Recommendations on the Treatment of Latent TB infection in HIV-positive Persons in Hong Kong

Scientific Committee on AIDS
of
Hong Kong Advisory Council on AIDS

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BACKGROUND

1. Tuberculosis (TB) is an important complication of human immunodeficiency virus (HIV) infection. In the United states, the Centers for Disease Control and Prevention (CDC) has classified TB as an AIDS-defining illness for surveillance purpose.[1] In Hong Kong, the Scientific Committee on AIDS proposed to include extrapulmonary TB as an AIDS-defining condition, while pulmonary TB is included only if one's CD4 count is below 200/ul.[2] This decision was made to take into consideration the low HIV rate and the endemicity of TB in the Hong Kong setting.

2. The prevention of TB in HIV infected individuals shall be achieved through the prevention of exposure to infectious TB in the first place. If infection has or has likely taken place, "preventive" treatment may be indicated. Preventive treatment using isoniazid (INH) monotherapy had been recommended by the American Thoracic Society (ATS) as early as in the 1960's.[3] In the recent guidelines by ATS, the term "treatment of latent TB infection (LTBI)" is preferred to "preventive therapy" or "chemoprophylaxis".[4] In as early as 1990, the United States CDC recommended INH for 12 months for treatment of LTBI in all HIV-infected persons with a positive tuberculin skin test (TST) as well as those who had recently been exposed to infectious TB.[5]

3. The applicability of such recommendations to Hong Kong was initially questioned because of a number of concerns: different TB epidemiology, higher prevalence of INH resistance, and wide coverage with BCG vaccination confounding interpretation of TST results. In subsequent years, 7 randomized controlled trials in the United States, Haiti and some Sub-Saharan African countries have evaluated different regimens for the treatment of LTBI in HIV-positive individuals.[6,7,8,9,10,11,12] These studies provided support to the regimens and their effectiveness in groups of subjects who would benefit from the strategy.

4. In February 1998, World Health Organisation (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued a policy statement indicating that *there can ... no longer be any doubt that treatment of PPD+ (and HIV infected) individuals living in a setting with a high prevalence of TB with INH will reduce the risk of developing active TB in the short term to around 40%*, and *INH preventive treatment should be part of the package of care for people living with HIV/AIDS*.[13]

5. Taking reference from the research findings and national/international strategies, the following recommendations are formulated by the Scientific Committee on AIDS to facilitate the development of protocols in the management of LTBI in Hong Kong. The likely benefits of the recommendations are the reduction of morbidity and possibly mortality related to TB in HIV infected persons, secondary transmission to others, and probable HIV progression aggravated by TB. The algorithm of the proposed management is in Appendix I.

GUIDING PRINCIPLES

6. To prevent the development of TB in HIV seropositive individuals, measures for the prevention of exposure to infectious sources should be emphasised.

7. HIV-associated tuberculosis is an opportunistic infection, the development of which decreases markedly once the CD4 count is over 100 cells/ml.[14] Highly active antiretroviral therapy (HAART) is effective in substantially reducing the risk of developing TB.[15]

8. INH preventive treatment (IPT) is the standard therapy for LTBI in the vast majority of individuals dually infected by TB and HIV. The high prevalence of primary INH resistance is however noted, the implications of which should be monitored over time.

9. The effectiveness of treatment for LTBI depends on its proper diagnosis, which is in turn reliant on the correct interpretation of the TST. A cutoff value of 5 mm as recommended by ATS[4] is appropriate for considering the initiation of treatment in HIV infected persons in the local setting.

10. Regimens for LTBI treatment are not only inadequate for active TB but would foster the development of resistance. Before treatment of LTBI is begun, active disease should be ruled out. It is necessary also to monitor for the development of TB symptoms during LTBI treatment.

