μL was a risk factor for new, incident TB disease independent of TST results in HIV infected patients.[8] Thus, dual testing with TST and IGRA at low CD4 counts could enhance case finding. By dispensing with the need to return for reading, IGRA should also improve the current suboptimal compliance to annual testing.

10. Therefore, we consider that in Hong Kong, IGRA is an acceptable alternative to TST for use in the HIV infected population. At a low CD4 count <100/μL, dual testing by TST and IGRA is advised. A positive result with either test is an indication for treatment. If convenient, blood should be drawn for IGRA before or on the same day as placing the TST to avoid potential PPD sensitisation.

11. It is equally important that all patients newly diagnosed with TB are screened for HIV. Diagnosis of coinfection allows the involvement of the HIV specialist who would make assessment of (a) other complications arising from HIV disease; (b) the patient's immune and virologic status; (c) the need to provide prophylactic treatment against other opportunistic infections; and (d) the timing of appropriate ART and necessary adjustments in anti-TB treatment. Recent guidelines published by this Committee emphasised that the process of informed consent should be simplified and need not be burdened with counselling that was irrelevant.[9]

Clinical diagnosis

12. In HIV disease, TB may present atypically, especially in those

with a low CD4 count. In 2012, among the 20 cases of coinfections reported by the Chest and HIV clinics of the Department of Health, the median presenting CD4 count was 192/μL and nine (45%) had extrapulmonary TB. Pretreatment susceptibility results were available in 16 patients; one was MDR-TB, and 13/16 (81%) were fully susceptible.[10]

13. Extrapulmonary TB commonly takes the form of lympahadenitis (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 generally presents with more typical findings, similar to those in HIV-negative patients.

14. Thus, a high index of suspicion is necessary for diagnosis. 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. In the presence of unexplained clinical or radiological findings, there should be a low threshold in proceeding to bronchoscopy. Depending on clinical circumstances, gastric aspiration, find needle aspiration of lymph node, blood culture, bone marrow biopsy and lumbar puncture may also be required for a definitive diagnosis.

15. AFB in the sputum is 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 (NAAT) 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 ART. *M. kansasii* may also rarely cause pulmonary disease and should be considered in the differential diagnosis.

16. After years of adoption, the use of fluorescence microscopy, automated liquid culture systems and NAAT is now commonplace. Recently recommended by WHO is GeneXpert MTB/RIF™, an automated, PCR-based molecular test for the rapid detection of *M. tuberculosis* with sensitivity and specificity that approach culture.[11] Notably, it can be used for selected extrapulmonary samples and it simultaneously detects rifampicin resistance, the majority of which is associated with isoniazid resistance, i.e. MDR-TB. Molecular tests for resistance to other anti-TB agents are also being evaluated.

Treatment of tuberculosis

17. Treatment should be initiated promptly on the basis of clinical grounds or rapid molecular tests before culture and drug susceptibility test 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 an antiretroviral regimen other than that based on efavirenz is contemplated. (**Appendix 1 and 2**)

18. Although a standard six-month regimen for pulmonary TB is considered adequate in some developed countries for HIV positive patients, studies have shown a higher risk of relapse.[12] 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, even longer durations of treatment are necessary.

19. 'Directly observed treatment' (DOT) should be employed for the treatment of all TB patients, including those who are HIV coinfected. This is also the standard practice of the TB and Chest Services 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.

20. Highly intermittent therapy such as 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 count <100/μL, drugs should preferably be given daily at least in the initial phase.

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.[13]

Concomitant anti-TB and antiretroviral therapy

22. If an HIV-positive patient has already been put on ART, it should be continued even if incident TB is diagnosed. Anti-TB treatment should be initiated without delay. ART should also be started in a timely manner if HIV is diagnosed in a patient with TB, as the occurrence of TB is indicative of significant immune deficiency. In either case, judicious choice of drugs and dosage adjustments may be needed to prevent adverse drug-drug interactions.