11. In an HIV-infected person diagnosed with LTBI, a course of treatment with INH for 12 months is recommended.

INITIAL EVALUATION

12. For persons newly diagnosed as having HIV infection, TST should be done as part of the initial evaluation. If the result is negative and the individual is at significant risk for exposure to MTB, annual repeat testing should be considered although the reliability of the TST might diminish as the CD4+ T-lymphocyte count declines. For persons whose immune function has improved because of HAART, repeat TSTs may also be considered. Testing with anergy panel is no longer appropriate as no benefit is demonstrated with treatment for LTBI in those who are TST negative or anergic.[16]

13. A proper diagnosis of LTBI is crucial in guiding its subsequent management. This is in turn reliant on the correct interpretation of the TST. It must be cautioned that recent conversion to TST positivity in an HIV infected individual may represent a boosted phenomenon, new TB infection, or improvement of cell mediated immune function. Active TB should be ruled out in all circumstances.

14. The cutoff value for the TST depends on the purpose of testing and the population tested. In the general population in Hong Kong including primary school children, a cutoff value of 10 mm has been used after testing with 2 units of PPD-RT23.[17] In relation to the purpose of deciding whether or not to give treatment for LTBI in HIV infected individuals, a lower cutoff value of 5 mm as recommended by ATS[4] is

more appropriate in the local setting.

COMMENCEMENT OF LTBI TREATMENT

Standard regimen

15. In an HIV-infected person diagnosed with LTBI, INH at a dose of 5mg/kg daily (maximum 300 mg daily) for 12 months is recommended. The maximal beneficial effect of LTBI treatment is usually achieved by 9 month, and minimal additional benefit is gained by extending therapy beyond 12 months[4]. Though these figures were elicited in HIV-negative individual, they are likely to be applicable in HIV-positive persons.

16. The main indication for LTBI treatment is a positive TST, which is defined as an induration of 5 mm or greater. Before initiating treatment, active TB must first be ruled out.[18]This is done by both a chest radiograph examination and noting relevant symptoms and/or signs. Sputum smears and cultures for AFB should be considered if there is any clinical suspicion. There must also be:

(a) Low suspicion of infection with INH or multi-drug resistant TB.

(b) No contraindication to INH.

17. The contraindications to treatment of LTBI with INH are:

(a) Previous treatment of TB or treatment of LTBI. However, repeat treatment may be considered for those who have recently been close contacts of infectious TB patients.

(b) Previous adverse reactions to INH.

18. Compliance is essential for treatment of LTBI to work. Proper counselling before starting treatment is essential. Rationale of treatment for LTBI, its limitations, possible side effects, and the need for good compliance are to be discussed. Available information suggests that directly observed treatment (DOT) is associated with higher rates of treatment completion compared to self-administered treatment, and is, under certain circumstances, more cost-effective.[19]

Alternative regimens

19. Treatment of LTBI with drugs other than INH should be considered in circumstances where infection with INH resistant TB is suspected, where there is contraindication to the use of INH, or when prolonged therapy is not desirable. Regimens using rifampicin (RIF) and/or pyrazinamide (PZA) with or without INH have been evaluated in comparison with INH monotherapy against TB in HIV positive individuals[9-12]. These regimens have the advantages of being of comparatively shorter duration. The use of RIF 600mg and PZA 20mg/kg daily for two months is one such alternative regimen, the efficacy of which is equivalent to 12 months of INH 300 mg daily[12]. Liver toxicity is a concern and intensive monitoring is recommended.[20] The other disadvantages are increased cost and pill burden. Moreover, potential drug-drug

interactions between RIF and a PI or an NNRTI should first be addressed and dosage adjusted. Rifabutin (RFB) may need to be considered in place of RIF to minimize drug interaction although, as treatment for LTBI, it has never been evaluated.

20. The generally accepted dosage when RIF or RFB is combined with some PI and NNRTI is as in Appendix II.[21]

21. Other authorities have advocated the treatment of HIV infected individuals who're close contacts of active TB. The best regimen for the treatment of LTBI in those who are close contacts of infectious MDR-TB has not been established. Some authorities recommend PZA+ethambutol or PZA+quinolone (levofloxacin or ofloxacin) for 12 months[4]. Consultation with experts is advisable.