For a patient on ART newly diagnosed with TB

23. 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 rifabutin induce the cytochrome P450 enzyme system. This may reduce plasma concentrations of certain antiretrovirals to subtherapeutic levels, resulting in the emergence of drug-resistant HIV. Conversely, the toxicity of rifamycins may also be increased when the same enzymes are inhibited by antiretrovirals. Of note, other mechanisms may also be at play and some commonly used drugs, such as the azole and macrolides, also inhibit the cytochrome system.

24. 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. Triple or quadruple nucleoside antiretroviral therapy may rarely be considered as a short term alternative only if the viral load is low. Otherwise, antiretroviral therapy should consist of at least three drugs from two classes.

25. Rifampicin or rifabutin should be included in the anti-TB regimen as far as possible because of their potency. Rifapentine should not be used because of the risk of acquired rifamycin resistance with its intermittent use and currently limited knowledge of its interaction with antiretrovirals. Based on proven clinical effectiveness, and susceptibilities permitting, an efavirenz-based antiretroviral regimen in combination with rifampicin-containing TB treatment is preferred. It is noted that the recommended dosage adjustments are only approximate, based on normal liver and kidney functions, and subject to significant inter-individual variation. In case of doubt, therapeutic drug monitoring should be considered.

For a patient diagnosed with TB who is not on ART

26. As a manifestation of immune deficiency, the occurrence of TB is a clinical indication of ART. However, the optimal timing of HIV treatment in the course of anti-TB treatment was not clear until recently. A series of clinical trials have confirmed that although early integration of ART into TB treatment was associated with adverse effects and IRIS, it also resulted in lower rates of new AIDS-defining illnesses or death.[14, 15, 16] Importantly, this is supported by local experience. Among 260 coinfected patients in Hong Kong, antiretroviral therapy within two months of TB treatment was associated with a favourable outcome (91% vs 67%).[17]

27. Synthesis of these data led to the recommendation that ART should be started

(a) within 2 weeks for those with CD4 count <50/μL;
(b) within 4 weeks for those with CD4 count 50-200/μL AND severe clinical disease; and
(c) within 8-12 weeks for the rest, i.e. in the continuation phase of TB treatment.

However, this is merely a general time frame intended to convey the degree of urgency of antiretroviral therapy commensurate with the extent of immune deficiency. Clinical circumstances are often difficult and may override the intention to start ART. Caution is especially advised for those with TB meningitis, in whom early initiation of ART (as compared to deferral of therapy to 8 weeks) does not confer survival benefit and is associated with more severe adverse events, in particular intracranial IRIS.[18]

28. As aforementioned, the risk of adverse events is high with concomitant ART and TB treatment. For instance, the risk of hepatotoxicity is significant even with recommended dosage adjustments, especially with nevirapine-containing regimens, double-dosing or superboosting of lopinavir, and coinfection with hepatitis B or C. ART interruption may result in resistance that is difficult to manage. Similarly, re-initiation of TB treatment is cumbersome and may also result in resistance.

29. If ART were to be interrupted, all components should generally be stopped together. If not, mono or dual therapy will effectively be given which can easily lead to viral resistance. However, 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.

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

31. 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 inappropriate.

Immune Reconstitution Inflammatory Syndrome

32. In one meta-analysis, TB-associated IRIS is among the most common variety of IRIS, occurring in 15.7% of patients.[19] It is similar to the paradoxical reaction in HIV-uninfected patients. In HIV infected individuals, the enhancement of immune responses by ART results in atypical or worsening of disease, often after initial improvement. This happens as early as 10 days of ART. Several definitions of TB-IRIS have been put forward with fairly good agreement.[20] They generally divide TB-IRIS into -

- Paradoxical TB-IRIS – new, atypical or worsening TB disease within 3 months of ART initiation in a patient already on anti-TB treatment, after excluding treatment failure or nonadherence, drug toxicity, and other opportunistic infection and neoplasms.
- ART-associated TB – occurrence of TB disease after a patient has already been put on ART. A subset of this will be unmasking of TB by immune reconstitution. Unmasked patients either manifest atypical TB within 3 months of ART or display a paradoxical reaction upon initiation of anti-TB treatment.

33. The major clinical challenge is to differentiate paradoxical IRIS from treatment failure and non-adherence, as the principles of management are very different (**Box 1**). In general, ART should be continued in the face of IRIS. Non-steroidal anti-inflammatory drugs are usually not helpful, but systemic steroid has been shown in a small trial to confer clinical benefit.[21] Additional therapies may be required for complications, e.g. aspiration of abscess to prevent rupture. In life-threatening situations such as neurological TB-IRIS, high dose

Box 1. Clues suggestive of IRIS

- Temporal association between ART 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 TST, etc
- Histopathological appearance of florid cell-mediated response
- Preceding fall in viral load

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

corticosteroids are indicated and interruption of ART considered.

Infection Control

34. *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 may be necessary 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. A local exhaust ventilation device (e.g. a HEPA booth) would be useful for this purpose.

35. 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).[22]

36. 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.[23] As a statutorily notifiable disease, TB should be promptly reported to the Centre for Health Protection. All TB patients should also be screened for HIV infection as explained above.

Outlook

37. The progress of science in the last two decades has successfully addressed the many controversies in the management of TB HIV coinfection.

However, 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. In particular, the evolution of MDR-TB, including XDR-TB, should be closely monitored.

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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)	10-12 (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)

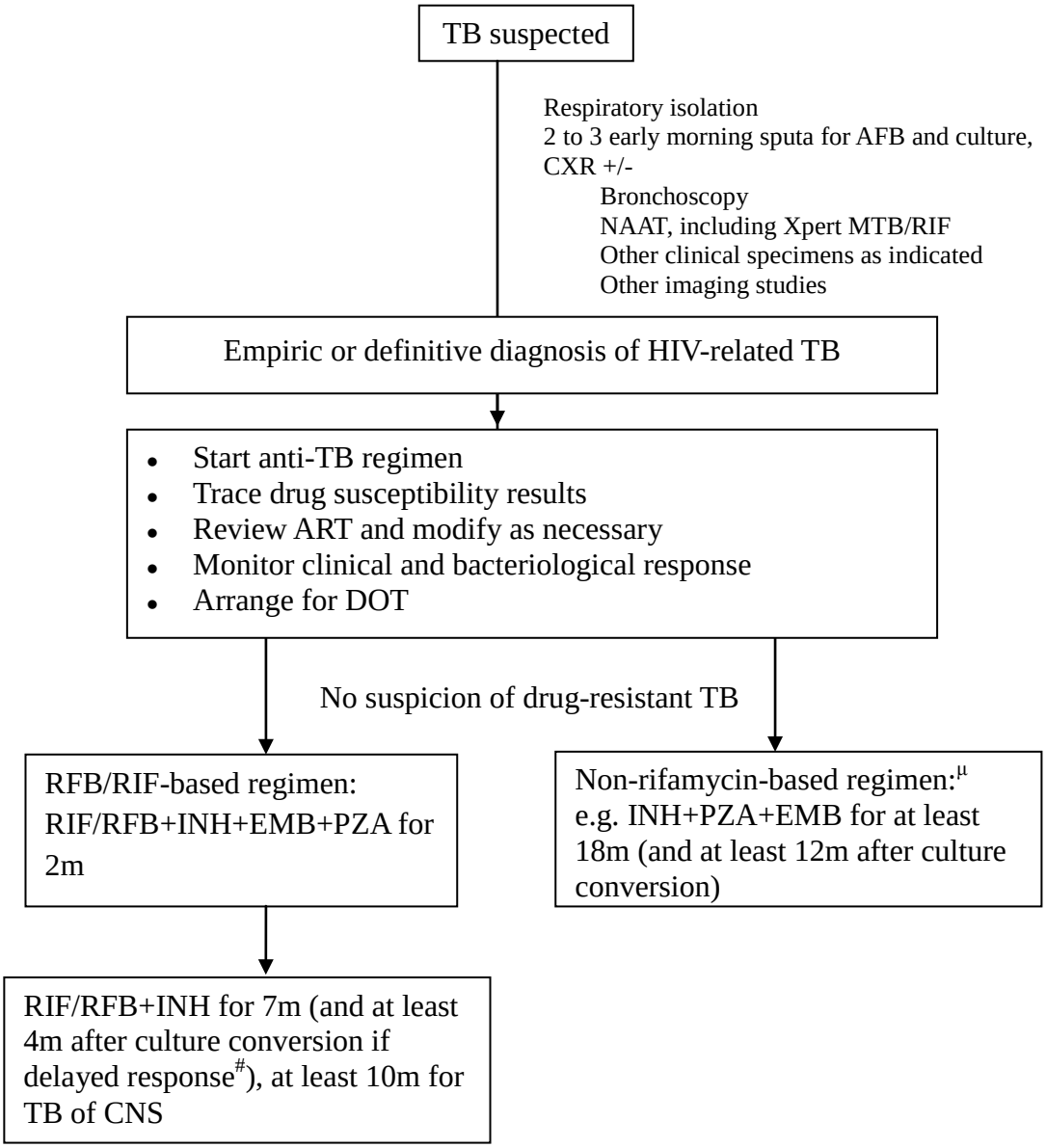
tiw, three times per week

Important adverse reactions

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

*Co-administer pyridoxine 10-50 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, Chan ACK, Leung CC. Tuberculosis in HIV/AIDS. In: Lee SS (ed). *HIV Manual 2013*. CEID, CUHK & CHP, DH
(Available at http://www.hivmanual.hk/content.html?gonum=30)

#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 efficacy. Considerusing fluoroquinolone to construct alternative regimens.

NAAT, Nucleic acid amplification test; INH, isoniazid; RIF, rifampicin; RFB, rifabutin; EMB, ethambutol;

PZA, pyrazinamide

Appendix 3. Dosage adjustments for concurrent use of rifamycins and certain antiretrovirals[24]

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

	EFV	NVP*	Kaletra™ tablet (LPV 200mg/RTV 50mg)*	MVC@	RAL@
ARV	600 qd	200 bid#	4 tablets bid or (2 tablets + RTV 300 mg) bid	600 bid	800 bid
RIF	***600 qd***	***600 qd***	***600 qd***	***600 qd***	***600 qd***

*Beware hepatotoxicity; # Initiate and maintain at 200 mg bid; @ Limited clinical experience

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

	NVP	EFV	ETR (without PI)	ATV	FPV	RTV-boosted ATV, FPV, TPV, DRV, LPV	MVC	RAL
ARV	200 bid	600 qd	200 bid	400 qd	1400 bid	Standard dosage	300 bid	400 bid
RFB	***300 qd***	***450-600 qd or 600 tiw***	***300 qd***	***150 qd or 300 tiw***	***150 qd or 300 tiw***	***150 qd or 300 tiw***	***300 qd***	***300 qd***

If RIF were to be replaced by RFB so that a PI could be given, preferably allow up to 2 weeks of full dose substitution (RFB 300 mg qd) before adding PI.

ARV, antiretroviral
RIF, rifampicin
RFB, rifabutin
NVP, nevirapine
EFV, efavirenz
ETR, etravirine
RTV, ritonavir SQV, saquinavir
ATV, atazanavir
FPV, fosamprenavir
TPV, tipranavir
DRV, darunavir
LPV, lopinavir (coformulated with RTV)
MVC, maraviroc
RAL, raltegravir

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