MONITORING TREATMENT

22. During treatment, the client should be evaluated for adverse effects or development of active TB. INH is associated with a relatively high incidence of peripheral neuropathy in HIV-infected persons. Concomitant pyridoxine is advisable. INH-induced hepatitis is more prone to occur in the older age groups. It is important to watch out for signs and symptoms of hepatitis, and to monitor with liver function tests when clinical suspicion of hepatitis arises.

23. Currently there are no data supporting the regular use of continuous or repeated courses of INH for treatment of LTBI in HIV-infected persons. Neither is the treatment of LTBI indicated after treatment of active TB. TST after a course of treatment for LTBI is unnecessary.

24. It must be noted that the efficacy of treatment for LTBI is never 100%. Exogenous re-infection is also a genuine possibility with passage of time, especially in high prevalence areas like Hong Kong. The clinician is advised to maintain a high index of suspicion of TB when the clinical presentation is compatible, regardless of whether treatment for LTBI has been given.

OTHER CONSIDERATIONS

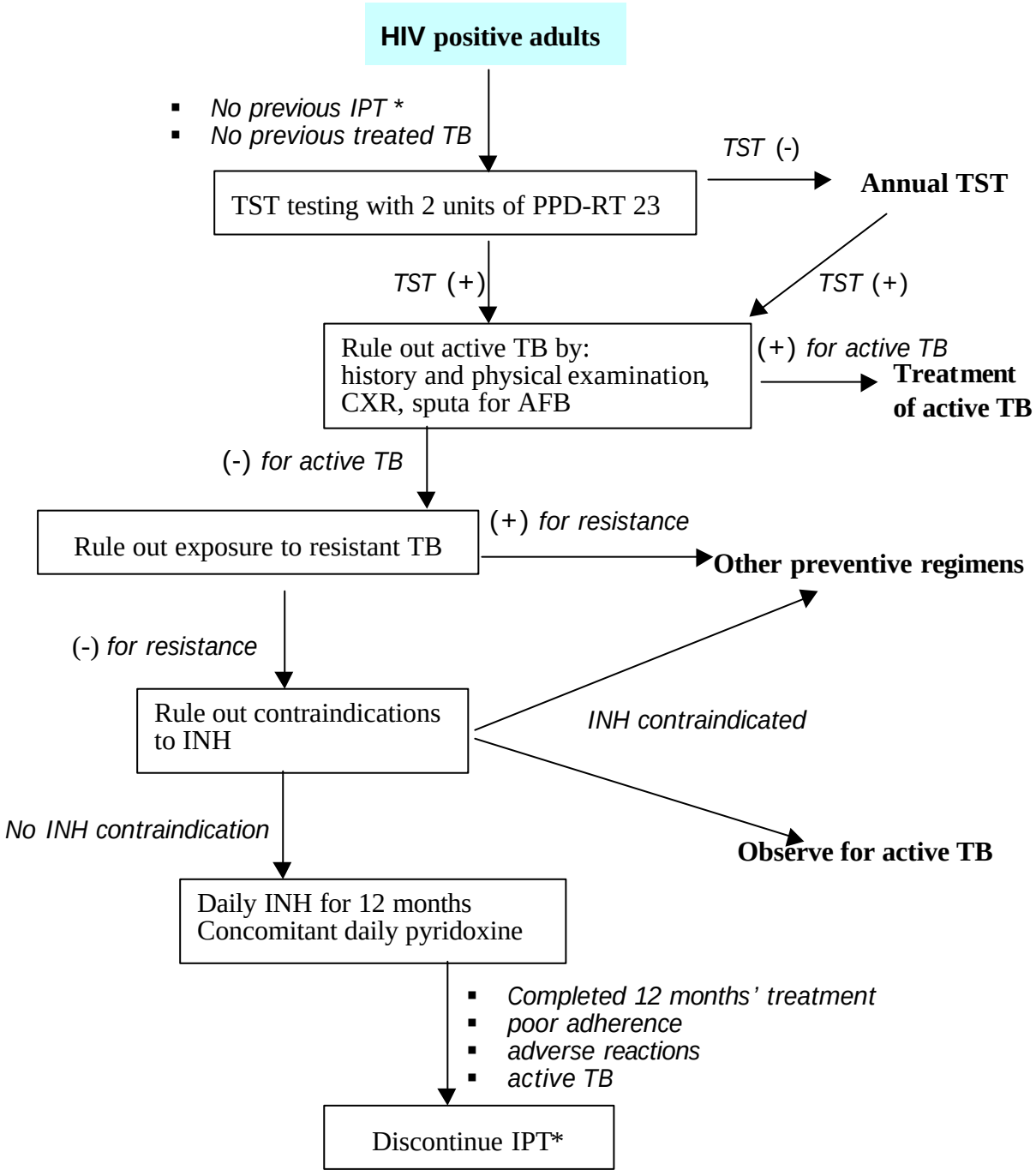
25. TB in HIV is an increasing health problem. The prevention of HIV-related TB depends on the ability to control TB as much as the control of HIV infection. HIV-associated tuberculosis is an opportunistic infection, the development of which decreases markedly once the CD4 count is over 100 cells/ml.[14] Highly active antiretroviral therapy (HAART) is effective in substantially reducing the risk of developing TB.[15] The provision of HAART therefore forms one important arm of the management of the dual infection of TB and HIV.

26. Some other areas are worth noting. There are the uncertain roles of repeat courses or continuous treatment of LTBI in high prevalence areas, and the impacts on

the prevalence of INH resistance when INH monotherapy for LTBI is widely prescribed without direct observation. The treatment of LTBI in paediatric HIV-infected patients who have been BCG vaccinated is another area which has not been adequately studied. Generation of local data on the treatment of LTBI among the HIV-infected is desirable to evaluate the approach relevant for the local setting. Continuous review of the literature will also be required for updating and/or revision of the recommendations in this document.

APPENDICES

Appendix I: Algorithm on the Treatment of LTBI in HIV infection



* IPT: INH preventive treatment

<u>Appendix II</u>. Dosage adjustment for LTBI treatment for concomitant antiretroviral therapy

Table 1. Dosage adjustment of Rifampicin (RIF) in combination with common antiretroviral regimens (daily dosage in mg)

	NVP 200 bid	EFV 600 qd	RTV/SQV combination 400/400 bid	RTV 600 bid
RIF	**600 qd** +	**600 qd** +	**600 qd** +	**600 qd** +

Table 2. Dosage adjustment of Rifabutin (RFB) in combination with common antiretroviral regimens (daily dosage in mg unless otherwise specified))

	NVP 200 bid	EFV 600 qd	SGC-SQV 1200 tid	APV 1200 bid	IDV 1000 q8h, or 1200 q8h	NFV 750 tid, or 1000 tid, or 1250 bid	RTV 600 bid
RFB qd	**300 qd** +	**450 qd** +	**300 qd** +	**150 qd** +	**150 qd** +	**150 qd** +	**Daily RFB contra-indicated;** **150 mg biw - tiw** +

ABBREVIATIONS: APV – amprenavir; EFV – effavirenz; IDV – indinavir; NFV – nelfinavir; NVP – nevirapine; RTV – ritonavir; SQV – saquinavir; SGC-SQV – soft gel capsule saquinavir.

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About the Scientific Committee on AIDS

The Scientific Committee on AIDS (SCA) works on the scientific, technical, professional and surveillance aspects of HIV/AIDS. It was renamed from the former Scientific Working Group on AIDS in 1990 to give it equal status to the other two committees under the Advisory Council on AIDS (ACA). It is now in its fourth term of ACA (1999-2002), with its first meeting held on 19 November 1999.

SCA has the following terms of reference:

(a) to evaluate the HIV/STD surveillance system in Hong Kong;

(b) to develop and recommend technical and professional guidelines/protocols on HIV/AIDS prevention, management and control;

(c) to provide scientific and clinical input to the process of planning and development of services in HIV/AIDS prevention, management and control, and the training of health and community care workers; and

(d) to recommend and coordinate researches on the clinical, scientific, epidemiological and sociological aspects of HIV/AIDS with special reference to Hong Kong.

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